Colloid Polym Sci (2008) 286:1653–1661
DOI 10.1007/s00396-008-1942-7

ORIGINAL CONTRIBUTION

Effect of end group polarity upon the lower critical solution temperature of poly(2-isopropyl-2-oxazoline)

Stephan Huber · Naima Hutter · Rainer Jordan

Received: 5 August 2008 / Revised: 29 September 2008 / Accepted: 1 October 2008 / Published online: 21 October 2008

Abstract Thermo-sensitive poly(2-isopropyl-2-oxazoline)s (P*i*PrOx) were functionalized with end groups of different polarity by living cationic ring-opening polymerization using the initiator and/or termination method as well as sequential block copolymerization with 2-methyl-2-oxazoline. As end groups, methyl, *n*-nonyl, piperidine, piperazine as well as oligo(ethylenglygol) and oligo(2-methyl-2-oxazoline) were introduced quantitatively. The lower critical solution temperature (LCST) of the aqueous solutions was investigated. The introduction of hydrophobic end groups decreases the LCST, while hydrophilic polymer tails raise the cloud point. In comparison to poly(*N*-isopropyl acrylamide), the impact of the end group polarity upon the modulation of the LCST was found to be significantly stronger. Surprisingly, terminal oligoethylenegycol units also decrease the LCST of P*i*PrOx, thus acting as moieties of higher hydrophobicity as compared to the poly(2-oxazoline) main chain. Together with the possible variation of the side group polarity, this allows a broad modulation of the LCST of poly(2-oxazoline)s.

Keywords Poly (2-oxazoline) · Thermo sensitive polymer · LCST · End group

Introduction

The temperature-dependent solubility of aqueous solutions of hydrophilic polymers is well known. Upon heating and crossing a lower critical solution temperature (LCST), the polymers precipitate at the so-called cloud point (CP) [1, 2]. The specific LCST of a respective polymer is a function of, e.g. the concentration of the polymer solution, additives such as salts, soaps, cosolvents etc. as well as the polymer molar mass, architecture, and composition, i.e. pendant or end group modification [3–8]. Since the LCST is an entropic phenomenon, the influence of the polymer terminal groups is expected to be significant. In the past, various poly(acrylamide)s were investigated in this respect, especially the most prominent poly(*N*-isopropyl acrylamide) (PNIPAAm) since its cloud point is located around the human body temperature. Thus, the thermo responsiveness of PNIPAAm is frequently discussed in the context of 'smart materials' for biomedical applications or nanotechnology [1, 2, 9–13]. Especially for these applications, well-defined polymers are needed as well as a precise adjustment of the LCST to a specific temperature. Both go hand in hand since the polymer architecture and composition strongly influences the cloud point. For PNIPAAm, the LCST tuning by the parameters mentioned above were subject of a controversial discussion until Stöver et al. [7, 8] developed the atom transfer radical polymerization of NIPAAm for the synthesis of defined polymers of the necessary narrow molar mass distribution and end group definition to allow a direct structure–property correlation.

For several reasons, another polymer class, the poly(2-oxazoline)s (POx), came recently into the focus of related research. POx with short alkyl side chains (methyl, ethyl, propyl) are water soluble and/or display a CP for several pendant side groups [3–6, 14, 15]. The polymer is nontoxic [16–20] and, due to the numerous possibilities for terminal [17, 21] and pendant group [22–33] functionalization, a versatile system to develop polymer–drug conjugates for biomedical applications [34].

POx is synthesized via living cationic ring-opening polymerization (LCROP) that allows for the synthesis of highly

S. Huber · N. Hutter · R. Jordan (✉)
Wacker-Lehrstuhl für Makromolekulare Chemie,
Department Chemie, Technische Universität München,
Lichtenbergstr.4,
85747 Garching, Germany
e-mail: Rainer.Jordan@tum.de

defined linear polymers with narrow molar mass distribution $\left(\mathrm{PDI} = \overline{M}w/\overline{M}n \sim 1.01 - 1.3\right)$ [35], defined copolymerization of various 2-oxazolines [4, 22, 24–27, 31, 33, 36, 37] and defined as well as quantitative introduction of end groups by the initiation and termination reaction [17, 21, 38, 39]. This was recently used to tune the LCST of various POx copolymers in a broad range from 9 to 75 °C [4–6]. Analogous to PNIPAAm, where the copolymerization of NIPAAm with more hydrophilic comonomers increases and copolymerization with more hydrophobic monomers deceases, the LCST of the resulting copolymer, i.e. poly(2-*n*-propyl-2-oxazoline) with an LCST of 23 °C, can be shifted to 75 °C by copolymerization with the more hydrophilic 2-ethyl-2-oxazoline [5]. The CP of poly(2-isopropyl-2-oxazoline) (P*i*PrOx) of 47 °C can be decreased to 9 °C when copolymerized with 2-nonyl-2-oxazoline (NonOx) [4]. We found that even slight changes in the average polymer composition of POx significantly modulate the LCST, much stronger as it was observed for poly(acryl amide)s. This might be due to the fact that, in general, the molar mass range of investigated POx is much smaller, and small changes of the molecular composition and/or architecture become augmented. The recent study of Stöver et al. [7, 8] comparing low and high molar mass PNIPAAm with different end groups supports this assumption. While for short PNIPAAm (M_n~3,000 g/mol), different end groups resulted in a shift of the CP of ~8 °C, this effect diminished completely for polymers with M_n>10.000 g/mol. It can be expected that also for POx the impact of the end group polarity is significant. However, until now only one study addressed the end group functionalization of POx in the context of its LCST behavior. Meyer et al. [40, 41] investigated the irreversible formation of fibers from P*i*PrOx having ionic end groups or as a P*i*PrOx-poly(L-glutamate) block copolymer. To the best of our knowledge, a dedicated study of the LCST of POx as a function of the end group polarity was not performed till now.

In this paper, we describe the synthesis of P*i*PrOx equipped with end groups of different polarity: from non-polar *n*-nonyl chains to highly polar oligo(2-methyl-2-oxazoline) blocks. Temperature-dependant turbidity measurements of the polymer aqueous solutions allowed a conclusive structure–property relationship of the polarity of the polymer termini upon the LCST of POx.

