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Versatile side chain modification via isocyanide-based multicomponent reactions: Tuning the LCST of poly(2-oxazoline)s

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Poly(2-oxazoline)s are receiving large current interest based on their potential use in biomedical applications. The development of novel methods to control the polymer side chains and to tune the polymer properties will further enhance this potential. In this contribution, the Passerini and Ugi multicomponent reactions are used to modify a random poly(2-oxazoline) copolymer of 2-ethyl-2-oxazoline (EtOx) and 2-methyl butyrate-2-oxazoline (C3-MestOx) with defined chain length and comonomer ratio. Hydrolysis of the pending methyl ester groups provided an easy access to carboxylic acid groups in the side chain, which were used for post-polymerization modification reactions *via* isocyanide-based multicomponent reactions (IMCRs) to simultaneously introduce various substituents. This allowed a straightforward adjustment of the properties of the random poly(2-oxazoline). Most importantly, control over the cloud point and glass transition temperatures was possible by simple variation of the components used in the multicomponent grafting approach.

1. Introduction

The living cationic ring-opening polymerization (CROP) of 2-oxazoline monomers was first reported in 1966 and yields polyamides exhibiting acyl groups in the side chain.[1-4] Poly(2-oxazoline)s impress, depending on their substituents, by their exceptional material properties, *i.e.* biocompatibility, good solubility, thermoresponsiveness, high thermal stability, and chemical resistance.[5] Especially due to their good biocompatibility, these materials found their way to several applications in biomedical chemistry, for instance drug delivery.[6, 7] Compared to poly(ethylene glycol) (PEG), a well-established biocompatible polymer, poly(2-oxazoline)s offer similar biocompatibility in combination with more structural diversity than only chain end modification as available for PEG.[8] For poly(2-oxazoline)s, variation of the monomers and their composition as well as side chain modification is enabled, allowing precise adjustment of the properties of the respective biomaterial. Moreover, poly(2-oxazoline)s are known for their remarkable "stealth" behavior, whereas the existence of PEG antibodies in animal as well as human studies starts to raise questions for the wide-spread usage of PEG.[9-11] Thus, the application and modification of poly(2-oxazoline)s is still a highly topical research field.[12, 13] Recent modifications of poly(2-oxazoline)s include, for instance, the synthesis of novel monomers that bear various functionalities in 2-position. Taton, Lecommandoux, Tam and coworkers synthesized an acetal protected 2-oxazoline, which was copolymerized with 2-methyl-2-oxazoline.[14, 15] The respective polymer unveiled pendant aldehyde groups under acidic treatment and post-modifications with amines were enabled. Poly(2-oxazoline)s with pendant alkenes proved also to be beneficial for further functionalization. Simple thiol-ene chemistry with several thiols yielded alterable thermal properties of the products, whereas in another study highly blood-tolerable polymers were obtained by generating zwitterionic structures in the side chain.[16, 17] Moreover, simple variation of the monomer ratio using 2-cyclopropyl-2-oxazoline and EtOx resulted in various gradient copolymers that enabled precise adjustment of the lower critical solution temperature (LCST) in the range of 47 °C to 81 °C.[18] Schubert *et al*. impressively exploited the whole variability of poly(2-oxazoline)s by the use of amine-functionalized comonomers, first reported by Jordan and coworkers,[19] to install a fluorescent tag, while amine end-functionalization was used to link the polymer on glass slides.[20] The resulting coating showed antifouling properties when exposed to different bacteria in water.

Within this study, we demonstrate a novel tool for simultaneous introduction of two or more functionalities into the side chain, and concurrent adjustment of the thermal properties of the respective poly(2-oxazoline)s. Simple modification reactions *via* IMCRs, namely the Passerini three-component reaction (Passerini-3CR) and Ugi four-component reaction (Ugi-4CR) were used for this purpose.[21, 22] The Passerini-3CR combining carboxylic acids, aldehydes, and isocyanides, and the Ugi-4CR additionally including amines, only recently gained high attention in polymer science due to their straightforward procedure and modular nature.[23-26]

Especially the latter Ugi-4CR found its way into the field of biomedical chemistry as PEGylation method of proteins under simultaneous introduction of fluorescent agents or other functional groups.[27, 28] Nonetheless, many other multicomponent reactions were introduced to polymer science as well, such as the Kabachnik-Fields,[29-31] Biginelli,[32, 33] Asinger,[34] Hantzsch,[35] or the Cu-catalyzed reaction of alkynes, sulfonyl azides and amines.[36] In most of these reactions, the MCRs were used for the polymer synthesis by a monomeric or polymeric approach, whereas post-polymerization modifications with MCRs were only rarely applied.[26] Here, the research groups of Theato, Tao and Meier performed pioneering work and established efficient grafting methodologies.[30, 32, 36-38] In this study, we utilize the concept of MCR-based side chain modification and exploit the versatility of this approach to specifically tune the material properties (LCST) of the respective poly(2-oxazoline)s.

2. Experimental Section

2.1 Materials

The following chemicals were used as received: lithium hydroxide (≥ 98 %, Sigma-Aldrich), hydrochloric acid (37 % solution in water, Acros Organics), acetaldehyde **1a** (≥99 %, Sigma-Aldrich), isobutyraldehyde **1b** (≥ 99 %, Sigma-Aldrich), benzaldehyde **1c** (≥ 99 %, Sigma-Aldrich), anisaldehyde **1d** (98 %, Sigma-Aldrich), *tert*-butyl isocyanide **2a** (98 %, Sigma-Aldrich), benzyl isocyanide **2b** (98 %, Sigma-Aldrich), 2-morpholinoethyl isocyanide **2c** (≥ 98 %, Sigma-Aldrich), *n*-propylamine **3a** (≥ 99 %, Fluka), benzylamine **3b** (99 %, Sigma-Aldrich), barium oxide (90 %, Acros Organics), methanol-*d4* (CD_3OD, 99.8 atom-% D, Euriso-Top), pre-packed disposable PD-10 desalting column (VWR). 2-Ethyl-2-oxazoline (EtOx, kindly donated by Polymer Chemistry Innovations), methyl *p*-toluenesulfonate (MeTos, ≥ 97 %, Sigma-Aldrich), and piperidine (99 %, Sigma-Aldrich) were all dried by distillation over barium oxide under inert argon atmosphere and stored in the glovebox. 2-Methyl butyrate-2-oxazoline (C3-MestOx) was synthesized in analogy to 2-methoxycarboxyethyl-2-oxazoline (MestOx).[39] Acetonitrile was purified over aluminum oxide by means of a solvent purification system from J.C. Meyer, custom-made. HPLC-grade solvents were used for the synthesis; water was used in a deionized form.

