

WATER-SOLUBLE OPTICALLY ACTIVE POLY(2-OXAZOLINE)S

Stephan Huber¹, Julia Hytry², Jing Tong³, Robert Luxenhofer², Alexander V. Kabanov^{3,4}, Rainer Jordan^{1,2}

¹ Wacker-Lehrstuhl für Makromolekulare Chemie, TU München, Lichtenbergstraße 4, 85747 Garching, Germany

² Professur für Makromolekulare Chemie, TU Dresden, Zellescher Weg 19, 01069 Dresden, Germany

³ Center for Drug Delivery and Nanomedicine, 985830 Nebraska Medical Center, Omaha, Nebraska 68198-5830, USA

⁴ Laboratory of Chemical Design of Bionanomaterials, Faculty of Chemistry, M.V. Lomonosov Moscow State University, Moscow 119992, Russia

Introduction

Materials that respond to external stimuli have been frequently investigated over the past years. Especially polymers that reversibly change their physicochemical properties - in particular their hydrophilicity - upon such stimulus, e.g. a change in temperature have been extensively discussed as smart biomaterials.¹ Many water-soluble polymer exhibit a lower critical solution temperature, i.e. the polymers precipitate upon heating their aqueous solutions. The temperature of this transition may depend in varying degrees on the nature, molar mass and architecture of the polymer, its concentration, solvent quality (co-solvents and co-solutes).^{2,3,4,5} Poly(2-oxazolines) are a versatile materials platform, which have gained more and more attention as a biomaterial in the last years.^{6,7,8,9,10} Hoogenboom et al. have recently investigated hydrophobic poly(2,4-disubstituted-2-oxazolines) as described the formation of dynamic secondary structures.^{3,11,12}

Here, we describe water-soluble chiral 2,4-disubstituted poly(2-oxazolines) and investigate their thermal responsiveness in aqueous solution. While poly(2-ethyl-4-methyl-2-oxazolines) exhibit a lower critical solution temperature, the more hydrophilic poly(2,4-dimethyl-2-oxazolines) forms temperature sensitive secondary structures in aqueous solution as evidenced by circular dichroism spectroscopy.

Experimental

Materials. 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. Solvents, methyl triflate (MeOTf) and all monomers used for the living cationic polymerization were dried by refluxing over CaH₂ for approx. 3 h and subsequent distillation. The monomers were stored under a dry nitrogen atmosphere and handled in a glove box.

Instrumentation. All polymerizations were performed using a CEM Discover microwave. ¹H-NMR spectra were recorded on a Bruker ARX 300 (¹H: 300.13 MHz) with TMS as internal standard at T=293 K in CDCl₃. Gel permeation chromatography (GPC) was performed on a Waters system (pump mod. 510, RI-detector mod. 410) with columns Resi Pore Guard (50x7.5 mm) and 2x Resi Pore (300 x 7.5mm) as the stationary and dimethylacetamide (DMAc) as the mobile phase using PMMA calibration standards. The mass spectrometry measurements were performed using a MAT 8200 Finnigan (EI, 70 eV) ion impact mass spectrometer. The optical rotation power was measured using a 241MC polarimeter from Perkin-Elmer at λ = 589 nm (Na-D-line), at 20 °C and dichloromethane as the solvent. Turbidity measurements were carried out on a Cary 50 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 5 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. CD Spectroscopy was performed at polymer concentrations of 0.25 g/L in deionized water using an Aviv Circular Dichroism Model 202SF Spectrometer (Lakewood, NJ) in a 1 mm pathlength cuvette. Scans were performed from 200 to 250 nm in 1 nm steps.

Monomer synthesis. The general procedure for the synthesis of the 2,4-oxazoline monomers was carried out as described before.² All Monomers were dried over calciumhydride for approximately 3h and followed by subsequent distillation. Exemplarily, (*R*)-2,4-dimethyl-2-oxazolin (**R**-**DMOx**) was synthesized from acetonitrile and D-alaninol under cadmium acetate dihydrate catalysis. Other monomers were prepared accordingly. boiling point (bp): 75°C at 240 mbar, yield: 27%. ¹H NMR (300MHz, CDCl₃, 293K): δ = 4.29 (t,

J = 8.0 Hz, 1H), 4.18 – 3.93 (m, 1H), 3.72 (t, *J* = 7.8 Hz, 1H), 1.93 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H). MS(70eV, EI): m/z 99.1 [M]. [α]_D20: +132° (S)-2,4-dimethyl-2-oxazolin (**S**-**DMOx**): bp: 75 °C at 250 mbar, yield: 17%. ¹H NMR (300MHz, CDCl₃, 293K): δ = 4.28 (t, *J* = 8.0 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.70 (t, *J* = 7.8 Hz, 1H), 1.92 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H). MS(70eV, EI): m/z 99.1 [M]. [α]_D20: -131° (R)-2-ethyl-4-methyl-2-oxazolin (**R**-**EMOx**): bp: 84 °C at 250 mbar, yield: 44%. ¹H NMR (300MHz, CDCl₃, 293K): δ = 4.31 (t, *J* = 8.0 Hz, 1H), 4.24 – 4.05 (m, 1H), 3.74 (t, *J* = 7.8 Hz, 1H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H). MS(70eV, EI): m/z 113.1 [M]. [α]_D20: +113° (S)-2-ethyl-4-methyl-2-oxazolin (**S**-**EMOx**): bp: 84 °C at 250 mbar, yield: 44%. ¹H NMR (300MHz, CDCl₃, 293K): δ = 4.29 (t, *J* = 8.0 Hz, 1H), 4.19 – 4.02 (m, 1H), 3.72 (t, *J* = 7.8 Hz, 1H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.6 Hz, 3H). MS(70eV, EI): m/z 113.2 [M]. [α]_D20: -111°