Experimental part

Materials and methods

All chemicals used for synthesis were purchased from Aldrich (Munich, Germany) or Acros Organics (Geel, Belgium) and were used without further purification unless otherwise stated. *n*-Nonyl-2-oxazoline was received from Henkel KGaA, Düsseldorf, Germany as a gift. Solvents, methyl triflate (MeOTf), nonylamine ($NonNH_2$) and all monomers used for the living cationic polymerization were dried by refluxing over CaH_2 for approximately 3 h and subsequent distillation. The monomers were stored under a dry nitrogen atmosphere and handled in a glove box. All polymerizations were performed using a CEM Discover microwave with a maximum power setting to 150 W. The microwave was set to reaction temperature of 130 °C that was continuously monitored by an internal infra-red detector.

^{1}H- and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX 300 (^{1}H, 300.13 MHz and ^{13}C, 75.48 MHz) with tetramethylsilane as internal standard at T=293 K in $CDCl_3$.

Gel permeation chromatography (GPC) was performed on a Waters system (pump model 510, RI-detector model 410) with columns Resi Pore Guard (50×7.5 mm) and 2x Resi Pore (300×7.5 mm) as the stationary and dimethylacetamide (DMAc) as the mobile phase. The calculation of the molar mass and number average (M_w, M_n) 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 as well as a Bruker-Daltonic, Ultraflex matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)/TOF with dithranol (1,8,9-trihydroxyanthracene) as the matrix. Elemental analysis was performed at the Microanalytical Laboratory of the Inorganic Chemistry Institute of the TU München using a ElementarVario EL instrument.

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 2-isopropyl-2-oxazoline monomer synthesis and characterization was performed as previously reported following the account by Witte and Seeliger [4, 42].

Initiators

Nonyltriflate (NonOTf) In a Schlenk flask with 5 mL dry chloroform, 2.4 g (5 eq. 17.33 mmol) of anhydrous K_2CO_3 and 0.5 g (3.47 mmol) nonanol, 1.27 g (1.3 eq., 4.5 mmol) trifluoromethanesulfonic anhydride was added dropwise

under a dry nitrogen atmosphere. After 3 h, the mixture was filtered through a polytetrafluoroethylene filter (Chromafil, 0.20 μm, Machery Nagel), and the solvent was evaporated. The nonyltriflate remained as colorless liquid (yield, 680 mg, 70%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=4.53 (t, J=4.5 Hz, 2H), δ=1.83 (q, J=1.82 Hz, 2H), δ=1.5-1.2 (m, br, 12H), δ=0.88 (t, J=0.88 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ=120.98, 78.03, 32.00, 29.49, 29.34, 29.06, 25.26, 22.84, 14.26.

Triethyleneglycolmonomethylethertosylate In a 100-mL Schlenk tube, 1 g (6 mmol) triethyleneglycolmonomethylether was dissolved in 0.95 g (2 eq., 12 mmol) pyridine at 0 °C, 1.26 g (6.6 mmol) *p*-toluenesulfonyl chloride was added, and the solution was allowed to equilibrate to room temperature. After 3.5 h, the reaction was quenched by addition of 10 mL toluene and 10 mL 10% HCl. The organic phase was separated and washed with saturated NaCl solution. The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. The triethyleneglycolmonomethylethertosylate (TEGTos) remained as colorless liquid (yield, 1.45 g, 76%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.78 (d, J=7.3 Hz, 2H), δ=7.32 (d, J=7.3 Hz, 2H), δ=4.15 (t, J=4.1 Hz, 2 H), δ=3.68 (t, J=3.7 Hz, 2H), δ=3.59 (m, 6H), δ=3.52 (m, 2H), δ=3.36 (s, 3H), δ=2.44 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ=144.7, 133.0, 129.8, 129.0, 71.9, 70.5, 70.5, 69.2, 68.7, 59.0, 21.6.

MS(70eV, EI): m/z 318 [M].

Termination agents

Triethyleneglycolmonomethylether amine The synthesis of the triethyleneglycolmonomethylether amine (TEG-NH_2) was performed as described previously (yield, 54%) [43].

^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.66 (m, 6H), δ=3.56-3.50 (m, 4H), δ=3.39 (s, 3 H), δ=2.87 (t, J=2.9 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ=73.5, 71.9, 70.6, 70.5, 70.2, 59.0, 41.8.

Elemental analysis:

$C_7H_{17}NO_3$: calculated: C 51.51, H 10.50, N 8.58; found: C 51.17, H 10.86, N 8.18.

Polymerization and termination reaction

All polymerization reactions were performed using a CEM Discover microwave (temperature setting, 130 °C; maximum power setting, 150 W; reaction time, 0.5 h). After full monomer conversion, approximately 5 eq. (with respect to the initial initiator amount) of the termination agent was directly injected into the reaction vial at room temperature. The termination reaction was allowed to complete overnight. The neutralization and workup procedures were carried out following a general procedure described previously [17, 21, 27, 44]. 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 polymers except for MeOx end-functionalized P*i*PrOx. The di- and triblock copolymers were synthesized by sequential monomer addition, starting and ending with a $MeOx_3$ block and MeOTf and piperidine as the initator and termination agent, respectively. As termination agent, piperidine was used unless otherwise mentioned. Please refer to Table 1 for the respective ratios and analytical values of the polymers.

Poly(2-isopropyl-2-oxazoline); $PiPrOx_{25}$ ^{1}H-NMR (300 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)$_2$).

$PiPrOx_{25}$-piperazine ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.44 (s, br, 100 H, *N*–(CH_2)$_2$–N); δ=2.91, 2.64 (s, br, 32 H, CO–C*H*–(CH_3)$_2$, H^{Pip}); δ=1.11 (s, br, 159 H, CH–(CH_3)$_2$).

Poly[(2-isopropyl-2-oxazoline)$_n$-co-(2-n-nonyl-2-oxazoline)$_m$]$_{ran.}$; P(iPrOx$_n$NonOx$_m$) P(iPrOx$_{24}$NonOx$_1$) ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.43 (s, br, 100 H, *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, 12 H, 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).

