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2-Isopropenyl-2-oxazoline: A Versatile Monomer for Functionalization of Polymers Obtained via RAFT

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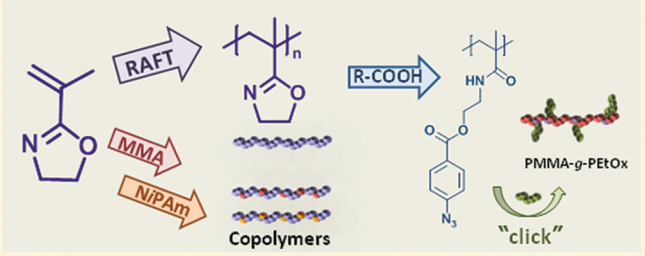
Supporting Information

ABSTRACT: 2-Isopropenyl-2-oxazoline (*i*POx) was polymerized for the first time via a controlled radical polymerization technique. Reversible addition−fragmentation chain transfer (RAFT) polymerization utilizing a dithiobenzoate-based chain transfer agent was employed to form a backbone that is highly reactive toward thiols and acids. Moreover, the statistical copolymerization of *i*POx with methyl methacrylate (MMA) and *N-iso*-propylacrylamide (N*i*PAm) was investigated resulting in two copolymer series with *i*POx content varying from 100% to 13% (PDI = 1.37 to 1.21). The P(*i*POx-*stat*-N*i*PAm) copolymers displayed thermoresponsive behavior in water as well as phosphate buffered saline at higher temperatures in comparison to homopolymers of N*i*PAm due to the hydrophilicity of the introduced *i*POx moieties (T_{cp} = 25 to 75 °C). Futhermore, *i*POx-based (co)polymers were functionalized by polymer analogous addition reactions with thiophenol, benzoic acid and 4-azidobenzoic acid in high conversions (74−100%). The latter adduct represented a suitable building block for the synthesis of a graft copolymer consisting of a PMMA backbone and poly(2-ethyl-2-oxazoline) (PEtOx) side chains via copper-catalyzed azide−alkyne cycloaddition (CuAAC) of PEtOx with alkyne terminus.



INTRODUCTION

2-Oxazolines are well-known in polymer chemistry for their ability to undergo a living cationic ring-opening polymerization to yield well-defined polymers for use in biomedical applications.[1−8] However, one might be less aware of the fact that the 2-oxazoline ring is also capable of addition reactions with a wide range of nucleophiles, such as carboxylic acids or thiols.[9] These reactions have been exploited for polyaddition reactions of bis-oxazolines and dicarboxylic acids yielding polyesteramides.[10−13] In addition, the 2-oxazoline ring provides a versatile tool for postpolymerization functionalization when it is connected in a pendant fashion to a polymer backbone. Such a structure can be obtained by the polymerization of 2-*iso*-propenyl-2-oxazoline (*i*POx), a commercially available monomer, via its vinylic moiety. This polymerization can be performed under either anionic[14] or free radical[15] polymerization conditions. On the other hand, attempts to polymerize *i*POx cationically via its oxazoline moiety resulted only in ill-defined oligomeric products.[14] It was already demonstrated that the pendant oxazoline ring can be readily used for further modification of the free radically polymerized P*i*POx by attack of acids or thiols, even in aqueous solution.[16] More recently, Jerca et al. reported the functionalization of statistical copolymers of *i*POx and methyl methacrylate (MMA) with a carboxylic acid functionalized azo dye.[17,18] In addition, MMA/*i*POx copolymers are commercially available as water-soluble cross-linking agents for carboxylic acid containing polymers.

Nowadays, controlled radical polymerization (CRP) techniques,[19−21] such as atom transfer polymerization,[22] nitroxide mediated polymerization[23] or reversible addition−fragmentation chain transfer (RAFT) polymerization[24,25] are widely applied for the synthesis of well-defined polymers from a large number of vinylic monomers, such as acrylates, acrylamides, methacrylamides, methacrylates or vinylesters. One major advantage of these polymerization techniques is the utilization of monomers and solvents without extensive purification procedures as well as the good tolerance against other functional moieties, compared to ionic polymerizations. In addition, the utilization of CRP and various click reactions[26−29] enables the engineering of advanced polymer structures, such as

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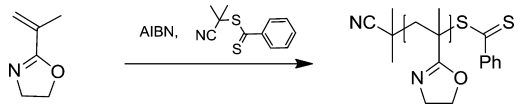
block or graft copolymers, or the copolymerization with other monomers providing further interesting properties, such as thermoresponsiveness.[30−33] However, to the best of our knowledge, the CRP of *i*POx has not been reported up to now, even though the oxazoline moiety should enable access to a range of interesting polymers via polymer analogous reactions when using a well-defined P*i*POx as a backbone.

In this contribution, we present the homo- and statistical copolymerization of *i*POx utilizing the RAFT polymerization technique (Scheme 1). To the best of our knowledge, this is the first report on a statistical copolymerization of *N-iso*-propylacrylamide (N*i*PAm) and *i*POx. Moreover, we have investigated the thermoresponsive behavior of the obtained polymers. Furthermore, selected polymers were subsequently functionalized with benzoic acid and thiophenol as model compounds to present the versatility of the addition reaction. Last but not least, 4-azidobenzoic acid was reacted as precursor material for the synthesis of graft copolymers via "click" chemistry.