Polymer synthesis. All polymerization reactions were performed at 130°C (max. power setting: 150W) for 17h. Alternatively, polymerization were carried out at 180 °C in an oil bath. All polymerizations were initiated with methyltriflate (MeOTf) and after full monomer conversion, approx. 5 eq. (with respect to the initial initiator amount) of the termination agent piperidine was directly injected into the reaction vial at room temperature. The termination reaction was allowed to complete over night. The neutralization and work-up procedures were carried out following a general procedure described previously.²

Results and Discussion

We synthesized a series of chiral homopolymers from both enantiomers of 2,4-dimethyl-2-oxazoline (**R**- and **S**-**DMOx**) and 2-ethyl-4-methyl-2-oxazoline (**R**- and **S**-**EMOx**) by ring-opening polymerization after initiation using methyltriflate (**Figure 1**, **Table 1**). For the majority of polymers we obtained only mediocre dispersity values which is in accordance with reports for other 2,4-disubstituted poly(2-oxazolines).¹¹ This is presumably due to the low reactivity of these monomers which requires in turn high polymerization temperature and/or long polymerization times.

Table 1. Analytical Values of Synthesized Polymers.

Polymer	Yield (%)	M _n , theo. (g mol ⁻¹) ^{a)}	M _n ^{b)} (g mol ⁻¹)	Đ ^{b)}
P(S)-DMOx₁₀	n.d.	1192	n.d.	n.d.
P(S)-DMOx₂₅₋₁	94	2577	2371	1.33
P(S)-DMOx₂₅₋₁₁	n.d.	2679	1784	1.59
P(S)-DMOx₅₀	n.d.	4859	3787	1.42
P(R)-DMOx₁₀	n.d.	1192	n.d.	n.d.
P(R)-DMOx₂₅	87	2577	2756	1.19
P(R)-DMOx₅₀	n.d.	5058	3770	1.70
P(R)-DMOx₈₀	n.d.	7932	8000	1.53
P(R)-EMOx₂₅	80	2928	3512	1.31
P(S)-EMOx₂₅	75	2928	3487	1.31
P(R,S)-EMOx₂₅	93	2928	2489	1.12

a) calculated from [M]₀/[I]₀ b) Determined by GPC analysis.

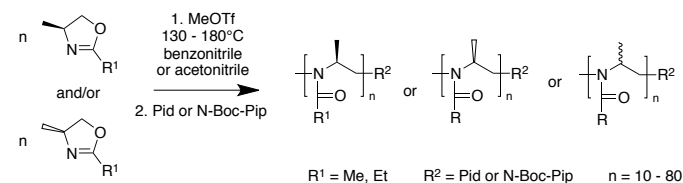


Figure 1. Synthetic scheme of the polymerization of 2,4-disubstituted 2-oxazolines.

Both parameters are expected to increase undesired side reactions. Nevertheless, the molar mass of the polymers could be controlled to some extent through the monomer to initiator ratio as expected. Interestingly, despite the lower dispersity of **P(R,S)-EMOx₂₅**, this polymer exhibited the

broadest transition during cloud point measurements (20 g/L). While both enantiopure polymers **P(R)-EMOX₂₅** and **P(S)-EMOX₂₅** the transition occurred within one Kelvin, the transition interval was about three times as broad for the racemic polymer (**Figure 2a**). The cloud points of the **PEMOx** are virtually identical with the value obtained for their non-chiral constitutional isomer poly(2-*iso*-propyl-2-oxazoline) **PiPrOx₂₅** of the same degree of polymerization. We hypothesized that the CP of the chiral samples may be influenced by chiral co-solutes. We therefore measured the cloud points in the presence of 50 g/l D- and L-alanine (**Figure 2b**). For all samples, including the achiral **PiPrOx₂₅**, the observed CP are lower in the presence of alanine, which can be interpreted as salting out of the polymers.³ However, for **P(R)-EMOX₂₅** and **P(S)-EMOX₂₅** the observed shift of CP is with approx. 5 K much more pronounced. On the other hand, the shift is identical for either combination of R- and S-POx and D- and L-alanine. The obtained CPs are summarized in **Table 3**.