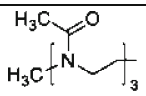
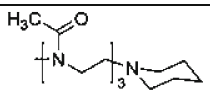
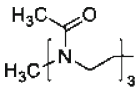
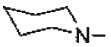
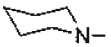
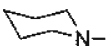
P(iPrOx$_{23}$NonOx$_2$) ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.44 (s, br, 100 H, *N*–(CH_2)$_2$–N); δ=2.88, 2.64 (s, br, 29 H, CO–C*H*–(CH_3)$_2$); δ=2.39 (s, br, 7 H, CO–CH_2–C_8H_{17}); δ=1.56 (s, br, 4 H, CH_2–CH_2–C_7H_{15}); δ=1.24 (s, br, 21 H, CH_2–(CH_2)$_6$–CH_3); δ=1.10 (s, br, 143 H, CH–(CH_3)$_2$; δ=0.85 (t, br, 6 H, C_8H_{16}–CH_3).

Non-$PiPrOx_{25}$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.43 (s, br, 96 H, *N*–(CH_2)$_2$–N); δ=2.88–2.62 (m, br, 25 H, CO–C*H*–(CH_3)$_2$), C_8H_{17}–CH_2–NH; δ=1.53–1.24 (m, br, 15 H, CH_3–(CH_2)$_7$–CH_2); δ=1.08 (s, br, 144 H, CH–(CH_3)$_2$; δ=0.85 (t, br, 3 H, C_8H_{16}–CH_3).

Non-$PiPrOx_{25}$-Non ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.43 (s, br, 104 H, *N*–(CH_2)$_2$–N); δ=2.88–2.65 (m, br, 31 H, CO–C*H*–(CH_3)$_2$), C_8H_{17}–CH_2–NH; δ=1.63–1.24 (m, br, 27 H, CH_3–(CH_2)$_7$–CH_2); δ=1.08 (s, br, 163 H, CH–(CH_3)$_2$; δ=0.85 (t, br, 6 H, C_8H_{16}–CH_3).

TEG-$PiPrOx_{25}$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.61, 3.44, 3.36 (m, br, 113 H, $C_6H_{13}O_3$–CH_2–N, *N*–(CH_2)$_2$–N); δ=2.88–2.65 (m, br, 26 H, $C_6H_{13}O_3$–CH_2–N, CO–C*H*–(CH_3)$_2$); δ=1.09 (s, br, 153 H, CH–(CH_3)$_2$).

Table 1 Compositions of all P*i*PrOx with hydrophobic and hydrophilic termini

R^1	R^2 (ratio)	R^3	Polymer
	$(CH_3)_2CH$-		$MeOx_3$-P*i*PrOx$_{25}$-$MeOx_3$
	$(CH_3)_2CH$-		$MeOx_3$-P*i*PrOx$_{25}$
CH_3-	$(CH_3)_2CH$-		P*i*PrOx$_{25}$-piperazine
CH_3-	$(CH_3)_2CH$-		P*i*PrOx$_{25}$
CH_3-$(O(CH_2)_2)_3$-	$(CH_3)_2CH$-		TEG-P*i*PrOx$_{25}$
CH_3-$(O(CH_2)_2)_3$-	$(CH_3)_2CH$-	CH_3-$(O(CH_2)_2)_3$-NH-	TEG-P*i*PrOx$_{25}$-TEG
CH_3-$(CH_2)_8$-	$(CH_3)_2CH$-		Non-P*i*PrOx$_{25}$
CH_3-$(CH_2)_8$-	$(CH_3)_2CH$-	CH_3-$(CH_2)_8$-NH-	Non-P*i*PrOx$_{25}$-Non
CH_3-	$(CH_3)_2CH$-/ CH_3-$(CH_2)_8$- (24/1)		P(*i*PrOx$_{24}$NonOx$_1$)
CH_3-	$(CH_3)_2CH$-/ CH_3-$(CH_2)_8$- (23/2)		P(*i*PrOx$_{23}$NonOx$_2$)

TEG-PiPrOx$_{25}$-TEG ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.61, 3.44, 3.36 (m, br, 126 H, $C_6H_{13}O_3$–CH_2–N, *N*–(CH_2)$_2$–N); δ=2.84–2.64 (m, br, 28 H, $C_6H_{13}O_3$–CH_2–N, CO–*CH*–(CH_3)$_2$); δ=1.09 (s, br, 147 H, CH–(CH_3)$_2$).

MeOx$_3$-PiPrOx$_{25}$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ=3.44 (s, br, 112 H, *N*–(CH_2)$_2$–N); δ=2.89, 2.66 (s, br, 26 H, CO–*CH*–(CH_3)$_2$); δ=2.13 (m, br, 9 H –CH–CH_3); δ=1.09 (s, br, 159 H, CH–(CH_3)$_2$).

MeOx$_3$-PiPrOx$_{25}$-MeOx$_3$ ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 3.44 (s, br, 124 H, *N*–(CH_2)$_2$–N); δ=2.89, 2.66 (s, br, 23 H, CO–*CH*–(CH_3)$_2$); δ=2.10 (m, br, 20 H –CH–CH_3); δ=1.09 (s, br, 161 H, CH–(CH_3)$_2$).

Results and discussion

Synthesis of P*i*PrOx$_n$ with end groups of different polarity

The defined and quantitative introduction of terminal groups into POx is possible by the initiator and/or the termination reaction of the LCROP as developed by Kobayashi et al. [45, 46, 47]. Besides the standard initiators, multifunctional initiators can also be used to synthesize POx of e.g. star-like architecture [48, 49]. For termination of the LCROP of 2-oxazolines, various nucleophilic reagents can be used such as water, alcohols or amines. Especially, cyclic amines are most suitable to ensure a quantitative termination reaction [17, 50, 51].

Alternatively, copolymerization to ABA block copolymers also results in bolaamphiphilic polymer structures. Figure 1 outlines the synthetic scheme of amphiphilic poly (2-isopropyl-2-oxazoline) bearing methyl-, nonyl- and triethylenglycol terminal groups as well as P*i*PrOx with one or two oligo(2-methyl-2-oxazoline) ($MeOx_3$) sequences as hydrophilic tails. The compositions of all synthesized polymers are summarized in Table 1.

