Chiral and Water-Soluble Poly(2-oxazoline)s

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ABSTRACT: We describe the synthesis and characterization of the first water-soluble and chiral poly(2,4-disubstituted-2-oxazoline)s. While poly(2,4-dimethyl-2-oxazoline)s are water soluble up to 100 °C, aqueous solutions of poly(2-ethyl-4-methly-2-oxazoline) exhibit a lower critical solution temperature. This is discussed in context with its constitutional isomers poly(2-oxazoline)s and poly(2-oxazine)s. Circular dichroism spectroscopy revealed strong Cotton effects, which are also responsive to temperature in aqueous solution. It is therefore hypothesized that structures, comparable to polyproline helices, are formed in aqueous solution. In contrast to polyproline, poly(2,4-disubstituted-2-oxazoline)s are highly water soluble and therefore represent very interesting pseudo-polypeptides that may be useful to develop responsive biomimetic biomaterials. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000–000, 2012

KEYWORDS: chiral polymer; circular dichroism; cloud point; hydrophilic; LCST; polyoxazoline

INTRODUCTION Optically active and water-soluble polymers may be considered particularly intriguing as a platform for biomaterials, in particular when considering biomimetic materials, as the chemistry of life is quintessentially chiral.[1] Although the origins of, or reasons for chirality in the biological realm remain unclear, it is obvious that chirality matters for, for example, interaction with cells.[2] However, among synthetic biomaterials, nonpeptidic chiral platforms, in particular water soluble, remain rather uncommon.

On the other hand, materials that respond to external stimuli, that is smart materials have gained increased interest over the last decades.[3] Especially, polymers that reversibly change their physicochemical properties—in particular their hydrophilicity—upon such stimulus, for example a change in temperature has been extensively discussed as smart biomaterials. Most water-soluble polymers exhibit a lower critical solution temperature (LCST), that is the polymers precipitate upon heating their aqueous solutions. The temperature of this transition may depend on varying degrees on the nature, molar mass and architecture of the polymer, its concentration, and solvent quality (cosolvents and cosolutes).[4–22] Poly(2-oxazoline)s (POx) are a versatile platform of biomaterials. For nonfouling surfaces,[23,24] hydrophilic POx are reportedly more stable as compared to PEGylated surfaces.[25] As for soluble systems, POx have promising preclinical results as polymer therapeutics in a variety of approaches (for recent reviews, see refs. 26–28]).[29–35] Hoogenboom and coworkers[36–39] have recently investigated hydrophobic poly(2,4-disubstituted-2-oxazoline)s and found conclusive evidence for the formation of dynamic secondary structures.

While Saegusa et al.[40] described 4-substituted POx as precursors for chiral poly(propyleneimine), we describe water-soluble chiral 2,4-disubstituted POx and investigate their thermal responsiveness in aqueous solution. Poly(2-ethyl-4-methyl-2-oxazoline) exhibits a LCST, while the more hydrophilic poly(2,4-dimethyl-2-oxazoline) forms temperature-sensitive secondary structures in aqueous solution as evidenced by circular dichroism (CD) spectroscopy.

EXPERIMENTAL

Materials

All chemicals used for synthesis were purchased from Aldrich (Steinheim, Germany) or Acros Organics (Geel, Belgium) and

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were used without further purification unless otherwise stated. Solvents, methyl triflate (MeOTf), and all monomers used for the living cationic polymerization were dried by refluxing over CaH_2 for approximately 3 h and subsequent distillation. The monomers were stored under a dry nitrogen atmosphere and handled in a glove box under dry argon.

Instrumentation

All polymerizations were performed using a CEM Discovery microwave. ^{1}H-NMR spectra were recorded on a Bruker ARX 300 (^{1}H: 300.13 MHz) with tetramethylsilane as internal standard at $T = 293$ K in $CDCl_3$. Gel permeation chromatography (GPC) was performed on a Waters system (pump mod. 510, RI-detector mod. 410) with columns Resi Pore Guard (50 × 7.5 mm) and 2× Resi Pore (300 × 7.5 mm) as the stationary and dimethylacetamide as the mobile phase using poly(methyl methacrylate) calibration standards. The mass spectrometry measurements were performed using a MAT 8200 Finnigan (EI, 70 eV) ion impact mass spectrometer. The optical rotation power [α] was measured using a 241MC polarimeter from Perkin-Elmer at $\lambda = 589$ 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 $\lambda = 500$ nm of the aqueous polymer solutions (2.0 wt %). The solution temperature was increased by a rate of 1 K/min 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 path length 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 adapted from the previously published literature.[37] Exemplarily, (*R*)-2,4-dimethyl-2-oxazoline **(*R*)-DMeOx** 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%.

