Poly(cyclic imino ether)s : from chiral poly(2-oxazoline)s to thermo-responsive polymers

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From chiral poly(2-oxazoline)s to thermo-responsive polymers

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Chapter 1

An introduction to the polymerization of cyclic imino ethers and chirality

Abstract

2-Oxazolines (2-OZO) are 5-membered cyclic imino ethers whose cationic ring-opening polymerization (CROP) mechanism and properties are extensively studied. Main-chain chiral poly(2-oxazoline)s are obtained when the 4th or 5th position of the 2-oxazoline ring is substituted, although only a limited number of reports deal with such polymers. Also 6- and 7-membered cyclic imino ethers can be polymerized via CROP. Even though these larger cyclic monomers further extend the scope of this class of polymers, they are also significantly less investigated compared to 2-OZO. Nonetheless, these compounds represent interesting monomers to enhance the versatility of (co)poly(cyclic imino ether)s. To emphasize the potential of such alternative cyclic imino ether monomers, this chapter provides an overview on the polymerizations of chiral 2-OZO and 2-oxazine (2-OZI) and the properties of the resulting polymers.

1. An introduction to the polymerization of cyclic imino ethers and chirality

1.1 Polymers

Both natural and synthetic polymers are omnipresent around us and a world without them has become unimaginable. Proteins, sugars and our DNA are natural polymers, while cosmetics, inks, and coatings are examples of materials that contain various synthetic polymers. Such bulk polymers are ill-defined; they are polydisperse, although this has no influence on the properties of most applications. Since the introduction of living and controlled polymerization techniques, more advanced polymer structures with defined molar mass and endgroups together with a narrow polydispersity index can be obtained in various architectures like gradient or block copolymers and comb polymers. Depending on the type of monomer, controlled radical polymerizations like reversible addition fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP) and/or living anionic or cationic polymerizations, including living ring-opening polymerizations, can be performed. 2-Oxazolines, for example, can be polymerized via a cationic ring-opening polymerization (CROP) process using a strong electrophile to initiate the reaction and a nucleophile as termination agent (Scheme 1.1). After the initiation, a cationic oxazolinium ring with a weakened C-O bond is formed followed by the nucleophilic attack of the next monomer onto this carbon atom. Both ionic and cationic active species can be present during the polymerization, although the polymerization process proceeds almost exclusively via the cationic species.

![Scheme 1.1 Schematic presentation of the cationic ring-opening polymerization of 2-oxazolines.](image-url)
1. An introduction to the polymerization of cyclic imino ethers and chirality

The polymer properties can be controlled by varying the side-chain on the 2-position. For example, small alkyl side-chains, like methyl, ethyl or n-propyl result in water soluble polymers, while larger hydrophobic side-chains result in hydrophobic polymers that cannot be dissolved in water. However, poly-2-ethyl-2-oxazoline (pEtOx) and poly-2-n-propyl-2-oxazoline (pnPropOx) precipitate from the aqueous solution when the temperature is increased which is known as lower critical solution temperature (LCST) behavior. Besides constructing a polymer from one 2-oxazoline monomer, it is also possible to synthesize copolymers either by a statistical copolymerization where both monomers are polymerized at the same time or via a block copolymerization whereby the second monomer is added after the first has polymerized completely. As such, both hydrophobic and hydrophilic monomers can be combined resulting in amphiphilic copolymers that can self-assemble in aqueous solution. Besides substituting the 2-oxazoline on the 2-position, also a side-chain can be added to the 4th or 5th position resulting in chiral 2-oxazolines that, upon polymerization, lead to chiral polymers. Like natural chiral polymers they might form, besides the primary structure, also secondary structures and might be useful for molecular recognition and enantioselective catalysis depending on their 3-dimensional tertiary structure. Besides introducing a chiral group, also the cyclic imino ether ring-size can be increased to for example 6-membered 2-oxazine monomers, further expanding the variety of monomers suitable for the CROP.

Early applications of such poly(cyclic imino ethers) are stabilizers/surfactants, compatibilizers and thermo-settings. However, several other applications have evolved in the last years like in biomedical applications such as drug delivery systems and antimicrobial surfaces due to their biocompatibility or in thermo-responsive materials, mostly in the form of hydrogels triggered by the LCST behavior of several poly(2-oxazoline)s.\(^4\)

1.2 Introducing chirality

We live in a chiral world since the majority of natural molecules and polymers are chiral, like proteins and DNA, which form secondary structures like helices or β-sheets. The most frequently investigated natural polymer class containing main-chain chirality are poly(amino-acid)s.\(^1,2\) In contrast to naturally occurring polymers, synthetic polymers with main-chain chirality forming a secondary helical structure are
1. An introduction to the polymerization of cyclic imino ethers and chirality

less common. 2-Oxazolines (2-OZO) can be made chiral by substituting the monomer on the 4th or 5th position and upon polymerization via the cationic ring-opening polymerization (CROP), chiral main-chain poly(2-oxazolines) are obtained which can be regarded as pseudo-peptides.\textsuperscript{3-10} The first reports on the CROP of 4- and 5-substituted 2-OZO appeared in the mid 70’s.\textsuperscript{5,11} In a first example by Saegusa, chiral S-4-methyl-2-oxazoline (S-4MeOx) was polymerized via CROP using ethyl tosylate (EtOTf) as initiator.\textsuperscript{5} The polymerization took 50 h at 80 °C to obtain a white solid polymer in 91% yield with a melting point (T\textsubscript{m}) of ~160 °C after purification (Table 1.1). The optical rotation changed from [α]\textsubscript{D} = –148 to +130° upon polymerization (Table 1.2). 2-Unsubstituted-5-Me-2-OZO could also be polymerized using methyl tosylate (MeOTs), methyl iodide (MeI), and EtOTf as initiators, although the resulting molar mass was not high, i.e. less than 1,000 g/mol.\textsuperscript{6} Polymerization of 2-unsubstituted-4S-carbomethoxy-5R-methyl-2-oxazoline (2-unsubstituted-4S-CO\textsubscript{2}Me-5R-Me-2-OZO) with MeI or MeOTf in dimethyl formamide (DMF) at 100 °C for 120 h, resulted in a light-brown solid after precipitation with a yield of 60%.\textsuperscript{11} The polymer revealed a T\textsubscript{m} of 186 °C and a molar mass (M\textsubscript{n}) of 1,340 g/mol. The specific rotation changed from [α]\textsubscript{D} = +231 to –11° upon polymerization (Table 1.2), and the optical rotatory dispersion (ORD) spectrum exhibited a positive Cotton effect near 253 nm.
1. An introduction to the polymerization of cyclic imino ethers and chirality

Table 1.1 *Thermal properties of optically active P-2-OZO.*

<table>
<thead>
<tr>
<th>Schematic representation of the repeating unit</th>
<th>$M_n$ (g/mol)</th>
<th>PDI</th>
<th>$T_g$ ($^\circ$C)</th>
<th>$T_m$ ($^\circ$C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Schematic 1" /></td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>160</td>
<td>5</td>
</tr>
<tr>
<td><img src="image2.png" alt="Schematic 2" /></td>
<td>1,340</td>
<td>n.r.</td>
<td>n.r.</td>
<td>186</td>
<td>11</td>
</tr>
<tr>
<td><img src="image3.png" alt="Schematic 3" /></td>
<td>n.r.</td>
<td>n.r.</td>
<td>122-143$^2$</td>
<td>170$^2$</td>
<td>12</td>
</tr>
<tr>
<td><img src="image4.png" alt="Schematic 4" /></td>
<td>2,500$^1$</td>
<td>n.r.</td>
<td>43-63$^2$</td>
<td>190$^2$</td>
<td>12</td>
</tr>
<tr>
<td><img src="image5.png" alt="Schematic 5" /></td>
<td>1,600$^1$</td>
<td>n.r.</td>
<td>83-102$^2$</td>
<td>171$^2$</td>
<td>12</td>
</tr>
</tbody>
</table>

n.r. = not reported. $^1$Obtained from SEC. $^2$Determined from the first heating run in DSC.
1. An introduction to the polymerization of cyclic imino ethers and chirality

Table 1.2 Optical rotation of chiral P-2-OZO.

<table>
<thead>
<tr>
<th>Schematic representation of the repeating unit</th>
<th>$M_n$ (g/mol)</th>
<th>PDI</th>
<th>$[\alpha]_D$ ($^\circ$) monomer</th>
<th>$[\alpha]_D$ ($^\circ$) polymer</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Schematic" /></td>
<td>n.r.</td>
<td>n.r.</td>
<td>$-148$ (C$_2$H$_5$OH)</td>
<td>$+130$ (CH$_3$OH)</td>
<td>5</td>
</tr>
<tr>
<td><img src="image2" alt="Schematic" /></td>
<td>1,340$^1$</td>
<td>n.r.</td>
<td>$+231$ (THF)</td>
<td>$-11$ (CH$_3$OH)</td>
<td>11</td>
</tr>
<tr>
<td><img src="image3" alt="Schematic" /></td>
<td>n.r.</td>
<td>n.r.</td>
<td>$+68.5$ (CH$_3$CN)</td>
<td>$+30.0$ (CH$_3$CN)</td>
<td>12</td>
</tr>
<tr>
<td><img src="image4" alt="Schematic" /></td>
<td>2,500$^2$</td>
<td>n.r.</td>
<td>$+25.6$ (CH$_3$CN)</td>
<td>$-114.2$ (CHCl$_3$)</td>
<td>12</td>
</tr>
<tr>
<td><img src="image5" alt="Schematic" /></td>
<td>1,600$^2$</td>
<td>n.r.</td>
<td>$+95.37$ (CH$_3$CN)</td>
<td>$+180.6$ (CH$_3$CN)</td>
<td>12</td>
</tr>
<tr>
<td><img src="image6" alt="Schematic" /></td>
<td>n.r.</td>
<td>n.r.</td>
<td>$-51.75$ (CH$_3$CN)</td>
<td>n.r.</td>
<td>12</td>
</tr>
<tr>
<td><img src="image7" alt="Schematic" /></td>
<td>2,371$^3$</td>
<td>1.33$^3$</td>
<td>$+89$</td>
<td>$-131$</td>
<td>15</td>
</tr>
<tr>
<td><img src="image8" alt="Schematic" /></td>
<td>2,756$^3$</td>
<td>1.19$^3$</td>
<td>$-89$</td>
<td>$+131$</td>
<td>15</td>
</tr>
</tbody>
</table>
In addition, the chiral $\text{R-2-phenyl-4-ethyl-2-oxazoline (2-Ph-4R-Et-2-OZO)}$, $\text{R-2-phenyl-4-phenyl-2-oxazoline (2-Ph-4R-Ph-2-OZO)}$, $\text{R-2-methyl-4-phenyl-2-oxazoline (2-Me-4R-Ph-2-OZO)}$, and $\text{S-2-phenyl-4-isopropyl-2-oxazoline (2-Ph-4S-iProp-2-OZO)}$ monomers have been investigated as monomers for CROP. The first three monomers could be polymerized in bulk with methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{CH}_3$) as initiator at a temperature of 100 °C or higher resulting in yellowish solids. 2-Ph-4S-iProp-2-OZO could not be polymerized under these conditions. All monomers and polymers are optically active (Table 1.2). The molar masses determined by SEC were low but comparable to the other reported optically active P-2-OZO. The polymers are semi-crystalline with a melting peak between 170 and 190 °C (Table 1.1) in the differential scanning calorimetry (DSC) trace during the first heating run. However, in the second heating run no melting peak was observed anymore. Furthermore, 2-unsubstituted-4S-benzyl-2-oxazoline (2-unsubstituted-4S-Bn-2-OZO) was polymerized via CROP by Breslow et al. using MeOTs as initiator, as well as poly(2-ethyl-4-benzyl-2-oxazoline (P-2-Et-4-Bn-2-OZO)). In general, the CROP of chiral 2-OZO was reported to be very slow yielding polymers with low molar masses, which can be ascribed to steric hindrance caused by the 4- and 5-substituents that hinder attack of the next monomer on the 5-position.

Jordan reported the influence of chirality on the lower critical solution temperature (LCST) behavior of P-2-OZO. Poly-2-methyl-4R-methyl-2-oxazoline (P-2-Me-4R-
1. An introduction to the polymerization of cyclic imino ethers and chirality

Me-2-OZO), P-2-Me-4S-Me-2-OZO, poly-2-ethyl-4R-methyl-2-oxazoline (P-2-Et-4R-Me-2-OZO), P-2-Et-4S-Me-2-OZO and the racemic polymer P-2-Et-4RS-Me-2-OZO were synthesized with MeOTf as initiator and piperidine as terminating agent; their molar masses and optical rotations are summarized in Table 1.2. The polymerizations required 17 h under microwave-assisted conditions at 130 °C. 2-Isopropyl-4-methyl-2-oxazoline (2-iProp-4-Me-2-OZO) did not polymerize presumably due to steric hindrance. P-2-Me-4R-Me-2-OZO and P-2-Me-4S-Me-2-OZO were found to be soluble in water up to 100 °C, indicating that they do not reveal a LCST behavior. However, when the side-chain on the 2\textsuperscript{nd} position is elongated to an ethyl group, the polymer does reveal a cloud point temperature (T\textsubscript{CP}) in water at 47 °C for P-2-Et-4S-Me-2-OZO and 48 °C for P-2-Et-4R-Me-2-OZO and p-2-Et-4RS-Me-2-OZO, respectively. The addition of 5 wt% of D- or L-alanine to the aqueous polymer solution lowered the T\textsubscript{CP} by 3 to 5 °C, which can be explained by a salting out effect, i.e. alanine binds to the chiral polymer and, therefore, decreases the solubility resulting in a decrease in T\textsubscript{CP}. Since the addition of alanine only decreases the T\textsubscript{CP} of the nonchiral P-2-iProp-2-OZO with 1 °C, it is speculated that the chiral alanine forms stronger bonds with the chiral centers in the chiral P-2-OZO.

A possible application for chiral P-2-OZO is their use for the separation of enantiomeric mixtures. Schmidt and Bott\textsuperscript{16} described in a patent the synthesis of poly-2-phenyl-4S-ethyl-2-oxazoline (P-2-Ph-4S-Et-2-OZO) (α\textsubscript{D} = −20° (CHCl\textsubscript{3})) with the use of methyl orthotoluenesulfonic acid as initiator. The resulting polymer was applied as a chiral stationary phase to separate D,L-2-chloro-4-methyl-phenoxypropionic acid methylester. In addition, the polymerization of S-2-pentadecyl-4-ethyl-2-oxazoline (2-C\textsubscript{15}H\textsubscript{31}-4S-Et-2-OZO) is described in the patent.

1.2.1 Polymerization mechanism of 4- and 5-substituted 2-oxazolines

Compared to 2-methyl-2-oxazoline (2-Me-2-OZO), the polymerization of 2-unsubstituted-5-Me-2-OZO is about 12 times slower with MeOTs as initiator due to steric hindrance. The sterical hindrance for 4-methyl-2-oxazoline (2-unsubstituted-4-Me-2-OZO) is less than for 2-unsubstituted-5-Me-2-OZO, since for 2-unsubstituted-4-Me-2-OZO the methyl group is not located on the C-atom, which is attacked by the nucleophile, resulting in a faster polymerization compared to 2-unsubstituted-5-Me-2-OZO.\textsuperscript{6}
1. An introduction to the polymerization of cyclic imino ethers and chirality

The polymerization of 2-OZO takes place via a SN2 reaction between the propagating species and the monomer. Therefore, it is expected that the polymerization proceeds with inversion of the chiral configuration at carbon-5 of the monomer in case of a substituent on the 5th position. On the other hand, the stereochemistry of carbon-4 should remain intact when the monomer is substituted on the 4th position, since C-4 is not involved in the propagating step. Kinetic investigations on the CROP of 5-methyl-2-oxazoline (2-unsubstituted-5-Me-2-OZO) revealed that the polymerization initiated by MeOTs proceeds via cationic oxazolinium tosylate species (Scheme 1.2), while during the polymerization initiated with MeI both ionic and covalent species are present during polymerization. This equilibrium during the polymerization causes racemization of the chiral center.

\[
\text{Scheme 1.2 Schematic representation of the polymerization of 2-unsubstituted-5-Me-2-OZO initiated with MeOTs.}
\]

Racemic and enantiopure polymers were obtained by the CROP of 2-propyl-4S-methoxycarbonyl-2-oxazoline (2-Prop-4S-CO\textsubscript{2}Me-2-OZO) initiated with dimethyl sulfate under vacuum at 120 °C (Scheme 1.3). The specific rotation changed from \([\alpha]_D = +152^\circ\) for the monomer to negative or zero optical activity after polymerization, which indicates that racemization occurs before or during the CROP. When no initiator is used, a polymer with a different structure is formed, which is most likely poly(methyl-N-butanimidopropenoate) that can also be obtained by polymerizing methyl-N-butanimidopropenoate with AIBN (Scheme 1.3). It was suggested that the dehydroalanine monomer is generated in situ at 120 °C by abstracting the relatively acidic hydrogen at the chiral carbon group by the nitrogen atom of another monomer followed by ring opening and proton transfer. In a similar way, the reversible occurrence of deprotonation and reprotonation during the CROP can cause racemization. Alternatively, deprotonation of a growing chain end to produce a dehydroalanine end group can occur. If another monomer adds to the vinyl group through a Michael addition, subsequent protonation should regenerate the chiral carbon with loss of optical activity (Scheme 1.4). Due to all these possible side reactions, the polymerizations of 2-Prop-4S-CO\textsubscript{2}Me-2-OZO are not very reproducible.
1. An introduction to the polymerization of cyclic imino ethers and chirality

However, optically active material is obtainable containing the amide and carboxylic acid pendent groups, available for functionalization.