Scheme 1. Schematic Representation of the RAFT Polymerization of 2-Isopropenyl-2-oxazoline



EXPERIMENTAL SECTION

Materials. The monomers *i*POx (99%), methyl methacrylate (MMA, 99%) and *N-iso*-propylacrylamide (N*i*PAm, 97%) were purchased from Aldrich. MMA was destabilized with inhibitor remover (Aldrich) prior to use. 2,2′-Azobis(2-methylpropionitrile) (98%, Acros, AIBN) was recrystallized from hexane and the chain transfer agent 2-cyanopropyl dithiobenzoate (CPDB, 97%) was obtained from Aldrich. Benzoic acid (99.5%) was purchased from Sigma-Aldrich, 4-azidobenzoic acid (98%) from ABCR, and thiophenol (98%), DMF (99.5%) as well as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 99%) from Fluka. Copper(I) iodide (CuI, 99.5%) was purchased from Aldrich. Poly(2-ethyl-2-oxazoline) (PEtOx-TB) was prepared according to a previously published procedure.[34] Preparative size exclusion chromatography was carried out using BioBeads-SX1 from BioRad with THF as eluent. For the cloud point measurements, demineralized water and phosphate buffered saline 10× concentrate (Aldrich) were used. All other chemicals and solvents were obtained from common commercial sources and used without further purification, unless otherwise noted.

Instrumentation. ^{1}H NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on a Bruker Avance 300 MHz using the residual solvent resonance as an internal standard. Size exclusion chromatography (SEC) was measured on a Shimadzu system equipped with a SCL-10A system controller, a LC-10AD pump, and a RID-10A refractive index detector using a solvent mixture containing chloroform, triethylamine, and isopropanol (94:4:2) at a flow rate of 1 mL min^{-1} on a PSS-SDV-linear M 5 μm column at 40 °C. The system was calibrated with PMMA (2−88 kDa) standards. For polymers containing secondary amides, a different SEC system was used. This system is equipped with a SCL-10A system controller, a LC-10AD pump, a RID-10A refractive index detector, and both a PSS Gram30 and a PSS Gram1000 column in series, whereby *N,N*-dimethylacetamide with 2.1 g·L^{-1} of LiCl was applied as an eluent at 1 mL min^{-1} flow rate and the column oven was set to 60 °C. GC measurements were performed on a Shimadzu GC-2010 equipped with a Restek Rtx-5 column, a FID detector and a PAL autosampler. IR spectra were recorded on an Affinity-1 Fourier transform infrared spectrophotometer from Shimadzu.

For the measurement of the matrix-assisted laser desorption/ionization (MALDI) mass spectra an Ultraflex III TOF/TOF (Bruker Daltonics, Bremen, Germany) was used. The instrument was equipped with a Nd:YAG laser and a collision cell. All spectra were measured in the positive reflector or linear mode. The instrument was calibrated prior to each measurement with an external PMMA standard from PSS Polymer Standards Services GmbH (Mainz, Germany). Electrospray ionization time-of-flight mass spectrometry (ESI TOF MS) measurements were performed with a micrOTOF (Bruker Daltonics) mass spectrometer equipped with an automatic syringe pump, which is supplied from KD Scientific for sample injection. The mass spectrometer was operating in the positive ion mode. The standard electrospray ion source was used to generate the ions. The ESI TOF MS instrument was calibrated in the m/z range from 50 to 3000 g mol^{-1} using an internal calibration standard (Tunemix solution), which was supplied from Agilent. Data were processed via Bruker Data Analysis software version 4.0. Cloud point temperatures (T_{cp}) were determined using a Crystal 16 from Avantium Technologies being connected to a chiller (Julabo FP 40) at a wavelength of 500 nm and a heating ramp of 1 K min^{-1}. The concentration of the polymer was kept constant at 5 mg mL^{-1}, and T_{cp} values are reported from 50% transmittance in the second heating cycle.

Synthesis. *Kinetic Studies RAFT Polymerization.* *i*POx (1.5 g, 13.5 mmol) was dissolved in 5.2 mL toluene and a solution of 11.1 mg (0.067 mmol) AIBN in toluene as well as a solution of 59.7 mg (0.27 mmol) CPDB in toluene were added. The concentration of the monomer was 2 mol L^{-1} and the ratio of [*i*POx]:[CPDB]:[AIBN] was 50:1:0.25. Subsequently, the mixture was degassed with a gentle flow of nitrogen for 30 min and divided over 7 separate vials that were

Table 1. Characterization Data of Statistical Copolymers of *i*POx with MMA and N*i*PAm

	comonomer type (M)	% *i*POx (feed)	% *i*POx (^{1}H NMR)	DP^c *i*POx:M	M_n [g mol^{-1}]	PDI	conv [%] *i*POx:M
P1	-	100	100	55:0	2700^a	1.37^a	16:0
P2	MMA	90	89	43:5	2840^a	1.34^a	16:19
P3	MMA	75	77	40:12	3350^a	1.34^a	20:19
P4	MMA	50	53	26:23	3820^a	1.31^a	11:16
P5	MMA	25	29	18:44	5360^a	1.23^a	22:22
P6	MMA	10	13	12:84	7370^a	1.21^a	43:39
P7	-	100	100	50:0	2760^b	1.33^b	11:0
P8	N*i*PAm	90	88	31:8	2880^b	1.24^b	32:14
P9	N*i*PAm	75	83	12:2	1960^b	1.36^b	21:5
P10	N*i*PAm	50	62	8:5	2680^b	1.23^b	26:7
P11	N*i*PAm	25	43	5:7	3080^b	1.20^b	29:10
P12	N*i*PAm	10	17	3:13	4000^b	1.22^b	32:12

^{a}Determined via SEC ($CHCl_3$) using PMMA calibration. ^{b}Determined via SEC (DMA) using PMMA calibration. ^{c}Degree of polymerization estimated from the integral ratio of the aromatic signals of the dithiobenzoate end group and signals of both repeating units in the ^{1}H NMR spectra.