The synthesis and analysis of P*i*PrOx$_{25}$ homopolymer as well as the copolymers P(*i*PrOx$_{24}$NonOx$_1$) and P(*i*PrOx$_{23}$ NonOx$_2$) with methyl on one and piperidine [4] or piperazine [17, 51] end groups on the other side is described elsewhere. The introduction of the *n*-nonyl groups via an *n*-nonyltriflate initator and by the termination

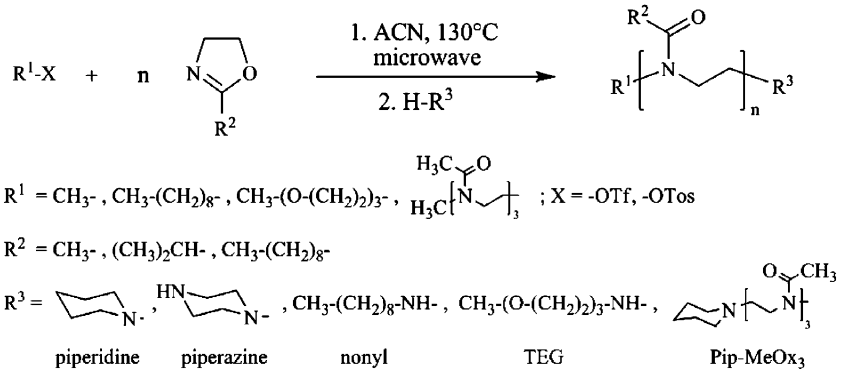


Fig. 1 General scheme of the microwave-assisted synthesis of poly(2-isopropyl-2-oxazoline) (P(*i*PrOx)) bearing methyl-, nonyl- and triethylenglycol terminal groups as well as P(*i*PrOx) with one or two oligo(2-methyl-2-oxazoline) ($MeOx_3$) sequences

method using *n*-nonylamine was straightforward. ^{1}H-NMR spectroscopy of the resulting mono- and difunctionalized P*i*PrOx (Non-P*i*PrOx$_{25}$, Non-P*i*PrOx$_{25}$-Non) confirmed the expected polymer composition with a quantitative end group functionalization. End-group analysis using the ^{1}H-NMR data gave, for both polymers, a good agreement between the theoretical ($[M]_0/[I]_0$) and experimental average degree of polymerization (DP) with a deviation of less than one monomer unit. Exemplarily, Fig. 2 shows the ^{1}H-NMR spectrum of Non-P*i*PrOx$_{25}$-Non.

Gel permeation chromatography revealed a narrow and monomodal molar mass distribution with a polydispersity index (PDI = M_w/M_n) of 1.04 in both cases. Additionally, characterization by MALDI-TOF/TOF mass spectrometry of e.g. Non-P*i*PrOx$_{25}$ gave a monomodal distribution of mass signal with a $\Delta(m/z)$=113.16 (M[monomer]=113.16 g/mol) with a maximum signal, M_p, at m/z=3,041.08 (calculated for [Polymer/H$^+$] and n=25: m=3,041.33 g/mol) and a PDI= M_w/M_n=3,072.89/2,979.78=1.03 (data not shown). A mass spectrometry analysis of Non-P*i*PrOx$_{25}$-Non was not possible due to insufficient signal intensity. Presumably, the desorption and/or ionization process is impaired by the formation of aggregates of the analyte within the matrix.

The introduction of triethylenegycol monomethyl ether units (TEG) as more hydrophilic terminal moieties was initially attempted analog to the *n*-nonyl groups. However, the synthesis of a TEG triflate from the corresponding alcohol resulted in a dark brown undefined product. Most probably, the triflate functionalization of TEG caused elimination, formation of a terminal vinyl function and

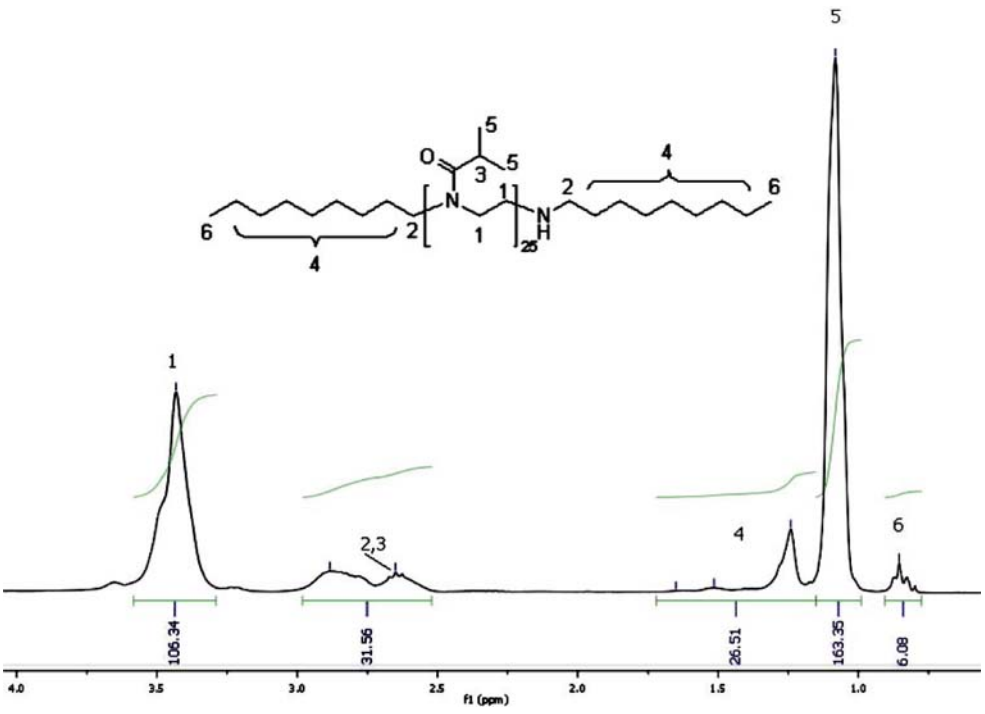


Fig. 2 ^{1}H-NMR spectrum of Non-P*i*PrOx$_{25}$-Non along with the peak assignments and integral signal values. For the determination of the average degree of polymerization, end group analysis of the integral intensity ratio of the CH_3- signals (6, 6 H) of the terminal alkyl chains against the integral intensity of the –CH_2– backbone signals (1, *n*4H) or the signals of the two CH_3– pendant groups (5, *n*6 H) was used

immediate polymerization or other side reactions, and no TEG-OTf could be isolated in a pure form. Hence, the less reactive tosylate compound, TEGTos, was synthesized as the initiator for LCROP of *i*PrOx. The termination agent TEG-NH_2 was obtained by azidation and reduction from TEGTos. Using TEGTos as the initiator, the PDI of both polymers, TEG-P*i*PrOx$_{25}$, TEG-P*i*PrOx$_{25}$-TEG, is with 1.23 slightly higher. However, the composition of both polymers is still well-defined, and the experimental DP=24 is almost identical to the $[M]_0/[I]_0$=25. Exemplarily, the ^{1}H-NMR spectrum of TEG-P*i*PrOx$_{25}$-TEG is displayed in Fig. 3.