2.2 Characterization

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 300 MHz spectrometer operating at room temperature. The chemical shifts δ are given relative to solvent residual peak of deuterated methanol at 3.31 ppm.

Size-exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler (ALS), a thermostatted column compartment (TCC) at 50 °C equipped with two PLgel 5 µm mixed-D columns and a mixed-D guard column in series, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). *N*,*N*-Dimethylacetamide (Dmac) was used as eluent containing 50mM of lithium chloride at optimized flow rate of 0.593 mL/min. Chromatograms were analyzed using Agilent Chemstation software with SEC add-on. Number average molar mass (M_n) and dispersities ($Đ$) values were determined against poly(methyl methacrylate) standards from PSS (Polymer Standards Service, Germany).

Differential scanning calorimetry (DSC) was performed on a Mettler-Toledo DSC1/700 STAR^e system equipped with a FRS5 (56 thermocouples) and an automatic sample robot. The samples were weighed into standard 40 µL aluminum pans and nitrogen flushed during the measurements. The glass transition temperature (T_g) of the polymers was recorded on the second heating scan by using the following method: heating from 25 °C to 150 °C at 10 °C/min, cooling from 150 °C to 25 °C at -10 °C/min and heating from 25 °C to 150 °C at 10 °C/min.

Turbidity measurements were performed on a Crystal 16^{TM} from Avantium Technologies. In the Crystal 16 four blocks of four parallel temperature controlled sample holders are connected to a Julabo FP40 cryostat allowing 16 simultaneous measurements. Samples of concentration of 5 mg/mL in water were analyzed in the temperature range from 5 °C to 105 °C with threefold heating and cooling ramps of 1 °C/min under stirring. Cloud points (T_c) were taken at 50 % transmittance during the second heating run.

All manipulations concerning the polymer synthesis of **P1** were carried out in a VIGOR Sci-Lab SG 1200/750 Glovebox System with a water concentration ≤ 0.1 ppm. For the polymerizations, a Biotage Initiator EXP Microwave System with Robot Sixty was used. During the polymerization, the microwave synthesizer operated at a constant set temperature, which is monitored by an IR-sensor, using the high absorption mode setting.

2.3 Synthesis

2.3.1 Synthesis of statistical copoly(2-oxazoline) (P1). A solution of MeTos (90.5 µL, 112 mg, 0.60 mmol), EtOx (4.76 mL, 4.76 g, 48.0 mmol) and C3-MestOx (2.05 mL, 2.05 g, 12.0 mmol) was made in dry acetonitrile (8.18 mL), leading to a total monomer concentration of 4.0 M in a 20 mL Biotage microwave vial. The reaction mixture was polymerized at 140 °C for 17 minutes, after which the reaction was terminated with 100 µL dry piperidine at room temperature while stirring overnight. Precipitation into cold diethyl ether yielded **P1** as white powder (5.50 g, 80 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 1.02-1.18 (m, 240 H, 80 $COCH_2CH_3$), 1.26-1.38 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.66-1.73 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.81-1.96 (m, 40 H, 20 $COCH_2CH_2$), 2.25-2.63 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COOCH_3, 2 NCH_2 piperidine end group), 3.08-3.14 (m, 2 H, CH_2 piperidine linkage), 3.35-3.89 (m, 461 H, 199 CH_2 backbone, CH_3 end group, 20 $COOCH_3$); T_g = 46 °C.

2.3.2 Hydrolysis of statistical copoly(2-oxazoline) P1 (P2). Polymer **P1** (2.00 g, 175 µmol) and lithium hydroxide (1.25 g, 52.4 mmol, 15.0 eq. with respect to carboxylic groups) were mixed in a 250 mL round-bottomed flask. 70 mL water was added and the solution was stirred for three hours. Afterwards, the solution was acidified to pH 1-2 with concentrated hydrochloric acid. The water was removed using a freeze-dryer and the residue was extracted with

200 mL THF to remove the major part of the formed LiCl. The crude product was dissolved in 10 mL Milli-Q water and chromatographed with a pre-packed disposable PD-10 desalting column. Final freeze-drying yielded white fluffy polymer **P2** (1.63 g, 84 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 1.02-1.17 (m, 240 H, 80 $COCH_2CH_3$), 1.27-1.34 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.60-1.74 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.78-1.95 (m, 40 H, 20 $COCH_2CH_2$), 2.27-2.58 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COOH, 2 NCH_2 piperidine end group), 3.04-3.10 (m, 2 H, CH_2 piperidine linkage), 3.37-3.81 (m, 401 H, 199 CH_2 backbone, CH_3 end group); T_g = 77 °C.

2.3.3 Modification *via* Passerini-3CR

General procedure. Polymer **P2** (100 mg, 8.95 µmol) was dissolved in a water : isopropanol = 1 : 2 (v/v) mixture (600 µL), then aldehyde **1a-c** (1.07 mmol, 6.00 eq. with respect to carboxylic groups) and isocyanide **2a-c** (1.07 mmol, 6.00 eq. with respect to carboxylic groups) were added. The reaction mixture was stirred for one day at room temperature. Afterwards, isopropanol was added until the cloudy solution got transparent; drying over sodium sulfate, filtering and evaporation of the solvent afforded the crude product. Twofold precipitation from 600 µL methanol into 40 mL ice-cold diethyl ether yielded modified polymer **P3-7** as white powder.

2.3.3.1 Poly(2-oxazoline) modified with acetaldehyde **1a** and *tert*-butyl isocyanide **2a** (**P3**)

P3 was obtained as white powder (84 mg, 68 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 1.01-1.18 (m, 240 H, 80 $COCH_2CH_3$), 1.27-1.34 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.33 (s, 180 H, 20 ^{t}Bu), 1.38 (d, J = 7.1 Hz, 60 H, 20 $CHCH_3$), 1.54-1.64 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.80-2.00 (m, 40 H, 20 $COCH_2CH_2$), 2.25-2.63 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COO, 2 NCH_2 piperidine end group), 3.04-3.10 (m, 2 H, CH_2 piperidine linkage), 3.37-3.83 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 4.78-4.98 (m, 20 H, 20 $CHCH_3$), 7.50 (br, 20 H, 20 NH); T_g = 77 °C.

