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ORIGINAL CONTRIBUTION

Modulation of the lower critical solution temperature of 2-Alkyl-2-oxazoline copolymers

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Abstract Living cationic copolymerization of 2-isopropyl-2-oxazoline with 2-*n*-propyl-, 2-*n*-butyl-, and 2-*n*-nonyl-2-oxazoline results in gradient copolymers of defined composition, narrow molar mass distributions (PDI=1.09–1.3), and defined overall degree of polymerization, set to $n=25$ for all polymers. The introduction of monomer units of stronger amphiphilic character results in a systematic decrease of the lower critical solution temperature (LCST). The LCST modulation can be controlled by the choice of the comonomer as well as the comonomer ratio and was tuned in the temperature range from 46 to 9 °C.

Keywords Poly(2-oxazoline) · LCST · Thermo-responsive polymer · Living cationic polymerization · Copolymer

Introduction

In the development of next-generation polymer therapeutics, hydrophilic and non-toxic or "biocompatible" [1–5] poly(2-oxazoline)s (POx) gained much interest recently because of the possibility to fine-tune the composition, molecular architecture, and functionality of this polymer class. As PEG, POx is synthesized by means of living ionic polymerization, and thus, well defined in terms of the molar mass distribution (polydispersity index, $\mathrm{PDI} = \overline{M}_w/\overline{M}_n \sim 1.01 - 1.3$) and chain end-functionality [6]. In contrast to the well-known poly(ethylene glycol) (PEG), POx can be equipped with defined chain-end functions [2, 8] and with various functional pendant groups. Besides the reported functions such as hydroxyl- [10, 11], phenyl- [12], carboxyl- [10, 13], carbazol-functionalities [14, 15], iodoaryl- [16], bipyridyl- [17, 18], furan-, and maleimide modifications [19], as well as thiol [20], we introduced recently the aldehyde [21], alkyne [22], and amine [23] functionalities for efficient and orthogonal polymer analogue reactions. Functional monomers or consecutive polymer analogue chemical ligation offers the possibility to introduce various, i.e., biologically relevant moieties such as short peptide motifs that can act as homing devices along with pharmacologically active groups or markers for targeted drug delivery [24] or as cross-linked hydrogels [25] for controlled drug release applications [2–5, 27]. Copolymerization of functionalized 2-oxazoline monomers with "inert" ones, having short alkyl chains (methyl-, ethyl-, *n*-propyl), results in well-defined functional polymer constructs of tunable water solubility and biodistribution [2].

Analogue to most of the water-soluble polymers, POx displays a lower critical solution temperature (LCST) above that which the polymer becomes insoluble in water and precipitates (referred to as the cloud point). This temperature sensitivity is frequently discussed in the frame of the development of stimulus-responsive or "smart" materials [28], with a focus on the popular poly(*N*-isopropylacrylamide) (PNIPAAm) and its use in biomedicine, as the LCST of PNIPAAm is within the physiological range, i.e., human body temperature. Although the mechanism is still not fully understood on the molecular scale [29], this behavior is

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well known and studied for polyacrylamides and their derivates [30, 31].

The LCST for a given polymer is generally dependant on the polymer concentration, the polymer architecture (linear, branched, star, etc.) [29, 32, 33], as well as the terminal functionalization by small moieties or as a block copolymer [32]. This was recently investigated by Meyer et al. [34] for poly(2-isopropyl-2-oxazoline) (P*i*PrOx) with ionic end-groups or P*i*PrOx-poly(L-glutamate) block copolymers [35].

Additionally, the broad range of, i.e., POx copolymer compositions can be used to tune its LCST. For example, while the LCST of poly(2-*n*-propyl-2-oxazoline) (P*n*PrOx) homopolymers is reported to range from 23 to 25 °C [36], of P*i*PrOx is from ~35 to ~47 °C [36–39] and of poly(2-ethyl-2-oxazoline) (PEtOx) from ~60 to 78 °C [37, 40–42]. Park and Kataoka [36] reported recently about the accurate control of the LCST by gradient and random copolymerization of these monomers resulting in POx of tunable LCSTs between 26.3 and 75.1 °C.

In general, the LCST of a given homopolymer can be increased by the incorporation of more hydrophilic comonomer units and lowered by the combination with more hydrophobic comonomer units. This has been systematically demonstrated for NIPAAM copolymerized with more hydrophilic (acrylamide) [43] or hydrophobic (*N*-*tert*-butylacrylamide) [44] monomers [45]. For the P*i*PrOx homopolymer system, only the recent account by Park and Kataoka [36] represents a systematic study. However, incorporation of monomers of higher hydrophobicity should result in still water-soluble copolymer with a further decreased LCST. Furthermore, regarding the impact of the polymer molar mass upon the biodistribution behavior and excretion of POx [1, 2], POx of lower molar mass with a cloud point in the physiological interesting temperature region around 37 °C might be more suitable for future use as polymer therapeutics.