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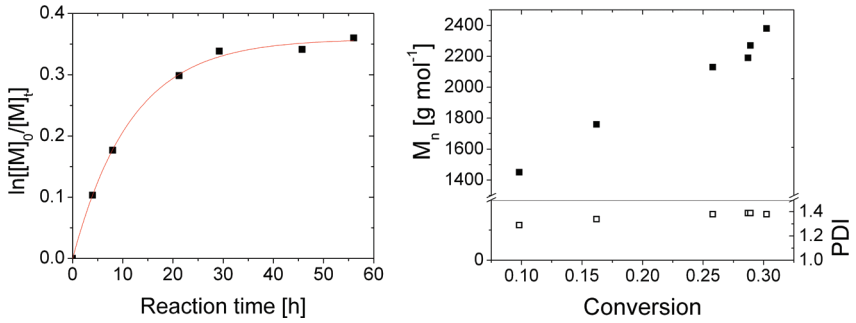

Figure 1. Kinetic plots for the RAFT homopolymerization of *i*POx utilizing CPDB as CTA. SEC traces can be found in ESI (Figure SI-2, Supporting Information).

capped and shortly degassed with nitrogen one more time. All vials were placed simultaneously in an oil bath at 70 °C and taken out after varying reaction times between 4 and 56 h. Subsequent to cooling with tap water, the vials were opened and samples were taken for ^{1}H NMR ($CDCl_3$) and SEC ($CHCl_3$). The conversions were determined by comparison of the integral ratios of the peaks in the ^{1}H NMR spectrum derived from the vinylic protons of *i*POx (5.72 and 5.32 ppm, respectively) and the methylene protons of the oxazoline ring (4.28−3.56 ppm).

RAFT Homo- and Statistical Copolymerization. According to the feed ratios given in Table 1, the appropriate amounts of *i*POx and MMA or *i*POx and N*i*PAm, respectively, were dissolved in toluene and AIBN as well as CPDB were added in a similar fashion as described above. For **P1−6** (MMA copolymers) the ratio of [Monomer]: [CPDB]: [AIBN] was set to 100: 1: 0.25, whereas it was set to 50: 1: 0.25 for **P7−12** (N*i*PAm copolymers). After capping the vials and gently degassing the reaction mixtures with nitrogen, initial samples were taken via syringe and the vials were placed in an oil bath at 70 °C to react for 19 h. Subsequent to cooling with tap water, the vials were opened and final samples were taken for GC ($CHCl_3$) and SEC ($CHCl_3$ for **P1−6** and DMA for **P7−12**) measurements. Monomer conversions were determined via GC using the reaction solvent as an internal standard. The P*i*POx homopolymers and statistical copolymers with MMA were precipitated into cold *tert*-butyl methyl ether and the N*i*PAm copolymers were purified by preparative size exclusion chromatography on a BioBeads-SX1 column with THF as eluent. The resulting pink polymers were dried in a vacuum oven. Yields: **P1**, 48 mg, 5%; **P2**, 115 mg, 11%; **P3**, 205 mg, 16%; **P4**, 397 mg, 21%; **P5**, 574 mg, 31%; **P6**, 812 mg, 45%; **P7**, 209 mg, 21%; **P8**, 144 mg, 13%; **P9**, 180 mg, 14%; **P10**, 311 mg, 16%; **P11**, 278 mg, 14%; **P12**, 322 mg, 16%. ^{1}H NMR (300 MHz, $CDCl_3$): **P1−6** δ/ppm = 4.3−4.1 N−CH_2−, 3.8−3.6 N−CH_2−, 3.9−3.5 O−CH_3, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3; **P7−12** δ/ppm = 4.3−4.1 N−CH_2−, 4.1−3.8 CH−$(CH_3)_2$, 3.8−3.6 N−CH_2−, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3.

Addition Reactions with Carboxylic Acids and Thiophenol. In a representative example, P*i*POx (85 mg, corresponding to 0.77 mmol of *i*POx units) and a 2-fold excess of *p*-azidobenzoic acid (106 mg, 1.53 mmol) were dissolved in 2 mL of DMF and stirred for 24 h at 60 °C. The crude product was dissolved in chloroform and extracted with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Subsequently, the polymer was precipitated into cold diethyl ether and dried in a vacuum oven. Yields: **A1**, 61 mg, 54%; **A2**, 209 mg, 63%; **A3**, 122 mg, 88%; **A4**, 134 mg, 52%. ^{1}H NMR (300 MHz, CD_2Cl_2): **A1** δ/ppm = 7.6−7.0 CH phenyl, 6.7−6.0 NH, 3.6−2.7 S−CH_2−CH_2−NH, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3; **A2** δ/ppm = 8.2−7.2 CH phenyl, 6.7−6.0 NH, 4.5−4.2 COO−CH_2, 3.8−3.3 CH_2−NH, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3; **A3** δ/ppm = 8.1−7.6 and 7.1−6.7 CH phenyl, 6.7−6.0 NH, 4.5−4.2 COO−CH_2, 3.8−3.3 CH_2−NH, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3; **A4** δ/ppm = 8.1−7.6 and 7.1−6.7 CH phenyl, 6.7−6.0 NH, 4.5−4.2 COO−CH_2, 3.8−3.3 CH_2−NH and O−CH_3, 2.3−1.5 C−CH_2−C, 1.5−0.8 C−CH_3.

*Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) of **A4** with Alkyne-Terminated Poly(2-ethyl-2-oxazoline).* The azide-containing copolymer **A4** (21 mg, corresponding to 0.017 mmol azide units), PEtOx-TB (20 mg, 0.02 mmol), and DBU (3.04 mg, 0.02 mmol) were dissolved in 0.25 mL of DMF and degassed for 30 min. Subsequently, CuI (3.8 mg, 0.02 mmol) was added under argon, and the reaction mixture was stirred overnight at ambient temperature. The CuI was removed by flushing the solution over a short aluminum oxide column. The solvent was removed under reduced pressure and the crude product was redissolved in THF in order to purify the polymer by preparative size exclusion chromatography on a BioBeads-SX1 column. Finally, the product (**A5**) was precipitated in ice-cold diethyl ether (yield 30 mg, 83%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ/ppm = 8.4−7.7 (C−H phenyl and C−H triazole), 4.5−4.3 COO−CH_2CH_2, 4.2−4.0 COO−CH_2 PEtOx, 3.9−3.5 O−CH_3 MMA, 3.6−3.3 N−CH_2 PEtOx, 3.1−3.0 N−CH_3 PEtOx, 2.5−2.2 CO−CH_2 PEtOx, 2.1−1.5 CH_2 backbone, 1.5−0.8 CH_3 backbone and CH_3−CH_2 PEtOx.

RESULTS AND DISCUSSION

Homopolymerization of *i*POx. In an initial screening, varying classes of chain transfer agents (CTAs), such as dithiobenzoate, trithiocarbonate, and dithiocarbamate, were applied in order to gain first insights into the RAFT polymerization conditions of *i*POx. All polymerizations were performed in 2 M solution in toluene for 18 h at 70 °C using AIBN as initiator, whereby the ratio of [*i*POx]: [CTA]: [AIBN] was set to 50: 1: 0.25. As depicted in Figure SI-1, Supporting Information, utilization of dithiocarbamate as well as trithiocarbonate-based CTAs resulted in broad molar mass distributions, whereas the RAFT polymerization with the dithiobenzoate-based CTA (CPDB) yielded polymers with a more narrow molar mass distribution (PDI = 1.38). In addition, the lower molar mass of the resulting polymer indicated that the polymerization could be controlled by CPDB to a certain extent. As a result, CPDB was selected for the performance of further experiments, such as kinetic studies and the synthesis of statistical copolymers of *i*POx with other monomers.

The kinetic studies of the RAFT polymerization of *i*POx utilizing CPBD as CTA were performed under similar reaction conditions as described above. The resulting kinetic plots are depicted in Figure 1. Even though the molar mass of the polymer increases in a linear fashion with monomer conversion and the PDI values remain well below 1.4, the semilogarithmic plot reveals that the polymerization slows down significantly at monomer conversions of around 30%. Since the kinetic studies were accomplished in separate vials this fact cannot simply be a result of contamination of the reaction mixture during sampling. Instead, after initiation by AIBN, the intermediate structure during the RAFT process might be too stable to reinitiate the polymerization once it has been formed. This assumption is supported by the fact that CPDB is frequently

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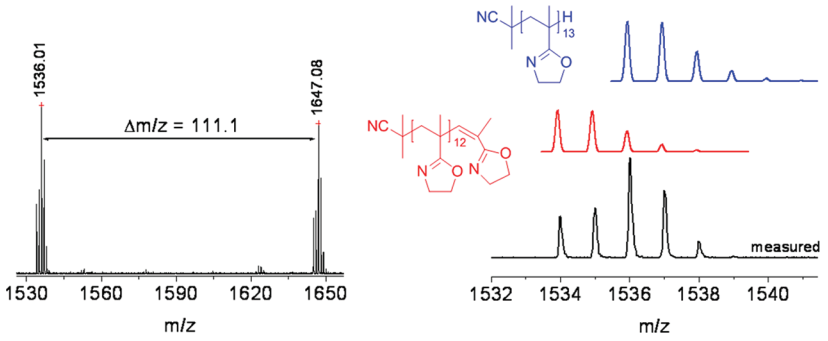

Figure 2. Zoom into the m/z range from 1520 to 1660 of the MALDI TOF mass spectrum of P*i*POx and overlay of measured and calculated isotopic patterns. Both structures are ionized with a sodium cation. The full spectrum is provided in Figure SI-3, Supporting Information.