2.3.3.2 Poly(2-oxazoline) modified with isobutyraldehyde **1b** and *tert*-butyl isocyanide **2a** (**P4**)

P4 was obtained as white powder (81 mg, 63 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 0.97 (d, J = 6.8 Hz, 120 H, 20 $CH(CH_3)_2$), 1.03-1.16 (m, 240 H, 80 $COCH_2CH_3$), 1.27-1.34 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.33 (s, 180 H, 20 ^{t}Bu), 1.36-1.47 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.82-2.00 (m, 40 H, 20 $COCH_2CH_2$), 2.02-2.19 (m, 20 H, 20 $CH(CH_3)_2$), 2.27-2.62 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COO, 2 NCH_2 piperidine end group), 3.04-3.11 (m, 2 H, CH_2 piperidine linkage), 3.37-3.84 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 4.65 (d, J = 5.0 Hz, 20 H, 20 $OCHCO$), 7.48 (br, 20 H, 20 NH); T_g = 68 °C.

2.3.3.3 Poly(2-oxazoline) modified with benzaldehyde **1c** and *tert*-butyl isocyanide **2a** (**P5**)

P5 was obtained as white powder (101 mg, 75 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 1.02-1.17 (m, 240 H, 80 $COCH_2CH_3$), 1.29 (s, 180 H, 20 ^{t}Bu), 1.32-1.38 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.47-1.52 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.80-2.00 (m, 40 H, 20 $COCH_2CH_2$), 2.24-2.64 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COO, 2 NCH_2 piperidine end group), 3.02-3.10 (m, 2 H, CH_2 piperidine linkage), 3.36-3.82 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 5.85 (s, 20 H, 20 $OCHCO$), 7.26-7.42 (m, 60 H, 60 Ar-H[a]), 7.42-7.52 (m, 40 H, 40 Ar-H[b]), 7.73 (br, 20 H, 20 NH); T_g = 82 °C.

2.3.3.4 Poly(2-oxazoline) modified with isobutyraldehyde **1b** and benzyl isocyanide **2b** (**P6**)

P6 was obtained as white powder (91 mg, 68 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 0.82-1.01 (m, 120 H, 20 $CH(CH_3)_2$), 1.01-1.23 (m, 240 H, 80 $COCH_2CH_3$), 1.26-1.37 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.72-1.78 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.78-2.00 (m, 40 H, 20 $COCH_2CH_2$), 2.09-2.25 (m, 20 H, 20 $CH(CH_3)_2$), 2.25-2.64 (m, 244 H, 100 $NCOCH_2$, 20 CH_2COO, 2 NCH_2 piperidine end group), 3.02-3.10 (m, 2 H, CH_2 piperidine linkage), 3.35-3.78 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 4.39 (s, 40 H, 20 $NHCH_2$), 4.71-4.95 (m, 20 H, 20 $OCHCO$), 7.05-7.40 (m, 120 H, 100 Ar-H, 20 NH); T_g = 68 °C.

2.3.3.5 Poly(2-oxazoline) modified with isobutyraldehyde **1b** and 2-morpholinoethyl isocyanide **2c** (**P7**)

P7 was obtained as beige powder (61 mg, 44 %). ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 0.98 (d, J = 5.3 Hz, 120 H, 20 $CH(CH_3)_2$), 1.04-1.22 (m, 240 H, 80 $COCH_2CH_3$), 1.27-1.37 (m, 2 H, $NCH_2CH_2CH_2$ piperidine end group), 1.60-1.71 (m, 4 H, 2 NCH_2CH_2 piperidine end group), 1.82-2.01 (m, 40 H, 20 $COCH_2CH_2$), 2.08-2.25 (m, 20 H, 20 $CH(CH_3)_2$), 2.26-2.76 (m, 364 H, 100 $NCOCH_2$, 20 CH_2COO, 20 $N(CH_2)_3$, 2 NCH_2 piperidine end group), 3.04-3.11 (m, 2 H, CH_2 piperidine linkage), 3.25-3.40 (m, 40 H, 20 $CONHCH_2$), 3.40-3.84 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 3.67 (t, J = 4.4 Hz, 80 H, 20 CH_2OCH_2), 4.75-4.92 (m, 20 H, 20 $OCHCO$); T_g = 61 °C.

2.3.4 Modification *via* Ugi-4CR

General procedure. Aldehyde **1b-d** (1.07 mmol, 6.00 eq. with respect to carboxylic groups) and amine **3a-b** (1.07 mmol, 6.00 eq. with respect to carboxylic groups) were mixed with 400 µL methanol and stirred at room temperature for 20 minutes. The resulting imine solution and isocyanide **2a-c** (1.07 mmol, 6.00 eq. with respect to carboxylic groups) were added to polymer **P2** (100 mg, 8.95 µmol) dissolved in 600 µL methanol, and the reaction mixture was stirred for one day. Afterwards, the solvent and volatile components were removed under reduced pressure and the residue was re-dissolved in 700 µL methanol. Twofold precipitation into 40 mL ice-cold diethyl ether yielded modified polymer **P8-13** as white powder.

2.3.4.1 Poly(2-oxazoline) modified with *n*-propylamine **3a**, isobutyraldehyde **1b** and *tert*-butyl isocyanide **2a** (**P8**)

P8 was obtained as white powder (83 mg, 61 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 2 : 1): δ (ppm) = 0.75-1.00 (m, 180 H, 20 $CH(CH_3)_2$, 20 $NCH_2CH_2CH_3$), 1.01-1.18 (m, 240 H, 80 $COCH_2CH_3$), 1.32, 1.35 (2s, 180 H, 20 ^{t}Bu), 1.50-1.70 (m, 42 H, 20 $NCH_2CH_2CH_3$, $NCH_2CH_2CH_2$ piperidine end group), 1.79-2.00 (m, 44 H, 20 $COCH_2CH_2$, 2 NCH_2CH_2 piperidine end group), 2.15-2.72 (m, 264 H, 120 $NCOCH_2$, 20 $CH(CH_3)_2$, 2

NC**H**$_2$ piperidine end group), 3.04-3.11 (m, 2 H, CH_2 piperidine linkage), 3.24-3.41 (m, 40 H, 20 NC**H**$_2$CH$_2$CH$_3$), 3.39-3.81 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 3.81-3.97, 4.18-4.34 (2m, 20 H, 20 NCHCO), 7.56-7.71, 7.76-8.06 (2m, 20 H, 20 NH); T_g = 76 °C.