In this account, we investigated the copolymerization behavior of *i*PrOx with 2-*n*-butyl-(*n*BuOx), 2-*tert*-butyl-(*t*BuOx), 2-*n*-propyl- (*n*PrOx), and 2-*n*-nonyl-2-oxazoline (NonOx). Furthermore, the LCST of the copolymers of fine-tuned composition and of relative low molar mass (degree of polymerization; DP=25) was determined by turbidity measurements of their aqueous solutions.

Experimental part

Materials and methods

All chemicals used for synthesis were purchased from Aldrich or Acros Organics and were used without further purification unless otherwise stated. Solvents, methyl triflate (MeOTf) and all monomers used for the living cationic polymerization were dried by refluxing over CaH_2 for approximately 3 h and subsequent distillation.

^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AC 250 (^{1}H, 250.13 MHz and ^{13}C, 62.90 MHz) with TMS as internal standard at T=300 K in $CDCl_3$.

Gel permeation chromatography was performed on a Waters system (pump mod. 510, RI-detector mod. 410) with columns Resi Pore Guard (50×7.5 mm) and 2× Resi Pore (300×7.5 mm) as the stationary and dimethyl acetamide (DMAc) as the mobile phase. The calculation of the molar mass average was performed using a calibration with poly(styrene) standards. The mass spectrometry measurements were performed using a MAT 8200 Finnagan (EI, 70 eV) ion impact mass spectrometer. Elemental analysis was performed at the Microanalytical Laboratory of the Inorganic Chemistry Institute of the TU München using an Elementar Vario EL instrument.

The in situ kinetic measurements of the copolymerization were carried out using a gas chromatograph (Hewlett-Packard 5890A) equipped with a FID-Detector and a Optima 1 column from Macherey Nagel (50 m×0.53-mm diameter, 5-μm film thickness) using toluene as external standard.

Turbidity measurements were carried out on a Cary 3 UV-vis spectrophotometer from Varian. The cloud point was determined by spectrophotometric detection of the changes in transmittance at λ=500 nm of the aqueous polymer solutions (2.0 wt%). The solution temperature was increased by a rate of 1 K min^{-1} followed by a 15-min period of constant temperature to ensure equilibration. Given values for the cloud point were determined as the temperature corresponding to a 10% decrease in optical transmittance.

Synthesis

Monomer synthesis

The general procedure for the synthesis of the 2-oxazoline monomers was carried out according to Witte and Seeliger et al. [46, 47].

2-Isopropyl-2-oxazoline (*i*PrOx)

In a Schlenk flask, 3 g (0.043 mol) of isobutyronitrile, 3.59 g (0.0516 mol, 1.2 eq) aminoethanol and 0.29 g (1.08 mmol) cadmium acetate dihydrat were stirred and heated to 130 °C. After 12 h, the reaction was cooled to room temperature. The red raw product was purified by vacuum distillation [boiling point (bp), 40 °C at 16 mbar] and then stored under a dry nitrogen atmosphere for further use (yield, 3.16 g, 65%).

^{1}H NMR (250 MHz, $CDCl_3$): δ=4.23 (t, J=9.3 Hz, 2 H), δ=3.78 (t, J=9.3 Hz, 2 H), δ=2.62 (sp, J=7.10 Hz, 3 H), δ=1.18 (d, J=7.10 Hz, 6 H).

^{13}C NMR (63 MHz, DMSO): δ=170.4, 66.4, 53.4, 27.0, 19.3.MS(70 eV, EI): m/z 113 [M].

Elemental analysis

$C_6H_{11}NO$: Calcd: C 63.68, H 9.80, N 12.38; Found: C 61.74, H 9.83, N 12.38.

The 2-*n*-butyl-2-oxazoline, 2-*tert*-butyl-2-oxazoline, and 2-*n*-propyl-2-oxazoline were synthesized accordingly. The 2-*n*-nonyl-2-oxazoline (NonOx) was a kind gift from Henkel KGaA, Düsseldorf, Germany.

2-*n*-Butyl-2-oxazoline (*n*BuOx)

bp, 56 °C at 10 mbar (yield, 61%).

^{1}H NMR (250 MHz, $CDCl_3$): δ=4.17 (t, J=9.2 Hz, 2 H), δ=3.77 (t, J=9.2 Hz, 2 H), δ=2.23 (t, J=7.8 Hz, 2 H), δ=1.60 (q, J=7.8 Hz, 2 H), δ=1.38 (sp, J=7.8 Hz, 2 H), δ=0.88 (t, J=7.3 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ=168.3, 66.7, 54.0, 27.7, 27.3, 21.9, 13.3.