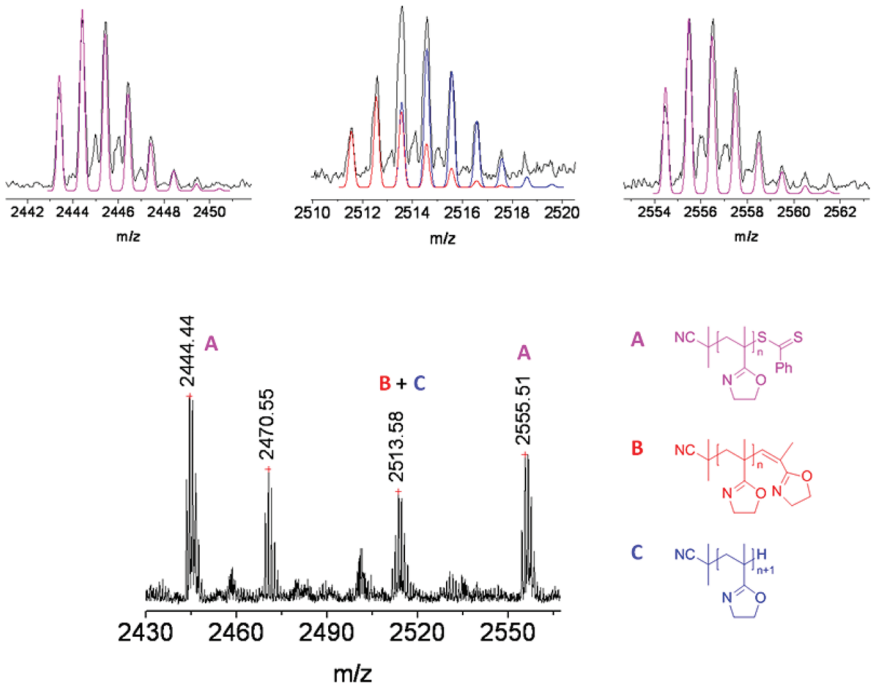

Figure 3. Zoom into the +1 charged region of the ESI TOF mass spectrum of P*i*POx and assignment of the main distributions. All structures are ionized with a proton.

applied for RAFT polymerization of more activated monomers as well as by the observation that free CTA was still present in the reaction solution, even at later stages of the polymerization, as confirmed by preparative SEC on a BioBeads column showing two pink fractions (i.e., P*i*POx and free CPDB) that eluted separately from each other.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectrometry analysis of the obtained P*i*POx revealed a single distribution with a m/z difference of 111.1 between two neighboring peaks, which corresponds to the molar mass of the *i*POx repeating unit (Figure 2). Because of the rather harsh ionization during the MALDI process, the dithiobenzoate end group is cleaved and polymer chains with both saturated as well as unsaturated end groups are formed. The m/z difference of 2 between those end groups results in an overlapping of the isotopic patterns of the assigned structures.

In contrast, the softer ionization taking place during electro spray ionization (ESI) partially preserved the dithiobenzoate end group, although also polymer chains with saturated and unsaturated end groups could be assigned. The peak assignment of the resulting ESI mass spectrum of P*i*POx is shown in Figure 3.

Statistical Copolymerization of *i*POx with MMA and NiPAm. Encouraged by the rather successful homopolymerization that delivered P*i*POx with much narrower molar mass distributions compared to the results obtained by free radical polymerization,[15] two series of statistical copolymers of *i*POx with other monomers, i.e., MMA and N*i*PAm, were prepared. In order to evaluate the amount of *i*POx that can be incorporated into a copolymer without suppressing reversible chain transfer, the *i*POx content was varied systematically from 100 to 10% for both series. Except for a ratio of [monomer]:[CTA] of 100:1 for the copolymer series with MMA as reactive monomer, all polymerizations were carried out under similar conditions as described above. The results of the characterization of the obtained copolymers by means of SEC and ^{1}H NMR spectroscopy are summarized in Table 1.

SEC analysis of the statistical copolymers consisting of *i*POx and MMA **P1**−**P6** (Figure 4, top) revealed that, with increasing amount of the more activated MMA in the feed, the molar mass distribution becomes much more narrow with PDI values

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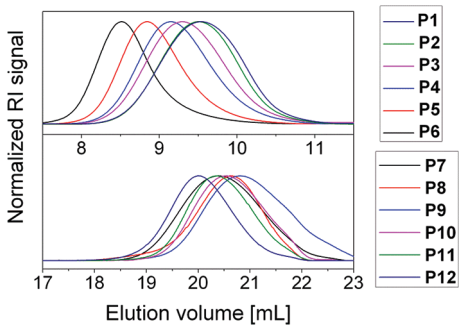

Figure 4. SEC traces of the statistical copolymers of *i*POx with MMA (top, eluent $CHCl_3$) and with N*i*PAm (bottom, eluent DMA).

between 1.37 for the P*i*POx homopolymer and 1.21 for the statistical copolymer containing only 13 mol % *i*POx. In addition, the molar mass of the copolymer increases with the MMA content. In order to evaluate if the latter is simply an effect of a variation in hydrodynamic volume of the polymers with altered composition, the degree of polymerization (DP) of each comonomer was roughly estimated from appropriate signals in the ^{1}H NMR spectra, assuming full end functionalization with the dithiobenzoate moiety. Indeed, keeping in mind the accuracy of the applied method, at least the two copolymers with the largest mole fraction of MMA (**P5** and **P6**) have significantly higher DP values than the copolymers with lower MMA content (see Table 1). In addition, as depicted in Figure 5, the copolymer composition,