Finally, P*i*PrOx$_n$ with hydrophilic oligo(2-methyl-2-oxazoline) blocks (MeOx$_3$) were synthesized via sequential block copolymerization. The obtained di- and triblock copolymer products had the expected composition and reasonably low PDIs of 1.18 and 1.24, respectively. All polymer analytical values are summarized in Table 2.

Temperature-dependent solubility—LCST behavior

The effect of end groups with different polarity dramatically influences the LCST behavior of thermo-sensitive polymers as discussed for PNIPAAm [7, 10, 12, 13]. Okano et al. [2] and Gil et al. [1] compared the LCST behavior for both hydrophobic and hydrophilic end-modified PNIPAAm. It could be shown that there is a significant difference of the temperature-dependant water solubility between end-group and pendant-group-modified PNIPAAm. In general, hydrophobic groups, e.g. methacrylic acid stearyl ester [2], phenyl 2-chloropropionamide [7] or octadecyl derivates [13] at the end of the polymer have a strong influence on the phase transition because this entropic dominated effect appears to be initiated from the ends of the polymer chains due to their high mobility and unique solvation [1]. Moreover, the terminal groups are able to form hydrophobic microdomains (micelles), which then become separated from the solvated PNIPAAm chains. Due to the formation of aggregates, the observed CP of the modified polymer is again close to that of the homopolymer [9, 10]. In contrast to end-group-modified PNIPAAm, copolymers with randomly distributed hydrophobic pendant groups form loose and undefined aggregates, and thus, the LCST decreases systematically with the introduction of more and/or larger hydrophobic side groups [2].

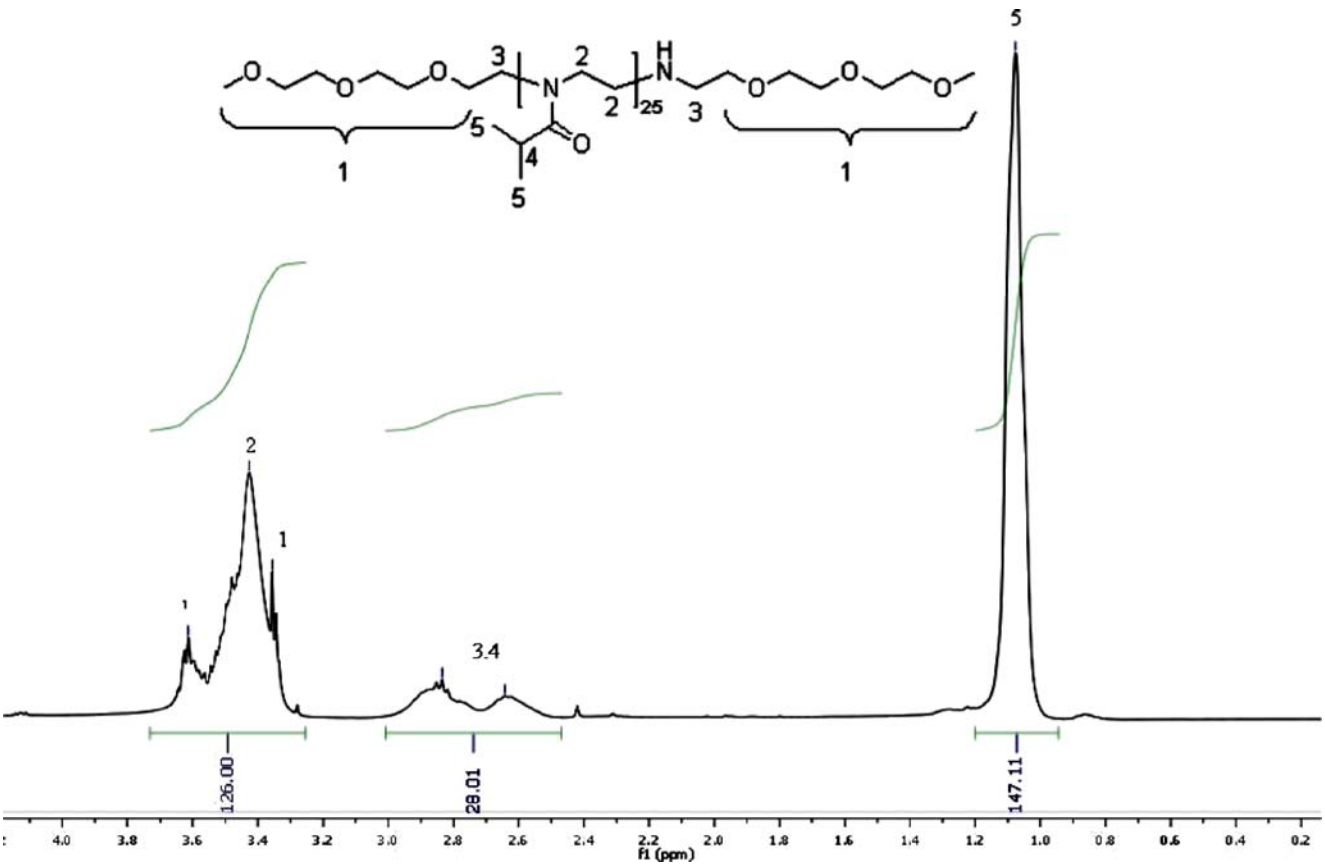


Fig. 3 ^{1}H-NMR spectrum of TEG-P*i*PrOx$_{25}$-TEG along with the peak assignments and integral signal values. Since no isolated end group signals are available, the determination of the average degree of polymerization was calculated from the ratio of the sum of signal integrals of 3 and 4 versus signals 5 or the sum of 1 and 2