MS(70 eV, EI): m/z 126 [M-1].

Elemental analysis

$C_7H_{13}NO$: Calcd: C 66.10, H 10.30, N 11.01; Found: C 64.69, H 10.30, N 11.36.

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

bp, 47 °C at 11 mbar (yield, 61%).

^{1}H NMR (250 MHz, $CDCl_3$): δ=4.27 (t, J=9.2 Hz, 2 H), δ=3.81 (t, J=9.2 Hz, 2 H), δ=2.23 (t, J=7.5 Hz, 2 H), δ=1.69 (st, J=7.5 Hz, 2 H), δ=0.95 (t, J=7.5 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ=168.3, 66.9, 54.2, 29.7, 19.2, 13.6.

MS(70 eV, EI): m/z 112 [M-1].

Elemental analysis

$C_6H_{11}NO$: Calcd: C 63.68, H 9.80, N 12.38; Found: C 63.48, H 8.35, N 11.01.

2-*tert*-Butyl-2-oxazoline (*t*BuOx)

Boiling point, 42 °C at 10 mbar (yield, 29%).

^{1}H NMR (250 MHz, $CDCl_3$): δ=4.2 (t, J=9.4 Hz, 2 H), δ=3.78 (t, J=9.4 Hz, 2H), δ=1.20 (s, 9H).

^{13}C NMR (63 MHz, $CDCl_3$): δ=131.5, 93.09, 67.26, 41.33, 27.62.

MS(70 eV, EI): m/z 126 [M-1].

Elemental analysis

$C_6H_{11}NO$: Calcd: C 66.17, H 10.20, N 11.82; Found: C 63.17, H 10.30, N 11.82.

Polymerization

All polymerization reactions and workup procedures were carried out following a general procedure described previously [2, 8, 9, 16]. At a constant initiator concentration, the theoretical chain length, adjusted by the initial $[M]_0/[I]_0$ ratio, was set to a total of 25 monomer units for all (co) polymers. In the following, the results and assignments of the ^{1}H NMR spectroscopy are given. For further details for each synthesized polymer, see Table 1; additionally, exemplary ^{1}H-NMR spectra of each copolymer are provided as Supplementary material.

Poly(2-isopropyl-2-oxazoline); **P*i*PrOx$_{25}$**

Table 1 Polymer compositions and analytical values

Polymer	*n*/*m* theor.	*n*/*m*[a] exp.	Yield (%)	$\overline{M}_n$,theor (g/mol)	$\overline{M}_n$[b] (g/mol)	PDI[c]	CP[d] (°C)
P*i*PrOx$_{25}$	–	–	80	2,928	3,907	1.09	47
P(*i*PrOx$_{24}$NonOx$_1$)	24/1	24/1.5	85	3,012	3,508	1.18	15
P(*i*PrOx$_{23}$NonOx$_2$)	23/2	24/2	93	3,096	3,143	1.17	11
P(*i*PrOx$_{22}$NonOx$_3$)	22/3	22/3	81	3,180	3,349	1.20	9
P(*i*PrOx$_{24}$*n*BuOx$_1$)	24/1	24.5/1.5	72	2,942	2,754	1.26	38
P(*i*PrOx$_{23}$*n*BuOx$_2$)	23/2	23/2	86	2,956	3,113	1.26	35
P(*i*PrOx$_{22}$*n*BuOx$_3$)	22/3	22/3	82	2,970	3,223	1.23	33
P(*i*PrOx$_{20}$*n*BuOx$_5$)	20/5	20/5	91	2,998	3,119	1.30	21
P*n*PrOx$_{25}$	–	–	75	2,942	3,068	1.13	25
P(*i*PrOx$_{22}$*n*PrOx$_3$)	22/3	23/3	75	2,928	2,661	1.23	46
P(*i*PrOx$_{20}$*n*PrOx$_5$)	20/5	21/5.5	77	2,928	2,860	1.29	37

[a] Determined by NMR analysis of the ratio of the backbone proton signals to the CH_3– side chain signals of the comonomer
[b] Determined by GPC analysis
[c] Polydispersity index; PDI=M_w/M_n calculated from GPC traces
[d] Determined by UV–vis photospectrometer at 10% decrease of optical transmittance of the polymer solution

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.45 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.90, 2.66 (s, br, 23 H, CO–C*H*–(CH_3)$_2$); δ=1.11 (s, br, 149 H, CH–(CH_3)$_2$).