2.3.4.2 Poly(2-oxazoline) modified with benzylamine **3b**, isobutyraldehyde **1b** and *tert*-butyl isocyanide **2a** (**P9**)

P9 was obtained as white powder (101 mg, 70 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 3 : 1): δ (ppm) = 0.86, 0.95 (2d, J = 6.1 and 6.3 Hz, 120 H, 20 CH(C**H**$_3$)$_2$), 1.00-1.18 (m, 240 H, 80 COCH$_2$C**H**$_3$), 1.23 (s, 180 H, 20 ^{t}Bu), 1.42-1.47 (m, 2 H, NCH$_2$CH$_2$C**H**$_2$ piperidine end group), 1.65-2.02 (m, 44 H, 20 COCH$_2$C**H**$_2$, 2 NCH$_2$C**H**$_2$ piperidine end group), 2.02-2.21 (m, 20 H, 20 C**H**(CH$_3$)$_2$), 2.21-2.82 (m, 244 H, 120 NCOCH$_2$, 2 NC**H**$_2$ piperidine end group), 3.03-3.10 (m, 2 H, CH_2 piperidine linkage), 3.35-3.87 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 3.96-4.17, 4.77-5.00 (2m, 20 H, 20 NCHCO), 4.54-4.95 (m, 40 H, 20 CH_2Ar), 6.97-7.40 (m, 100 H, 100 Ar-H), 7.70-8.05 (m, 20 H, 20 NH); T_g = 94 °C.

2.3.4.3 Poly(2-oxazoline) modified with *n*-propylamine **3a**, benzaldehyde **1c** and *tert*-butyl isocyanide **2a** (**P10**)

P10 was obtained as white powder (100 mg, 71 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 2 : 1): δ (ppm) = 0.56 (t, J = 6.9 Hz, 60 H, 20 NCH$_2$CH$_2$C**H**$_3$), 0.70-0.92 (m, 40 H, 20 NCH$_2$C**H**$_2$CH$_3$), 0.98-1.17 (m, 240 H, 80 COCH$_2$C**H**$_3$), 1.32, 1.36 (2s, 180 H, 20 ^{t}Bu), 1.49-1.55 (m, 2 H, NCH$_2$CH$_2$C**H**$_2$ piperidine end group), 1.59-1.66 (m, 4 H, 2 NCH$_2$C**H**$_2$ piperidine end group), 1.82-2.02 (m, 40 H, 20 COCH$_2$C**H**$_2$), 2.26-2.66 (m, 244 H, 120 NCOCH$_2$, 2 NC**H**$_2$ piperidine end group), 3.05-3.09 (m, 2 H, CH_2 piperidine linkage), 3.17-3.35 (m, 40 H, 20 NC**H**$_2$CH$_2$CH$_3$), 3.36-3.80 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 5.67, 5.97 (2s, 20 H, 20 NCHCO), 7.28-7.46 (m, 100 H, 100 Ar-H), 7.55, 7.81 (2br, 20 H, 20 NH); T_g = 85 °C.

2.3.4.4 Poly(2-oxazoline) modified with *n*-propylamine **3a**, anisaldehyde **1d** and *tert*-butyl isocyanide **2a** (**P11**)

P11 was obtained as white powder (93 mg, 63 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 2 : 1): δ (ppm) = 0.58 (t, J = 6.4 Hz, 60 H, 20 NCH$_2$CH$_2$C**H**$_3$), 0.70-0.93 (m, 40 H, 20 NCH$_2$C**H**$_2$CH$_3$), 0.96-1.20 (m, 240 H, 80 COCH$_2$C**H**$_3$), 1.31, 1.35 (2s, 180 H, 20 ^{t}Bu), 1.51-1.57 (m, 2 H, NCH$_2$CH$_2$C**H**$_2$ piperidine end group), 1.62-1.73 (m, 4 H, 2 NCH$_2$C**H**$_2$ piperidine end group), 1.78-2.02 (m, 40 H, 20 COCH$_2$C**H**$_2$), 2.24-2.66 (m, 244 H, 120 NCOCH$_2$, 2 NC**H**$_2$ piperidine end group), 3.03-3.10 (m, 2 H, CH_2 piperidine linkage), 3.14-3.30 (m, 40 H, 20 NC**H**$_2$CH$_2$CH$_3$), 3.38-3.78 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 3.80 (s, 60 H, 20 OCH$_3$), 5.61, 5.88 (2s, 20 H, 20 NCHCO), 6.94 (d, J = 7.7 Hz, 40 H, 40 Ar-H^a), 7.26 (d, J = 7.3 Hz, 40 H, 40 Ar-H^b), 7.44, 7.72 (2br, 20 H, 20 NH); T_g = 92 °C.

2.3.4.5 Poly(2-oxazoline) modified with *n*-propylamine **3a**, isobutyraldehyde **1b** and benzyl isocyanide **2b** (**P12**)

P12 was obtained as white powder (111 mg, 79 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 3 : 2): δ (ppm) = 0.75-0.90 (m, 60 H, 20 NCH$_2$CH$_2$C**H**$_3$), 0.81, 0.93 (2d, J = 6.6 and 5.9 Hz, 120 H, 20 CH(C**H**$_3$)$_2$), 0.99-1.20 (m, 240 H, 80 COCH$_2$C**H**$_3$), 1.35-1.65 (m, 46 H, 20 NCH$_2$C**H**$_2$CH$_3$, 2 NCH$_2$C**H**$_2$CH$_2$ and NCH$_2$CH$_2$C**H**$_2$ piperidine end group), 1.77-1.99 (m, 40 H, 20 COCH$_2$C**H**$_2$), 2.19-2.74 (m, 264 H, 120 NCOCH$_2$, 20 C**H**(CH$_3$)$_2$, 2 NC**H**$_2$ piperidine end group), 3.03-3.10 (m, 2 H, CH_2 piperidine linkage), 3.14-3.80 (m, 441 H, 199 CH_2 backbone, CH_3 end group, 20 NC**H**$_2$CH$_2$CH$_3$), 3.86-4.06, 4.49-4.61 (2m, 20 H, 20 NCHCO), 4.25-4.55 (m, 40 H, 20 NHC**H**$_2$), 7.12-7.43 (m, 120 H, 100 Ar-H, 20 NH); T_g = 82 °C.