Table 2 Analytical values of the synthesized polymers featuring end groups of different polarity along with the cloud points of the aqueous solutions (2 wt%)

Polymer	*n*		Yield[b] (%)	M_n (g/mol) theoretical	M_n[c,d] (g/mol) experimental	PDI[e]	CP[f] (°C)
	n/m theoretical	n/m[a] experimental					
$MeOx_3$-P*i*PrOx_{25}-$MeOx_3$	6/25	6.5/25	88	3,438	3,200	1.24	53
$MeOx_3$-P*i*PrOx_{25}	3/25	3/25	90	3,183	2,800	1.18	47
P*i*PrOx_{25}-piperazine	25	25	75[b]	2,930	2,900[d]	1.16	48
P*i*PrOx_{25}	25	25	80	2,928	3,900	1.09	47
TEG-P*i*PrOx_{25}	25	24	93	3,060	4,100	1.23	42
TEG-P*i*PrOx_{25}-TEG	25	24	88	3,138	4,000	1.23	42
Non-P*i*PrOx_{25}	25	24	83	3,040	3,000[d]	1.04	28
Non-P*i*PrOx_{25}-Non	25	26	84	3,098	3,200[d]	1.04	32
P(*i*PrOx_{24}NonOx_1)	24/1	24/1.5	85	3,012	3,500	1.18	15
P(*i*PrOx_{23}NonOx_2)	23/2	24/2	93	3,096	3,100	1.17	11

For comparison, copolymers with hydrophobic pendant groups are listed [4]
[a] Determined by NMR analysis from the intensity ratio of the backbone proton signals to the CH_3– side chain signals of the comonomer.
[b] Yield after dialysis (molar mass cut-off, 1,000 g/mol)
[c] Determined by GPC analysis
[d] Calculated by end group analysis from the intensity ratio of the nonyl-CH_3 end group or the piperazine protons to the backbone protons
[e] Polydispersity index; PDI = M_w/M_n calculated from GPC traces
[f] Determined by UV-vis spectroscopy at 10% decrease of optical transmittance of the polymer solution

Table 2 summarizes the cloud points for the aqueous solutions (2 wt%) of the synthesized polymers featuring nonyl end groups along with POx equipped with one or two nonyl side chains [4]. In Fig. 4, the CP measurements for hydrophobic modified POx are summarized.

Changing the terminal function from a methyl to a nonyl moiety significantly downshifts the cloud point by 19 °C from 47 °C for P*i*PrOx_{25} to 28 °C for Non-P*i*PrOx_{25}.

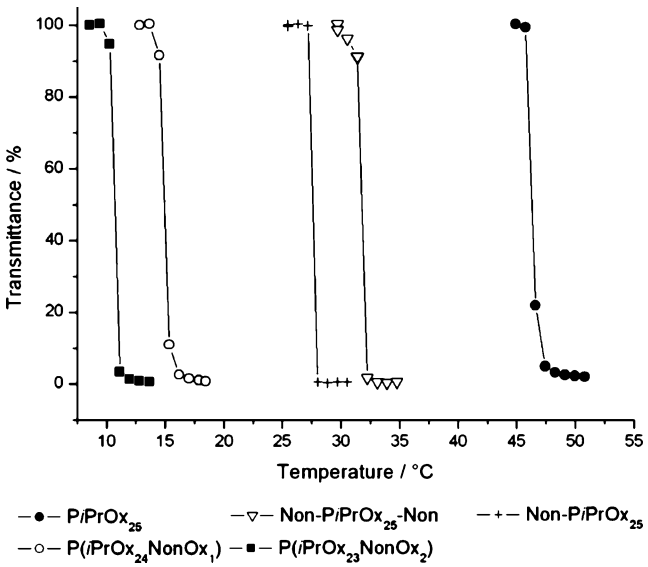


Fig. 4 Measurement of the cloud points for aqueous solutions of hydrophobic modified POx (2 wt%)

However, a side-chain-situated nonyl group decreases the CP even more by 32 to 15 °C for P(*i*PrOx_{24}NonOx_1). This LCST modulation is far more significant when compared to low molar mass PNIPAAm systems as studied by Stöver et al. [7] and Okano et al. [52], i.e. replacing a terminal hydrophilic amine group by a *n*-nonyl moiety changes the LCST of a linear PNIPAAm just by 2 °C and the introduction of a *n*-dodecyl chain by 8 °C [52]. Even the slightly higher molar mass of the compared PNIPAAm (M_W=7,300) does not fully explain this difference.

Replacing the terminal piperidine group of Non-P*i*PrOx_{25} by a second nonyl end function (Non-P*i*PrOx_{25}-Non) results in a smaller decrease of the CP by 15 to 32 °C. As discussed above for PNIPAAm, the introduction of terminal hydrophobic moieties often leads to aggregation into micelles, and the observed CP decrease becomes less pronounced. In fact, the aqueous solution of Non-P*i*PrOx_{25}-Non appears slightly turbid, indicating the formation of aggregates. The introduction of a second nonyl side group, however, decreases the CP as expected by 36 to 11 °C. The aqueous solution appeared clear. In this context, it is important to mention previous results on amphiphilic block as well as random copolymers. Also, in this case, P(NonOx-*b*-MeOx) block copolymers formed defined micelles at a defined critical micelle concentration of 10^{-5} mol/L, whereas random copolymers formed larger and less-defined aggregates [53–56].