**Scheme 1.3** Schematic representation of the polymerization of 2-propyl-4S-MeCO₂-2-OZO by CROP (top) and formation of racemic poly(methyl-N-butanoamidopropenoate) in two different ways (bottom).
1. An introduction to the polymerization of cyclic imino ethers and chirality

**Scheme 1.4** Schematic representation of the racemization due to reprotonation (counterions are omitted for clarity).

### 1.2.2 Block copolymerizations

Several copolymers involving chiral 2-OZO have been reported as intermediates for the synthesis of polyamines. Examples are the block copolymerization of THF and 4-benzyl-2-oxazoline (2-unsubstituted-4-Bn-2-OZO) by first cationically polymerizing THF and endcapping it with 2-unsubstituted-4-Bn-2-OZO followed by CROP (Scheme 1.5), the statistical copolymerization of 2-unsubstituted-4-Bn-2-OZO and unsubstituted-2-OZO via CROP (Scheme 1.6), and the termination of cationically polymerized 2-unsubstituted-4-Bn-2-OZO with poly(ethylene glycol) (PEG) methyl ether, all using MeOTf as the initiator.
1. An introduction to the polymerization of cyclic imino ethers and chirality

Scheme 1.5 Schematic representation of the block copolymerization of THF with 2-unsubstituted-4-Bn-2-OZO.

Scheme 1.6 Schematic representation of the statistical copolymerization of 2-unsubstituted-4-Bn-2-OZO with 2-unsubstituted-2-OZO.

1.2.3 Secondary structure formation

Due to the presence of a chiral group, it can be expected that the main-chain chiral p-2-OZO forms a secondary structure like polypeptides. The structure formed by such peptide analogs has been investigated by $^{13}$C NMR spectroscopy, molecular mechanics calculations and circular dichroism (CD).

In the decoupled $^{13}$C NMR spectrum of p-2-unsubstituted-S-4-Me-2-OZO, each of the four carbon resonances exhibits fine structures. This can be explained by four possible dyad structures, in which each of the two formyl groups may take up either the syn or anti conformation, as is usual for compounds containing the peptide linkage. The most probable structure is given in Figure 1.1a in which both carbonyl groups are turned away from the more substituted side of the nitrogen atom. The other three expected structures are displayed in Figure 1.4b, c and d. It was speculated that the population of the four dyad structures are in the order $1.4a > 1.4b \sim 1.4c > 1.4d$ and roughly in the ratio 50:20:20:10, assuming a Bernouilli distribution. The fine-structure indicates restricted rotation about the N-CHO bond in a similar way as in polyproline (PP) where there is restricted rotation about the main-chain peptide link. However, unlike PP it appears that P-2-unsubstituted-4-Me-2-OZO cannot be brought into a single conformation with respect to the peptide linkage. The spectrum of the racemic polymer was too complicated for a detailed analysis.
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Figure 1.1 Schematic representation of the possible structures of P-2-unsubstituted-4-Me-2-OZO.

Figure 1.2 Preferred structure of P-2-unsubstituted-4-Me-2-OZO (n=20) established by conformational energy minimizations. The structure is defined by a 14/3 left-handed helix with the identity period of 17.8 Å. Reprinted from ref. 20.

Molecular mechanics calculations were performed for P-2-unsubstituted-4-Me-2-OZO to model the chain conformation. Six conformations were found with energy minima over a range of 10.5 kJ/mol above the global minimum. Five out of the six possible conformations were possible for the dimer and tetramer. For the polymer (n=20) two stable helical arrays were calculated. One being a right-handed helix containing 23 residues per four turns with an identity period of 25.2 Å, and the other being a left-handed helical structure of 14 residues per three turns with an identity period of 17.8 Å (Figure 1.2). These calculations were supported by CD measurements of the optically active P-2-Me-4-Me-2-OZO, P-2-unsubstituted-4-Me-2-OZO, P-2-Me-4-Bn-2-OZO and P-2-unsubstituted-4-Bn-2-OZO in hexafluoroisopropanol (HFIP), which gave the same shape and intensities as the corresponding
1. An introduction to the polymerization of cyclic imino ethers and chirality
tetrameric model compound. This observation supports the assumptions that
copolymers and tetrameric model compounds have the same conformations as
established from the molecular mechanics calculations.

1.3 Cationic ring opening polymerization of 2-oxazines
Poly(2-oxazoline)s (P-2-OZO) are an important class of polymers since well-defined
polymers can be obtained via a living cationic ring opening polymerization (CROP)
of the 2-oxazoline (2-OZO) monomers. In the mid 1960s the polymerization of 2-
OZO were described for the first time independently by four groups. The
properties of the polymer can be widely tuned by varying the substituent on the 2-
position of the 2-OZO monomer and, due to the living nature of the polymerization,
block copolymers can easily be obtained by sequential monomer addition procedures.
The polymerization mechanism and the properties of these P-2-OZO have been
extensively described in several recent reviews. However, the CROP is not
limited to 5-membered cyclic imino ethers, also 6-membered 2-oxazine (2-OZI) rings
can be polymerized in a similar manner. Due to the increased ring-size the
polymerization kinetics are different compared to 2-OZO. In addition, the increased
number of methylene units in the main-chain will change the physical properties of
such polymers compared to P-2-OZO while the 2-substituent can still be used to
further tune the polymer properties.
2-OZI can be polymerized via the CROP, like 2-OZO, using electrophilic initiators
such as methyl paratoluensulfonate (MeOTs), methyl trifluoromethanesulfonate
(MeOTf) and methyl iodide (MeI). The synthesis of a series of P-2-substituted-2-OZI
(Figure 1.3) was already reported in 1967 by Litt et al., shortly after the first reports
on poly(2-oxazoline)s. The glass transition temperature (T_g) (Table 1.3) of P-2-OZI
is about 30 to 50 °C lower than the T_g of the corresponding P-2-OZO due to the
increased chain flexibility resulting from the additional methylene unit in the main
chain. Saegusa and coworkers synthesized P-2-unsubstituted-2-OZI which is a semi-
crystalline white solid with a melting point of ~120 °C. This polymer is soluble in
water as well as organic solvents in contrast to P-2-unsubstituted-2-OZO which is
soluble in water and insoluble in most organic solvents.
1. An introduction to the polymerization of cyclic imino ethers and chirality

![Chemical structure of P-2-OZI](image)

**Figure 1.3** Schematic overview of the reported P-2-OZI.

**Table 1.3** Thermal properties of P-2-OZI

<table>
<thead>
<tr>
<th>Side-chain P-2-OZI</th>
<th>[M]/[I]</th>
<th>T_g (°C)</th>
<th>T_m (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>~67</td>
<td>n.r</td>
<td>~120³</td>
</tr>
<tr>
<td>CH₃</td>
<td>200</td>
<td>~16²</td>
<td>n.r</td>
</tr>
<tr>
<td>CH₃CH₂</td>
<td>200</td>
<td>8</td>
<td>n.r</td>
</tr>
<tr>
<td>(CH₃)₃C</td>
<td>200</td>
<td>n.r</td>
<td>177⁴</td>
</tr>
<tr>
<td>CH₃(CH₂)₄</td>
<td>200</td>
<td>−16</td>
<td>n.r</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>2,500</td>
<td>72</td>
<td>165⁴</td>
</tr>
<tr>
<td>CF₃(CF₂)₆</td>
<td>2,500</td>
<td>25</td>
<td>110⁴</td>
</tr>
</tbody>
</table>

n.r. = not reported. ¹ Measured by DTA or by disappearance of birefringence on the heating stage of a microscope. ² Samples prepared later under improved conditions show a T_g of 30 °C. ³ Measured in a sealed capillary tube. ⁴ Determined by measurement of torsional modulus on a molded bar.

The structural conformation of P-2-unsubstituted-2-OZI was determined by ¹³C NMR spectroscopy in dioxane-d₈. ³¹ When looking at one repeat unit of the polymer, four different conformations can be drawn (Figure 1.4a) whereby subscripts s and a can be used to indicate whether the α, β and γ carbons are syn (s) or anti (a) to the neighboring oxygen atom. At ambient temperature, the ratio of βₐβₐ : βₕβₕ = βₕβₕ : βₐβₐ is 1:2:1 as expected for freely rotating small molecules. However, upon decreasing the temperature the main-chain takes up a conformation which brings a third nitrogen close to the αₕ carbon as indicated by broadening of the signal (Figure 1.4b). The fine structure indicates a random orientation of the formyl groups. The behavior of P-2-Ph-2-OZI was found to be similar to P-2-unsubstituted-OZI, but with a much lower coalescence temperature.
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Figure 1.4 Schematic presentation of (a) the possible structures of P-unsubstituted-2-OZI and (b) structure of P-2-unsubstituted-2-OZI at low temperature.

Besides the conventional electrophilic initiators, also an N-methylated salt formed by reaction of 3-methyl-2-p-styryl-2-oxazoline and MeOTf was reported to initiate the polymerization of 2-Me-2-OZI (Scheme 1.7), resulting in a polymer with a styryl endgroup and a molar mass that is well controlled by the initial feed ratio and a narrow polydispersity index (PDI) (1.08 to 1.18). This example illustrates the potential of the living CROP for the introduction of functional end-groups during initiation and/or termination.

Scheme 1.7 Schematic representation of the polymerization of 2-Me-2-OZI initiated with an N-methylated salt from 2-p-styryl-2-oxazoline.

Saegusa et al. determined that the CROP of the 2-unsubstituted-2-OZI, 2-Ph-2-OZI and 2-Me-2-OZI takes place via a S_N2 mechanism similar to the CROP of 2-OZO. The rate of propagation depends on whether ionic and/or covalent propagating species
are formed since the polymerization is slower when less reactive covalent propagating species are present. When both types of propagating species are in equilibrium, the polymerization proceeds almost exclusively on the more reactive ionic species. The type of propagating species that are formed during the polymerization depends on the nucleophilicity of the monomer and the basicity of the initiator leaving group. Ionic propagating species are formed when the basicity of the counter ion is lower than the nucleophilicity of the monomer, and covalent propagating species are formed when the basicity of the counter ion is higher compared to the nucleophilicity of the monomer. The polarity of the polymerization solvent also strongly influences the equilibrium between covalent and ionic propagating species, i.e. more polar solvents stabilize the ionic species pushing the equilibrium toward the cationic propagation resulting in a faster polymerization. During the polymerization of 2-unsubstituted-2-OZI in deuterated acetonitrile or nitrobenzene only ionic propagating species were observed, independent of the employed initiator (MeOTs, MeI, methyl methanesulfonate, methyl or p-nitrobenzensulfonates, ethyl trifluoromethanesulfonate (EtOTf), or 2,4,6-trinitrophenetole) (Scheme 1.8, top).33 2-Me-2-OZI initiated with MeOTs or MeI in nitrobenzene also polymerizes via ionic propagating species35 while for 2-Ph-2-OZI the polymerization proceeds via ionic propagating species when MeOTs is used in nitrobenzene and both ionic as well as covalent propagating species (Scheme 1.8, bottom) were found in the case of MeI as initiator in nitrobenzene.34 As a consequence, the polymerization with MeOTs is faster. The rate of initiation (k_i) increases when going from 2-unsubstituted-2-OZI to 2-Me-2-OZI due to the higher nucleophilicity of 2-Me-2-OZI. In contrast, the rate of propagation (k_p) decreases for 2-Me-2-OZI compared to 2-unsubstituted-2-OZI due to the decreased ring-opening tendency of 2-Me-2-OZI.35 For 2-Ph-2-OZI initiated with MeOTs both k_i and k_p are lower compared to 2-unsubstituted-2-OZI, even though both polymerizations proceed via cationic oxazinium tosylate propagating species. The lower k_i and k_p of 2-Ph-2-OZI can be ascribed to the lower nucleophilicity resulting from conjugation of the phenyl ring with the imine. The k_p is lower in case of MeI as initiator since besides ionic propagating species also covalent propagating species are present.34
The polymerization of 2-unsubstituted-2-OZI initiated with MeOTs is much slower compared to 2-unsubstituted-2-OZO, due to the lower reactivity of the propagating oxazinium species. This can be explained by the lower ring-tension of 2-oxazine as well as the non-planar conformation of the propagating species of 2-oxazine. This non-planar conformation causes steric hindrance when the next nucleophilic 2-oxazine monomer attacks the C-6 carbon atom of the electrophilic oxazolinium species due to the staggered hydrogen attached to the C-5 carbon atom; in contrast, the propagating species of 2-oxazoline are planar resulting in less sterical hindrance (Figure 1.5). When MeI is used as initiator, 2-unsubstituted-2-OZI is more reactive than 2-unsubstituted-2-OZO since the propagating species for 2-unsubstituted-2-OZI are the ionic oxazinium species, while for 2-unsubstituted-2-OZO these are the covalent alkyl iodide species. Based on this result, it can be concluded that 2-OZI has a higher nucleophilicity than 2-OZO.

Ritter and coworkers studied the polymerization of 2-Ph-2-OZI initiated with MeOTs and butyl iodide (BuI) in butyronitrile under conventional heating and microwave-assisted heating. The polymerization initiated with MeOTs proceeds via an ionic propagating mechanism and with BuI via covalent propagating species. Therefore, the $k_p$ was lower when the polymerization was initiated with BuI, and additionally an initiation period was observed when BuI was utilized as the initiator. Independent of the initiator used, the polymerization was faster under microwave-assisted conditions compared to conventional heating at 140 °C (however, it is known that exact temperature measurements of the microwave-assisted reactions are very difficult).
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![Figure 1.5 Schematic representation on top and Newman projection at the bottom of the nonplanar conformation of 2-unsubstituted-2-OZI and the planar conformation of 2-unsubstituted-2-OZO. Reprinted from ref. 33.](image)

### 1.3.1 Block copolymers

Sequence controlled cyclic imino ether dimers and trimers were successfully synthesized by the one-pot multi-stage feeding method. A dimer of 2-Ph-2-OZO and 2-Me-2-OZI was obtained by reacting an equimolar amount of MeOTf initiator and 2-Ph-2-OZO, followed by the addition of 1 eq. 2-Me-2-OZI. The trimer was formed by the equimolar reaction between the initiator and 2-C_{2}F_{5}-2-OZO, followed by the addition of 1 eq. 2-Me-2-OZO and subsequently 1 eq. 2-Me-2-OZI. Homopropagation was not observed as a side reaction since $k_i$ is larger than $k_p$ and, therefore, sequence controlled oligomers were obtained.

By choosing the substituent on the second position of the 2-OZI, either hydrophilic or lipophilic polymers can be formed. By combining such polymers in a block copolymer, amphiphilic surfactants that exhibit excellent surface activities can be obtained. Various combinations of 2-Me-2-OZO, 2-unsubstituted-2-OZI or 2-Me-2-OZI as the hydrophilic chain and 2-Ph-2-OZO or 2-Ph-2-OZI as the lipophilic chain have been combined in amphiphilic block copolymers employing a one-pot two-stage copolymerization with MeOTs as the initiator. All block copolymers are soluble in water and show moderate surfactant properties with surface tensions varying between 46.5 and 52.5 dyn/cm (Table 1.4).
1. An introduction to the polymerization of cyclic imino ethers and chirality

Table 1.4 Surface tension of block copolymers containing at least one block of 2-OZI.

<table>
<thead>
<tr>
<th>Block A</th>
<th>Block B</th>
<th>Unit ratio A:B</th>
<th>(M_n) (g/mol)</th>
<th>PDI</th>
<th>(\gamma) (dyn/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me-2-OZO</td>
<td>2-Ph-2-OZO</td>
<td>11.5:7.3(^1)</td>
<td>2,310(^4)</td>
<td>n.r.</td>
<td>46.5(^6)</td>
</tr>
<tr>
<td>2-Unsubstituted-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>14.4:8.5(^1)</td>
<td>2,650(^4)</td>
<td>n.r.</td>
<td>52.0(^6)</td>
</tr>
<tr>
<td>2-Unsubstituted-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>13.4:6.1(^1)</td>
<td>2,310(^4)</td>
<td>n.r.</td>
<td>52.5(^6)</td>
</tr>
<tr>
<td>2-Me-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>10.5:5.6(^1)</td>
<td>2,060(^4)</td>
<td>n.r.</td>
<td>48.4(^6)</td>
</tr>
<tr>
<td>2-Me-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>10.5:9.9(^1)</td>
<td>2,680(^4)</td>
<td>n.r.</td>
<td>51.0(^6)</td>
</tr>
<tr>
<td>2-Me-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>10.5:4.4(^1)</td>
<td>1,940(^4)</td>
<td>n.r.</td>
<td>46.6(^6)</td>
</tr>
<tr>
<td>2-Me-2-OZI</td>
<td>2-Ph-2-OZO</td>
<td>10.5:8.8(^1)</td>
<td>2,640(^4)</td>
<td>n.r.</td>
<td>49.9(^6)</td>
</tr>
<tr>
<td>(n)-C(<em>8)H(</em>{17})OTf</td>
<td>2-Me-2-OZI</td>
<td>2.9:1(^2)</td>
<td>n.r.</td>
<td>1.33(^5)</td>
<td>32.9(^7)</td>
</tr>
<tr>
<td>(n)-C(<em>8)H(</em>{17})OTf</td>
<td>2-Me-2-OZI</td>
<td>5.2:1(^2)</td>
<td>n.r.</td>
<td>1.35(^5)</td>
<td>33.5(^7)</td>
</tr>
<tr>
<td>(n)-C(<em>8)H(</em>{17})OTf</td>
<td>2-Me-2-OZI</td>
<td>8.2:1(^2)</td>
<td>n.r.</td>
<td>1.32(^5)</td>
<td>34.2(^7)</td>
</tr>
<tr>
<td>C(_8)F(_3)CH(_2)CH(_2)OTf</td>
<td>2-Me-2-OZI</td>
<td>4.3:1(^2)</td>
<td>n.r.</td>
<td>1.26(^5)</td>
<td>29.4(^7)</td>
</tr>
<tr>
<td>C(_8)F(_3)CH(_2)CH(_2)OTf</td>
<td>2-Me-2-OZI</td>
<td>6.0:1(^2)</td>
<td>n.r.</td>
<td>1.26(^5)</td>
<td>29.6(^7)</td>
</tr>
<tr>
<td>(n)-C(<em>8)H(</em>{17})OTs</td>
<td>2-Me-2-OZI</td>
<td>1:5.1(^2)</td>
<td>n.r.</td>
<td>1.35(^5)</td>
<td>33.5(^7)</td>
</tr>
<tr>
<td>(i)-Octyl vinyl ether</td>
<td>2-Me-2-OZI</td>
<td>2.9:4.2(^3)</td>
<td>1,000(^4)</td>
<td>1.47(^5)</td>
<td>30.6(^8)</td>
</tr>
<tr>
<td>2-Me-2-OZI</td>
<td>THF</td>
<td>n.r.</td>
<td>778(^3)</td>
<td>1.10(^5)</td>
<td>40.8(^8)</td>
</tr>
</tbody>
</table>

n.r. = not reported. \(^1\)Determined by assuming that each polymer contains one molecule of initiator. \(^2\)Determined from \(^1\)H NMR analysis. \(^3\)Determined from VPO and \(^1\)H NMR analysis. \(^4\)Measured by VPO. \(^5\)Determined from SEC. \(^6\)Measured by Du Noüy tensiometer at a concentration of 1.0 wt% in water at 29 °C. \(^7\)As \(f\) except for measured at ambient temperature and recalculated for a value at 20 °C. \(^8\)As \(f\) except for measured at a concentration of 0.5 wt% at ambient temperature and recalculated for a value at 25 °C.