Poly[(2-isopropyl-2-oxazoline)$_n$-*co*-(2-n-nonyl-2-oxazoline)$_m$]; **P(*i*PrOx)$_n$(NonOx)$_m$**

P(*i*PrOx)$_{24}$(NonOx)$_1$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.43 (s, br, 100H, N–(CH_2)$_2$–N); δ=2.88, 2.66 (s, br, 28 H, CO–C*H*–(CH_3)$_2$); δ=2.36 (s, br, 4 H, CO–CH_2–C_8H_{17}); δ=1.57 (s, br, 2 H, CH_2–CH_2–C_7H_{15}); δ=1.23 (s, br, 12H, CH_2–(CH_2)$_6$–CH_3); δ=1.10 (s, br, 146 H, CH–(CH_3)$_2$; δ=0.85 (t, br, 4 H, C_8H_{16}–CH_3).

P(*i*PrOx)$_{23}$(NonOx)$_2$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.44 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.88, 2.64 (s, br, 29 H, CO–C*H*–(CH_3)$_2$); δ=2.39 (s, br, 7H, CO–CH_2–C_8H_{17}); δ=1.56 (s, br, 4 H, CH_2–CH_2–C_7H_{15}); δ=1.24 (s, br, 21 H, CH_2–(CH_2)$_6$–CH_3); δ=1.10 (s, br, 143 H, CH–(CH_3)$_2$; δ=0.85 (t, br, 6H, C_8H_{16}–CH_3).

P(*i*PrOx)$_{22}$(NonOx)$_3$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.43 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.88, 2.66 (s, br, 26 H, CO–C*H*–(CH_3)$_2$); δ=2.34 (s, br, 9 H, CO–CH_2–C_8H_{17}); δ=1.57 (s, br, 6 H, CH_2–CH_2–C_7H_{15}); δ=1.23 (s, br, 35 H, CH_2–(CH_2)$_6$–CH_3); δ=1.09 (s, br, 134 H, CH–(CH_3)$_2$; δ=0.84 (t, br, 9H, C_8H_{16}–CH_3).

Poly[(2-isopropyl-2-oxazoline)$_n$-*co*-(2-n-butyl-2-oxazoline)$_m$]; **P(*i*PrOx)$_n$(*n*BuOx)$_m$**

P(*i*PrOx)$_{24}$(*n*BuOx)$_1$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.42 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.87, 2.64 (s, br, 29 H, CO–C*H*–(CH_3)$_2$); δ=2.34 (s, br, 5 H, CO–CH_2–C_3H_7); δ=1.54 (s, br, 3 H, CH_2–CH_2–C_2H_5); δ=1.32 (s, br, 3 H, (CH_2–CH_2–C_2H_5); δ=1.07 (s, br, 145 H, CH–(CH_3)$_2$); δ=0.88 (t, br, 4 H, C_3H_6–CH_3).

P(*i*PrOx)$_{23}$(*n*BuOx)$_2$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.43 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.86, 2.65 (s, br, 27 H, CO–C*H*–(CH_3)$_2$); δ=2.33 (s, br, 6 H, CO–CH_2–C_3H_7); δ=1.56 (s, br, 5 H, CH_2–CH_2–C_2H_5); δ=1.32 (s, br, 5 H, (CH_2–CH_2–C_2H_5); δ=1.08 (s, br, 137 H, CH–(CH_3)$_2$); δ=0.89 (t, br, 7 H, C_3H_6–CH_3).

P(*i*PrOx)$_{22}$(*n*BuOx)$_3$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.39 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.84, 2.60 (s, br, 27 H, CO–C*H*–(CH_3)$_2$); δ=2.29 (s, br, 8 H, CO–CH_2–C_3H_7); δ=1.51 (s, br, 7 H, CH_2–CH_2–C_2H_5); δ=1.27 (s, br, 7H, (CH_2–CH_2–C_2H_5); δ=1.04 (s, br, 133 H, CH–(CH_3)$_2$); δ=0.85 (t, br, 9 H, C_3H_6–CH_3).

P(*i*PrOx)$_{20}$(*n*BuOx)$_5$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.41 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.86, 2.65 (s, br, 26 H, CO–C*H*–(CH_3)$_2$); δ=2.32 (s, br, 12 H, CO–CH_2–C_3H_7); δ=1.54 (s, br, 10 H, CH_2–CH_2–C_2H_5); δ=1.29 (s, br, 11 H, (CH_2–CH_2–C_2H_5); δ=1.08 (s, br, 120 H, CH–(CH_3)$_2$); δ=0.87 (t, br, 15 H, C_3H_6–CH_3).