2.3.4.6 Poly(2-oxazoline) modified with *n*-propylamine **3a**, isobutyraldehyde **1b** and 2-morpholinoethyl isocyanide **2c** (**P13**)

P13 was obtained as white powder (96 mg, 66 %). ^{1}H NMR (CD_3OD, 300 MHz, mixture of *cis*/*trans*-amide bonds, ratio of 1 : 1): δ (ppm) = 0.77-1.03 (m, 180 H, 20 CH(C**H**$_3$)$_2$, 20 NCH$_2$CH$_2$C**H**$_3$), 1.02-1.25 (m, 240 H, 80 COCH$_2$C**H**$_3$), 1.48-1.68 (m, 42 H, 20 NCH$_2$C**H**$_2$CH$_3$, NCH$_2$CH$_2$C**H**$_2$ piperidine end group), 1.79-2.01 (m, 44 H, 20 COCH$_2$C**H**$_2$, 2 NCH$_2$C**H**$_2$ piperidine end group), 2.19-2.73 (m, 384 H, 120 NCOCH$_2$, 20 C**H**(CH$_3$)$_2$, 20 N(CH$_2$)$_3$, 2 NC**H**$_2$ piperidine end group), 3.04-3.11 (m, 2 H, CH_2 piperidine linkage), 3.12-3.39 (m, 80 H, 20 NC**H**$_2$CH$_2$CH$_3$, 20 CONHC**H**$_2$), 3.41-3.83 (m, 401 H, 199 CH_2 backbone, CH_3 end group), 3.67 (t, J = 4.6 Hz, 80 H, 20 CH$_2$OCH$_2$), 3.84-4.00, 4.40-4.52 (2m, 20 H, 20 NCHCO); T_g = 74 °C.

2.3.5 Synthesis of statistical copoly(2-oxazoline) P1a and its derivatives

P1a was analogously synthesized to **P1** with a monomer ratio of EtOx : C3-MestOx = 85 : 15. Subsequent modifications resulting in **P2a**, **P4a** and **P8a** were conducted in analogy to the procedure for **P2**, **P4** and **P8**.

3. Results and Discussion

Carboxylic acids, which are required for the desired post-polymerization modification *via* IMCRs, are incompatible with the CROP of 2-oxazolines as they are nucleophilic and will terminate the polymerization on the one hand, and can react with the 2-oxazoline monomer on the other hand. Thus, the related methyl ester functionalized monomer was employed for the CROP, which can be transformed to the desired carboxylic acid after the polymerization process. For this purpose, C3-MestOx was used as functional monomer, and copolymerization with EtOx in ratio of 1 : 4 with a degree of polymerization of 100 yielded poly(2-oxazoline) **P1**, exhibiting a relatively high degree of functionalization while the functional groups had sufficient spacing (**Scheme 1**). Due to the similar reactivity of C3-MestOx and EtOx, **P1** was featured by a near-ideal random distribution of the methyl ester along the polymer backbone.[40] SEC analysis of **P1** confirmed the living nature of the polymerization process by a narrow molecular weight distribution ($Đ$ = 1.21) with a M_n value of 16150 g/mol. Nevertheless, a shoulder at higher molecular weight was observed (**Figure 1**, **top**), which can be attributed to always present side reactions in CROP of 2-oxazolines, *e.g.* β-elimination, leading to coupling reactions towards the end of

the polymerization.[41] Determination of the thermal properties revealed a T_g at 46 °C and a cloud point temperature (T_c) at 75 °C in water for **P1** (see **Table 1**). The T_c of **P1** is, as expected, in between those of the EtOx homopolymer, which has a T_c around 95 °C with a degree of polymerization of 100,[42] and the C3-MestOx homopolymer, which has a T_c of 25 °C.[40]