The synthesis of surfactants containing 2-OZI with other types of monomers is also possible. The block copolymerization of polyalkylene glycol terminated with a sulfonate ester initiator group with 2-unsubstituted-2-OZI for the preparation of surfactants has been patented.\(^38\) \(n\)-Octyl ethyl triflate, 2-(perfluoroctyl)ethyl triflate
1. An introduction to the polymerization of cyclic imino ethers and chirality

and n-octyl tosylate have been used as initiator for the CROP of 2-Me-2-OZI yielding surfactants in which the initiator provides the hydrophobic group and 2-Me-2-OZI the hydrophilic chain. The initiation of 2-Me-2-OZI via an onium salt was fast and the polymerization was slow resulting in a controlled degree of polymerization (DP) close to the initial monomer to initiator feed ratio. The surfactant behavior was good as evidenced by the low surface tension. With the 2-(perfluorooctyl)ethyl as the hydrophobic group the lowest surface tension of 29.4 dyn/cm was obtained.

2-Me-2-OZI was also copolymerized by cationic polymerization with i-octyl vinyl ether to form a block copolymer with good surface activities. First the vinyl ether was polymerized with hydrogen iodide (HI) as initiator to form poly(vinyl ether) followed by the addition of the cyclic imino ether to produce poly(vinyl ether) having oxazolinium groups at their termini and after polymerization, poly(vinyl ether)-block-poly(2-Me-2-OZI) was formed (Scheme 1.9). The polymer was obtained in high yield with a fairly narrow PDI value of 1.47 and a surface tension of 30.6 dyn/cm.

Scheme 1.9 Schematic representation of the copolymerization of i-octyl vinyl ether with 2-Me-2-OZI.

The CROP of 2-Me-2-OZI was also combined with the CROP of THF to obtain AB block copolymers and BAB triblock copolymers. THF was first polymerized using EtOTf as the initiator followed by the addition of the 2-Me-2-OZI to obtain an oxazolinium group at the polymer terminus. After polymerization of 2-Me-2-OZI the block copolymer was obtained (Scheme 1.10). The polymer showed good surfactant properties with a surface tension of 40.8 dyn/cm. The BAB-type triblock copolymer was synthesized starting with a bifunctional initiator, trifluoromethanesulfonic anhydride (Tf₂O) followed by propagation at both ends via a two-stage copolymerization in one pot. The initiation of THF was fast and the length of the polymer was very close to the initial monomer to initiator feed ratio with a molar mass of 1,280 g/mol and narrow PDI value of 1.21. The surface activity of the
1. An introduction to the polymerization of cyclic imino ethers and chirality

triblock, having a surface tension of 35.1 dyn/cm, was better compared to the diblock (40.8 dyn/cm).

Scheme 1.10 Schematic representation of the block copolymerization of THF with 2-Me-2-OZI terminated with water.

1.4 Aim of the thesis

The polymerization rate of the CROP is significantly decreased when introducing substituents in the 4th or 5th position. However, the polymerizations might be accelerated at high temperatures under pressurized microwave-assisted conditions. When polymerizing enantiomerically pure R- or S-substituted-2-OZO monomers, main-chain chiral polymers are obtained. Due to the chirality, such polymers have been speculated to form a defined secondary structure. According to a model and circular dichroism (CD) measurements the formation of a helical structure is possible, which might result in potential applications in the biological field like separating racemic mixtures into their enantiomers. Therefore the aim of the first chapters are to synthesize new chiral poly(2-oxazoline)s under microwave-assisted conditions and to evaluate whether they form a secondary structure in solution as well as in the solid state similar to polypeptides. Polymers with different side-chains were synthesized to investigate selected structure-property relationships and copolymers of the two enantiomers were synthesized to further elucidate the secondary structure formation.

Due to the living nature of the CROP, it is possible to synthesize block copolymers as well. Therefore the aim of the third chapter was to synthesize statistical copolymers and block copolymers containing a chiral hydrophobic part as well as a hydrophilic part and to study their self-assembly behavior in aqueous solution. Besides 2-oxazolines (2-OZO), which are 5-membered cyclic imino ethers, also 6-membered cyclic imino ethers, named 2-oxazines (2-OZI), can be polymerized via the cationic ring-opening polymerization (CROP) in a living manner. Like 2-OZO, 2-OZI can be hydrophilic or lipophilic depending on the side-chain, which makes it possible to form block copolymers that can act as a surfactant. The possibility to use 2-OZI in block
1. An introduction to the polymerization of cyclic imino ethers and chirality
copolymers for the use as surfactants is the only reported application of 2-OZI so far. It might be possible that poly(2-oxazine)s (P-2-OZI) with certain side-chains also have thermo-responsive properties like poly(2-oxazoline)s (P-2-OZO), further expanding the versatility of these synthetic polyamides. Therefore the aim of the last chapter was to synthesize p-2-OZI with LCST behavior. Additionally, the cloud point temperature of the thermo-responsive P-2-OZO was investigated in the presence of Hofmeister salts and the number of thermo-responsive P-2-OZO was expanded by the synthesis of a new polymer based on 2-cyclopropyl-2-oxazoline.
Overall the aim of this thesis was to explore the synthesis and properties of poly(cyclic imino ether)s beyond the well studied poly(2-oxazoline)s.

1.5 Outline of the thesis
The synthesis and controlled polymerization of chiral R-2-butyl-4-ethyl-2-oxazoline (R-BuEtOx) and S-BuEtOx as well as racemic RS-BuEtOx under microwave-assisted conditions are described in Chapter 2. Moreover, the difference in solution properties between the racemic and the enantiopure polymers is illustrated based on solubility tests, optical rotation, circular dichroism (CD) and small angle neutron scattering (SANS). The solid state properties studied by differential scanning calorimetry (DSC), x-ray diffraction (XRD) and CD of polymer films are also described in Chapter 2. The effect of varying the 2-substituent of the 2-alkyl-4-ethyl-2-oxazoline polymers on the secondary structure formation is discussed in Chapter 3. Whether the majority rule effect occurs was studied by copolymerizing the two enantiomers R-BuEtOx with S-BuEtOx in different ratios. Moreover, the polymer properties as function of the enantiomeric excess are described in Chapter 4. The formation of self-assembled nanostructures of amphiphilic chiral block and gradient copolymers and the influence of the hydrophilic to hydrophobic ratio on the type of nanostructure formed are discussed in Chapter 4. Besides chiral poly(2-oxazoline)s, also a new thermo-responsive poly(2-cyclopropyl-2-oxazoline) was synthesized and characterized, which is described in Chapter 5. Furthermore, the effect of Hofmeister salts on the cloud point temperature of various thermo-responsive poly(2-oxazoline)s is illustrated in this chapter as well. Finally, the influence of the ring-size on the aqueous thermal transition was investigated by synthesizing and polymerizing 2-
oxazines yielding thermo-responsive polymers, which is also described in the last chapter.

1.6 References and notes

1. An introduction to the polymerization of cyclic imino ethers and chirality

(38) T. Saegusa, K. Aoi, H. Yamanaka, European patent, 0 434 223 A1, **1990**.
Chapter 2

Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Abstract

In nature most polymers are chiral, like proteins and DNA, which form defined secondary structures like helices or β-sheets. In contrast to naturally occurring polymers, synthetic polymers with main-chain chirality forming a secondary structure are less common. Chiral poly(2-oxazoline)s could be regarded as polypeptide analogues and, because of that, it might be anticipated that they form secondary structures like helices, sheets or turns. Motivated on this assumption new 2,4-disubstituted-2-oxazoline monomers, namely R-2-butyl-4-ethyl-2-oxazoline, RS-2-butyl-4-ethyl-2-oxazoline and S-2-butyl-4-ethyl-2-oxazoline were synthesized and polymerized under microwave-assisted conditions. A kinetic investigation was performed revealing that the enantiopure and racemic monomers have comparable polymerization rates and the polymerizations take place in a controlled manner. The difference in solubility between the racemic and enantiopure polymers was the first indication that there must be a difference in the polymer structures. The formation of an ordered chiral structure was further investigated by measuring the short range structure with circular dichroism (CD) and the long-range structure by small angle neutron scattering (SANS). The combination of the CD and SANS results revealed that the enantiopure polymers form a flexible and dynamic structure in which only a certain fraction of the polymer adopts an ordered secondary structure. In contrast, the racemic polymer forms a random coil. The influence of the type of solvent, temperature, concentration and molar mass of the polymer on the secondary structure was studied with CD as well. Furthermore, differential scanning calorimetry (DSC) measurements revealed that the enantiopure polymers are semi-crystalline revealing cold crystallization and a double melting peak due to a melt-recrystallization process during heating, while the racemic polymer is completely amorphous. The crystallinity was confirmed by X-ray diffraction (XRD) measurements and CD of a spin coated film of the enantiopure polymer revealed that the formed crystals are chirally ordered.

2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

2.1 Introduction

The most frequently investigated natural polymer class containing main-chain chirality are poly(amino-acids), also called poly(peptides).\(^1,^2\) Even though stable secondary, tertiary and even quaternary structures are formed, proteins exhibit chain flexibility resulting in conformational dynamics in solution. In contrast to naturally occurring polymers, synthetic polymers with main-chain chirality forming a secondary helical structure are less common. Main-chain chiral polymers can be synthesized via the so called ‘helix-sense-selective’ polymerization from achiral monomers using either a chiral initiator or catalyst.\(^3\) Even though such methods can control the main-chain chirality to a large extent, the formation of some defect structures is unavoidable. Nonetheless, the chain conformation and the properties of polymers, such as poly(propylene)\(^4,^5\) and poly-(methacrylate),\(^6\) depend on the stereoregularity. The chains of a stereoregular polymer can adopt a stable, specific overall conformation, which can be a helical structure for isotactic or syndiotactic polymers. In contrast, fully atactic poly(propylene) forms a random coil. Alternatively, optically active monomers can be polymerized resulting in enantiopure polymers with main-chain chirality. Poly(lactide) is the most common example of a synthetic chiral polymer with main-chain chirality. This polymer can be synthesized in a controlled manner by the ring-opening polymerization of lactide.\(^7,^8\) The macroscopic properties of poly(lactide) are strongly influenced by the chirality.\(^9,^{10}\) Recently, polyurethanes and polythiourethanes with main-chain chirality were synthesized by self-polyaddition followed by ring-opening polymerization.\(^11\) The enantiopure polymers formed higher ordered structures, which were stabilized by stronger internal hydrogen bonds, compared to the internal hydrogen bonds formed in an unordered racemic polymer.

The cationic ring opening polymerization (CROP) of 2-oxazolines with substituents on the 4- and/or 5-position can also result in chiral polymers with main-chain chirality (Scheme 2.1). Although the living CROP of 2-substituted-2-oxazolines is well-known since 1966,\(^12-16\) only a few examples of main-chain chiral poly(2-oxazolines), which might be regarded as pseudo-peptides,\(^17,^{18}\) were reported.\(^19-23\) In fact, chiral poly(2-oxazoline)s can be considered as poly(proline) isomers and, thus, it might be anticipated that they could form poly(proline) type helices\(^24\) or other types of secondary structures like sheets or turns, also found for non-hydrogen bonded β-
peptide oligomers. So far only a few publications have addressed the potential secondary structure formation of chiral poly(2-oxazoline)s. Oh et al. modeled the structure of poly(N-acetyl-1-methylethlenimine) with 20 repeating units as well as the corresponding tetramer indicating the formation of left-handed helices containing 14 residues per 3 turns with an identity period of 17.8 Å. Even though the tetramer and the polymer did indeed show similar Cotton effects with circular dichroism (CD), the formation of a helical structure was not unambiguously proven. In addition, Fischer et al. proposed a helical structure for both chiral and achiral N-acetylated-poly(ethylenimine) in bulk, based on the characteristic X-ray diffraction (XRD) pattern for a hexagonal columnar arrangement. Up to this moment, these CD spectra and XRD patterns are the only preliminary reports that suggest helical structure formation of main-chain chiral poly(2-oxazoline)s.

Scheme 2.1 Schematic representation of the cationic ring-opening polymerization of BuEtOx.

Furthermore, optically active poly(2-oxazoline)s were found to be semi-crystalline according to differential scanning calorimetry (DSC) measurements, since they reveal a melting peak in the first heating scan while the second heating scan only showed a glass transition temperature (T_g). The crystallization of chiral polymers is somewhat more complex since the crystals can contain a secondary structure like helices, which are for example found in isotactic and syndiotactic polypropylene (PP). Atactic PP, on the other hand, is amorphous. The exact conformation that is formed in the crystal depends on the degree of stereoregularity and the mechanical and thermal histories of the samples as well as the molar mass and polydispersity index. This chapter describes the synthesis and the microwave-assisted polymerization of new 2,4-disubstituted oxazoline monomers, namely R-2-butyl-4-ethyl-2-oxazoline (R-BuEtOx), RS-BuEtOx and S-BuEtOx (Scheme 2.2; section 2.2). The influence of the
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Chirality on the properties in solution were investigated (section 2.3) based on the solubility, optical activity and the formation of an ordered structure with combined CD and small angle neutron scattering (SANS) experiments. In addition, the properties of the polymers were investigated in the solid state by determining the presence of chiral crystals with DSC, powder XRD and CD of a polymer film, which is described in section 2.4.

![Scheme 2.2 Schematic representation of the chemical structures of the investigated poly(2-oxazoline)s.](image)

### 2.2 Polymerization of chiral 2-butyl-4-ethyl-2-oxazoline

The 2,4-disubstituted-2-oxazoline monomers, \( R\)-BuEtOx, \( RS\)-BuEtOx and \( S\)-BuEtOx, were synthesized through the reaction of valeronitrile with the corresponding amino alcohol using zinc acetate as catalyst.\(^{35}\) The polymerization of these monomers was performed under microwave-assisted conditions to investigate the possibility of increasing the polymerization rate for these rather low reactive monomers; the sterical hindrance caused by the 4-substituent lowers the polymerization rates. The polymerization kinetics were determined at 140 and 180 °C, using an initial monomer concentration of 4 M and a monomer to initiator ratio of 60, with methyl tosylate (MeOTs)\(^{36}\) as initiator (see ref. 37-39 for the optimization of the polymerization conditions). The resulting kinetic plots are depicted in Figure 2.1. At polymerization temperatures of 140 and 180 °C both the racemic monomer and the enantiopure monomer revealed linear first-order kinetics up to ~80% conversion (\( \ln([M]_0/[M]) \approx 2 \)) as well as a linear increase of the molar mass (\( M_n \)) with conversion, demonstrating that the polymerizations proceeded in a living manner. It is evident that there are no differences in the polymerization rate between the enantiopure monomer and the racemic monomer up to ~80% conversion. However, the polymerization rates
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

decreased after ~80% conversion at a reaction temperature of 180 °C, which is probably due to a limited diffusion of the monomer to the living polymer chains due to the increase in viscosity. This effect seems to be stronger for RS-BuEtOx.

Figure 2.1 (a) Kinetic plots for 4-butyl-2-ethyl-2-oxazoline polymerizations initiated with methyl tosylate ([M]/[I] = 60) in acetonitrile ([M] = 4 M) at 140 (closed symbols) and 180 °C (open symbols). (b) Corresponding molar mass (M_n) against conversion plot, including polydispersity indices; the dotted line represents the theoretical molar mass.

In addition, size exclusion chromatography (SEC) revealed monomodal molar mass distributions for the polymers with polydispersity index (PDI) values below 1.3 demonstrating that the polymers were prepared in a living manner. The observed difference between the theoretical molar mass and the measured molar mass is most likely due to the determination of the molar masses from SEC using a polystyrene calibration; although the occurrence of some chain transfer reactions cannot be excluded.