Poly(2-*n*-propyl-2-oxazoline); **P(*n*PrOx)$_{25}$**

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.44 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.32 (s, br, 52 H, CO–CH_2–C_2H_5); δ=1.64 (s, br, 55 H, CH_2–CH_2–CH_3); δ=0.94 (s, br, 70 H, C_2H_4–CH_3).

Poly[(2-isopropyl-2-oxazoline)$_n$-*co*-(2-n-propyl-2-oxazoline)$_m$]; **P(*i*PrOx)$_n$(*n*PrOx)$_m$**

P(*i*PrOx)$_{20}$(*n*PrOx)$_5$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.42 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.85, 2.64 (s, br, 28 H, CO–C*H*–(CH_3)$_2$); δ=2.30 (s, br, 11 H, CO–CH_2–CH_2); δ=1.60 (s, br, 11 H,CH_2–CH_2–CH_3); δ=1.08 (s, br, 127 H, CH–(CH_3)$_2$); δ=0.91 (t, br, 16 H, C_2H_4–CH_3).

P(*i*PrOx)$_{22}$(*n*PrOx)$_3$

^{1}H NMR (250 MHz, $CDCl_3$): δ=3.44 (s, br, 100 H, N–(CH_2)$_2$–N); δ=2.89, 2.66 (s, br, 25 H, CO–C*H*–(CH_3)$_2$); δ=2.34 (s, br, 7 H, CO–CH_2–CH_2); δ=1.61 (s, br, 6H,CH_2–CH_2–CH_3); δ=1.09 (s, br, 149 H, CH–(CH_3)$_2$); δ=0.94 (t, br, 8 H, C_2H_4–CH_3).

Results and discussion

The different 2-oxazoline monomers are directly accessible in high yields via different synthetic routes [6, 48] but, in general, by a one- or two-step synthesis from the corresponding nitrile compound [46, 47]. Thus, a broad choice of 2-oxazolines are accessible for fine tuning of the

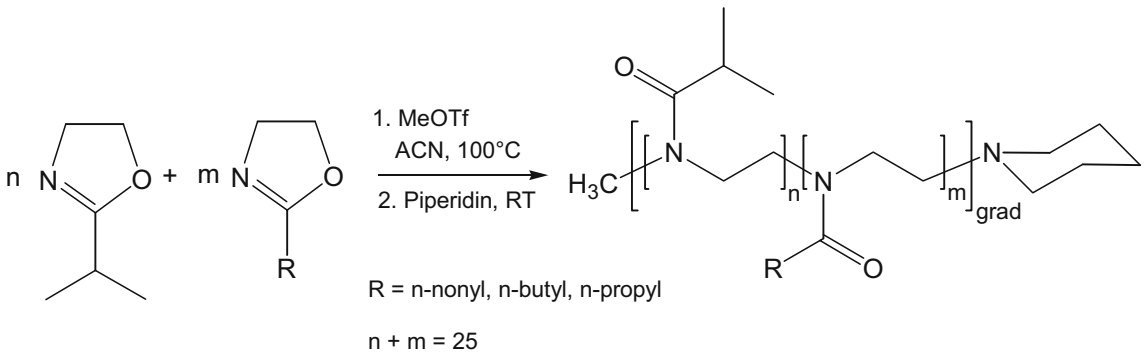

Fig. 1 Copolymerization of 2-isopropyl-2-oxazoline (*i*PrOx) with different 2-alkyl-2-oxazolines