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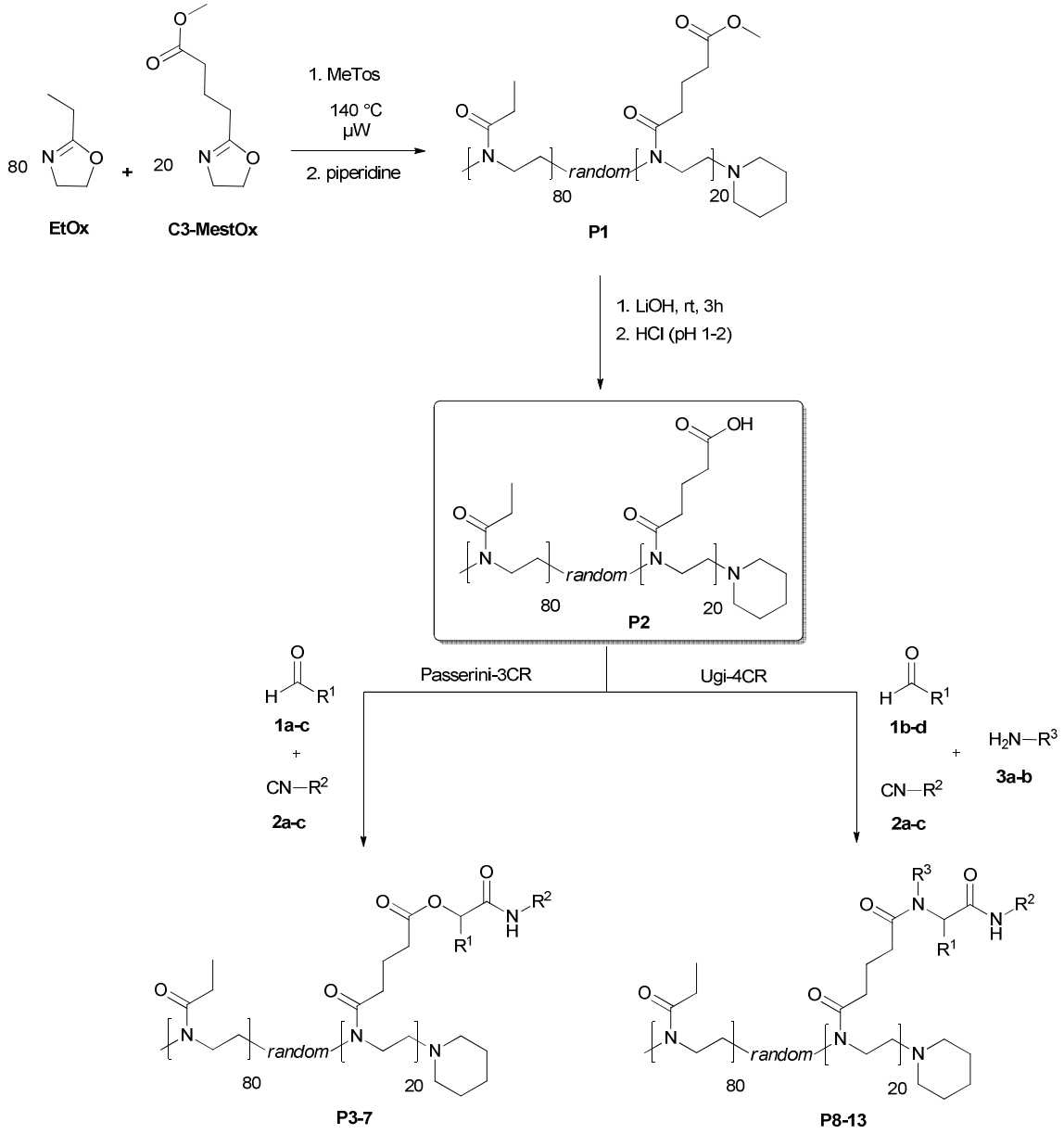

Scheme 1. Synthesis of functional poly(2-oxazoline) **P1** by CROP of EtOx and C3-MestOx with MeTos as initiator and piperidine as chain stopper. Subsequent saponification of the pending methyl ester yielded **P2**, which was modified *via* Passerini-3CR to yield ester linkages (left, **P3**-**7**) and *via* Ugi-4CR to yield amide linkages (right, **P8**-**13**).

In order to install carboxylic acid groups along the polymer backbone of **P1**, the pending methyl ester groups were transformed to carboxylic acid groups by basic hydrolysis using lithium hydroxide as reagent. After three hours, full conversion of the methyl esters was detected and acidification with hydrochloric acid yielded the carboxylic acid groups along the polymer chain. Prior to modifying **P2**, the formed lithium chloride and residual *p*-toluenesulfonic acid resulting from the initiation of the CROP of C3-MestOx and EtOx had to be removed, since salts influence the cloud point measurements and the *p*-toluenesulfonic acid was found to catalyze transesterifications in the following MCRs. Due to the similar solubility behavior of poly(2-oxazoline)s **P1** and **P2**, purification by precipitation or extraction was not feasible. Alternatively, dialysis or chromatography *via* PD-10 desalting

column were tested as purification method, whereby the latter revealed to be more efficient and the pure product **P2** could be obtained in 84 % yield. The purified polymer revealed an increased T_g of 77 °C, ascribed to stronger interchain interactions due to hydrogen bonding. The *T*c only mildly increased to 78 °C indicating marginally increased hydrophilicity of the copolymer by conversion of the methyl ester groups into carboxylate groups (see **Table 1**). This unexpected minor increase is most likely related to increased polymer-polymer interactions resulting from hydrogen bonding of the protonated fraction of the carboxylic acid units in milliQ water; analogous to a previous report on decreased T_c upon incorporation of hydrophilic sugar units into poly(2-oxazoline)s.[43]