Based on the kinetic investigations, larger amounts of S-BuEtOx, RS-BuEtOx and R-BuEtOx were polymerized under microwave-assisted conditions with an initial monomer concentration of 4.5 M in acetonitrile and a [M]/[I] of 50, using methyl tosylate as initiator at a reaction temperature of 180 °C for 60 min. Based on the similar polymerization rates of R-BuEtOx and RS-BuEtOx, it was assumed that S-BuEtOx also has a similar polymerization rate. The resulting polymers were purified by precipitation in water resulting in white solid powders. All polymers displayed monomodal SEC traces (Figure 2.2). The molar masses and PDI values determined by SEC (PS calibration) are M_n = 4,950 g/mol, PDI = 1.27 for p-S-BuEtOx,
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

\[ M_n = 5,100 \text{ g/mol, PDI} = 1.25 \] for \( p\text{-RS-BuEtOx} \) and \( M_n = 4,100 \text{ g/mol, PDI} = 1.24 \) for \( p\text{-R-BuEtOx} \), respectively. The observed differences in the molar masses between the three polymers can be the result of small differences in the actual \([M]/[I]\) values, a different level of impurities and/or slight variations in the precipitation procedure.

![Graph of SEC traces](image)

**Figure 2.2** SEC traces of \( p\text{-S-BuEtOx} \), \( p\text{-RS-BuEtOx} \) and \( p\text{-R-BuEtOx} \) dissolved in dimethylacetamide.

To investigate the influence of the molar mass on the polymer properties, \( p\text{-R-BuEtOx} \) with various \([M]/[I]\) ratio’s were also synthesized. Even though the molar mass increases with increasing \([M]/[I]\), the increase in molar mass becomes less steep when the \([M]/[I]\) increases (Figure 2.3a), indicative of chain transfer reactions. The observed fronting in the SEC traces led to an increase in the PDI values with increasing \([M]/[I]\) (Figure 2.3b) when the molar mass reaches 10,000 g/mol, indicating that the polymerization becomes less controlled with increasing \([M]/[I]\).

The fronting in the SEC traces of the polymers with the highest molar masses is probably the result of chain transfer reactions causing chain-chain coupling.\(^{40}\)
2. Properties in solution

To investigate whether the enantiopure polymers have a different chain conformation in solution and have different solubility properties compared to the racemic polymer, solubility tests were performed in different solvents with a sample concentration of 5 mg/mL. The transmittance of light through the different solutions, i.e. turbidimetry, was measured at different temperatures. The results in Table 2.1 demonstrate that the enantiopure polymers do not dissolve in most of the investigated solvents at 5 mg/mL, except for n-butanol and tetrahydrofuran (THF) in which the polymers dissolve upon heating and remain in solution upon cooling. There seems to be a relatively small range of solvents in which the enantiopure polymers dissolve having an intermediate dipole moment around 1.6 and an intermediate dielectric constant (2.0 < $\varepsilon$ < 25.3). In contrast, the racemic polymer readily dissolved in all investigated solvents except water. These results clearly demonstrate that the enantiopure polymers behave different in solution compared to the racemic polymer. In fact, this difference in solubility provides an indirect proof that the racemic monomer mixture indeed results in the formation of a racemic polymer, rather than a mixture of two enantiopure polymers. Furthermore, the observed differences in solubility represent a first indication that the enantiopure polymers might form ordered secondary structures, which are more difficult to dissolve compared to the unordered structure of the racemic polymer.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Table 2.1 Solubility of the chiral and racemic polymers measured at 5 mg/mL and the dielectric constants and dipole moments of the solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>p-R-BuEtOx</th>
<th>p-RS-BuEtOx</th>
<th>p-S-BuEtOx</th>
<th>(\varepsilon^1)</th>
<th>(\mu^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)-Heptane</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>1.92</td>
<td>~0</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>2.02</td>
<td>~0</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>7.52</td>
<td>1.75</td>
</tr>
<tr>
<td>(n)-Butanol</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>17.8</td>
<td>1.66</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>25.3</td>
<td>1.69</td>
</tr>
<tr>
<td>Methanol</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>33.0</td>
<td>1.70</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>36.6</td>
<td>3.92</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Insoluble</td>
<td>38.3</td>
<td>3.82</td>
</tr>
<tr>
<td>Water</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>80.4</td>
<td>1.85</td>
</tr>
</tbody>
</table>

\(^1\) Dielectric constant \((\varepsilon)\) and dipole moment \((\mu)\) taken from the CRC handbook of chemistry and physics 86th edition.

The chain length of the polymer also influences the solubility. A shorter polymer chain usually becomes better soluble and this was also observed for p-R-BuEtOx. P-R-BuEtOx with a molar mass \((M_n)\) of 3,160 g/mol \((\text{[M]/[I]} = 17)\) is also soluble in the protic polar solvents ethanol as well as methanol and when the \(M_n\) decreases to 1,960 g/mol \((\text{[M]/[I]} = 9)\), p-R-BuEtOx also dissolves in the aprotic polar solvents acetonitrile and N,N-dimethylformamide as well as the apolar solvent cyclohexane, while p-R-BuEtOx with a higher \(M_n\) of 7,450 g/mol \((\text{[M]/[I]} = 75)\) is insoluble in all investigated solvents.

2.3.1 Optical properties

To further investigate the proposed formation of a secondary structure, the optical rotation and circular dichroism of the polymers were studied. The optical rotation of the monomers S-BuEtOx and R-BuEtOx are approximately the same although opposite in sign. As expected, RS-BuEtOx is optically inactive. Upon polymerization a remarkable change in optical activity was observed for the enantiopure polymers as
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

can be seen from Table 2.2. The inversion in sign upon polymerization is commonly observed for polymers that form a higher structure, most likely a secondary helical structure.41-44

Table 2.2 Optical rotation

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_D$ ($^\circ$) monomer</th>
<th>$\alpha_D$ ($^\circ$) polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$-BuEtOx</td>
<td>+68.2</td>
<td>−26.1</td>
</tr>
<tr>
<td>$R$-$S$-BuEtOx</td>
<td>−0.1</td>
<td>−0.2</td>
</tr>
<tr>
<td>$R$-BuEtOx</td>
<td>−68.9</td>
<td>+25.8</td>
</tr>
</tbody>
</table>

$^1$Measured by polarimetry using a concentration of 30 mg/mL in CHCl$_3$ at room temperature.

Figure 2.4 (a) UV and (b) CD data of R-BuEtOx dissolved in TFE at 20 °C and in HFIP at −10 °C, 20 °C and 50 °C, respectively.

Since the monomer $R$-BuEtOx is optically active, a single Cotton effect is observed when the monomer is dissolved in trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) (Figure 2.4). The monomer absorbs the UV light at 194 nm when dissolved in TFE and reveals a Cotton effect around the same wavelength. In case the monomer is dissolved in HFIP, the UV absorption and the CD maximum shifts to a higher wavelength with a decrease in temperature. Most likely the interaction between the solvent and the monomer is responsible for this shift.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

The possible formation of an ordered structure is further investigated with CD, whereby strong Cotton effects are expected when the polymer forms a secondary structure. Figure 2.5 shows that p-R-BuEtOx possesses a dichroic Cotton effect with strong negative and positive CD signals at 194 and 213 nm with a crossover point close to the position of the maximum UV absorption at 203 nm, caused by the amide chromophore, when dissolved in trifluoroethanol (TFE). The Cotton effect at 213 nm can be assigned to the n-π* transition and the Cotton effect at 194 nm can be assigned to π-π* transition of the amide chromophore. The CD spectra of p-R-BuEtOx and p-S-BuEtOx are mirror images of each other when dissolved in TFE or hexafluoroisopropanol (HFIP), indicating that both polymers have the same conformation, which is most likely helical with opposite handedness, as proposed by Oh et al.26 As expected, the racemic p-RS-BuEtOx does not show a Cotton effect. The different CD spectra obtained in HFIP at 20 ºC compared to TFE will be addressed in further detail in the following.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Figure 2.5 (a) UV and (b) CD data of p-S-BuEtOx, p-R-BuEtOx and p-RS-BuEtOx dissolved in TFE at 20 °C. (c) UV and (d) CD data of p-S-BuEtOx, p-R-BuEtOx and p-RS-BuEtOx dissolved in HFIP at 20 °C.

The effect of temperature on the secondary structure has also been investigated by CD. Figures 2.6a and 2.6b depict the temperature dependence of the UV and CD spectra of p-R-BuEtOx dissolved in TFE. The intensities of the Cotton effect and UV absorption slightly decreased in a linear manner with the increase of temperature from −10 to 70 °C and the shape of the CD spectra did not change (Figures 2.6c and 2.6d). This small decrease in Cotton effect with the increase in temperature is most likely caused by a small decrease in persistence length of the ordered domains due to increased chain dynamics. The presence of an isodichroic point at the cross-over point around the wavelength of 203 nm is an indication of a two-state transition between a folded state and an unfolded random coil state, like in polypeptides. Therefore, it might be speculated that the enantiopure polymers do not form rigid
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

secondary structures, but that the chain conformation consists partly of ordered coils and partly of random coils.

**Figure 2.6** (a) Temperature dependence of the UV absorption and (b) the Cotton effects of p-R-BuEtOx dissolved in TFE. (c) Linear decrease of the UV-maximum with increasing temperature. (d) Linear decrease of the Cotton effects with increasing temperature.

When p-S-BuEtOx is dissolved in acetonitrile, a similar temperature effect is observed as for p-R-BuEtOx dissolved in TFE (Figure 2.7). However, in acetonitrile the negative and positive Cotton effects are similar in amplitude, while in TFE the Cotton effect caused by the n-π* transition is stronger compared to the Cotton effect caused by the π-π* transition. This indicates that the structure formed in acetonitrile is different compared to the structure formed in the fluorinated ethanol and that the solvents influences the type or the amount of secondary structure formed.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Figure 2.7 Temperature dependence of (a) the UV absorption and (b) the Cotton effects of p-S-BuEtOx dissolved in acetonitrile. (c) Linear decrease of UV-maximum with decreasing temperature. (d) Linear decrease of the Cotton effects with decreasing temperature.

Figures 2.8a and 2.8b depict the temperature dependence of the UV and CD spectra of p-R-BuEtOx measured in HFIP. Like in TFE, the intensity of the UV absorbance decreases linearly with the increase in temperature from –10 to 50 ºC (Figures 2.7c and 2.7d). At 50 ºC the CD spectrum is comparable with the CD spectra obtained when the polymer is dissolved in TFE. However, with a decrease in temperature to 20 ºC, the Cotton effect at 211 nm decreased in intensity and blue shifted to 207 nm while the Cotton effect at 194 nm loses its intensity. At 20 ºC the maximum Cotton effect is located approximately at the isodichroic point at 207 nm. Further decreasing the temperature to –10 ºC results in the reappearance of a positive Cotton effect. This Cotton effect increases in intensity and blue shifts from 232 nm at 20 ºC to 224 nm at
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline) –10 °C. The negative Cotton effect also increases in intensity and blue shifts from 207 to 204 nm. Similar observations were made for p-S-BuEtOx with opposite CD signs.

Figure 2.8 Temperature dependence of (a) the UV absorption and (b) the Cotton effects of p-R-BuEtOx dissolved in HFIP. (c) Linear decrease of UV-maximum with decreasing temperature. (d) Linear decrease and increase of the Cotton effects with decreasing temperature.

This unique thermo-responsive behavior indicative of a change in secondary structure is most likely due to a solvent effect. From literature it is known that HFIP can exist in different conformations and that it can form aggregates. At high temperatures, HFIP is in such a conformation that the hydrogen bond donor ability is low, resulting in a similar CD spectrum for p-R-BuEtOx in HFIP at 50 °C as in TFE. With the decrease in temperature the hydrogen bond donor ability of HFIP increases resulting in HFIP hydrogen bonding to the polymer amide groups. With the decrease in temperature, the strength of the hydrogen bonds increases, resulting in a blue shift of
the Cotton effect and, eventually, in an inversion of the Cotton effects indicating that the chain conformation of the p-R-BuEtOx has changed due to HFIP hydrogen bonding. The same is observed for p-S-BuEtOx while no Cotton effect for p-RS-BuEtOx is observed at any given temperature.

![Graphs showing concentration dependence on UV absorption and Cotton effects](image)

**Figure 2.9** Concentration dependence on the (a) UV absorption and (b) the Cotton effects of p-S-BuEtOx dissolved in TFE at 20 °C. Concentration dependence on (c) the UV absorption and (d) the Cotton effects of p-S-BuEtOx dissolved in HFIP at 20 °C.

Bisignate Cotton effects as well as the inversion in sign of the Cotton effect like observed when the polymer is dissolved in HFIP, can also occur due to the aggregation of a single polymer chain.⁵² To rule out this possibility, a concentration range of 0.1 to 0.5 mg/mL of p-S-BuEtOx in TFE and HFIP were measured. It turned out that the maximum UV absorption and maximum CD signals were linearly dependent on the polymer concentration (Figure 2.9) demonstrating that no aggregation occurs in this concentration range. As a result, it can be concluded that
the observed change in Cotton effect with temperature is due to HFIP hydrogen bonding inducing a change in the secondary structure of the polymer.

![Figure 2.10](image)

**Figure 2.10** (a) UV absorption and (b) Cotton effects of p-S-BuEtOx dissolved in polar and apolar solvents at 20 °C.

The influence of the solvent on the structure formation has been further studied by measuring CD of p-S-BuEtOx dissolved in different solvents (Figure 2.10). Since a low concentration of 0.25 mg/mL is sufficient to measure CD, the polymers could also be measured in bad solvents. In the polar solvents methanol, ethanol and n-butanol the Cotton effects are similar, indicating that in all these polar solvents the same type of secondary structure is formed with the same persistence length. The type of secondary structure slightly changes when the polar solvent is fluorinated since the Cotton effect caused by the π-π* transition is stronger in the polar solvents while the Cotton effect caused by the n-π* transition is similar in strength. In the aprotic polar solvent acetonitrile the Cotton effects slightly decreases compared to the protic polar solvents. However, when the solvent is changed to an apolar solvent, the decrease of the Cotton effects becomes stronger, indicating that the persistence length decreases when the polymer is dissolved in apolar solvents. Furthermore, the type of secondary structure is also different in apolar solvents since the Cotton effect caused by the n-π* transition is weaker compared to the Cotton effect of the π-π* transition, while in the polar solvents this is the other way around. In cyclohexane this effect is even stronger compared to n-heptane. This can be understood by the fact that the polar N-C=O group of the chiral polymer prefers to be dissolved in polar solvents, while the butyl side-chains of the chiral polymer is soluble in apolar solvents. The presence of both
polar and apolar groups in the polymer chain makes the polymer fold in different ways depending on the type of solvent.

Figure 2.11 (a) UV absorption (b) and CD spectra of p-R-BuEtOx with different molar masses dissolved in TFE at 20 ºC and (c) UV absorption and (d) CD spectra of p-R-BuEtOx with different molar masses dissolved in HFIP at 20 ºC.

The molar mass of the polymer might influence the secondary structure formation as well. For example polyisocyanides only forms a predominantly one-handed helical structure when the DP is at least 30.\textsuperscript{53} The polyamide poly(p-benzamide) is known to show dynamic helical properties, whereby the Cotton effects depend both on temperature and molar mass.\textsuperscript{54} However, the molar mass of p-S-BuEtOx was found to hardly influence the secondary structure formation, whether it is dissolved in TFE or in HFIP (Figure 2.11). Only the Cotton effect due to the n-\pi* transition in TFE becomes somewhat stronger when the molar mass is increased. This means that the
type of secondary structure hardly depends on the $M_n$ in the range of 2,000 to 11,000 g/mol, like it was modeled by Oh et al.\textsuperscript{26}

### 2.3.2 Structure formation in solution measured by SANS

The CD results revealed that the enantiopure polymers form a secondary structure which is most likely helical. Nonetheless, CD only provides information about the short-range structure and, therefore, SANS measurements were performed in collaboration with Sarah Rogers at the ISIS facility to investigate the long-range structure of the polymers. Information on both the radius of gyration ($R_g$) and the conformation of the polymer structures can be determined from the SANS data by using the Guinier approximation\textsuperscript{55} and Kratky plots,\textsuperscript{56} respectively. Mathematical modeling can also be employed to provide further structural information on the polymer conformations.

It is expected that if the enantiopure polymers form a rigid ordered structure then the data would be best presented by a rigid rod or an ellipsoid model and that the racemic mixture would be best described as a random coil. This hypothesis was tested by fitting each data set obtained to both the ellipsoid and coil model and then comparing the values obtained from FISH modeling for the ellipsoid scale factor and Gaussian coil absolute scattering intensity with those calculated from known parameters.

Figure 2.12a represents the SANS data, plotted on a double logarithmic scale, of all three polymers dissolved in TFE-$d_3$ at a concentration of 5 mg/mL. By comparison of the scale factors and absolute intensities it was found that all three polymers were best described by the random coil model (the fit lines are also shown on Figure 2.12a), which is not in agreement with the CD data that indicated the formation of a secondary structure. $R_g$ values obtained from modeling compared well to those found from Guinier analyses (Table 3 and Figure 2.12b). The differences between the $R_g$ of the three polymers can be explained solely by their differences in molar mass rather than a difference in shape; p-$R$-BuEtOx has the smallest $M_n$ and therefore the smallest $R_g$ whereas p-$S$-BuEtOx and p-$RS$-BuEtOx have a comparable $M_n$ and also a comparable $R_g$. The random coil chain conformation of all three polymers is further confirmed from the Kratky plots (Figure 2.12c). All plots are typical for a random chain in a good solvent as the lack of a distinct peak in all plots is representative of an unordered and random coil structure.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Similar contradictory results, whereby CD reveals an ordered helical structure and SANS reveals a random coil, have also been observed for polyproline II (PPII) type polypeptides. These results have been explained in the literature by the theory that the PPII type polymer forms a very flexible, fluctuating structure which possesses a helical structure along a certain amount of repeating units but is never, or only rarely in the ideal helical conformation. As such, it is proposed that the here investigated main-chain chiral poly(2-oxazoline)s form similar dynamic flexible structures as some PPII-type peptides indicating that poly(2-oxazoline)s might indeed be regarded as pseudo-polypeptides. It is evident that no difference in structure is observed between the racemic polymer and the enantiopure polymers when the polymers are dissolved in a good solvent like TFE-d₃.