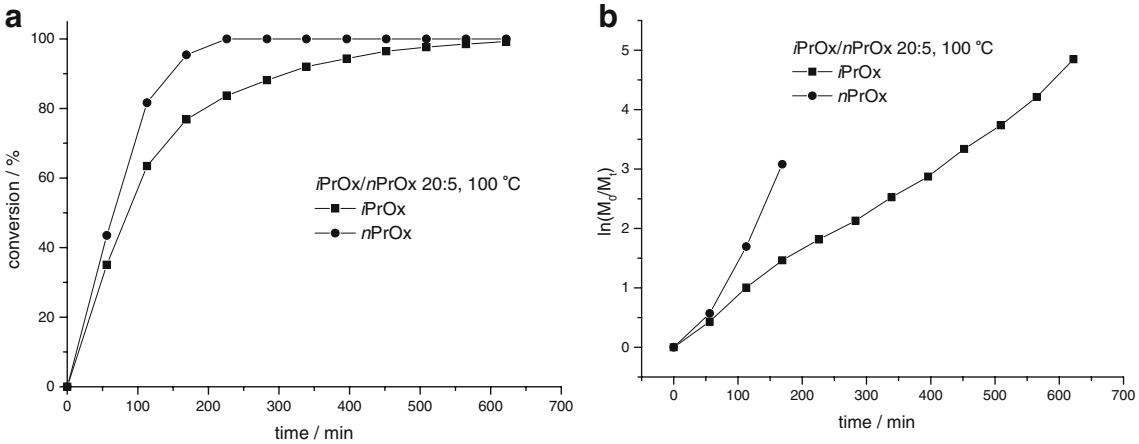

Fig. 2 First-order kinetic plots of the copolymerization of 2-isopropyl-2-oxazoline (*i*PrOx) and 2-propyl-2-oxazoline (*n*PrOx) as monitored by in situ GC sampling. **a** Diagram of the conversion of *i*PrOx and *n*PrOx during copolymerization in dependence of the time at T=100 °C and the monomer ratio of 20/5. **b** Logarithmic plot of data from **a**

solubility and aggregation behavior of POx homo- and copolymers.

The hydrophilicity of poly(2-oxazoline)s (POx) is determined by the length of the alkyl group the 2-position of the respective monomers. Longer pendant alkyl chains of the monomer unit results in an increasingly stronger amphiphilic character, and POx becomes a non-ionic polysoap. POx block copolymers with a strong amphiphilic contrast in the monomer units as well as along the entire chain show the typical low critical micelle concentration in water of ~10^{-5} M [49, 50], and defined spherical micelles are formed [51]. However, copolymers of the same composition but random or gradient distribution of the hydrophilic and amphiphilic monomer units along the copolymer chain results in significant changes of the solubility, aggregation behavior, as well as the morphology of the resulting aggregates of POx [52–54].

Hence, not only the copolymer composition but also the copolymer architecture has to be known so as to evaluate the solubility behavior and LCST characteristics of POx copolymers. Park and Kataoka [36] recently found that *n*PrOx copolymerizes with EtOx in a strictly random fashion, but forms gradient copolymers with *i*PrOx. Moreover, the NonOx copolymerization behavior was extensively studied before by Schulz [55], and it can be reasonably assumed that copolymerization with the more reactive *i*PrOx will also result in gradient copolymers as determined by matrix-assisted laser desorption/ionization–time of flight mass spectrometry. Thus, in a first step, the copolymerization behavior of *i*PrOx with 2-*n*-butyl-(*n*BuOx), 2-*tert*-butyl-(*t*BuOx), as well as with *n*PrOx was investigated by in situ GC monitoring of the polymerization reaction. The copolymerization reactions are summarized in Fig. 1.

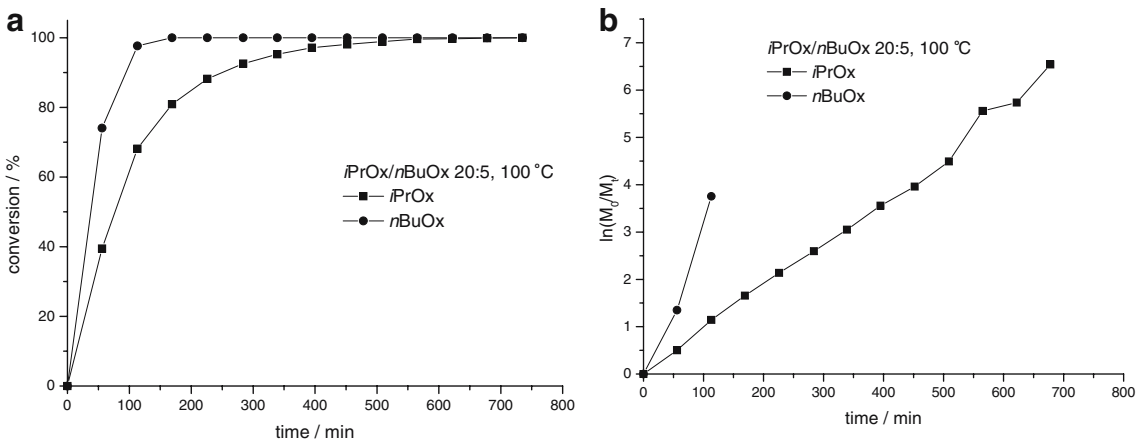

Fig. 3 First-order kinetic plots of the copolymerization of 2-isopropyl-2-oxazoline (*i*PrOx) and 2-*n*-butyl-2-oxazoline (*n*BuOx) as monitored by in situ GC sampling. **a** Diagram of the conversion of *i*PrOx and *n*BuOx during copolymerization in dependence of the time at T=100°C and the monomer ratio of 20/5. **b** Logarithmic plot of data from **a**