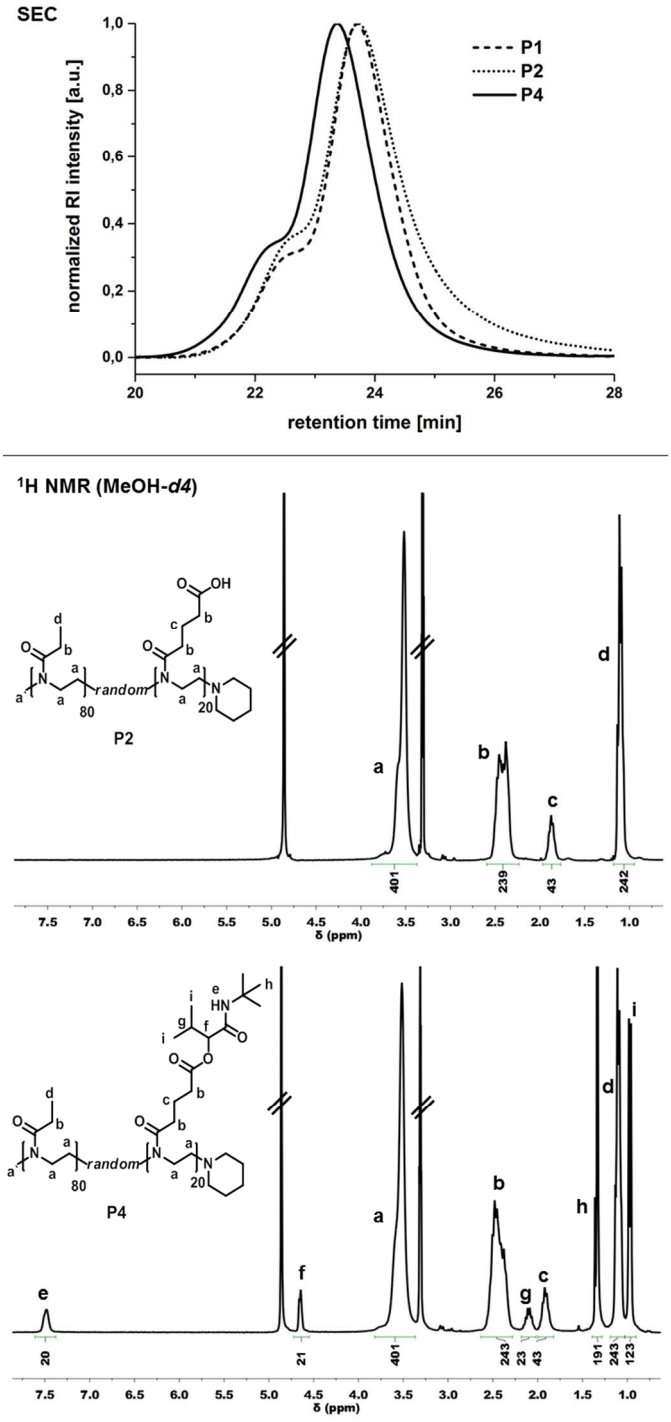

Figure 1. (top) SEC traces of pristine poly(2-oxazoline) **P1**, its carboxylic acid analogue **P2** and Passerini-3CR derivative **P4**. (bottom) ^{1}H NMR spectra (300 MHz, methanol-*d4*) of reactant **P2** and successfully modified polymer **P4** with assigned signals.

After preparation and purification of **P2**, the reaction conditions for the modification of **P2** *via* Passerini 3-CR and Ugi 4-CR were optimized (**Scheme 1**). Passerini-3CRs are conventionally performed in concentrated solutions in tetrahydrofuran, dichloromethane, chloroform or toluene, and stirred at ambient temperature for 24

hours. Reactions in these solvents utilizing four equivalents of isobutyraldehyde **1b** and *tert*-butyl isocyanide **2a** as components showed only marginal product formation since neither reactant **P2** nor product **P4** were soluble in these reaction media. Only alcohols and water could dissolve poly(2-oxazoline) **P2**. Luckily, it has been reported that the Passerini-3CR also proceeds in aqueous reaction media, even with an accelerated reaction rate.[44, 45] Thus, the reaction was conducted in water and already after 30 seconds the product precipitated as white powder since **P4** shows a T_c of 21 °C, which was below room temperature when performing these experiments. Subsequent analysis by ^{1}H NMR spectroscopy revealed incomplete conversion (ca. 73 %), as the polymer precipitated before being fully reacted. To prevent precipitation of the product, a solvent mixture of water : isopropanol = 1 : 2 (v/v) was used, which resulted in full conversion of the acid groups and formation of the desired fully modified copolymer **P4**. SEC analysis confirmed an increased molar mass of M_n = 19150 g/mol along with a nearly unchanged dispersity ($Đ$ = 1.19) compared to the initial polymer **P1** (**Figure 1**, **top**). Moreover, the ^{1}H NMR spectrum of **P4** showed new characteristic signals of the *tert*-butyl (1.33 ppm) and isopropyl moieties (0.97 ppm) in the expected integral ratio. The assignment of all resonances is illustrated in **Figure 1**.

For the Ugi-4CR, the similar reaction conditions as for the Passerini-3CR were adopted, whereby *n*-propylamine was additionally added and methanol was used as solvent, being the standard solvent for these reactions. However, in some modification reactions only 19 instead of 20 units of **P2** were functionalized and full conversion could be reached by increasing the excess of the components to six equivalents (evidenced by ^{1}H NMR spectroscopy). In order to provide a general procedure, six equivalents of components were used in every subsequent experiment. Purification by double precipitation into ice-cold diethyl ether afforded pure modified poly(2-oxazoline) **P8**, which was obtained in 61 % yield. Its cloud point was determined to be 15 °C and its M_n value increased to 21900 g/mol ($Đ$ = 1.17).

Once these general procedures were established for the post-polymerization modification reactions of **P2** *via* Passerini-3CR and Ugi-4CR, the reaction components were varied to influence the thermal material properties and solubility behavior (see **Table 1**). In the Passerini-3CR, acetaldehyde **1a** and benzaldehyde **1c** were used as aldehyde components resulting in poly(2-oxazoline)s **P3** and **P5**, respectively. Whereas the alteration of R^1 only minimally influenced the amorphous behavior as all Passerini-derived polymers have a T_g in the range of 61 – 82 °C, the thermoresponsiveness was extremely affected by changing the aldehyde component. Along with the reduced polarity of **P2** to **P5**, the T_c decreased from 78 °C for **P2** to 41 °C for **P3**, and 21 °C for **P4**, whereas **P5** was not soluble in water anymore (**Figure 2**). Water-insoluble polymers were also obtained when introducing benzyl isocyanide **2b** along with isobutyraldehyde **1b**, resulting in **P6** (68 % yield). In contrast, the application of polar 2-morpholinoethyl isocyanide **2c** in the

Table 1. Characterization of the pristine poly(2-oxazoline) **P1** (EtOx : C3-MestOx = 80 : 20) and its modified derivatives **P2**-**13**.

product	R^1	R^2	R^3	M_n [g/mol][a]	$Đ$[a]	yield [%]	T_g [°C][b]	T_c [°C][c]
P1	---	---	---	16150	1.21	80	46	75
P2	---	---	---	14350	1.26	84	77	78
P3	-Me (**1a**)	-*t*-Bu (**2a**)	---	17850	1.21	68	77	41
P4	-*i*-Pr (**1b**)	-*t*-Bu (**2a**)	---	19150	1.19	63	68	21
P5	-Ph (**1c**)	-*t*-Bu (**2a**)	---	20050	1.28	75	82	ns
P6	-*i*-Pr (**1b**)	-Bn (**2b**)	---	23450	1.18	68	68	ns
P7	-*i*-Pr (**1b**)	-morpholinoethyl (**2c**)	---	19150	1.22	44	61	64
P8	-*i*-Pr (**1b**)	-*t*-Bu (**2a**)	-*n*-Pr (**3a**)	21900	1.17	61	76	15
P9	-*i*-Pr (**1b**)	-*t*-Bu (**2a**)	-Bn (**3b**)	22000	1.20	70	94	ns
P10	-Ph (**1c**)	-*t*-Bu (**2a**)	-*n*-Pr (**3a**)	19850	1.20	71	85	ns
P11	-PhOMe (**1d**)	-*t*-Bu (**2a**)	-*n*-Pr (**3a**)	22200	1.19	63	92	ns
P12	-*i*-Pr (**1b**)	-Bn (**2b**)	-*n*-Pr (**3a**)	22950	1.19	79	82	ns
P13	-*i*-Pr (**1b**)	-morpholinoethyl (**2c**)	-*n*-Pr (**3a**)	22850	1.20	66	74	51

[a]determined by SEC analysis (Dmac) relative to narrow PMMA standards.