Table 2.3 Comparison of best fit parameters for the SANS data obtained in TFE-d₃ and methanol-d₄ determined by Guinier analyses and mathematical modeling.

<table>
<thead>
<tr>
<th>Dissolved in TFE-d₃</th>
<th>System</th>
<th>Concentration (mg/mL)</th>
<th>Molar mass (g/mol)</th>
<th>Rₖ (Å)¹</th>
<th>Guinier</th>
<th>FISH model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-S-BuEtOx</td>
<td>5</td>
<td>4,950</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-RS-BuEtOx</td>
<td>5</td>
<td>5,100</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-R-BuEtOx</td>
<td>5</td>
<td>4,100</td>
<td>16</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolved in Methanol-d₄</th>
<th>System</th>
<th>Concentration (mg/mL)</th>
<th>Molar mass (g/mol)</th>
<th>Rₖ (Å)¹</th>
<th>Guinier</th>
<th>FISH model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-R-BuEtOx</td>
<td>2</td>
<td>4,480</td>
<td>14</td>
<td>3</td>
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</tr>
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<td></td>
<td>p-R-BuEtOx</td>
<td>5</td>
<td>4,480</td>
<td>18</td>
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<tr>
<td></td>
<td>p-RS-BuEtOx</td>
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<td>5,100</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

¹ Uncertainties in absolute intensity is ± 5% and in Rₖ is ± 2 Å.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Figure 2.12 SANS analysis of p-S-BuEtOx, p-RS-BuEtOx and p-R-BuEtOx dissolved in TFE-d\textsubscript{3} at a concentration of 5 mg/mL. (a) SANS profiles that fit to a model of a random coil (solid lines). (b) Guinier analysis and fits (solid lines) of the R\textsubscript{g}. (c) Kratky plots.

In light of this result, further SANS measurements were performed employing methanol-d\textsubscript{4} as solvent rather than TFE-d\textsubscript{3}. Methanol was chosen since it is a bad solvent for the enantiopure polymer and a good solvent for the racemic polymer. It is anticipated that the difference in solubility of the polymers would result in a difference in chain conformation. Figure 2.13a represents the SANS profiles, plotted on a double logarithmic scale, of p-R-BuEtOx (at concentrations of both 5 and 2 mg/mL) and p-RS-BuEtOx (5 mg/mL only) dissolved in methanol-d\textsubscript{4}. All three data sets were modeled using both ellipse and random coil form factors. By comparison of absolute intensities and scale factors a difference in conformation between the enantiopure and racemic systems was found; the enantiopure polymer was best...
described as an ellipse and the racemic polymer as a coil. Using the parameters of primary radius, $R$, and aspect ratio, $X$, which are obtained from fitting when using the ellipse model, the $R_g$ of an ellipse structure is calculated using the following equation:\textsuperscript{49}

$$R_g = \frac{\sqrt{2R^2 + (XR)^2}}{5}$$

Again, $R_g$ values found from mathematical modeling compared well to those obtained from Guinier analyses (Figure 2.13b and Table 2.3) and it can be concluded that even though the enantiopure polymer has a lower molar mass it has a larger $R_g$ when compared to that of the racemic polymer. This implies that there must be a difference in chain conformation between the two systems. Furthermore, from the Guinier plot (Figure 2.13b) it can be seen that there is no significant interparticle interaction present when the polymer is dissolved in methanol-$d_4$ as no difference in the $R_g$ of p-R-BuEtOx was observed between the two concentrations. The Kratky plots (Figure 2.13c) also reveal a difference in conformation between the enantiopure and racemic polymer. The lack of a peak in the plot for the racemic polymer is again indicative of a random coil structure, as found for all systems in TFE, whereas the peak present at $Q \sim 0.11 \text{ Å}^{-1}$ in both the enantiopure polymer measurements is representative of a more compact structure even though the curvature is not as strong as expected for a rod-like structure. Nonetheless, these results demonstrate that the enantiopure polymer partially forms a secondary structure in methanol-$d_4$.

The ellipsoidal chain conformation obtained by SANS for the chiral polymer indicates an increased persistence length of the ordered segments, causing an anisotropic chain conformation. This result demonstrates that the ordered structure is better preserved in a bad solvent, which might be due to a decreased solvation of the structure reducing its conformation flexibility. As a result, the fraction of the dynamic polymer structure that forms a secondary structure is larger in methanol-$d_4$ compared to TFE-$d_3$. 

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2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Figure 2.13 SANS analysis of p-R-BuEtOx (2 mg/mL and 5 mg/mL) and p-RS-BuEtOx (5 mg/mL) dissolved in methanol-d$_4$. (a) SANS profiles and fits (solid lines) for an ellipse form factor for p-R-BuEtOx and a random coil for p-RS-BuEtOx. (b) Guinier analysis and fits (solid lines) of the $R_g$. (c) Kratky plots.

To elucidate how the long-range structure of p-R-BuEtOx in HFIP-d$_2$ changes with the change in temperature was investigated as well by measuring the polymer dissolved in HFIP-d$_2$ at different temperatures. The scattering profiles, absolute intensities and data fittings (fit lines shown in Figure 2.14a) all revealed that p-R-BuEtOx adopts an ellipsoidal chain conformation in HFIP-d$_2$ at all three temperatures, indicating that the long-range structure of the polymer does not change when the short-range chiral structure is altered from one conformation into the other, as determined by CD. The combination of CD and SANS demonstrates that this polymer also forms a flexible and dynamic secondary structure in HFIP-d$_2$ too. Therefore, it may be expected that
both chiral chain conformations are simultaneously present in each polymer chain together with unordered segments.

**Figure 2.14** SANS analysis of p-R-BuEtOx dissolved in HFIP-d$_2$ at a concentration of 5 mg/mL. (a) SANS profile and fits (solid lines) for an ellipse form factor at –10 °C, 20 °C and 50 °C (solid lines); and (b) the Guinier analysis.

**Table 2.4** Comparison of best fit parameters to SANS data found from mathematical modeling and Guinier analyses of p-R-BuEtOx dissolved in HFIP-d$_2$.

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>R1 ellipse (Å)</th>
<th>X ellipse (Å)</th>
<th>R$_g$ (Å) FISH</th>
<th>R$_g$ (Å) Guinier</th>
</tr>
</thead>
<tbody>
<tr>
<td>−10</td>
<td>16</td>
<td>3</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>20</td>
<td>15</td>
<td>3</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>50</td>
<td>17</td>
<td>3</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

$^1$ Uncertainty in absolute intensities is 5% and in R$_g$ is ± 2 Å.

The R$_g$ values obtained from mathematical modeling compared well with those found from the Guinier analysis (Figure 2.14b; Table 2.4). At low Q range the intensity increases due to interparticle interaction (aggregation) and, therefore, these values are not included in the fits of R$_g$ (open symbols in Figure 2.14b). The similar sizes found for the polymer structure at the three different temperatures confirm that the long-range structure of the polymer is not influenced by the temperature.
2.4 Properties in the solid state

In this section the properties of the chiral p-BuEtOx polymers in the solid state are investigated by measuring the thermal properties by thermal gravimetric analysis (TGA) as well as differential scanning calorimetry (DSC); the formation of a secondary structure in the solid state was also investigated by CD of polymer films. In addition, x-ray diffraction (XRD) measurements were performed to see if the polymer structure changes after thermal treatment. New batches of polymers had to be synthesized for the XRD measurements resulting in polymers with slightly different molar masses \( M_n \) and PDI values of 6,140 g/mol and 1.27 for p-R-BuEtOx, 6,850 g/mol and 1.31 for p-S-BuEtOx and 5,100 g/mol and 1.25 for p-RS-BuEtOx, respectively, as determined by SEC (PS standards).

2.4.1 Thermal properties

From the TGA measurements (Figure 2.15a) it was observed that the polymers looses 5 wt% between 283 and 294 °C, indicating that the polymers are stable up to at least 250 °C. The thermal transitions of the enantiopure and racemic poly(2-oxazoline)s were measured by DSC from \(-30\) to 250 °C with a heating rate of 20 °C/min. In the first heating run, the enantiopure poly(2-oxazoline)s revealed a glass transition temperature \( T_g \) followed by cold crystallization \( T_{cc} \) and double melting peaks \( T_{m1} \) and \( T_{m2} \) while the racemic polymer only revealed a \( T_{cc} \). The DSC results from the second heating run are shown in Figure 2.15b and the results are summarized in Table 2.5. All polymers have approximately the same glass transition temperature \( T_g \) around 50 °C with a heat capacity \( \Delta C_p \) of about 0.3 J/(g K). However, the enantiopure polymers show an exothermic crystallization \( T_{cc} \) due to cold crystallization and two melting peaks \( T_{m1} \) and \( T_{m2} \) in the second heating run, while the racemic polymer does not. The cooling rate of 20 °C/min was obviously too fast for the enantiopure polymers to completely crystallize from the melt and, therefore, the crystallization takes place from the rubbery state during the heating run. In general double melting transitions can be explained by three major proposed mechanisms, namely melt-recrystallization, dual lamellae population, and dual crystal structures. The thermal behavior of the polymers was further investigated after annealing above the \( T_g \) at 110 °C for one hour. Then, the polymer crystallizes and the cold-crystallization exotherm is eliminated in p-R-BuEtOx and almost completely
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline) disappeared in p-S-BuEtOx (Figure 2.15b). Again two melting peaks are observed. The first melting endotherm ($T_{m1}$) is probably the result of crystals formed during annealing and the second melting peak ($T_{m2}$) is broad and is probably a combination of $T_{m1}$ and $T_{m2}$ that were observed in the second heating scan. The melt enthalpy ($\Delta H_m$) increased after annealing, which means that the crystallinity of the enantiopure polymers is increased after the thermal treatment. After annealing, still no melting peak appears for the racemic polymer indicating its amorphous behavior. The melting peaks observed for the enantiopure polymers might be due to the melting of polymer crystals containing an ordered chiral structure, which might be helices or ordered arrays of helices, while the racemic polymer forms an unordered amorphous structure.

When a 50:50 mixture of both enantiopure polymers is measured with DSC, $\Delta H_{cc}$ and $\Delta H_m$ are much lower during the second heating run compared to the individual enantiopure polymers (Figure 2.15b), which indicates a partial suppression of crystallization after mixing. However, the formation of some kind of superstructure upon mixing, similar to the stereocomplexes formed by poly-L-lactide and poly-D-lactide, might be possible.\textsuperscript{60,61} Alternatively, the presence of both enantiomers could obstruct the formation of crystals of single enantiomers resulting in a smaller crystalline fraction. After annealing, $\Delta H_m$ is increased, but still not to the same extent as the individual enantiopure polymers.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

![Figure 2.15](image)

**Figure 2.15** (a) TGA traces of p-R-BuEtOx, p-RS-BuEtOx and p-S-BuEtOx indicating the temperature at which 5% of the weight (wt%) was lost. (b) DSC traces of the second heating scan and after annealing the sample for 1 hour at 110 °C of p-R-BuEtOx, p-RS-BuEtOx, p-S-BuEtOx and a 50:50 mixture of p-R-BuEtOx and p-S-BuEtOx, respectively.

**Table 2.5** Thermal properties obtained by the DSC measurements.

<table>
<thead>
<tr>
<th>Polymer BuEtOx</th>
<th>Second heating run¹</th>
<th>After annealing¹,²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tg (°C)</td>
<td>ΔCp (J/(g K))</td>
</tr>
<tr>
<td>S</td>
<td>50</td>
<td>0.33</td>
</tr>
<tr>
<td>RS</td>
<td>50</td>
<td>0.34</td>
</tr>
<tr>
<td>R</td>
<td>52</td>
<td>0.36</td>
</tr>
<tr>
<td>Mixture</td>
<td>46</td>
<td>0.38</td>
</tr>
</tbody>
</table>

¹ Heating rate: 20 °C/min. ² Annealed at 110 °C for 1 hour.

The melting behavior of p-S-BuEtOx was further investigated by varying the heating rate between 10 and 70 °C/min and by annealing the sample at different temperatures ranging from 110 to 180 °C for 1 hour. The results, summarized in Table 2.6 and in Figure 2.16a, reveal that Tm1 is shifting to higher temperatures with increasing heating rate, while Tm2 remains at the same temperature until only one melting peak is observed. Such a behavior is indicative for melt-recrystallization in which the first melting peak is caused by the initially formed crystals which recrystallize into more perfect crystals that are responsible for the second melting peak. ⁵⁹,⁶² Furthermore,
when the heating rate is increased, cold crystallization ($T_{cc}$) is suppressed and shifted to higher temperature resulting in a smaller fraction of initially formed crystals, causing a decrease in $\Delta H_{m1}$ and, subsequently, less melt-recrystallization takes place which also leads to a decrease in $\Delta H_{m2}$. Syndiotactic polypropylene (sPP) also reveals the melt-recrystallization mechanism when the stereoregularity is relatively low ((rrrr $< 90\%$)). In that case a double melting peak is observed in the DSC trace, whereby the first melting peak is due to the partial melting of irregular crystals in the disordered helical form followed by successive recrystallization into the more ordered helical form which melts at higher temperatures causing the second melting peak. As a consequence, it is also possible that p-S-BuEtOx initially forms crystals with a disordered secondary structure that recrystallizes during melting into crystals with a more defined secondary structure.

Figure 2.16 DSC traces of p-S-BuEtOx (a) of the second heating run at different heating rates and (b) after annealing at different temperatures for 1 hour (heating rate: 20 °C/min).
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Table 2.6 Thermal properties of p-S-BuEtOx obtained by DSC at different heating rates.

<table>
<thead>
<tr>
<th>Heating rate (°C/min)</th>
<th>T_{cc} (°C)</th>
<th>ΔH_{cc} (J/g)</th>
<th>T_{m1} (°C)</th>
<th>T_{m2} (°C)</th>
<th>ΔH_{m} (J/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>158</td>
<td>21</td>
<td>195</td>
<td>215</td>
<td>37</td>
</tr>
<tr>
<td>20</td>
<td>173</td>
<td>12</td>
<td>206</td>
<td>217</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>176</td>
<td>1.9</td>
<td>208</td>
<td>215</td>
<td>3.9</td>
</tr>
<tr>
<td>40</td>
<td>-</td>
<td>-</td>
<td>208</td>
<td>215</td>
<td>2.7</td>
</tr>
<tr>
<td>50</td>
<td>-</td>
<td>-</td>
<td>208</td>
<td>214</td>
<td>2.0</td>
</tr>
<tr>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>214</td>
<td>1.3</td>
</tr>
<tr>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>214</td>
<td>1.15</td>
</tr>
</tbody>
</table>

The annealing temperature further influences the thermal properties as illustrated in Table 2.7 and Figure 2.16b. With the increase in annealing temperature from 110 to 180 °C, T_{m1} shifts to higher temperature and increases in intensity, while T_{m2} remains around the same temperature and decreases in intensity. Although still two melting peaks are present after annealing at 180 °C for 1 hour, such a shift in T_{m} and change in ΔH_{m} was also observed for PLLA, where both melting peaks relate to the helical α form\textsuperscript{63,64} and also to the helical comb polymer PLLA.\textsuperscript{65} The authors attributed the double melting peaks to melt-recrystallization. It seems that with increasing annealing temperature more initial crystals are formed that cause an increase in ΔH_{m1}. These initial crystals are more perfect, which causes the increase in T_{m1}. Another indication that the second melting peak is due to melt-recrystallization is the dip between the two melting endotherms present after annealing the sample at 120 to 150 °C.\textsuperscript{29}
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Table 2.7 Thermal properties obtained by DSC after annealing p-S-BuEtOx at different temperatures for 1 hour.

<table>
<thead>
<tr>
<th>T_a (°C)</th>
<th>T_cc (°C)</th>
<th>ΔH_cc (J/g)</th>
<th>T_m1 (°C)</th>
<th>T_m2 (°C)</th>
<th>ΔH_m (J/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>-</td>
<td>-</td>
<td>184</td>
<td>215</td>
<td>30</td>
</tr>
<tr>
<td>120</td>
<td>191</td>
<td>0.9</td>
<td>185</td>
<td>213</td>
<td>43</td>
</tr>
<tr>
<td>130</td>
<td>193</td>
<td>1.1</td>
<td>188</td>
<td>211</td>
<td>32</td>
</tr>
<tr>
<td>140</td>
<td>197</td>
<td>1.2</td>
<td>192</td>
<td>213</td>
<td>43</td>
</tr>
<tr>
<td>150</td>
<td>200</td>
<td>1.1</td>
<td>194</td>
<td>214</td>
<td>40</td>
</tr>
<tr>
<td>160</td>
<td>-</td>
<td>-</td>
<td>198</td>
<td>215</td>
<td>39</td>
</tr>
<tr>
<td>170</td>
<td>-</td>
<td>-</td>
<td>202</td>
<td>216</td>
<td>38</td>
</tr>
<tr>
<td>180</td>
<td>-</td>
<td>-</td>
<td>206</td>
<td>217</td>
<td>36</td>
</tr>
</tbody>
</table>

Exothermic dip between two melting peaks.