^{1}H NMR (300 MHz, $CDCl_3$, 293 K): $\delta = 4.29$ (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 (70 eV, EI): $m/z = 99.1$ [M]. [α]: +132°

(*S*)-2,4-dimethyl-2-oxazoline **(*S*)-DMeOx**: bp: 75 °C at 250 mbar, yield: 17%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): $\delta = 4.28$ (t, $J = 8.0$ Hz, 1H), 4.13–4.03 (m, 1H), 3.70 (t, $J = 8.0$ Hz, 1H), 1.92 (s, 3H), 1.21 (d, $J = 6.6$ Hz, 3H). MS(70 eV, EI): $m/z = 99.1$ [M]. [α]: −131°

(*R,S*)-2,4-dimethyl-2-oxazoline **(*R,S*)-DMeOx**: bp: 50 °C at 100 mbar, yield: 20%. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): $\delta = 4.25$ (t, $J = 8.75$ Hz, 1H), 4.14–4.00 (m, 1H), 3.68 (t, $J = 7.8$ Hz, 1H), 1.90 (s, 3H), 1.17 (d, $J = 6.5$ Hz, 3H).

(*R*)-2-ethyl-4-methyl-2-oxazoline **(*R*)-EtMeOx**: bp: 84 °C at 250 mbar, yield: 44%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): $\delta = 4.31$ (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(70 eV, EI): $m/z = 113.1$ [M]. [α]: +113°

(*S*)-2-ethyl-4-methyl-2-oxazoline **(*S*)-EtMeOx:** bp: 84 °C at 250 mbar, yield: 44%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): $\delta = 4.29$ (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(70 eV, EI): $m/z = 113.2$ [M]. [α]: -111°

Polymer Synthesis

All polymerization reactions were performed at 130 °C (max. power setting: 150 W) for 17 h using MeOTf as the initiator and after full monomer conversion, approx. 5 eq. (with respect to the initial initiator amount) of the termination agent (piperidine or BOC-protected piperazine) 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 by following a general procedure described previously.[41]

RESULTS AND DISCUSSION

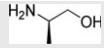
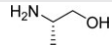
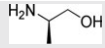
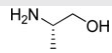
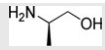
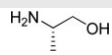
Chiral 2,4-disubstituted 2-oxazolines are directly accessible in low to moderate yields via a one-step synthesis from chiral D- or L-alaninol and the corresponding nitriles by following the well-established route of 2-oxazoline synthesis.[42,43] In total, we synthesized six different chiral monomers, namely 2,4-dimethyl-2-oxazoline (***R***- and ***S*-DMeOx**), 2-ethyl-4-methyl-2-oxazoline (***R***- and ***S*-EtMeOx**), 2-isopropyl-4-methyl-2-oxazoline (***R***- and ***S*-*i*PrMeOx**), and one racemic (***R,S*-DMeOx**) that have not been reported previously.[44] The used educts, yields, and optical activities are summarized in Table 1. As the chiral center of the monomers does not participate in the later polymerization, no racemization can occur.

The first who described the synthesis of 2,4-disubstituted-2-oxazolines and their polymerization were Guo and Schulz.[42] As the substituent in 2-position phenyl or methyl moieties was chosen, whereas the 4-position was substituted by an ethyl-, *iso*-propyl,- phenyl-, or methyl group. After polymerization, partly crystalline, isotactic polymers could be obtained in high yields which were water insoluble. Notably, 2-phenyl-4-isopropyl-2-oxazoline did not polymerize. More recently, Bloksma et al.[38,39] studied chiral, water-insoluble poly(2-butyl-4-ethyl-2-oxazoline)s in detail.

We synthesized a series of chiral homopolymers from the enantiomers of **R-** and **S-DMeOx** and **R-** and **S-EtMeOx** by ring-opening polymerization using MeOTf (Fig. 1 and Table 2). For the majority of polymers, slightly broader dispersities were found which is in accordance with the earlier reports for 2,4-disubstituted POx.[38,39,43]

Nevertheless, the average molar mass of the polymers could be controlled reasonably well through the monomer-to-initiator ratio as expected for a living cationic polymerization. Chiral POx with an average degree of polymerization (DP) of 10, 25, 50, and 80 were prepared (Table 2). A more precise

TABLE 1 Synthesis and Analytical Values of the Optically Active 2,4-Oxazoline Monomers

Monomer	Nitrile	Alaninol	Yield (%)	$[\alpha]_D^{20}$ (deg)
(*R*)-DMeOx			27	+132
(*S*)-DMeOx			17	−131
(*R*)-EtMeOx			44	+113
(*S*)-EtMeOx			44	−111
(*R*)-*i*PrMeOx			47	+94
(*S*)-*i*PrMeOx			48	−95

determination of the DP from end-group analysis based on ^{1}H-NMR spectroscopy data was not possible because of strong signal overlap. In addition, one racemic sample, **P(R,S)-EtMeOx$_{25}$** was synthesized. In comparison, the monomer **(*R*) and (*S*)-*i*PrMeOx** exhibited a very low tendency for polymerization because of the steric hindrance by the substituents and were not further studied.