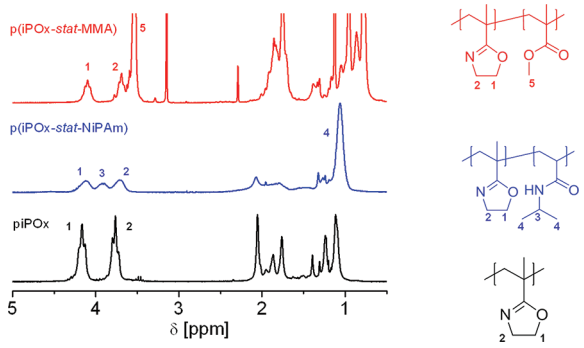

Figure 5. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of a P*i*POx homopolymer (bottom) and statistical copolymers of *i*POx with MMA (top) as well as with N*i*PAm (middle), respectively.

which was calculated from the ratio of the peak integrals of the methylene protons of the 2-oxazoline ring of the *i*POx and the methyl protons of MMA, was found to be close to the feed ratio of both monomers. All these results indicate that the low ability of the intermediate species that is formed during RAFT polymerization of *i*POx to undergo reversible chain transfer can be overcome by utilization of MMA as more activated comonomer.

As next step, *i*POx functionalities were incorporated into a polymer displaying thermo-responsive properties, namely PN*i*PAm. For this second series of statistical copolymers **P7–12**, SEC analysis (Figure 4, bottom) revealed a significant increase of the molar mass and a satisfying peak shape only for **P12**, the copolymer with the highest mole fraction of N*i*PAm (83%), even though the PDI values for all copolymers remained well below 1.3, except for **P9**. In addition, the conversion of *i*POx was found to be higher than that of N*i*PAm, which is reflected in an increased mole fraction of *i*POx in the polymers with respect to the feed ratios. However, it was possible to obtain polymers with varying *i*POx content from roughly 17 to 88% (as determined by ^{1}H NMR spectroscopy, Figure 5), that could be used for an investigation of the effect of the *i*POx moieties upon the lower critical solution temperature (LCST) behavior of PN*i*PAm.

Aqueous Solution Behavior of P(*i*POx-*stat*-NiPAm) Copolymers. The thermoresponsive properties of **P7–12** in aqueous solution were investigated by means of turbidimetry at a polymer concentration of 5 mg mL^{-1} in water as well as phosphate buffered saline (PBS). In order to determine the reversibility of the coil to globule transition two heating cooling cycles were conducted for each sample with a heating rate of 1 K min^{-1}. Turbidity curves from the second heating run are displayed in Figure 6 (left). The P*i*POx homopolymer **P7** remained water-soluble during the whole investigated temperature range up to 100 °C indicative of its high hydrophilicity. The latter also caused complete solubility of the copolymer with the highest *i*POx content **P8**. Consequently, an increasing mole fraction of *i*POx in the statistical copolymers **P9–12** was expected to result in elevated cloud point temperatures (T_{cp}) of the aqueous solutions. Surprisingly, as shown in Figure 6 (right), this holds true only for copolymers with mole fractions of *i*POx above 50%. Below that value, T_{cp} remained rather unaffected by the copolymer composition around 25 to 26 °C in PBS and around 33 to 35 °C in water. As a result of the hydrophilic *i*POx moieties, the latter value is slightly higher than the T_{cp} of a comparable PN*i*PAm solution at 30 °C under similar measurement conditions. In addition, the transition becomes less sharp with increasing *i*POx/N*i*PAm ratio in the copolymer. Possible explanations for this unexpected behavior

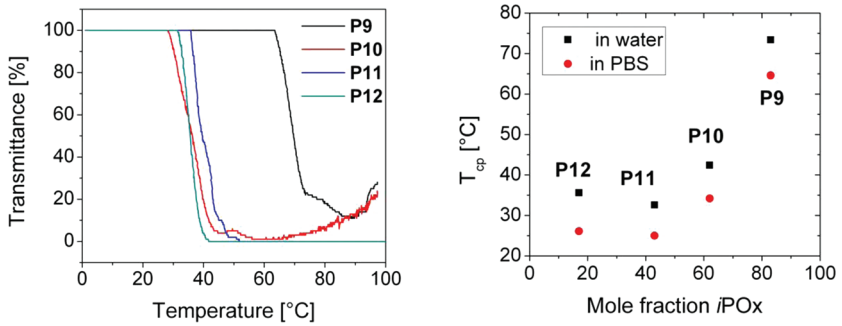

Figure 6. Left: Turbidity curves of aqueous solutions of **P9–12** in water (c = 5 mg mL^{-1}, second heating run). Right: Dependence of the cloud point temperature (T_{cp}) of solutions of **P9–12** in water and PBS on the copolymer composition (c = 5 mg mL^{-1}, second heating run, 50% transmittance).

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Scheme 2. Schematic Representation of the Addition Reaction of P*i*POx with Thiophenol and Carboxylic Acids

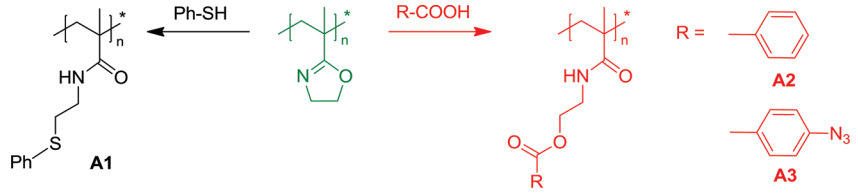

Table 2. Characterization Data of Addition Products Obtained after Reaction of P*i*POx with Thiophenol and Carboxylic Acids

		premodification		postmodification		theoretical	
code	reactant	M_n [a] [g mol^{-1}]	PDI	M_n [a] [g mol^{-1}]	PDI	M_n [b] [g mol^{-1}]	F [c] (%)
A1	thiophenol	2130	1.45	11 200	1.21	11 000	quant.
A2	benzoic acid	2930	1.45	6200	1.35	9500	74
A3	4-azidobenzoic acid	2130	1.45	8070	1.40	12 700	88