The influence of the molar mass of p-R-BuEtOx on the thermal properties was measured by TGA and DSC, respectively. From the TGA measurements it can be observed that the thermal stability increases with increasing molar mass (M_n), since the temperature at which the polymer loses 5 wt% increases almost linearly with increasing M_n (Figure 2.17a). The T_g also increases linearly with increasing M_n up to 8,000 g/mol. (Figure 2.17b). Due to the increased number of chain ends with decreasing M_n, both the thermal stability and T_g decreases with decreasing M_n. The polymers with a M_n of 1,960 g/mol and 3,160 g/mol do not crystallize from the melt or from the rubbery state, making them amorphous (Figure 2.17c). When the polymer reaches a M_n of 4,040 g/mol, cold crystallization (T_cc) followed by a double melting peak (T_m1 and T_m2) is observed. With increasing M_n, T_cc as well as T_m1 and T_m2 shift to higher temperature up to a M_n of 9,490 g/mol, probably due to the formation of larger crystals with increasing molar mass. The polymers with a M_n of 9,490 g/mol or higher only reveal a small exotherm due to cold crystallization followed by one melting endotherm. It is commonly observed that polymers with increasing molar mass have a lower crystallization rate and a lower ability to crystallize due to the increase in melt-viscosity, which can explain the increase in T_cc and the decrease in ΔH_m with increasing molar mass in the M_n range of 4,000 to 9,000 g/mol.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Upon annealing the polymers at 110 °C for 1 hour, p-R-BuEtOx with a $M_n$ of 1,960 g/mol remains completely amorphous, however a double melting peak appears for p-R-BuEtOx with a $M_n$ of 3,160 g/mol, which did not reveal a melting transition during the second heating run (Figure 2.17d). With increasing $M_n$ both $T_{m1}$ and $T_{m2}$ shift to higher temperature until only one melting enotherm is observed when the polymer reaches a $M_n$ of 8,360 g/mol. The double melting peak is due to melt-recrystallization like discussed before, since a small exothermic dip can be observed in between the two melting peaks when the polymer has a $M_n$ of 4,040 g/mol or 6,000 g/mol, respectively. When the polymer reaches a $M_n$ of 8,360 g/mol no initial crystals that recrystallize into more perfect crystals are formed anymore and only $T_{m2}$ is observed.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

![Graphs showing thermal stability and Tg of p-R-BuEtOx with increasing molar mass.](image)

**Figure 2.17** (a) Thermal stability and (b) Tg of p-R-BuEtOx with increasing molar mass (Tg taken from the 2nd heating run, heating rate = 20 °C/min). (c) 2nd Heating run and (d) after annealing for 1 h at 110 °C of p-R-BuEtOx with increasing molar mass (heating rate = 20 °C/min).
2.4.2 Crystal structure

The XRD measurements were performed on p-R-BuEtOx and p-S-BuEtOx powders before and after annealing at 110 and 140 °C to investigate if the polymers are already crystalline after synthesis, i.e. after precipitation, drying at 40 °C and storage at ambient conditions, and if the crystal structure changes upon annealing. For comparison also p-RS-BuEtOx was analyzed with XRD before and after annealing at 110 °C. Figures 2.18a and 2.18b demonstrate that the enantiopure polymers are obtained as semi-crystalline materials after synthesis and purification. No significant change is observed in the XRD pattern after annealing at 110 or 140 °C indicating that the crystal structure does not change after the thermal treatment, despite the differences that are observed by DSC after annealing. The diffraction peaks corresponds to a d-spacing of respectively 9.7 Å, 7.9 Å, 6.5 Å, 5.2 Å, 4.3 Å and 3.4 Å. P-RS-BuEtOx (Figure 2.18c) shows broad bands before and after annealing indicating that this polymer is amorphous. The broad peak between 2θ of 15 and 30 with sharp peaks on top arises from the Vaseline that was used for the sample preparation and is also present in the XRD-patterns of the enantiopure polymers. The XRD of the 50:50 mixture of p-S-BuEtOx and p-R-BuEtOx revealed the same crystal structure compared to the separate enantiopure polymers. Also after thermal treatment the crystal structure of the mixture does not change, indicating that no stereocomplexes are formed.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

![Graphs showing XRD patterns](image)

**Figure 2.18** XRD patterns of (a) p-R-BuEtOx, (b) p-S-BuEtOx, (c) p-RS-BuEtOx and (d) 50:50 mixture of p-R-BuEtOx and p-S-BuEtOx, before and after annealing.

Furthermore, the 2D XRD patterns of the p-R-BuEtOx powder were measured at different temperatures to investigate if the crystalline structure changes upon heating. From Figure 2.19 it can be seen that the polymer was initially semi-crystalline at room temperature (Figure 2.19a) and that the crystalline structure does not change upon heating up to 200 °C. At 225 °C, the polymer starts to become amorphous (Figure 2.19d) and during the second measurement at 225 °C, the polymer was completely amorphous (Figure 2.19e). These results confirm that the double melting peak is caused by the melt-recrystallization mechanism and not due to the presence of a second crystalline structure. Upon slow cooling, the polymer crystallizes again below 100 °C. By further decreasing the temperature to room temperature, the crystallization occurs faster and the final crystalline fraction is similar to the initial sample before heating.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

Figure 2.19 XRD 2D patterns of p-R-BuEtOx during heating and cooling, respectively (a) room temperature (RT), (b) 100 °C, (c) 150 °C, (d) 225 °C first measurement, (e) 225 °C second measurement, (f) 250 °C, (g) 175 °C, (h) 150 °C, (i) 100 °C and (j) RT, respectively.

2.4.3 Optical properties

To determine if the melting peaks are the result of the melting of crystals that contain an ordered chiral structure, CD measurements were carried out on a thin polymer film spin-coated onto a quartz slide. CD spectra of the polymer film were taken at different temperatures starting at 25 up to 250 °C (Figures 2.20a and 2.20b). Below 100 °C, only a small dichroic Cotton effect was observed indicating that only a minor fraction of the polymer is present in an ordered chiral structure. However, when the temperature reached 100 °C, a significant increase in the Cotton effect around 200 nm was observed indicating the formation of an ordered chiral structure at this temperature. With the further increase in temperature up to 150 °C, the Cotton effect remains constant and decreases again with the increase in temperature until almost no Cotton effect was observed anymore at 230 °C demonstrating that the ordered chiral structure disappeared, probably due to melting of the crystals. Even though the CD results clearly show the formation of an ordered chiral structure, it cannot be assigned to a certain type of secondary structure due to the absence of model compounds.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

![Figure 2.20](image.png)

**Figure 2.20** (a) CD spectra of p-R-BuEtOx spincoated onto quartz glass at different temperatures. (b) CD maxima obtained (from 2.17a) plotted against temperature. (c) Melting curve of p-R-BuEtOx obtained with CD at a wavelength of 202 nm (heating rate: 1 °C/min). (d) First heating scan of p-R-BuEtOx obtained by DSC (heating rate: 1 °C/min).

In order to compare the DSC results with the CD results, a melting curve of the polymer was measured by both techniques using a heating rate of 1 °C/min (Figures 2.20c and 2.20d). Since the maximum Cotton effect stays around 202 nm in the CD spectra over the whole temperature range, the CD melting curve was recorded at this wavelength. By comparing the DSC with the CD results, it is evident that the Cotton effect increases significantly during the cold crystallization, which is indicated by a dip in the DSC trace at 100 °C. This means that during cold crystallization crystals are formed, which contain an ordered chiral structure. In addition, the melting peaks observed in the DSC trace can be related to the melting of this ordered chiral structure into a disordered melt, since the Cotton effect completely disappears at a temperature just above the end of the melting endotherm.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

2.5 Conclusion

Chiral 2-oxazoline monomers could be synthesized by the reaction of valeronitrile with the chiral starting materials R-2-amino-1-butanol, RS-2-amino-1-butanol or S-2-amino-1-butanol, with zinc acetate as catalyst. The resulting new monomers could be polymerized in a living manner by a cationic ring-opening polymerization, yielding in the corresponding optically active polymers. By increasing the [M]/[I] ratio, a higher molar mass polymer was obtained, although the polymerization became less controlled with increasing [M]/[I] ratio’s.

According to the solubility tests and the CD measurements, the enantiopure polymers form a secondary, most likely helical structure, while the racemic polymer forms a random coil. In TFE and acetonitrile the enantiopure polymers form a thermally stable conformation with only a small decrease in persistence length with increasing temperature. However, in HFIP an inversion in the Cotton effect was observed with a decrease in temperature due to the formation of hydrogen bonds between the solvent and the polymer causing a change in the secondary structure of the enantiopure polymer. Furthermore, the type of secondary structure formed in apolar solvents differs from the secondary structure formed in polar solvents most likely due to preferential solvation since the chiral polymer consists of polar amide groups and apolar side-chains.

In contrast to the CD data, SANS revealed a random coil for the long range structure of the enantiopure polymers dissolved in TFE-\(d_3\), like the racemic polymer. This behavior is proposed to be similar to polyproline II type helices; the structure of the polymer is very flexible and fluctuates around an ordered secondary structure but only a few monomeric units are in an ordered conformation at the same time. When the enantiopure polymer was dissolved in a bad solvent, methanol-\(d_4\), the SANS measurements revealed that the enantiopure polymer does form a more compact ellipsoidal structure compared to the racemic polymer. The ordered conformation is proposed to be better preserved in a bad solvent due to decreased solvation of the polymer chain causing an increase in persistence length leading to anisotropy.

Furthermore, the enantiopure p-R-BuEtOx and p-S-BuEtOx are semi-crystalline polymers with \(T_g\) values around 50 °C and double melting peaks caused by melt-recrystallization, which were determined by DSC measurements. In the second heating run, an exothermic dip was observed in the DSC thermograph due to cold
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

crystallization, which could not be observed anymore after annealing the polymer. In contrary, the racemic p-RS-BuEtOx is amorphous with a similar T\textsubscript{g} around 50 °C. The thermal stability and T\textsubscript{g} increased with increasing molar mass due to the decrease in chain ends. The crystallization rate and crystallization ability decreased with increasing molar mass due to the increase in melt-viscosity. The XRD measurements confirmed that the enantiopure polymers are semi-crystalline and that the crystal structure does not significantly change after annealing. Furthermore, the XRD measurements revealed that the crystal structure does not change during heating, which confirms that the double melting peaks observed with DSC are caused by the melt-recrystallization mechanism.

By comparing the DSC data with the CD data it could be concluded that the crystals formed in the enantiopure polymer contain an ordered chiral structure. As a consequence, it was proposed that these chiral poly(2-oxazoline)s initially form disordered chiral structures that recrystallize during melting into a more perfect chiral structure. Upon further heating, these crystals melt into a disordered structure.

These findings represents the first demonstration that synthetic polymers, i.e. main-chain chiral poly(2-oxazoline)s, can form flexible structures in solution similar to polyproline type II helices. In bulk the amount of crystallization and type of crystals formed in the chiral poly(2-oxazoline)s can be controlled by the thermal history, which has a direct influence on the formation of the ordered chiral structure.

2.6 Experimental section

*Materials and Instrumentation*

Valeronitrile (Aldrich), \(R\)-2-aminobutanol (ee 96%, Aldrich), \(S\)-2-aminobutanol (ee 96%, Aldrich) and \(RS\)-2-aminobutanol (Aldrich) were used as received. Acetonitrile (Aldrich) was dried in a solvent purification system (Pure Solv EN, Innovative Technology) before use as a polymerization solvent. Methyl tosylate (Aldrich) was distilled over barium oxide and stored under argon.

Small-scale reactions of 1 or 5 mL were carried out in capped reaction vials designed for the Emrys Liberator microwave system (Biotage) equipped with an IR temperature sensor. The vials were dried in the oven at 105 °C and cooled under argon to room temperature before use.

\(^1\text{H} \) NMR and \(^{13}\text{C} \) NMR spectra were recorded in CDCl\textsubscript{3} on a Varian AM-400 spectrometer. Chemical shifts are given in ppm relative to TMS.
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

GC measurements were performed on an Interscience Trace GC equipped with a Trace Column TX-5 and a PAL autosampler.

HRMS-ESI spectra were recorded on a Bruker BioTOF III.

GC-MS measurements were performed using a Shimadzu GC-17A (Column: DB-SMS, 5% phenyl-/95% dimethylpolysiloxane, length = 30 m, inner diameter = 0.25 mm, film thickness = 0.1 μm) connected to an AOC-20i autoinjector and a GCMS-QP5050A mass spectrometer. Ionization was managed by EI (electron impact).

Size exclusion chromatography (SEC) was measured on a Shimadzu system with a LC-10AD pump, a RID-10A refractive index detector, a system controller SCL-10A, a degasser DGU-14A, a CTO-10A column oven and two PSS GRAM 10 μm, 8 mm × 300 mm, 1000/30 Å columns using N,N-dimethylacetamide (DMA) with ~ 2 mg/L LiCl at a flow rate of 0.5 mL/min as the eluent (the column oven set to 50 °C, polystyrene calibration) or on a Shimadzu system equipped with a LC-10AD pump, a RID-10A refractive index detector, a SCL-10A system controller, and a Polymer Laboratory Mixed-D column utilizing a chloroform:triethylamine:isopropanol (93:5:2) mixture eluent at a flow rate of 1 mL/min (a column temperature of 50 °C, polystyrene calibration).

Solubility tests were performed using a Crystal-16 from Avantium Technologies with a concentration of 5 mg/mL. The transmittance was measured at a temperature range from −15 to 65 °C using methanol, ethanol, n-butanol, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, n-heptane and cyclohexane as solvent. When water was used as solvent, a temperature range from 0 to 65 °C was used.

Optical rotation at the Na-D line was measured with a sample concentration of 30 mg/mL in chloroform at room temperature with a polarimeter using a quartz cell with a path length of 10 mm.

UV and CD absorption spectra were measured simultaneously on a Jasco J815 spectropolarimeter equipped with a PTC-348WI temperature controller for temperatures ranging from −10 to 110 °C. Measurements of solutions were performed in a 1 mm quartz cell using sample concentrations of 0.25 mg/mL, unless stated differently. For measurements in bulk the samples were spin coated from chloroform (40 mg/mL) onto a quartz slide for 2 minutes with 2,000 rpm. The following scanning conditions were used: 50 nm/min scanning rate; 1 nm bandwidth; 0.1 nm datapitch;
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

0.5 s response time; and 10 accumulations. The melting curve was obtained by heating the sample with 1 °C/min.

SANS experiments were conducted on the time-of-flight LOQ diffractometer at the ISIS neutron facility. The incident wavelength range of 2.2 to 10 Å gave rise to a Q-range of 0.009 to 0.249 Å⁻¹. Absolute intensities for I(Q) (cm⁻¹) were determined within 5% by measuring the scattering from a partially deuterated polymer standard. Standard procedures for data treatment were employed. Measurements were performed in a 2 mm quartz cell using sample concentrations of 5 mg/mL in TFE-d₃ or in a 5 mm quartz cell using sample concentrations of 2 or 5 mg/mL in methanol-d₄ after which they remained soluble upon cooling to ambient temperature. Heating was necessary to dissolve the enantiopure polymer in methanol-d₄. The solutions were filtrated over 200 nm filters before the measurements. Solvent-scattering profiles were subtracted for background correction. The FISH analysis program was used for data modeling. Either an ellipsoid form factor P(Q) or a Gaussian coil model were employed depending on the conformation of the chain being studied. There are two structural dimensions in the ellipsoidal form factor mode; the primary and secondary radii R₁ and R₃ with the aspect ratio X = R₃/R₁. The value of X is unity for a spherical, < 1 for an oblate and > 1 for a prolate structure. Although estimates of the limiting radii can be made from the length and structure of the polymer, all three parameters were allowed to float during the fitting process. Values for I(0), flat background and radius of gyration are obtained from the Gaussian coil model and again these were allowed to adjust freely during the modeling process. In all cases absolute intensity and scale factor checks were made to ensure the values obtained were physically realistic. Further detail on the models used can be found in the FISH manual. The radii of gyration and chain conformation were also determined by Guinier analysis and Kratky plots, respectively.

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netsch under a nitrogen atmosphere with cooling rates of 20 °C/min and heating rates of 20 °C/min. Thermal transitions measured with a heating rate of 1 °C/min were measured on a DSC Q2000 by TA under nitrogen atmosphere.

X-ray diffraction (XRD) measurements were performed on a Rigaku Geigerflex Bragg-Brentano Powder Diffractometer as well as on a Bruker D8 discover with GADDS, a two-dimensional (2D) detector, and parallel beam optics. The XRD powder patterns were recorded with a Rigaku apparatus using Cu radiation,
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

wavelength 1.54056 Å, at 40 kV and 30 mA. The scans were performed with a 0.02 step in 2θ and a dwell time of 1.5 s. The samples were mounted with Vaseline, pure petroleum jelly, as a powder on a glass plate. The 2D diffraction patterns were obtained with a Bruker system using Cu radiation, wavelength 1.54184 Å, at 40 kV and 40 mA and a exposure time of 20 minutes. In this case the samples were prepared in a glass capillary and heated with a Linkam system, TMS94, to elevated temperatures.

**Monomer synthesis**

*R*-BuEtOx was synthesized as follows: a mixture of 40 g (0.481 mol) valeronitrile and 2.74 g (0.0125 mol) zinc acetate dehydrate was heated to 130 °C under argon in a three neck flask. To this mixture 45.27 g (0.508 mol) *R*-2-aminobutanol was added dropwise. The resulting mixture was stirred and heated under reflux overnight at 130 °C. To the reaction mixture 200 mL of dichloromethane was added at room temperature and the organic phase was washed three times with water and once with brine. The dichloromethane was removed by rotary evaporation and the crude product was purified and dried by distillation over barium oxide. The yield of the obtained monomer was 56%. *S*-BuEtOx and *R*S*-BuEtOx were obtained in a similar manner.