In a second set of POx polymers, different hydrophilic end functions were introduced. Again, the LCST behavior of the P*i*PrOx_{25} homopolymer with methyl and piperidine end groups serves as the reference (Fig. 5). Exchange of the

terminal piperidine with a piperazine moiety, thus introducing a polar secondary amine group function (P*i*PrOx$_{25}$-piperazine), increases the LCST noticeably by 1 °C. A "PEGylation" of P*i*PrOx$_{25}$ or, in other words, the introduction of one or two oligo(ethyleneglycol) blocks (TEG-P*i*PrOx$_{25}$, TEG-P*i*PrOx$_{25}$-TEG), however, *decreases* the LCST significantly by 5 °C. Interestingly, with 42 °C, there was no difference between the LCST of the single (TEG-*i*PrOx$_{25}$) and double (TEG-*i*PrOx$_{25}$-TEG) modified polymer. Apparently, the PEGylation modifies the temperature-dependant solubility of P*i*PrOx$_n$ similar to a hydrophobic moiety—approximately what could be expected by the introduction of, e.g. a single hydrophobic butyl group. In previous studies, we investigated poly(2-oxazoline) lipopolymers equipped with mono- (MEG) and triethyleneglygol (TEG) pendant groups [44]. Also there, the modification of the hydrophilic POx backbone with MEG or TEG resulted in an amphiphilic character of the polymer segment. This was noticeable by the appearance of an extended plateau in the pressure-area isotherms that was attributed to a reversible adsorption of the MEG- or TEG-modified POx at the air–water interface. This behavior was also found for PEG-based lipopolymers. Thus, it is noteworthy that PEG cannot be regarded as a simple water-soluble polymer but has a noticeable amphiphilic character. Apparently, POx with short alkyl chains (methyl, ethyl and isopropyl) has a higher hydrophilic character than PEG. This is corroborated by the temperature-dependant solubility experiments with POx with one and two oligomeric MeOx$_3$ tails. While with one terminal MeOx$_3$ segment, no noticeable influence upon the LCST of P*i*PrOx$_{25}$ could be observed, the CP for the bolaamphiphilic MeOx$_3$-P*i*PrOx$_{25}$-MeOx$_3$ was found to be 6 °C higher.

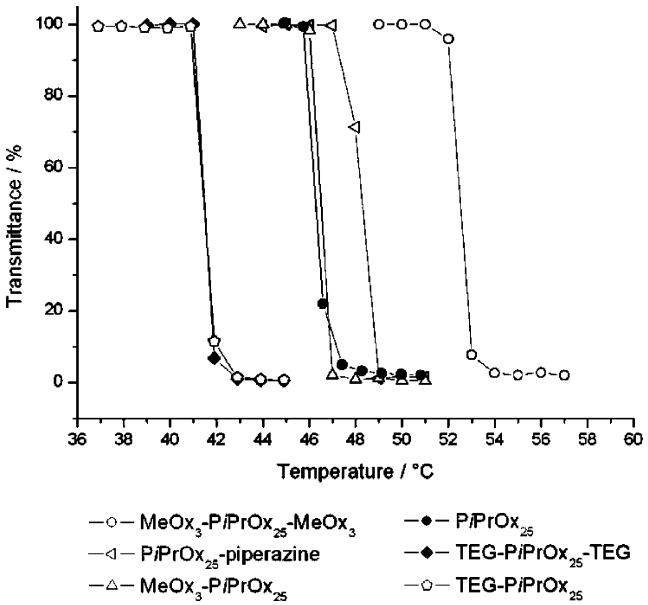


Fig. 5 Measurement of the cloud points for aqueous solutions of hydrophilic modified POx (2 wt%)

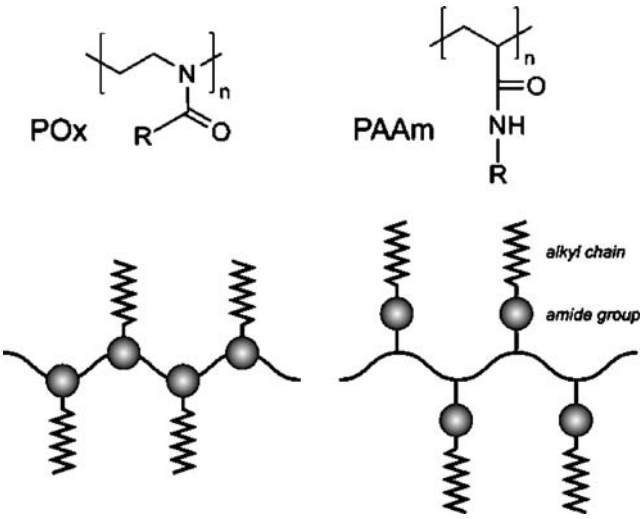


Fig. 6 Chemical and amphiphilic structure of the structural isomers poly(2-alkyl-2-oxazoline)s (POx) and poly(*N*-alkyl acrylamide)s (PAAm)

After comparison of the influence of pendant and end functionalization with groups of different polarity upon the LCST behavior of POx and PNIPAAm, it can be stated that the introduction of hydrophobic end groups has a stronger influence for POx systems as compared to PNIPAAm. However, introduction of non-polar side groups has an even stronger influence on POx-based systems, while the effect of terminal modification on PNIPAAm upon the LCST is more significant than side group modification [1]. Although P*i*PrOx and PNIPAAm are structural isomers (Fig. 6), PNIPAAm monomer units have a pendant secondary amide group, while the tertiary amide group in P*i*PrOx forms the link between backbone and the side chain. Attachment of larger hydrophobic pendant groups results in non-ionic polysoap motifs as depicted in Fig. 6. While the polar moiety in POx is part of the backbone, the 'soap' motif in poly(acrylamide)s (PAAm) is attached to a hydrophobic hydrocarbon backbone. Hence, the influence of hydrophobic moieties located in the side groups upon the temperature-dependant solubility in water is different for both polymers.

Conclusions

Poly(2-isopropyl-2-oxazoline) with end groups of different polarity can be synthesized by quantitative initiation and/or termination reaction or by sequential block copolymerization of 2-oxazolines. The lower critical solution temperature

in water strongly depends on the polarity of the terminal moiety. As expected, introduction of hydrophobic units decreases the LCST while hydrophilic increases the phase transition temperature. In comparison with poly(isopropyl acrylamide), the influence of the chain end polarity upon the cloud point is bigger, i.e. 19 °C between P*i*PrOx$_{25}$ with a *n*-nonyl chain instead of a methyl group. However, POx pendant group modification results in an even stronger shift of the LCST [4] due to the different location of the amide groups in the POx and PAAm monomer units. Attachment of oligo(ethyleneoxide) decreases the LCST of P*i*PrOx$_{25}$ due to its amphiphilic character.