[a]Determined via SEC (DMA) using PMMA calibration. [b]Calculated from the DP of the used P*i*POx and the degree of functionalization. [c]Degree of functionalization determined from ^{1}H NMR.

might either be a gradient composition of the copolymers facilitating the solubilization of already collapsed N*i*PAm rich parts by *i*POx rich parts below T_{cp}, or the rather small overall DP of the copolymers **P9**−**12** that exhibit LCST behavior (in the range of 12 to16). Because of the latter small variations of the composition of individual polymer chains directly result in a mixture of thermoresponsive polymers with varying T_{cp}.[35] In this case, polymer chains containing a similar mole fraction of N*i*PAm might be present in both copolymers (**P9** and **P10**) and would collapse prior to chains with smaller N*i*PAm content.

Functionalization of iPOx-Containing Polymers with Carboxylic Acids and Thiols. In order to evaluate the possibility to synthesize functionalized polymers from the *i*POx containing copolymers, polymer analogous addition reactions with benzoic acid and thiophenol as model substances were performed under mild conditions (at 60 °C) using P*i*POx homopolymers as starting material. In addition, 4-azidobenzoic acid was applied as reactant in order to obtain a polymer that is functionalized with multiple azide moieties. The poly(methacrylamide) structure of the resulting addition products **A1**−**3** is depicted in Scheme 2, and analytical data are supplied in Table 2.

Characterization of **A1**−**3** by means of SEC (Figure SI-4, Supporting Information) revealed a significant increase of the hydrodynamic volume of the polymers after the addition reactions and, especially for the addition product with thiophenol **A1**, smaller PDI values when compared to the P*i*POx starting material. It should be noted that the dithiobenzoate end group is cleaved during the reaction process (as indicated by the whitish instead of pink color of **A1**−**3**).

Utilizing ^{1}H NMR spectroscopy the degree of functionalization with the respective acid or thiol could be easily determined by comparison of the peak integrals in the aromatic region with the peak integrals derived from residual oxazoline moieties and the four methylene protons between amide and ester functionalities. As depicted in Figure 7, the reactions with both carboxylic acids reached conversions of 74% for **A1** and 88% for **A2**, respectively. Small residual peaks of the pendant oxazoline rings could be detected in both ^{1}H NMR spectra that were overlapping with the corresponding proton signals of the opened methacrylamide structure. On the other hand, the

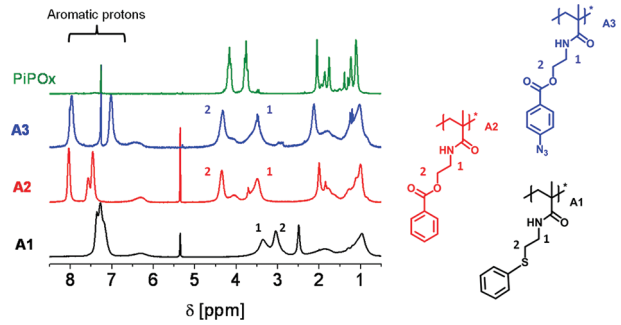

Figure 7. ^{1}H NMR spectra (300 MHz, CD_2Cl_2 or $CDCl_3$) of a P*i*POx homopolymer (top) and of the addition products with thiophenol (**A1**), benzoic acid (**A2**) as well as 4-azidobenzoic acid (**A3**).

addition of thiophenol proceeded quantitatively as demonstrated by the disappearance of the oxazoline derived signals.

The formation of ester functionalities after the polymer analogous reactions with carboxylic acids could be confirmed by means of FT-IR spectroscopy (Figure 8). The IR spectra of

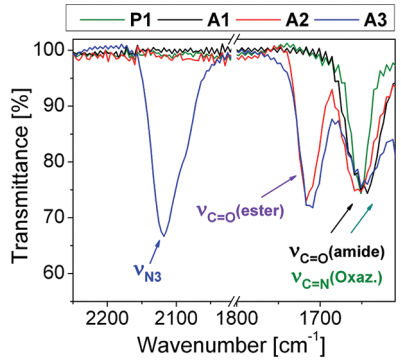

Figure 8. Zoom into the azide and carbonyl vibration region of the FT ATR IR spectra of P*i*POx (**P1**) and addition products with thiophenol, benzoic acid, and 4-azidobenzoic acid, respectively (**A1**−**3**).

both **A2** and **A3** clearly show a characteristic band at 1720 cm^{-1} that can be assigned to the carbonyl stretching vibration of the formed ester. In addition, the IR spectrum of **A3** provides evidence of the presence of azide moieties due to the characteristic ν_{N_3} band at 2120 cm^{-1}. It should be noted that