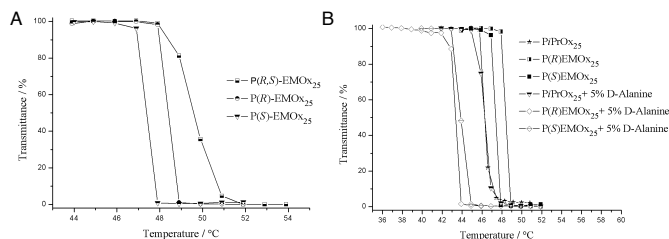


Figure 2. Optical transmittance measured at various temperatures for a) enantiopure and racemic **PEMOx₂₅** and b) compared with the constitutional isomer **PiPrOx₂₅** in the presence and absence of 50 g/L D-Alanine.

Table 3. Influence of chiral additives on the LCST of the thermosensitive chiral polymers as well as the achiral **PiPrOx₂₅**.

Polymer	Additive	CP ^{a)} (°C)
PiPrOx₂₅	No additive	47
P(R)-EMOX₂₅		48
P(S)-EMOX₂₅		47
PiPrOx₂₅	5% L-Alanine	46
P(R)-EMOX₂₅		43
P(S)-EMOX₂₅		43
PiPrOx₂₅	5% D-Alanine	46
P(R)-EMOX₂₅		44
P(S)-EMOX₂₅		44

a) Determined by UV-vis spectrophotometer at 10% decrease of optical transmittance of the polymer solution.

No melting point below 200 °C was observed, while glass transition temperature between 75 – 80 °C for **PEMOx₂₅**. In the case of **PDMOx**, the T_g increased with the degree of polymerization (DP) from 90 °C (DP = 10) to 120 °C (DP = 80) was observed. Thus, the T_g are somewhat higher as compared to their linear non-chiral conformation isomers poly(*n*-propyloxazoline) (T_g approx. 40 °C) and **PEtOx**, respectively. On the other hand, the glass transition temperature is similar to the value observed for poly(*cyclo*-propyloxazoline) (T_g approx. 80 °C).^{13,14} We also investigated these water-soluble chiral **PDMOx**, which did not exhibit a cloud point at 20 g/L, by circular dichroism (CD) spectroscopy. CD spectra were measured between 200 and 250 nm from dilute aqueous solutions (0.25 g/L). We observed pronounced Cotton effects with maximum values between 215 and 220 nm which is in excellent agreement with earlier reports on chiral poly(2-ethyl-4-butyloxazoline)s (**PBuEtOx**) (**Figure 3**).^{3,11,12} The CD spectra did not show a significant influence of the DP suggesting that the extent of secondary structure formation does not depend on the DP for $10 \leq DP \leq 80$ in water. On the other hand and in contrast to earlier reports on hydrophobic **PBuEtOx** in trifluoroethanol or hexafluoroisopropanol, when we measured aqueous solution of **P(S)-DMOX₅₀** at temperature ranging from 5 °C to 85 °C we observed an influence on both the maximum intensity and wavelength (**Figure 4a**). Notably, and consistently through the various samples the maximum wavelength shifts to lower values as the temperature increases by about 4 nm. The intensity of the Cotton effect increases with increasing temperature to 60 °C before it decreases again, exemplarily shown for **P(R)-DMOX₂₅** and **P(S)-DMOX₂₅** (**Figure 4b**). Hence, it appears that around 60 °C a maximum of helical character is formed.

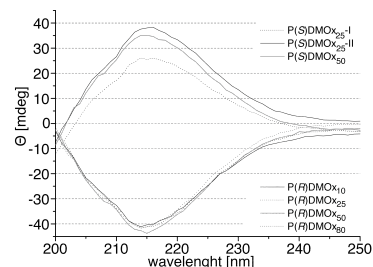


Figure 3. Circular dichroism spectra of aqueous solutions (0.025 wt.%) of a different chiral **PDMOx** with varying degrees of polymerization at 45 °C.

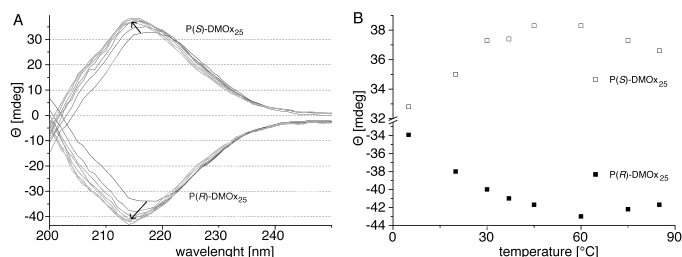


Figure 4. a) CD-spectra of 0.025 wt.% of **P(S)-DMOX₂₅** and **P(R)-DMOX₂₅** measured at 5 to 85 °C. b) Maximum intensity of the observed Cotton effect at different temperatures. Please note the break in the y-axis.

Conclusions

We reported on the temperature responsiveness of water-soluble 2,4-disubstituted poly(2-oxazolines). While poly(2-ethyl-4-methyl-2-oxazoline)s exhibit a cloud point around 50 °C, the secondary structure formed by poly(2,4-dimethyl-2-oxazoline) in water (presumably helices similar as polyproline helices) apparently stabilizes with increasing temperatures to about 60 °C before it become less stable at higher temperatures.

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