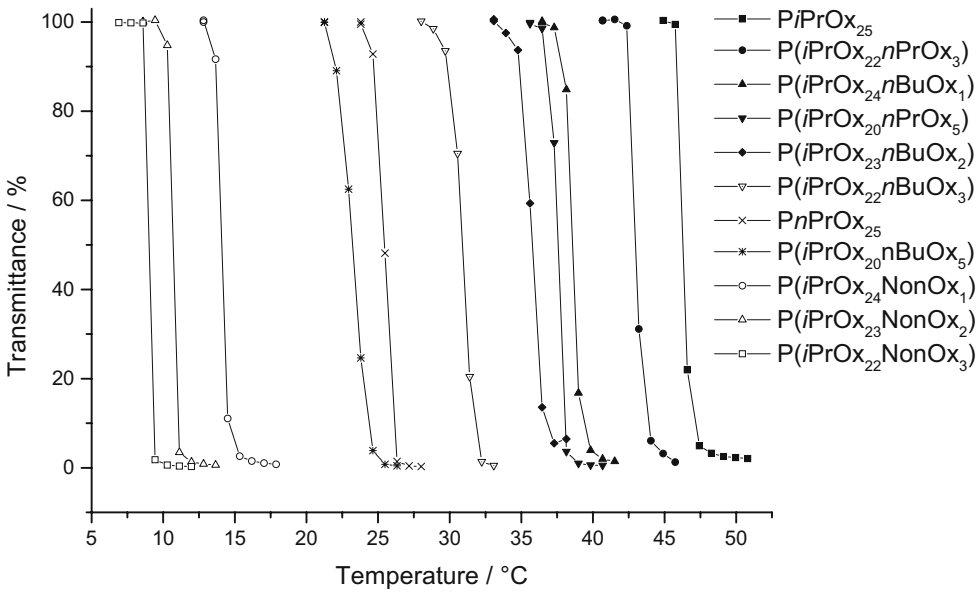

Fig. 4 Measurements of the cloud points of all aqueous polymer solutions (2.0 wt%)

Analog to the LCST tuning of acryl amides using *N*-*t*BAAm copolymerization to decrease the LCST of PNIPAAm, we synthesized the 2-oxazoline analogue *t*BuOx and attempted homo- as well as copolymerization with methyl triflate as the initiator and acetonitrile as the solvent. However, in no case was a polymer product containing *t*BuOx obtained. Neither increase of the reaction temperature nor change of the solvent or initiator system was successful. Presumably, the steric demand of the 2-substitution is too high to allow a cationic ring-opening polymerization of *t*BuOx.

The results of the copolymerization studies of the *i*PrOx with *n*POx at a ratio of 20:5 are shown in Fig. 2.

As apparent from the kinetic data (Fig. 2), the *i*PrOx/*n*PrOx copolymerization results in the formation of a copolymer gradient with enrichment of the less reactive *i*PrOx towards the polymer chain end. This corroborates the recent findings for the same copolymer system by Park and Kataoka [36] using a significantly lower reaction temperature of 42 °C, a different initiator (methyl tosylate), and other comonomer ratios. In our case, we could not observe copolymer side products even for the used reaction temperature of 100 °C. All analytical data indicated a living cationic polymerization resulting in the desired polymers with high yields and low PDIs from 1.09 to 1.3. However, side reactions of the living cationic polymerization of 2-alkyl substituted 2-oxazolines become only noticeable for elongated reaction times at high temperatures while attempting higher DPs [56–58]. In this study, we purposely kept the DP low to elucidate the LCST behavior