The stronger influence of the polarity of pendant as well as end groups of POx upon the LCST in aqueous solutions allows a tuning of the phase transition in a much broader range as compared to the commonly used PNIPAAm.

Acknowledgements This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG) through the project JO287/4-3.

References

1. Gil ES, Hudson SA (2004) Prog Polym Sci 29:1173
2. Chung JE, Yokoyama M, Aoyagi T, Sakurai Y, Okano TJ (1998) Control Release 53:119
3. Uyama H, Kobayashi S (1992) Chem Lett 9:1643
4. Huber S, Jordan R (2008) Colloid Polym Sci 286:395
5. Park JS, Kataoka K (2007) Macromolecules 40:3599
6. Park JS, Kataoka K (2006) Macromolecules 39:6622
7. Xia Y, Burke NAD, Stöver HDH (2006) Macromolecules 39:2275
8. Xia Y, Yin XC, Burke NAD, Stöver HDH (2005) Macromolecules 38:5937
9. Ringsdorf H, Venzmer J, Winnik FM (1991) Macromolecules 24:1678
10. Ringsdorf H, Simon J, Winnik FM (1992) Macromolecules 25:5353
11. Bae YH, Okano T, Hsu R, Kim SW (1987) Makromol Rapid Commun 8:481
12. Kujawa P, Segui F, Shaban S, Diab C, Okada Y, Tanaka F, Winnik FM (2006) Macromolecules 39:341
13. Winnik FM, Davidson AR, Hamer GK, Kitano H (1992) Macromolecules 25:1876
14. Christova D, Velichkova R, Loos W, Goethals EJ, Du Prez F (2003) Polymer 44:2255
15. Lin PY, Clash C, Pearce EM, Kwei TK, Aponte MA (1988) J Polym Sci, Part B: Polym Phys 26:603
16. Goddard P, Hutchinson LE, Brown J, Brookmann LJ (1989) J Control Release 10:5
17. Gaertner FC, Luxenhofer R, Blechert B, Jordan R, Essler MJ (2007) Control Release 119:291
18. Zalipsky S, Hansen CB, Oaks JM, Allen TM (1996) J Pharm Sci 85:133
19. Woodle MC, Engbers CM, Zalipsky S (1994) Biocon Chem 5:493
20. Lee SC, Kim C, Kwon IC, Chung H, Jeong SY (2003) J Control Release 89:437
21. Jordan R, Martin K, Räder HJ, Unger KK (2001) Macromolecules 34:8858
22. Zarka MT, Nuyken O, Weberskirch R (2003) Chem Europ J 9:3228
23. Krause JO, Zarka MT, Anders U, Weberskirch RO, Nuyken MR Buchmeiser A (2003) Chem Int Ed 42:5965
24. Odian G, Shi F (1993) Macromolecules 26:17
25. Hsieh BR, Litt MH (1986) Macromolecules 19:516
26. Hsieh BR, Litt MH (1985) Macromolecules 18:1388
27. Persigehl P, Jordan R, Nuyken O (2000) Macromolecules 33:6977
28. Chujo Y, Sada K, Saegusa T (1993) Macromolecules 26:6315
29. Chujo Y, Sada K, Saegusa T (1990) Macromolecules 23:2636
30. Kotre T, Nuyken O, Weberskirch R (2002) Macromol Rapid Commun 23:871
31. Cesana S, Auernheimer J, Jordan R, Kessler H, Nuyken O (2006) Macromol Chem Phys 207:183
32. Cesana S, Kurek A, Baur MA, Auernheirner J, Nuyken O (2007) Macromol Rapid Commun 28:608
33. Taubmann C, Luxenhofer R, Cesana S, Jordan R (2005) Macromol Biosci 5:603
34. Luxenhofer R, Lopez-Garzia M, Frank A, Kessler H, Jordan R (2006) PMSE Reprints 95:283
35. Kobayashi S (1990) Prog Polym Sci 15:751
36. Chujo Y, Sada K, Saegusa T (1990) Macromolecules 23:2693
37. Luxenhofer R, Jordan R (2006) Macromolecules 39:3509
38. Chujo Y, Ihara E, Kure S, Saegusa T (1993) Macromolecules 26:5681
39. Park JS, Akiyama Y, Winnik FM, Kataoka K (2004) Macromolecules 37:6786
40. Meyer M, Antonietti M, Schlaad H (2007) Soft Matter 3:430
41. Meyer M, Schlaad H (2006) Macromolecules 39:3967
42. Witte H, Seeliger W (1974) Liebigs Ann Chem 1974:996
43. Schmidt M, Amstutz R, Crass G, Seebach D (1980) Chem Ber 113:1691
44. Lüdtke K, Jordan R, Hommes P, Nuyken O, Naumann CA (2005) Macromol Biosci 5:384
45. Kobayashi S, Iijima S, Igarashi T, Saegusa T (1987) Macromolecules 20:1729
46. Kobayashi S, Uyama H, Higuchi N, Saegusa T (1990) Macromolecules 23:54
47. Aoi K, Okada M (1996) Prog Polym Sci 21:151
48. Kobayashi S, Uyama H, Narita Y, Ishiyama JI (1992) Macromolecules 25:3232
49. Luxenhofer R, Bezen M, Jordan R (2008) Macromol Rapid Commun 29:1509
50. Gross A, Maier G, Nuyken O (1996) Macromol Chem Phys 197:2811
51. Bonne TB, Papadakis CM, Lüdtke K (2007) Jordan R Colloid Polym Sci 285:491
52. Chung JE, Yokoyama M, Suzuki K, Aoyagi T, Sakurai Y, Okano T (1997) Colloids and Surfaces B-Biointerfaces 9:37
53. Bonne TB, Lüdtke K, Jordan R, Stepanek P, Papadakis CM (2004) Colloid Polym Sci 282:1425
54. Papadakis CM, Ivanova R, Lüdtke K, Mortensen K, Pranzas PK, Jordan R (2007) J Appl Crystallogr 40:S361
55. Bonne TB, Lüdtke K, Jordan R, Papadakis CM (2007) Macromol Chem Phys 208:1402
56. Bortenschlager M, Schöllhorn N, Wittmann A, Weberskirch R (2007) Chem Europ J 13:520