Thermoresponsiveness of Water-Soluble Poly(2,4-disubstituted-2-oxazoline)s

The prepared polymers are constitutional isomers of poly(2-ethyl-2-oxazoline) (PEtOx) and poly(2-iso-/*n*-propyl-2-oxazoline)s (PnPrOx or PiPrOx), poly(2-methyl-2-oxazine) (PMeOz), and poly(2-ethyl-2-oxazine) (PEtOz), respectively, as shown in Figure 2. Although the temperature sensitivity of aqueous solutions of various POx was intensively investigated,[9,11,14,16,18–21,45–47] thermoresponsive poly(2-oxazine)s have only recently been investigated.[48] The prepared 2,4-disubstituted POx are, in contrast to the previously described ones, highly water soluble at ambient conditions. To the best of our knowledge, **P(R)-** and **P(S)-EtMeOx** as well as **P(R)-** and **P(S)-DMeOx** represent the first chiral water-soluble POx described so far. As judged from the structural comparison (Fig. 2), both 2,4-disubstituted POx are structural analogs of thermoresponsive POx, therefore, we investigated the behavior of their aqueous solutions. **P(R)-** and **P(S)-DMeOx** are

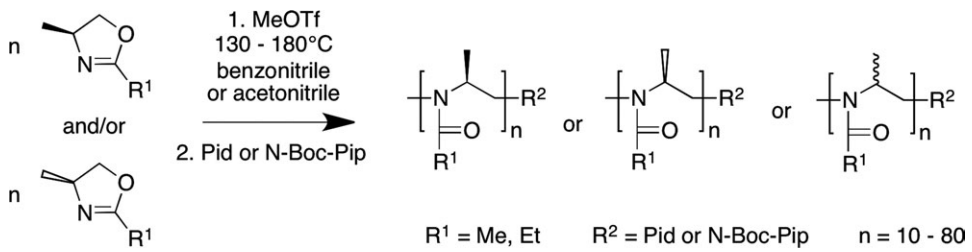


FIGURE 1 Schematic representation of the polymerization of chiral 2,4-disubstituted 2-oxazolines to give chiral or racemic poly(2,4-disubstituted-2-oxazoline)s as described in the text.

TABLE 2 Analytical Values of Synthesized Polymers

Polymer	Yield (%)	$M_n^{theoretical}$ (g/mol)[a]	M_n^{b} (kg/mol)	Đ[b]
P(*S*)-DMeOx$_{10}$	n.d.	1,192	n.d.	n.d.
P(*S*)-DMeOx$_{25\text{-I}}$	94	2,577	2.4	1.33
P(*S*)-DMeOx$_{25\text{-II}}$	n.d.	2,679	1.8	1.59
P(*S*)-DMeOx$_{50}$	n.d.	4,859	3.8	1.42
P(*R*)-DMeOx$_{10}$	n.d.	1,192	n.d.	n.d.
P(*R*)-DMeOx$_{25}$	87	2,577	2.8	1.19
P(*R*)-DMeOx$_{50}$	n.d.	5,058	3.8	1.70
P(*R*)-DMeOx$_{80}$	n.d.	7,932	8.0	1.53
P(*R*)-EtMeOx$_{25}$	80	2,928	3.5	1.31
P(*S*)-EtMeOx$_{25}$	75	2,928	3.5	1.31
P(*R,S*)-EtMeOx$_{25}$	93	2,928	2.5	1.12

[a] Calculated from $[M]_0/[I]_0$
[b] Determined from GPC traces.

constitutional isomers of PEtOx and PMeOz. While PEtOx solutions yield cloud points from 50 to <100 °C, depending on the architecture (linear, brush) and molar mass,[49,50] PMeOz does not precipitate from its aqueous solutions below 100 °C at ambient pressure.[48] Similarly, **P(*R*)-DMeOx$_{80}$** did not

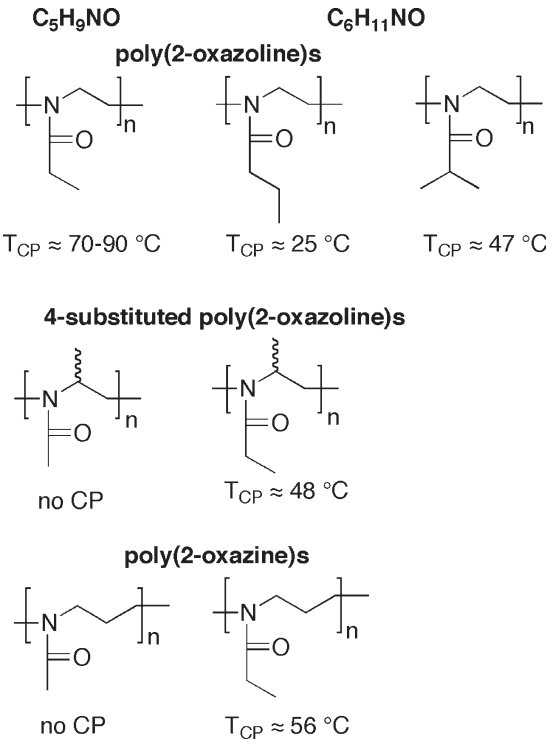


FIGURE 2 Comparison of polymer structures of structural isomers of POx, 4-substituted POx and poly(2-oxazine)s along with cloud point temperatures (T_{CP}) reported in the literature and in this account. It must be noted that the T_{CP} may depend strongly on the degree of polymerization, in particular for DP < 100, polymer concentration, and solvent quality. For a recent review, please refer to ref. 21.