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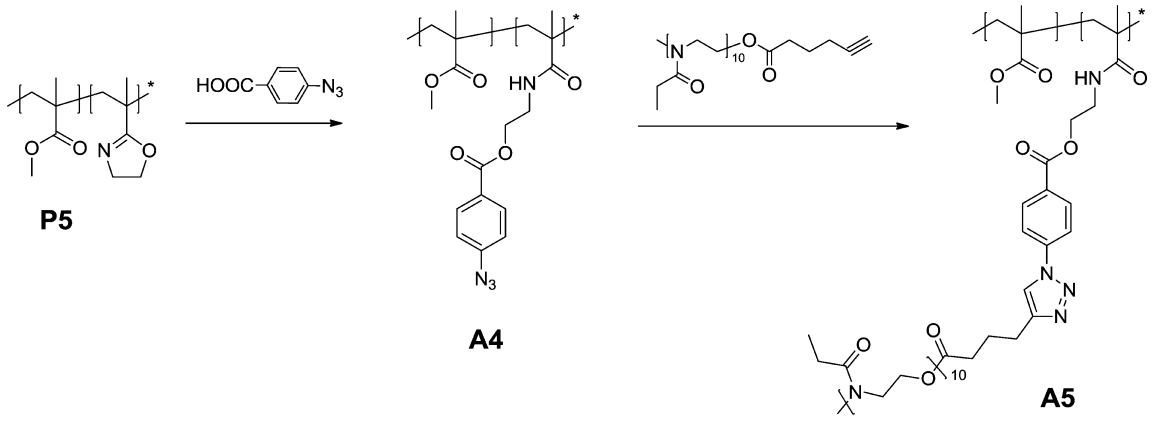
Scheme 3. Schematic Representation of the Synthesis Route toward PMMA-*g*-PEtOx



the carbonyl stretching vibration of the amide moiety at 1655 cm^{-1} in the IR spectra of all addition products **A1−3** is overlapping with the −C═N vibration of the oxazoline ring in P*i*POx.

The fact that the copper-catalyzed azide−alkyne cycloaddition (CuAAC) has become a common and versatile method in polymer chemistry led to the availability of a wide range of interesting building blocks for this type of "click" reaction. In this context, addition products of P*i*POx-based copolymers with 4-azidobenzoic acid could serve as starting material for further functionalization, or the synthesis of graft copolymers if the utilized alkyne represents an end functionalized polymer. As depicted in Scheme 3, the latter route was applied in order to obtain a graft copolymer having a PMMA-based backbone and poly(2-ethyl-2-oxazoline) (PEtOx) side chains.

A first hint toward a successful grafting of alkyne-terminated PEtOx onto the azide functionalized PMMA-based copolymer **A4** is provided by SEC analysis of the graft copolymer **A5** (Figure 9). The SEC trace of **A5** is shifted to smaller elution

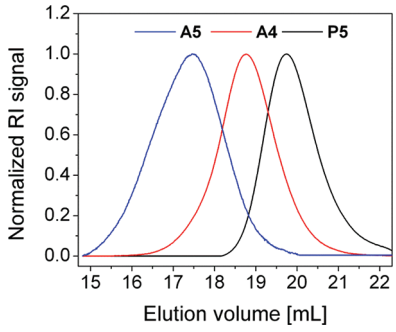


Figure 9. SEC traces (DMA) of **P5** (M_n = 4760 g mol^{-1}, PDI = 1.26), its addition product with 4-azidobenzoic acid **A4** (M_n = 10 220 g mol^{-1}, PDI = 1.29), and the graft copolymer **A5** (M_n = 25 780 g mol^{-1}, PDI = 1.39).

volume when compared to **A4** indicative of its larger hydrodynamic volume due to the grafting process. In addition, the complete removal of the excess of PEtOx after preparative size exclusion chromatography is confirmed by the monomodal peak shape.

With this knowledge it is possible to gain further insights regarding the copolymer composition by interpretation of the ^{1}H NMR spectrum of **A5**. As depicted in Figure SI-5, Supporting Information, the signals of the PEtOx side chains are clearly visible, and the formation of the triazole ring is manifested by a change of the signals in the aromatic region. Most likely due to steric hindrance by already grafted PEtOx, around 20% of the attached azide functionalities underwent no 1,3-dipolar cycloaddition, as could be roughly estimated from the peak integrals of residual 4-azidobenzoate moieties.

CONCLUSION

P*i*POx homopolymers bearing a dithiobenzoate end group could be obtained with PDI values below 1.4 utilizing CPDB as CTA. The irreversible chain transfer taking place during RAFT homopolymerization of *i*POx could be overcome by statistical copolymerization with MMA as well as with N*i*PAm resulting in two copolymer series with varying *i*POx content. The copolymers of N*i*PAm with *i*POx revealed thermoresponsive properties in aqueous media at elevated temperatures compared to PN*i*PAm due to the hydrophilicity of the incorporated *i*POx moieties. In addition, the *i*POx functionalities provided a versatile tool for post polymerization modification of the synthesized homo- and copolymers via addition reactions with nucleophiles, such as carboxylic acids and, in particular, thiophenol. The polymer analogous reaction with 4-azidobenzoic acid supplied polymers carrying multiple azide functionalities that represent suitable building blocks for the subsequent grafting of alkyne-terminated PEtOx onto PMMA by copper-catalyzed 1,3-dipolar cycloaddition. Future work will focus on the full exploitation of the potential to functionalize the well-defined copolymers with biologically active thiols, such as sugars or proteins, and on the development of more challenging copolymer architectures.

ASSOCIATED CONTENT

Supporting Information

SEC traces obtained with varying CTA's and during kinetic studies, full MALDI TOF mass spectrum of P*i*POx, SEC traces of **A1−3**, and ^{1}H NMR spectra of **A4** and **A5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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