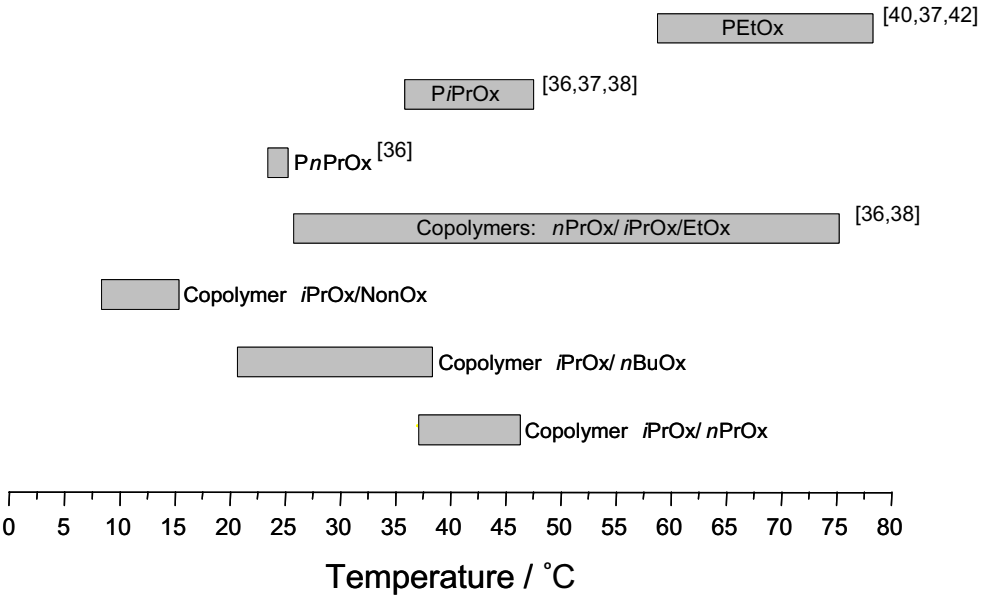

Fig. 5 Overview of the LCST modulation of poly (2-oxazoline)s as reported in the literature as well as in this account

of short POx copolymers. Similarly, the *i*PrOx/*n*BuOx copolymer system was investigated under identical conditions, and the kinetic data in Fig. 3 show the formation of *i*PrOx/*n*BuOx copolymers with increasing *i*PrOx content towards the polymer chain end.

The LCSTs of all synthesized homo- and copolymers in water (2.0 wt%) were determined by turbidity measurements. In Table 1, all polymers are summarized along with their composition, analytical values, and the determined cloud points. The transmittance changes at $\lambda=500$ nm as a function of the solution temperature are depicted in Fig. 4.

Park and Kataoka [36] reported a sharp LCST of a 1.0 wt% phosphate buffer solution of 23.8 °C. Giving the different experimental setup and conditions of the measurement, this coincides well with our determination of the cloud point for P*n*PrOx$_{25}$ of 25 °C. Interestingly, our determined cloud point for P*i*PrOx$_{25}$ of 47 °C deviates significantly from the therein reported cloud point value for P*i*PrOx$_{100}$ of 38.7 °C. Otherwise, we observe similar sharp and fast transitions for the P*n*PrOx as well as for the investigated copolymers, although of gradient architecture. A complete precipitation of the polymer from the water was observed within a temperature range of 1–2 °C. Repeated heating–cooling cycles verified the reversibility of the transition with no or only a slight temperature hysteresis. Recently, Meyer et al. [34] reported on the formation of stable and insoluble aggregates of double-charged P*i*PrOx when the precipitated polymer was kept for approximately 24 h above the LCST (65 °C). We repeated this experiment with our neutral and short P*i*PrOx25, and, in fact, after prolonged heating, also P*i*PrOx$_{25}$ remained water-insoluble as a fibrous material. Apparently, the presence of a terminal charge is not necessary for the formation of insoluble P*i*PrOx aggregates.

While the copolymerization of the monomers *n*PrOx with *i*PrOx results in a linear increase of the LCST from about 26 to 38.7 °C and with the even more hydrophilic EtOx in a further increase from approximately 35 to 75.1 °C [39], the incorporation of more hydrophobic comonomers decreases the phase transition temperature (Table 1, Fig. 4). Increasing incorporation of *n*BuOx modulates the LCST from 38 °C for P(*i*PrOx$_{24}$BuOx$_1$) to 21 °C for P(*i*PrOx$_{20}$*n*BuOx$_5$). Accordingly, a further decrease was observed in the case of the *i*PrOx/NonOx system with LCSTs ranging form 15 °C for P(*i*PrOx$_{24}$NonOx$_1$) down to 9 °C for P(*i*PrOx$_{22}$NonOx$_3$). Interestingly, the LCST of the short copolymers are well defined within a small temperature change and highly sensitive to the average copolymer composition. Even the introduction of, in average, only one hydrophobic monomer unit changes the overall solubility behavior in a defined way. This may indicate the formation of large micellar aggregates above the critical solution temperature. Overall, with the investigated systems, the LCST can be modulated over a broad temperature range from 46 °C down to 9 °C. Taking together the already reported cloud point values of POx homo- and copolymers, the LCST of POx can be tuned from 75 to 9 °C as shown in Fig. 5.

Conclusions

Living cationic copolymerization of 2-isopropyl-2-oxazoline with 2-*n*-propyl-, 2-*n*-butyl-, and 2-*n*-nonyl-2-oxazoline results in gradient copolymers of defined composition, narrow molar mass distributions (PDI=1.09–1.3), and defined overall degree of polymerization ($n=25$). The introduction of monomer units of stronger amphiphilic character results in a systematic decrease of the lower critical solution temperature. The LCST modulation can be controlled by the choice of the comonomer as well as the comonomer content and was tuned in the temperature range from 46 to 9 °C. Interestingly, even the relatively short poly(2-oxazoline)s showed a defined LCST behavior as a function of the average degree of comonomer content.

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