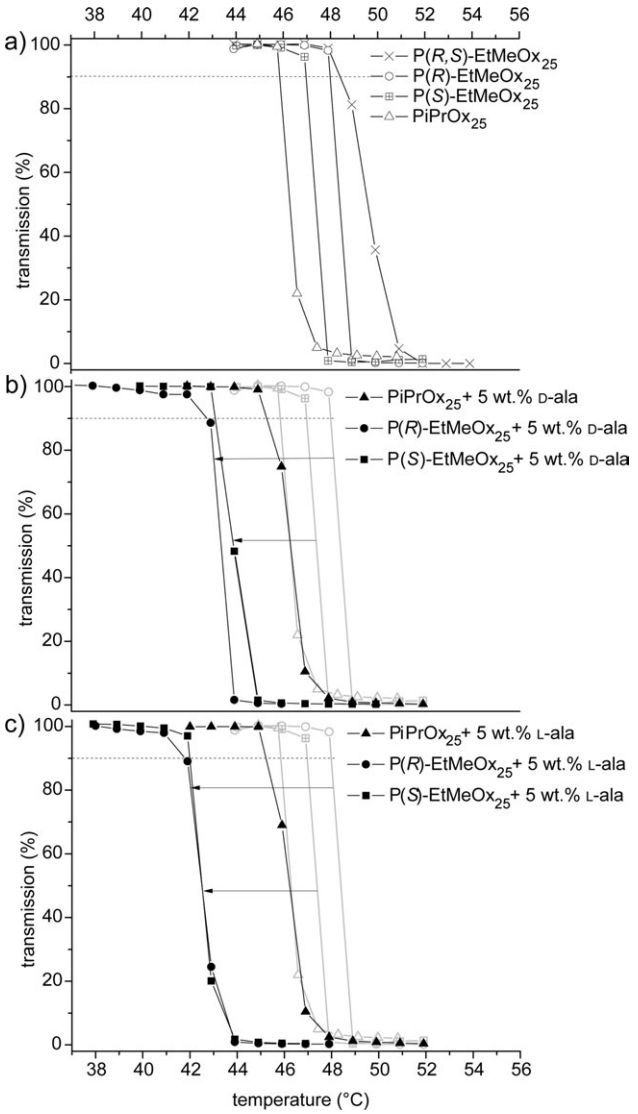


FIGURE 3 Optical transmittance measured at various temperatures for (a) enantiopure and racemic **PEtMeOx$_{25}$** and their achiral constitutional isomer **PiPrOx** (all 20 g/L) in deionized water and in the presence of 50 g/L (5 wt%), (b) D-, or (c) L-alanine.

show a cloud point at a concentration of 20 g/L in deionized water.

In contrast, aqueous solutions of **PEtMeOx**, a constitutional isomer of PEtOz (T_{CP} = 56 °C) and PnPrOx (T_{CP} = 25 °C)/PiPrOx (T_{CP} = 47 °C), exhibit defined cloud points at $T_{CP} \approx$ 47 °C. Interestingly, for both enantiopure polymers **P(*R*)-EtMeOx$_{25}$** and **P(*S*)-EtMeOx$_{25}$**, the transition occurred within 1 K, whereas the transition interval was found to be about three times as broad for the racemic polymer [Fig. 3(a)]. It is important to note that the molar mass and dispersity, as obtained from GPC, were somewhat lower for the racemic polymer. Moreover, the T_{CP} of the **PEtMeOx** was found to be almost identical with the value obtained for their non-chiral constitutional isomer **PiPrOx$_{25}$** with the same DP, whereas **PnPrOx** has a significantly lower T_{CP} of around

TABLE 3 Influence of Chiral Additives on the T_{CP} of the Thermosensitive Chiral POx as well as the Achiral **PiPrOx$_{25}$** (all at 20 g/L)[a]

Polymer	Additive	CP (°C)
P*i*PrOx$_{25}$		47
P(*R*)-EtMeOx$_{25}$	None	48
P(*S*)-EtMeOx$_{25}$		47
P*i*PrOx$_{25}$		46
P(*R*)-EtMeOx$_{25}$	5% L-Alanine	43
P(*S*)-EtMeOx$_{25}$		43
P*i*PrOx$_{25}$		46
P(*R*)-EtMeOx$_{25}$	5% D-Alanine	44
P(S)-EtMeOx$_{25}$		44

[a] The cloud points were determined by UV–vis spectrophotometer at 10% decrease of optical transmittance of the polymer solution.