[b]determined by DSC at heating rate of 10 °C/min.

[c]determined by turbidity measurement in water at 50 % transmittance.

ns = not soluble in water

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Passerini-3CR yielding **P7** (M_n = 19150 g/mol, $Đ$ = 1.22) resulted only in a slight decrease of the cloud point, which was determined at 64 °C. Thus, these simple post-polymerization modifications impressively show the wide range of accessible cloud points that are available by this concept resulting from the accurate control over the hydrophilic-hydrophobic balance of the newly introduced side chains, despite that these new side chains only constitute 20% of the side chains.

For the post-polymerization modification reactions *via* Ugi-4CR, the three different components – amine, aldehyde and isocyanide – were successfully altered as well and products **P8-13** were obtained in a yield of about 70 % (see **Table 1**). Here, SEC traces of all polymers showed an increased molar mass with slightly narrower dispersities in the range of 1.17 – 1.20 compared to initial poly(2-oxazoline) **P1**. The glass transition temperatures were mostly higher than for **P1-7**, which might be due to the introduced bulky phenyl rings, the additional side chain as introduced through the amine, as well as by the introduced hydrogen bonding (donor) capabilities. Especially **P9**, derived from isobutyraldehyde **1b**, *tert*-butyl isocyanide **2a** and benzylamine **3b**, exhibited a high T_g of 94 °C. Regarding their LCST behavior, only **P8** and **P13** showed a T_c at 15 °C and 51 °C, respectively, whereas all other modified polymers **P9-12** were water-insoluble (**Table 1** and **Figure 2**).

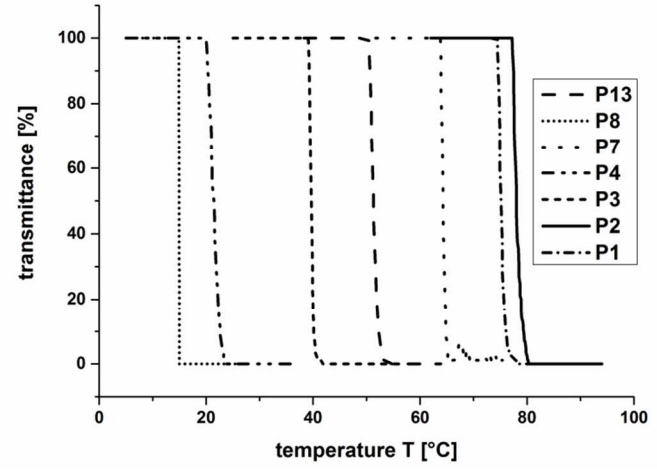

Figure 2. Turbidity measurements of thermoresponsive poly(2-oxazoline)s **P1-4, P7-8** and **P13** in water (5 mg/mL concentration), showing LCSTs in the range of 15 °C to 78 °C.

Since polymers with LCSTs just below the body temperature are of great interest for medical use, the most promising candidates **P4** and **P8** were further investigated to fine-tune the T_c by small variation of the polymer composition. For this purpose, another copolymer with a monomer ratio of 85 : 15 (EtOx : C3-MestOx) was synthesized having a M_n = 16150 g/mol and $Đ$ = 1.12 (**P1a**). Subsequent hydrolysis of the methyl ester led to a slight shift of the T_c of **P1a** from 91 °C to 88 °C for **P2a** (**Table 2**). **P1a** and **P2a** have an increased T_c compared to **P1** and **P2** due to the higher fraction of more hydrophilic EtOx units. For the post-polymerization modification *via* IMCRs, the analogous reaction conditions as for the synthesis of **P4** and **P8** were used resulting in poly(2-oxazoline)s **P4a** and **P8a**. ^{1}H NMR analysis revealed full conversion of the carboxylic acid groups by integration of all newly appeared signals indicating 15 functionalized side chains. SEC analysis gave higher M_n values for the modified polymers while the shape of the chromatogram remained unchanged. To our delight, the respective T_c's were in the desired range at T_c = 32 °C for **P4a** and T_c = 24 °C for **P8a**.

Table 2. Characterization of the pristine poly(2-oxazoline) **P1a** (EtOx : C3-MestOx = 85 : 15) and its modified derivatives **P2a, P4a** and **P8a**.

product	R^1	R^2	R^3	M_n [g/mol][a]	$Đ$[a]	yield [%]	T_g [°C][b]	T_c [°C][c]
P1a	---	---	---	16150	1.12	82	49	91
P2a	---	---	---	16400	1.17	84	99	88
P4a	-*i*-Pr (**1b**)	-*t*-Bu (**2a**)	---	16250	1.21	54	65	32

P8a	-*i*-Pr (**1b**)	-*t*-Bu (**2a**)	-*n*-Pr (**3a**)	17500	1.14	84	65	24

[a]determined by SEC analysis (Dmac) relative to narrow PMMA standards.

[b]determined by DSC at heating rate of 10 °C/min.

[c]determined by turbidity measurement in water at 50 % transmittance.

4. Conclusions

We have demonstrated a novel concept to functionalize a defined poly(2-oxazoline) copolymer in a simple one-pot procedure *via* isocyanide-based MCRs. Due to the modular nature of these reactions, simultaneous introduction of two different moieties using the Passerini-3CR, or even three different moieties using the Ugi-4CR, was enabled. Alteration of the single components resulted in different thermal material properties, which was expressed in variable T_c's ranging from 78 °C for the unmodified poly(2-oxazoline) to even insolubility in water. Moreover, glass transition temperatures could be influenced through the post-polymerization modification reactions. This proof of concept of post-polymerization modification of poly(2-oxazoline)s offers many possibilities to adjust the material properties and to introduce specific functionalities, which will be part of ongoing research.

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† Electronic Supplementary Information (ESI) available: ^{1}H NMR spectra of all polymers, turbidity measurements. See DOI: 10.1039/b000000x/

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