**R*-BuEtOx: **

**1H NMR** (400 MHz, δ in ppm, CDCl₃): 4.19 (t, CH₂O, 1H), 3.95 (q, CHN, 1H), 3.76 (t, CH₂O, 1H), 2.20 (t, OCCH₂(CH₂)₂CH₃, 2H), 1.2-1.7 (br, OC(CH₂)₂CH₃ and NCHCH₂CH₃, 6H), 0.8-1.0 (br, OC(CH₂)₂CH₃ and NCHCH₂CH₃, 6H). **13C NMR** (400 MHz, δ in ppm, CDCl₃): 167.6 (N=C=O, 1C), 71.7 (CH₂O=C, 1C), 67.2 (N=CH₂, 1C), 28.1 (CH₂, 3C), 22.3 (CCCH₂(CH₂)₂CH₃, 1C), 13.6 (CH₃, 1C), 9.76 (CH₃, 1C).

**HR-MS (ESI-TOF):** calculated for C₉H₁₇NO + H⁺ = 156.2456, found = 156.1383; calculated for C₉H₁₇NO + Na⁺ = 178.2275, found = 178.1202.

**GC-MS:** 154 [M⁺], 140 [M⁺-CH₃], 126 [M⁺-C₂H₆], 113 [M⁺-C₃H₈], 98 [M⁺-C₄H₁₀], 84 [M⁺-C₅H₁₃], 69 [M⁺-C₆H₁₅], 55 [M⁺-C₇H₁₆] 42 [M⁺-C₈H₁₇].

**S*-BuEtOx: **

**1H NMR** (400 MHz, δ in ppm, CDCl₃): 4.19 (t, CH₂O, 1H), 3.95 (q, CHN, 1H), 3.76 (t, CH₂O, 1H), 2.20 (t, OCCH₂(CH₂)₂CH₃, 2H), 1.2-1.7 (br, OC(CH₂)₂CH₃ and NCHCH₂CH₃, 6H), 0.8-1.0 (br, OC(CH₂)₂CH₃ and NCHCH₂CH₃, 6H). **13C NMR** (400 MHz, δ in ppm, CDCl₃): 167.6 (N=C=O, 1C), 71.7 (CH₂O=C, 1C), 67.2 (N=CH₂, 1C), 28.1 (CH₂, 3C), 22.3 (CCCH₂(CH₂)₂CH₃, 1C), 13.6 (CH₃, 1C), 9.76 (CH₃, 1C). **HR-MS (ESI-TOF):** calculated for C₉H₁₇NO + H⁺ = 156.2456, found = 156.1383; calculated for C₉H₁₇NO + Na⁺ = 178.2275, found = 178.1202. GC-MS:
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

154 [M⁺], 140 [M⁺-CH₃], 126 [M⁺-C₅H₆], 113 [M⁺-C₃H₈], 98 [M⁺-C₄H₁₀], 84 [M⁺-C₅H₁₃], 69 [M⁺-C₆H₁₅], 55 [M⁺-C₇H₁₆], 42 [M⁺-C₈H₁₇]

S-BuEtOx: \(^1\)H NMR (400 MHz, δ in ppm, CDCl₃): 4.19 (t, CH₂O, 1H), 3.95 (q, CHN, 1H), 3.76 (t, CH₂O, 1H), 2.20 (t, OCCH₂(CH₂)₂CH₃, 2H), 1.2-1.7 (br, OC(CH₂)₃CH₃ and NCHCH₂CH₃, 6H), 0.8-1.0 (br, OC(CH₂)₃CH₃ and NCHCH₂CH₃, 6H). \(^{13}\)C NMR (400 MHz, δ in ppm, CDCl₃): 167.6 (N=O, 1C), 71.7 (CH₂O=C, 1C), 67.2 (NCCCH₂, 1C), 28.1 (CH₂, 3C), 22.3 (CCH₂(CH₂)₂CH₃, 1C), 13.6 (CH₃, 1C), 9.76 (CH₃, 1C).

GC-MS: 154 [M⁺], 140 [M⁺-CH₃], 126 [M⁺-C₅H₆], 113 [M⁺-C₃H₈], 98 [M⁺-C₄H₁₀], 84 [M⁺-C₅H₁₃], 69 [M⁺-C₆H₁₅], 55 [M⁺-C₇H₁₆], 42 [M⁺-C₈H₁₇]

**Kinetic investigation of the microwave-assisted polymerization**

A stock solution of the monomer (R- or RS-BuEtOx) and methyl tosylate as initiator with a monomer-to-initiator ratio ([M]/[I]) of 60 was prepared in acetonitrile with an initial monomer concentration of 4 M. Five microwave vials were filled with 1 mL of this stock solution and heated in the microwave to 140 or 180 °C for different times. After the desired polymerization time, the mixture was cooled by compressed nitrogen and quenched by the addition of water. The resulting mixtures were analyzed by GC and SEC to determine the monomer conversion and the molar mass (distribution) of the polymer, respectively.

**Polymer synthesis**

The chiral p-R-BuEtOx, p-RS-BuEtOx and p-S-BuEtOx were synthesized using an initial monomer concentration of 4.5 M in acetonitrile and a [M]/[I] (I = methyl tosylate) ratio of 50. These polymerization mixtures were heated to 180 °C under microwave irradiation for 60 min. After the polymerizations, the mixtures were quenched by the addition of water. After drying, the polymers were redissolved in tetrahydrofuran and precipitated in demineralized water before further characterization.

**SANS theory**

The Guinier approximation relates to the low Q (QRₕ < 1) part of the scattering plot providing the radius of gyration (Rₕ) of the particle. The normalized scattered intensity I(Q) is given by the following expression:
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

\[ I(Q) = N_p \Delta \rho^2 V_p^2 P(Q,R)S(Q) \]

where \( N_p \) is the number of particles in the sample, \( \Delta \rho = \rho_p - \rho_m \), \( V_p \) is the volume of a particle, \( P(Q, R) \) is the single particle form factor arising from the intra-particle scattering and \( S(Q) \) is the structure factor which arises from inter-particle interactions. At low \( Q \) (the Guinier regime) and in dilute non-interacting systems, \( S(Q) = 1 \) and therefore \( P(Q, R) \) simplifies to the following:

\[ P(Q,R) = 1 - \frac{Q^2 R_g^2}{3} \]

Assuming that \( 1 - X^2 \approx \exp(-X^2) \) the expression for \( I(Q) \) then becomes:

\[ I(Q) \approx N_p \Delta \rho^2 V_p^2 \exp\left(-\frac{Q^2 R_g^2}{3}\right) \]

Plotting a graph of \( \ln[I(Q)] \) vs. \( Q^2 \) should give a linear section in the Guinier regime and the \( R_g \) can be obtained from the slope of this section:

\[ \text{Slope} = -\frac{R_g^2}{3} \]

For the systems being examined in this study \( R_g \) is expected to be larger for an ordered structure when compared to a random coil.

A Kratky plot is obtained by plotting \( I(Q)Q^2 \) vs. \( Q \) and contains information on the conformation of the polymer molecules within a system. The graph consists of three distinct regimes (Figure 2.20): the low \( Q \) section consists of a steep rising slope and can be related to the \( R_g \) of the entire molecule, the steep gradient then decays into the intermediate (Debye) section which contains information on the random arrangement of the polymer chain elements. The tail section of the Kratky plot will again begin to increase with a steep slope, the start of which can be related to the persistence length of the molecule. A more compact or structured molecule will have a more pronounced peak at low \( Q \) when compared to a random coil whose form will be more like a plateau.70
Mathematical modeling of the systems was performed using the multi-model FISH fitting program. This program is based on an iterative least-squares algorithm and allows for various common scattering laws to be tested. The best structural parameters and a measure of the fit residuals are obtained. The models employed were not chosen at random; the general form factors of the obtained scattering curves were taken into account as were results from Guinier analyses and Kratky plots along with data from other techniques such as CD. Absolute intensities and scale factors were determined for each data set to ensure that the most suitable structural model had been chosen. The fitting analyses used for this data was either the ellipsoid form factor or a Gaussian coil model. There are two structural dimensions in the ellipsoid model; the primary and secondary radii, \( R_1 \) and \( R_3 \) with an aspect ratio \( X = R_3/R_1 \). The value of \( X \) is unity for a spherical, \( < 1 \) for an oblate (Figure 2.21a) and \( > 1 \) for a prolate (Figure 2.21b) structure.

Estimates of the limiting radii can be made from the length and structure of the polymer and, although all three parameters were allowed to float during the fitting process, the values obtained were always kept within reason to these estimates. For an ellipsoidal particle the scale factor, \( S_F \), is defined as:

\[
\frac{1}{\text{Q}^2 \times I(Q)}
\]
2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

\[ S_F = \phi_p \Delta \rho^2 V_p \]

where \( \phi_p \) is the volume fraction of the particles, \( \Delta \rho \) the scattering length density difference between the particle and the solvent and \( V_p \) is the volume of the particle. The volume is found using:

\[ V_p = \frac{4}{3} \pi R^3 X \]

where \( R \) is the primary axis and \( X \) the axial ratio of the ellipsoid.

When using the Gaussian coil model, values for \( I(0) \), flat background and the radius of gyration can be obtained. Again these parameters were allowed to float during fitting, but not allowed to become physically unrealistic (taking the polymer molar mass and structure into account, alongside results from Guinier analyses). For the Gaussian coil model employed, the absolute scattering intensity, \( I(0) \), is given by:

\[ I(0) = \phi \Delta \rho^2 V \]

where \( \Delta \rho \) the scattering length density difference between the polymer and the solvent, \( \phi = \text{concentration of polymer (in g/cm}^3\text{) / density (in g/cm}^3\text{)} \) and \( V \) is the volume of polymer in one scattering object (the coil), and is given by:

\[ V = \frac{M_n}{d \cdot N_A} \]

where \( M_n \) is the molar mass of the polymer (in g/mol), \( d \) the density and \( N_A \) is Avogadro’s constant.

2.7 References and notes

2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)

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2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)


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2. Chiral poly(2-butyl-4-ethyl-2-oxazoline)


(68) R. K. Heenan, FISH Data Analysis Program; Rutherford Appleton Laboratory, Report RAL-89-129; CCLRC, Didcot, UK, **1989**.

(69) The FISH manual can be downloaded from: http://www.small-angle.ac.uk/small-angle/Software.html.

Chapter 3

Library of chiral main-chain poly(2-oxazoline)s

Abstract

The synthesis and microwave-assisted polymerization of a small library of chiral 2-oxazolines with varying alkyl pendant groups and bulky aromatic side-chains is described. A kinetic investigation of the polymerization of R-2-ethyl-4-ethyl-2-oxazoline (R-EtEtOx) revealed a living polymerization mechanism with a similar rate as for R-2-butyl-4-ethyl-2-oxazoline (R-BuEtOx). Circular dichroism (CD) measurements showed that the polymers containing ethyl, butyl and octyl pendant groups form a similar chiral structure, which changes when the side-chain length is elongated to nonyl-groups. While CD indicated that the short-range structure of 2 p-R-BuEtOx in hexafluoroisopropanol (HFIP) is thermoresponsive in a complex way, the long-range structure measured with small angle neutron scattering (SANS) is an ellipsoid that is insensitive to temperature demonstrating that only the local secondary structure changes with temperature, most likely due to HFIP hydrogen bonding to the polymeric amide groups. The bulky groups in poly(R-2-phenyl-4-ethyl-2-oxazoline) (6 p-R-PhEtOx) prevented the formation of hydrogen bonds between HFIP and the polymer, resulting in a temperature insensitive CD signal in HFIP. In addition, the short-range as well as the long-range chiral structure of 5 p-R-UndeEtOx was found to depend on the polarity of the solvent due to a difference in solvation. The influence of the side-chains on the thermal properties was investigated using differential scanning calorimetry (DSC) and the nature of the obtained melting endotherms was further investigated by thermal treatments of the polymers. 1 P-R-EtEtOx and 6 p-R-PhEtOx were found to be amorphous, while polymers with longer side-chains are semi-crystalline. Elongating the side-chains from butyl to octyl chains decreased the crystallization rate and melting temperature. Further elongating the side-chain length increases the crystallization rate again and an additional melting endotherm at a lower temperature appears upon annealing due to a dual crystal size population. CD measurements of the semi-crystalline polymer films revealed the presence of chirally ordered crystals.

3. Library of chiral main-chain poly(2-oxazoline)s

3.1 Introduction

In nature most polymers are chiral, like proteins and DNA. The chirality of these polymers together with the presence of non-covalent interactions, such as hydrogen bonds, electrostatic interactions and van der Waals interactions controls the formation of secondary structures like helices or β-sheets. In contrast to natural polymers only a few examples of synthetic polymers with a secondary conformation stabilized with hydrogen bonds are known.\(^1\)\(^2\) The majority of synthetic polymers that adopt a secondary structure are stabilized by van der Waals interactions. The main-chain of these polymers are often rigid or semi-flexible, which also contributes to the stability of their secondary structure. Since side-chains can significantly influence the rigidity of the backbone, side-chains also affect the potential formation of a secondary conformation. For example, polysilanes can adopt collapsed coil, flexible coil, stiff, or rigid-rod-like conformations depending on the alkyl side-chain length.\(^3\) Nilsson et al. hypothesized that the degree of planarity in the polymer backbone depends on electrostatic, H-bonding, steric, or van der Waals interactions within or between polymer chains, which again controls secondary structure formation.\(^4\) The effect of the side-chain on the chiral structure of poly(propiolic esters) with long alkyl side-chains was illustrated by a helix-sense inversion driven by the change in temperature or solvent composition.\(^5\) Furthermore, the side-chain can influence the thermal properties. For comb polymers it is observed that side-chain melting can occur with a minimum of eight carbon atoms in the pendant group when the backbone is semi-flexible and with a minimum of twelve carbon atoms when the main-chain is rigid.\(^6\) Main-chain chiral poly(2-oxazolines)\(^7\)\(^-\)\(^11\) can be regarded as pseudo-peptides,\(^12\)\(^13\) and, form secondary structures as described in Chapter 2. It is hypothesized that varying the alkyl side-chain length or changing the side-chain into a more bulky group could make the backbone more rigid or more flexible and, therefore, could stabilize or destabilize the formation of the chiral secondary structure. Moreover, changing the length of the alkyl side-chain and bulkiness of the side-chain controls the polymer solubility in more or less polar solvents, which controls the strength of non-covalent interactions and, thus, might also influence the secondary structure formation. The crystallinity can also be influenced by the side-chains, which can affect the optical properties in the solid state.
In this chapter the synthesis and the microwave-assisted polymerization of a series of new 2,4-disubstituted 2-oxazoline monomers with varying side-chains is described in section 3.1. The influence of the alkyl side-chain length on the solubility of the resulting polymers (Figure 3.1) was investigated and the formation of an ordered chiral structure in solution is discussed based on circular dichroism (CD) as well as small angle neutron scattering (SANS) measurements (section 3.2). Moreover, the temperature responsiveness of the secondary structures formed in solution was evaluated by temperature dependent CD for all polymers and SANS for 2 p-R-BuEtOx and the influence of the polarity of the solvent on the secondary structure formed by 5 p-R-UndeEtOx was investigated by both CD and SANS. The formation of chiral crystals by differential scanning calorimetry (DSC) and CD of polymer films is described in section 3.2. Furthermore, the influence of the bulky aromatic side-chains was investigated by DSC and CD, which is described in section 3.3, together with the synthesis.

Figure 3.1 Schematic representation of the investigated poly(2-oxazoline)s.

3.2 Varying the side-chain length of poly(2-alkyl-4-ethyl-2-oxazoline)
To investigate the effect of the side-chain length on the secondary structure formation of main-chain chiral poly(2-oxazoline)s a series of monomers with different side-chains on the 2-position was prepared. The 2,4-disubstituted-2-oxazoline monomers were synthesized through the reaction of R-2-amino-1-butanol with the corresponding nitrile using zinc acetate as the catalyst. After overnight heating under reflux and washing the reaction mixture with water followed by vacuum distillation, the monomers were obtained in high purity, which is essential for the living cationic ring-opening polymerization (CROP).

The polymerization kinetics of R-EtEtOx were determined under microwave-assisted conditions at 180 °C, using an initial monomer concentration of 4.5 M and a [M]/[I] of 60, with MeOTs as initiator and acetonitrile as solvent. These conditions are similar to the conditions used earlier for determining the polymerization kinetics
3. Library of chiral main-chain poly(2-oxazoline)s

of R-BuEtOx (Chapter 2), to be able to compare the results. Both monomers revealed linear first-order kinetics as well as a linear increase of the molar mass with conversion (Figure 3.2), demonstrating that the polymerizations proceeded in a living manner. Furthermore, it can be concluded that the kinetics indeed are similar and, thus, it may be assumed that all monomers have approximately the same polymerization rate constant ($k_p$) as it was demonstrated previously for a series of 2-alkyl-2-oxazolines.$^{16}$

![Figure 3.2](image)

**Figure 3.2** (a) Kinetic plots for the polymerizations of R-BuEtOx and R-EtEtOx initiated with methyl tosylate ([M]/[I] = 60) in acetonitrile ([M]$_0$ = 4 M and 4.5 M, respectively) at 180 °C. (b) Corresponding molar mass ($M_n$) against conversion plot, including the polydispersity index (PDI).