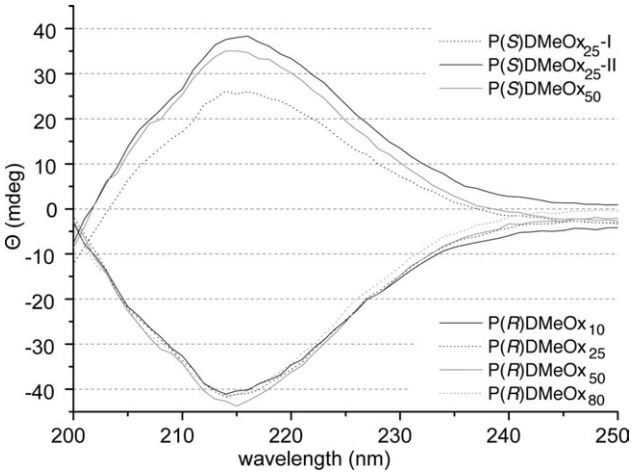


FIGURE 4 CD spectra of aqueous solutions (0.025 wt %) of different chiral **PDMeOx** with different DPs at 45 °C.

25 °C. It should be noted that at ambient conditions, it was found that **PEtMeOx** is miscible with water at all concentrations.

Therefore, it can be concluded that among the constitutional isomers of the POx/POz system, POz are the most hydrophilic, followed by 2,4-disubstituted POx and POx being the most hydrophobic polymers. In other words, a methylene moiety in the backbone exerts less hydrophobicity as compared to pending moieties and splitting a pending moiety into two appears to have a similar effect as branching of a side chain. It would be interesting to investigate the effect of branched substituents at the 2-, and/or 4-position in 2,4-disubstituted POx and whether branching at either position gives a different effect with respect to the solution behavior of the polymer. However, the low reactivity of 2,4-substituted oxazoline monomers bearing branched alkyl chains most probably does not allow the preparation of defined polymers of reasonable dispersities. Similarly, it would be interesting to investigate whether the observed trend holds for a further extension of the backbone methylene units for the monomer, that is to compare the solubility of polymers from 2,4- or 2,5-disubstituted oxazines and 2-oxazepines. However, to the best of our knowledge, only one example of the polymerization of 2-oxazepine, namely 2-pyrrolidino-4,5,6,7-tetrahydro-4H-1,3-oxazepine, has been reported so far.[51]

It is well known that water solubility and the LCST of hydrophilic polymers is influenced by cosolutes. We hypothesized that the T_{CP} of our chiral polymers may be influenced by chiral cosolutes; therefore, the T_{CP} was measured in the presence of 50 g/L D- and L-alanine [Fig. 3(b,c)] (Table 3). For all samples, including the achiral **PiPrOx$_{25}$**, the observed T_{CP} are lower in the presence of either stereoisomer of alanine, which could be interpreted as a salting out-effect for the polymer solution.[52] However, for **P(*R*)-EtMeOx$_{25}$** and **P(*S*)-EtMeOx$_{25}$**, the observed shift of the T_{CP} is with approx. 5 K much more pronounced as compared to the very small shift in the case of **PiPrOx**, which may be accounted to differences in steric accessibility of the amide moiety. On the other hand, the T_{CP} shift was found to be identical for, for example, **P(*R*)-EtMeOx$_{25}$** and **P(*S*)-EtMeOx$_{25}$** with either D- or L-alanine. Thus, no noticeable sensitivity for the chirality of cosolutes can be postulated at this point.

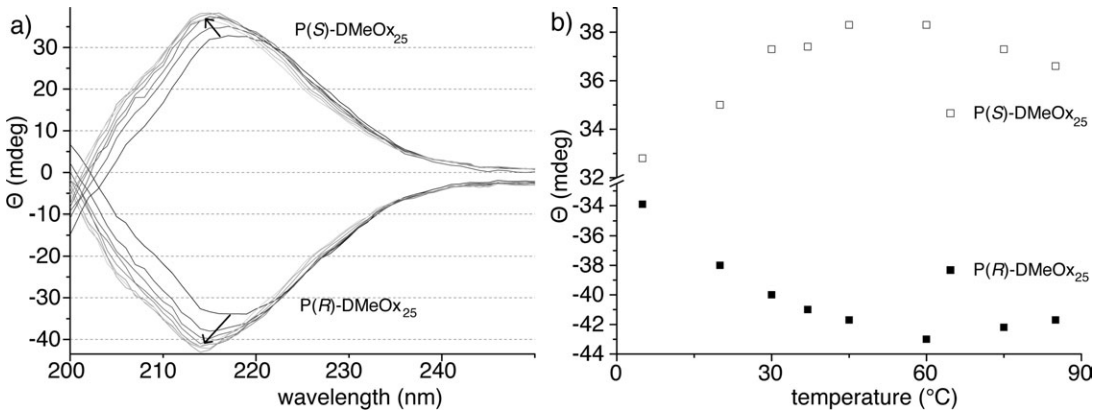


FIGURE 5 (a) CD spectra of 0.025 wt % of **P(*S*)-DMeOx$_{25}$** and **P(*R*)-DMeOx$_{25}$** measured from 5 to 85 °C. (b) Maximum intensity of the observed Cotton effect at different temperatures. Please note the break in the *y*-axis.

Thermogravimetric analysis showed that polymer degradation started around 280 °C. By differential scanning calorimetry, no melting points were found and the chiral polymers appear amorphous. As for glass transition temperature (T_g), we found values between 75 and 80 °C for **PEtMeOx$_{25}$**. In the case of **PDMeOx**, the T_g increased as expected as the DP increased from 90 °C (DP = 10) to 120 °C (DP = 80). Thus, the T_g are somewhat higher as compared to their linear non-chiral constitutional isomers P*n*PrOx (approx. T_g = 40 °C) and PEtOx, respectively,[53] because of the reduced mobility of the polymer main chain introduced by the additional substituent at the 4-position. On the other hand, the glass transition is similar to the value observed for poly(2-*cyclo*-propyl-2-oxazoline) (approx. T_g = 80 °C).[54]

Circular Dichroism in Aqueous Solution

To further elucidate the secondary structure of chiral POx, Schubert and coworkers performed X-ray and neutron scattering as well as CD analysis of the hydrophobic chiral poly(2-ethyl-4-butyloxazoline)s (PBuEtOx). From the scattering experiments, a (semi-)crystalline nature could be concluded; however, direct evidence for a helical structure could not be found so far. In CD spectroscopy, pronounced Cotton and anti-Cotton effects were found and tentatively attributed to secondary structure formation. As these secondary structures cannot be stabilized via intramolecular hydrogen bonding, their formation is attributed to steric reasons, similar as is the case in polyproline helices. The intensity and positions of the ellipticities shifted with the temperature. Although in trifluoroethanol, the intensity steadily decreased with the temperature, the Cotton effect intensity reached a minimal plateau around room temperature in hexafluoroisopropanol.

Zhang and co-workers investigated chiral polypeptoids by CD spectroscopy and found similar, yet distinct results.[55] In this case, chirality stems from chiral side chains, as the main-chain of polypeptoids is achiral. Similar as with the PBuEtOx, the polypeptoids were not water soluble due to nature of the side chains. While an effect on the chain length of the polymers was not reported for PBuEtOx, in the case of polypeptoids a pronounced effect was observed. In addition, cyclic polypeptoids appear to have a higher helical content as compared to linear ones. Interestingly, the intensity of the Cotton effect was reduced upon heating from 0 °C to 20°C but leveled out above this temperature.[55] Accordingly, the water soluble **PDMeOx** and **PEtMeOx** were studied by CD spectroscopy. CD spectra were measured between 200 and 250 nm from dilute aqueous solutions (c = 0.25 g/L) and pronounced Cotton effects with maximum values between 215 and 220 nm where observed, which is in excellent agreement with earlier reports on the chiral hydrophobic PBuEtOx (Figure 4).[37] The CD spectra of **PDMeOx** did not show a significant influence on the DP suggesting that the hypothesized secondary structure formation does not depend on the DP for 10 $\leq$ DP $\leq$ 80 in water (Fig. 4). On the other hand and in contrast to earlier reports on hydrophobic PBuEtOx in trifluoroethanol or hexafluoroisopropanol,[37] when we measured the aqueous solution of **PDMeOx** at temperature ranging from 5 °C to 85 °C, we observed an influence on both the maximum intensity and wavelength [Fig. 5(a)]. Notably, and consistently through the various samples, the maximum wavelength is shifted to lower values as the temperature increases by about 4 nm. The intensity of the Cotton effect increases when the temperature was increased to 60 °C before it decreases again as exemplarily shown for **P(*R*)-DMeOx$_{25}$** and **P(*S*)-DMeOx$_{25}$** [Fig. 5(b)]. Hence, it appears that around 60 °C, a maximal secondary structure formation occurs in our case while Schubert et al. and Zhang and coworkers observed a steady decrease in the intensity of Cotton effects.[37,55] The difference, in part, is likely to be attributed to the different solvent, in which the studies were performed. It is hypothesized that the maximum in the helical content reflects a turning point with respect to the enthalpic and entropic contributions for the formation of the helices. As such, upon heating, partial dehydration may lead to increased intramolecular interaction before further heating weakens the hypothesized transient structures again. Thus, future study will focus on the effect of a variety of solvents upon the formation of secondary structures and on the use of alternative analytical tools to investigate the presence of the proposed secondary structures therein.

CONCLUSIONS

We reported on the preparation and characterization of the first water-soluble chiral POx. The temperature-dependent water solubility of poly(2,4-disubstituted-2-oxazoline)s was studied and compared to constitutional isomers. While poly(2-ethyl-4-methyl-2-oxazoline) exhibit cloud points around 50 °C and thus very similar to its branched constitutional isomer poly(2-isopropyl-2-oxazoline), no cloud point could be found for poly(2,4-dimethyl-2-oxazoline)s. From CD spectroscopy measurements, poly(2,4-dimethyl-2-oxazoline) from secondary structures in water, presumably helices similar to polyproline. Such structures are apparently stabilized at temperatures around 60 °C. Poly(2,4-dimethyl-2-oxazoline) represents probably the first nonionic highly water-soluble chiral polymer that forms secondary structures without intramolecular hydrogen bonding.

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REFERENCES AND NOTES

1 M. Zhang, G. Qing, T. Sun, *Chem. Soc. Rev.* **2012,** *41*, 1972–1984.

2 X. Wang, H. Gan, M. X. Zhang, T. Sun, *Langmuir* **2012,** *28*, 2791–2798.

3 M. A. Stuart, W. T. Huck, J. Genzer, M. Müller, C. Ober, M. Stamm, G. B. Sukhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko, *Nat. Mater.* **2010,** *9*, 101–113.

4 X. Yin, A. S. Hoffman, P. S. Stayton, *Biomacromolecules* **2006,** *7*, 1381–1385.

5 J. Akimoto, M. Nakayama, K. Sakai, T. Okano, *J. Polym. Sci. Part A: Polym. Chem.* **2008,** *46*, 7127–7137.

6 P. Lin, C. Clash, E. M. Pearce, T. K. Kwei, M. A. Aponte, *J. Polym. Sci. Part B: Polym. Phys.* **1988,** *26*, 603–619.

7 S. Furyk, Y. Zhang, D. Ortiz-Acosta, P. S. Cremer, D. E. Bergbreiter, *J. Polym. Sci. Part A: Polym. Chem.* **2006,** *44*, 1492–1501.

8 H. Uyama, S. Kobayashi, *Chem. Lett.* **1992,** *21*, 1643–1646.

9 D. Christova, R. Velichkova, W. Loos, E. J. Goethals, F. D. Prez, *Polymer* **2003,** *44*, 2255–2261.

10 J. F. Lutz, K. Weichenhan, O. Akdemir, A. Hoth, *Macromolecules* **2007,** *40*, 2503–2508.

11 R. Hoogenboom, H. M. L. Thijs, M. J. H. C. Jochems, B. M. van Lankvelt, M. W. M. Fijten, U. S. Schubert, *Chem. Commun.* **2008, 5758–5759**.

12 O. Kretschmann, S. W. Choi, M. Miyauchi, I. Tomatsu, A. Harada, H. Ritter, *Angew. Chem. Int. Ed.* **2006,** *45*, 4361–4365.

13 J. F. Lutz, Ö. Akdemir, A. Hoth, *J. Am. Chem. Soc.* **2006,** *128*, 13046–13047.

14 J. S. Park, K. Kataoka, *Macromolecules* **2006,** *39*, 6622–6630.

15 F. M. Winnik, A. R. Davidson, G. K. Hamer, H. Kitano, *Macromolecules* **1992,** *25*, 1876–1880.

16 M. Meyer, M. Antonietti, H. Schlaad, *Soft Matter* **2007,** *3*, 430–431.

17 M. Meyer, H. Schlaad, *Macromolecules* **2006,** *39*, 3967–3970.

18 J. S. Park, K. Kataoka, *Macromolecules* **2007,** *40*, 3599–3609.

19 S. Huber, N. Hutter, R. Jordan, *Colloid Polym. Sci.* **2008,** *286*, 1653–1661.

20 S. Huber, R. Jordan, *Colloid Polym. Sci.* **2008,** *286*, 395–402.

21 C. Weber, R. Hoogenboom, U. S. Schubert, *Prog. Polym. Sci.* **2012,** *37*, 686–714.

22 L. T. T. Trinh, H. M. L. Lambermont-Thijs, U. S. Schubert, R. Hoogenboom, A. L. Kjøniksen, *Macromolecules* **2012,** *45*, 4337–4345.

23 R. Konradi, B. Pidhatika, A. Mühlebach, M. Textor, *Langmuir* **2008,** *24*, 613–616.

24 N. Zhang, T. Pompe, I. Amin, R. Luxenhofer, C. Werner, R. Jordan, *Macromol. Biosci.* **2012,** *7*, 926–936.

25 B. Pidhatika, M. Rodenstein, Y. Chen, E. Rakhmatullina, A. Mühlebach, C. Acikgöz, M. Textor, R. Konradi, *Biointerphases* **2012,** *7*, 1

26 K. Knop, R. Hoogenboom, D. Fischer, U. S. Schubert, *Angew. Chem. Int. Ed.* **2010,** *49*, 6288–6308.

27 M. Barz, R. Luxenhofer, R. Zentel, M. J. Vicent, *Polym. Chem.* **2011,** *2*, 1900–1918.

28 R. Luxenhofer, Y. Han, A. Schulz, J. Tong, Z. He, A. V. Kabanov, R. Jordan, *Macromol. Rapid Commun.* **2012,** *33*, 1613–1631.

29 R. Luxenhofer, A. Schulz, C. Roques, S. Li, T. K. Bronich, E. V. Batrakova, R. Jordan, A. V. Kabanov, *Biomaterials* **2010,** *31*, 4972–4979.

30 J. Tong, M. C. Zimmerman, S. Li, X. Yi, R. Luxenhofer, R. Jordan, A. V. Kabanov, *Biomaterials* **2011,** *32*, 3654–3665.

31 R. Hoogenboom, H. Schlaad, *Polymers* **2011,** *3*, 467–488.

32 R. Luxenhofer, G. Sahay, A. Schulz, D. Alakhova, T. K. Bronich, R. Jordan, A. V. Kabanov, *J. Control. Release* **2011,** *153*, 73–82.

33 T. X. Viegas, M. D. Bentley, J. M. Harris, Z. Fang, K. Yoon, B. Dizman, R. Weimer, A. Mero, G. Pasut, F. M. Veronese, *Bioconjug. Chem.* **2011,** *22*, 976–986.

34 A. Mero, G. Pasut, L. Dalla Via, M. W. Fijten, U. S. Schubert, R. Hoogenboom, F. M. Veronese, *J. Control. Release* **2008,** *125*, 87–95.

35 A. Mero, Z. Fang, G. Pasut, F. M. Veronese, T. X. Viegas, *J. Control. Release* **2012,** *159*, 353–361.

36 M. M. Bloksma, M. M. R. M. Hendrix, U. S. Schubert, R. Hoogenboom, *Macromolecules* **2010,** *43*, 4654–4659.

37 M. M. Bloksma, S. Rogers, U. S. Schubert, R. Hoogenboom, *Soft Matter* **2010,** *6*, 994–1003.

38 M. M. Bloksma, U. S. Schubert, R. Hoogenboom, *Polym. Chem.* **2011,** *2*, 203–208.

39 M. M. Bloksma, S. Hoeppener, C. D'Haese, K. Kempe, U. Mansfeld, R. M. Paulus, J. F. Gohy, U. S. Schubert, R. Hoogenboom, *Soft Matter* **2012,** *8*, 165–172.

40 T. Saegusa, S. Kobayashi, M. Ishiguro, *Macromolecules* **1974,** *7*, 958–959.

41 F. C. Gaertner, R. Luxenhofer, B. Blechert, R. Jordan, M. Essler, *J. Control. Release* **2007,** *119*, 291–300.

42 H. Witte, W. Seeliger, *Liebigs Ann. Chem.* **1974,** *174*, 996–1009.

43 X. Q. Guo, R. C. Schulz, *Polym. Int.* **1994,** *34*, 229–233.

44 M. M. Bloksma, U. S. Schubert, R. Hoogenboom, *Macromol. Rapid Commun.* **2011,** *32*, 1419–1441.

45 S. Salzinger, S. Huber, S. Jaksch, P. Busch, R. Jordan, C. M. Papadakis, *Colloid Polym. Sci.* **2012,** *290*, 385–400.

46 N. Zhang, R. Luxenhofer, R. Jordan, *Macromol. Chem. Phys.* **2012,** *213*, 1963–1969.

47 N. Zhang, R. Luxenhofer, R. Jordan, *Macromol. Chem. Phys.* **2012,** *213*, 973–981.

48 M. M. Bloksma, R. M. Paulus, H. P. van Kuringen, F. van der Woerdt, H. M. Lambermont-Thijs, U. S. Schubert, R. Hoogenboom, *Macromol. Rapid Commun.* **2012,** *33*, 92–96.

49 C. Weber, C. R. Becer, R. Hoogenboom, U. S. Schubert, *Macromolecules* **2009,** *42*, 2965–2971.

50 N. Zhang, S. Huber, A. Schulz, R. Luxenhofer, R. Jordan, *Macromolecules* **2009,** *42*, 2215–2221.

51 M. Miyamoto, K. Aoi, T. Saegusa, *J. Polym. Sci. Part A: Polym. Chem.* **1997,** *35*, 933–945.

52 M. M. Bloksma, D. J. Bakker, C. Weber, R. Hoogenboom, U. S. Schubert, *Macromol. Rapid Commun.* **2010,** *31*, 724–728.

53 E. F. J. Rettler, J. M. Kranenburg, H. M. L. Lambermont-Thijs, R. Hoogenboom, U. S. Schubert, *Macromol. Chem. Phys.* **2010,** *211*, 2443–2448.

54 M. M. Bloksma, C. Weber, I. Y. Perevyazko, A. Kuse, A. Baumgärtel, A. Vollrath, R. Hoogenboom, U. S. Schubert, *Macromolecules* **2011,** *44*, 4057–4064.

55 L. Guo, J. Li, Z. Brown, K. Ghale, D. Zhang, *Biopolymers* **2011,** *96*, 596–603.