Based on these kinetic investigations, larger amounts of all five polymers were synthesized under microwave-assisted conditions (180 °C for 1 to 1.5 h, depending on the monomer concentration) using MeOTs as initiator and acetonitrile as solvent. After the polymerization, the polymers were precipitated in water resulting in white solid powders. Most polymers showed some tailing in SEC at low molar mass (Figure 3.3), probably due to the occurrence of some chain transfer and/or termination reactions during the polymerization. P-R-EtEtOx represents an exception and revealed fronting, probably due to the occurrence of chain transfer reactions followed by coupling during the polymerization as previously also observed for the polymerization of 2-ethyl-2-oxazoline (EtOx).$^{17}$ The molar masses and PDI values determined by SEC (PS calibration) are $M_n = 6,170$ g/mol, PDI = 1.35 for 1 p-R-EtEtOx, $M_n = 4,100$ g/mol, PDI = 1.32 for 2 p-R-BuEtOx, $M_n = 8,240$ g/mol, PDI = 1.25 for 3 p-R-
OctEtOx, $M_n = 6,680 \text{ g/mol}$, PDI = 1.28 for 4 p-R-NonEtOx and $M_n = 8,510 \text{ g/mol}$, PDI = 1.24 for 5 p-R-UndeEtOx, respectively. The difference in molar mass between the polymers is most likely due to variations in the [M]/[I] values as well as the utilization of a relative PS calibration.

**Figure 3.3** SEC traces of all five synthesized polymers (eluent: CHCl$_3$:triethylamine:i-so-propanol = 94:2:4).

### 3.2.1 Solubility

The solubility of this series of chiral polymers was investigated in different solvents with a sample concentration of 5 mg/mL to study the effect of the side-chain length. The transmittance of light through different solutions, i.e. turbidimetry, was measured at different temperatures between −5 and 65 °C. The results demonstrate that 1 p-R-EtEtOx is soluble in all polar solvents (Table 3.1), due to the relatively small apolar side-chain which makes the polar amide group accessible. In the apolar solvent $n$-heptane this polymer is insoluble as expected. However, in the apolar solvent cyclohexane 1 p-R-EtEtOx is soluble, most likely due to the chemical chair conformation of cyclohexane and the slightly higher dielectric constant.
3. Library of chiral main-chain poly(2-oxazoline)s

Table 3.1 Solubility of the chiral polymers measured at 5 mg/mL together with the dielectric constants and dipole moments of the solvents.

+ = soluble; - = insoluble

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Side-chain</th>
<th>Et</th>
<th>Bu</th>
<th>Oct</th>
<th>Non</th>
<th>Und</th>
<th>ε&lt;sup&gt;1&lt;/sup&gt;</th>
<th>μ&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>n-Heptane</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+&lt;sup&gt;2&lt;/sup&gt;</td>
<td>+</td>
<td>1.92</td>
<td>-0</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>N,N-Dimethylformamide</td>
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<td>-</td>
<td>-</td>
<td>38.3</td>
<td>3.82</td>
</tr>
</tbody>
</table>

<sup>1</sup>Dielectric constant (ε) and dipole moment (μ) taken from the CRC handbook of chemistry and physics 86th edition. <sup>2</sup>Soluble only at high temperatures. <sup>3</sup>Soluble after heating to 80 °C.

2 P-R-BuEtOx has a longer apolar side-chain, which makes the accessibility of the polar amide group more difficult resulting in a decrease in solubility in polar solvents. The side-chain is also not long enough to make the polymer soluble in apolar solvents. There seems to be only a small range of solvents in which 2 p-R-BuEtOx dissolves, which is related to its chirality, since the racemic polymer is soluble in most organic solvents (Chapter 2). Specifically the difference in solubility between 1 p-R-EtEtOx and 2 p-R-BuEtOx in cyclohexane can be pointed out. This is most likely caused by a difference in crystallinity between the two polymers, since side-chain crystallization can occur in the butyl side-chains,<sup>18</sup> which is not possible for the ethyl side-chains. As a result, 1 p-R-EtEtOx can be directly solvated, while in the case of 2 p-R-BuEtOx, solvation can only occur after disruption of the crystalline fraction. When the side-chain is elongated further, the polymers do become soluble in apolar solvents. 4 P-R-NonEtOx is only soluble in apolar solvents at high temperature, which might be due to a balance between crystallization and solubilization of the side-
3. Library of chiral main-chain poly(2-oxazoline)s

chains, since side-chain crystallization occurs in poly(2-oxazoline)s with an alkyl side-chain length of four carbons or more.\textsuperscript{16} \textbf{4} P-R-NonEtOx and \textbf{5} p-R-UndeEtOx are soluble in ethanol after heating, which is required to melt the crystals to enhance the accessibility of the polar solvent to the polar amide groups.\textsuperscript{19} In methanol and the aprotic polar solvents these polymers are insoluble, indicating that solvents with a dielectric constant up to 26 are capable to dissolve these polymers.

\subsection*{3.2.2 Secondary structure formation in solution}

The effect of the alkyl side-chain length on the formation of an ordered secondary structure was investigated with CD. All polymers revealed double Cotton effects in trifluoroethanol (TFE, Figures 3.4a, 3.5a, 3.6a, 3.7a and 3.8a), which slightly decreased in a linear manner with increasing temperature, indicating a small decrease in persistence length. \textbf{3} P-R-OctEtOx, \textbf{2} p-R-BuEtOx and \textbf{1} p-R-EtEtOx exhibited similar Cotton effects meaning that minor changes in the secondary structure occur when the alkyl side-chain is altered. Nonetheless, the persistence length slightly decreases with decreasing side-chain length demonstrated by the small decrease in the Cotton effects.\textsuperscript{20}

When the alkyl side-chain length is elongated to \textbf{4} p-R-NonEtOx and \textbf{5} p-R-UndeEtOx, a more pronounced decrease in the Cotton effects, in particular in the negative Cotton effect caused by the n-\(\pi^*\) transition of the amide chromophore, is observed and the maximum UV absorption is blue shifted (Figures 3.4b, 3.5b, 3.6b, 3.7b and 3.8b) indicating the formation of a different chiral structure. This change in secondary structure might be caused by a decrease in solubility of the apolar alkyl side-chains in the polar solvent TFE, resulting in a distinct conformational change when going from octyl to nonyl side-chains. With the increase in temperature the persistence length of all chiral polymers slightly decreased in a linear way.

The chiral structures of the polymers were also studied by CD using hexafluoroisopropanol (HFIP) as solvent (Figures 3.4c, 3.5c, 3.6c, 3.7c and 3.8c). At 50 °C the influence of the side-chain length on the Cotton effects are similar in HFIP and TFE. However, in HFIP the observed Cotton effects are more thermo-responsive and are significantly altered upon decreasing the temperature. The presence of an isosbestic point demonstrates that the polymer chains can adopt at least two different conformations that are interconvertible by temperature changes.
For the interpretation of the complex CD spectra at lower temperature, it is assumed that there are two different secondary structures formed: the same secondary structure as formed in TFE, referred to as conformation I, together with another conformation, referred to as conformation II. To validate this assumption, the Cotton effects measured in TFE (conformation I) were subtracted from the Cotton effects measured in HFIP, resulting in the CD spectra of conformation II (Figures 3.4e, 3.5e, 3.6e, 3.7e and 3.8e), which have inverse Cotton effects compared to conformation I and are slightly shifted to higher wavelengths, in particular at lower temperature. It may be speculated that conformation II has a slightly different secondary, presumably helical, structure due to hydrogen bonding of HFIP to the polymeric amide groups causing expansion of the secondary structure and inducing a shift in the UV-absorption (Figures 3.4d, 3.5d, 3.6d, 3.7d and 3.8d).

The amount of both secondary conformations is quantified based on the intensity of the Cotton effect of the n-π* absorption of the amide bond (~ 220 nm; Figure 3.4f, 3.5f and 3.6f) revealing a linear variation in the fraction of conformers with temperature. For \(1\) p-R-EtOx, \(2\) p-R-BuEtOx and \(3\) p-R-OctEtOx conformation I is mostly present above 20 °C and conformation II is predominant below 20 °C while at 20 °C both conformations are present in approximately equal amounts. The coexistence of both conformations is enabled by the dynamic flexible structure of these main-chain chiral poly(2-oxazoline)s allowing different parts of the chain to adopt different secondary structures while the remainder of the chain that is not involved in the secondary structures will form a random coil conformation. The increase in conformation II fraction with decreasing temperature indicates that indeed HFIP molecules that form hydrogen bonds with the polymer amide groups are involved in this secondary structure, which becomes stronger at lower temperatures as speculated in Chapter 2.

Upon increasing the side-chain length from \(3\) p-R-OctEtOx to \(4\) p-R-NonEtOx (Figure 3.7f) and \(5\) p-R-UndeEtOx (Figure 3.8f) the formation of conformation II is more and more suppressed. For \(4\) p-R-NonEtOx (Figure 3.7f) the formation of conformation I is predominated at all temperatures except at −10 °C where both conformations are present in equal fractions. Further increasing the side-chain length to undecyl chains leads to an almost complete loss of conformation II at 50 and −10 °C only 30% of the chiral fraction of the chain is present in conformation II compared to 60% for polymers with shorter side-chains (ethyl, butyl and octyl). These
results suggest that conformation II, which is correlated to the formation of hydrogen bonds with HFIP, is strongly suppressed possibly due to the steric hindrance of the long alkyl side-chains that decrease the hydrogen bonding ability and accessibility of the polymer amide groups. All together, CD spectroscopy of these main-chain chiral poly(2-oxazoline)s in both TFE and HFIP revealed that the secondary structure formation is significantly influenced by the length of the alkyl side-chains. The polymers with relatively short side-chains up to octyl groups revealed very similar secondary structure formation, while longer alkyl side-chains suppressed the secondary structure formation.
Figure 3.4 (a) UV absorption spectra and (b) CD traces of 1-p-R-EtEtOx in TFE (conformation I), (c) UV absorption spectra and (d) CD traces of 1-p-R-EtEtOx in HFIP and (e) CD traces in HFIP – CD traces in TFE (conformation II) of 1-p-R-EtEtOx. (f) Fraction of conformation I and conformation II in HFIP at different temperatures, calculated from the intensity of the Cotton effect by the π-π* bands of the amide chromophore.
Figure 3.5 (a) UV absorption spectra and (b) CD traces of 2 p-R-BuEtOx in TFE (conformation I), (c) UV absorption spectra and (d) CD traces of 2 p-R-BuEtOx in HFIP and (e) CD traces in HFIP – CD traces in TFE (conformation II) of 2 p-R-BuEtOx. (f) Fraction of conformation I and conformation II in HFIP at different temperatures, calculated from the intensity of the Cotton effect by the π-π* bands of the amide chromophore.
Figure 3.6 (a) UV absorption spectra and (b) CD traces of 3 p-R-OctEtOx in TFE (conformation I), (c) UV absorption spectra and (d) CD traces of 3 p-R-OctEtOx in HFIP and (e) CD traces in HFIP – CD traces in TFE (conformation II) of 3 p-R-OctEtOx. (f) Fraction of conformation I and conformation II in HFIP at different temperatures, calculated from the intensity of the Cotton effect by the π-π* bands of the amide chromophore.
Figure 3.7 (a) UV absorption spectra and (b) CD traces of 4 p-R-NonEtOx in TFE (conformation I), (c) UV absorption spectra and (d) CD traces of 4 p-R-NonEtOx in HFIP and (e) CD traces in HFIP – CD traces in TFE (conformation II) of 4 p-R-NonEtOx. (f) Fraction of conformation I and conformation II in HFIP at different temperatures, calculated from the intensity of the Cotton effect by the π-π* bands of the amide chromophore.
Figure 3.8 (a) UV absorption spectra and (b) CD traces of 5 p-R-UndeEtOx in TFE (conformation I), (c) UV absorption spectra and (d) CD traces of 5 p-R-UndeEtOx in HFIP and (e) CD traces in HFIP – CD traces in TFE (conformation II) of 5 p-R-UndeEtOx. (f) Fraction of conformation I and conformation II in HFIP at different temperatures, calculated from the intensity of the Cotton effect by the π-π* bands of the amide chromophore.
3.2.3 Influence of the solvent on the secondary structure formation

The effect of solvent polarity on the secondary structure formation is investigated in detail by CD and SANS, in collaboration with Sarah Rogers of the ISIS facility, for 5 p-R-UndeEtOx, which is soluble in a wide range of solvents (Table 3.1). CD revealed that the solvent polarity indeed influences the secondary structure formation (Figure 3.9). The maximum UV absorption in the apolar solvents is located at higher wavelengths compared to more polar solvents and the intensity of the Cotton effects are higher in apolar solvents indicating that the fraction of secondary chiral structure, i.e. persistence length, increases in apolar solvents due to the difference in solubility. In apolar solvents the long alkyl side-chains are solubilized while the polar amide groups are insoluble, resulting in a more pronounced secondary structure formation due to dipole interactions between the tertiary amide groups. In more polar solvents, the polar amide group is better solubilized than the long alkyl side-chains. As a result of solvation, the amide groups cannot interact resulting in a less defined secondary structure. The strong influence of subtle changes in the solvent polarity is demonstrated by red shifts of the UV absorption maxima and the increase in Cotton effects when changing from n-hexane to n-heptane. Moreover, in cyclohexane the ratio between the Cotton effects is different compared to the other apolar solvents, indicating that also the conformation of the solvent influences the formed secondary chiral structure of the main-chain chiral poly(2-oxazoline)s.

**Figure 3.9** (a) CD spectra and (b) UV absorption of 5 p-R-UndeEtOx in polar and apolar solvents at 20 °C.
The influence of the solvent polarity on the secondary structure formation of 5 p-R-UndeEtOx was further investigated with SANS (Figure 3.10 and Table 3.2). 5 P-R-UndeEtOx is not soluble in TFE-$d_3$ or HFIP-$d_2$ at a concentration of 2 mg/mL required for SANS measurements and, therefore $n$-butanol-$d_{10}$ was used as a polar solvent and $n$-hexane-$d_{14}$ and cyclohexane-$d_{12}$ were used as the apolar solvents, respectively. The resulting SANS profiles were modeled using ellipse, rod/disc and random coil models, whereby the calculated scale factors could be compared to those given from modeling and thereby used to identify the best fit. By comparison of the absolute intensities and the scale factors a difference in chain conformation was found depending on whether the polymer is dissolved in an apolar or in a polar solvent. 5 P-R-UndeEtOx dissolved in $n$-hexane-$d_{14}$ is best described with an ellipse model and 5 p-R-UndeEtOx dissolved in $n$-butanol-$d_{10}$ is best described with a rod model (fit lines are also shown in Figure 3.10a). In cyclohexane-$d_{12}$ the data fit equally well to an ellipse model and a rod model and, therefore, it cannot be concluded which chain conformation the polymer adopts in this solvent. The rather unexpected higher ordering in the polymer chain conformation in $n$-butanol-$d_{10}$ is most likely not due to the formation of a chiral secondary structure as indicated by the small Cotton effects determined in TFE and HFIP (CD in $n$-butanol was not measured due to the absorption of the solvent). Instead, the rigid rod chain conformation is most likely driven by solvophobic van der Waals interactions between long alkyl chains.
Figure 3.10 SANS analysis of 5 p-R-UndeEtOx dissolved in n-hexane-d$_{14}$ and cyclohexane-d$_{12}$ at a concentration of 5 mg/mL and in n-butanol-d$_{10}$ at a concentration of 2 mg/mL. (a) SANS profile and fits (solid lines) for an ellipse form factor when dissolved in n-hexane-d$_{14}$ or cyclohexane-d$_{12}$ and/or fits (solid lines) for a rod form factor when dissolved in cyclohexane-d$_{12}$ or n-butanol-d$_{10}$ (solid lines); and (b) the Guinier analysis.

The investigated polymer consists of approximately 37 monomer units and when the polymer backbone is completely stretched, the length of the polymer chain is calculated to be approximately 74 Å. The length of the alkyl side-chain is 4 Å when it is fully stretched so the total width of the polymer is maximum 8 Å when the side-chains stick out on both sides. The fitted length (L) of the polymer chains in n-butanol were determined to be 78 Å indicating full stretching of the chains in n-butanol. The width of the structures in n-butanol is larger than the maximum theoretical width of 8 Å indicating that multiple chains aggregate, presumable by solvophobic side-chain interactions leading to close packing of the side-chains.

The $R_g$ can be calculated from the ellipse structure, as explained before in Chapter 2 and from the rod model by using the parameters of the primary radius, R, and the length, L, which are obtained from fitting using the rod model which has the following equation$^{43}$

$$R_g = \sqrt{\frac{R^2}{2} + \frac{L^2}{12}}$$

The $R_g$ values from the mathematical modeling do not compare well to those found from the Guinier analysis (Figure 3.10b) as can be seen from Table 3.2. Again at low
Q range the intensity increases due to interparticle interaction (aggregation) and, therefore, these values are not included in the fits of $R_g$ (open symbols in Figure 3.10b). However, $qR_g > 1.3$ for the linear range, indicating that the $R_g$ values calculated from Guinier analysis are not reliable. Nonetheless, the $R_g$ values are similar in all three solvents.

Table 3.2 Comparison of best fit parameters to SANS data found from mathematical modeling and Guinier analyses.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>R1 ellipse fit (Å)</th>
<th>X ellipse (Å)</th>
<th>R rod (Å)</th>
<th>L rod (Å)</th>
<th>$R_g$ (Å) FISH</th>
<th>$R_g$ (Å) Guinier</th>
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<tr>
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<td>37</td>
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<tr>
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<td>5</td>
<td>13</td>
<td>74</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>n-Butanol-$d_{10}$</td>
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<td>-</td>
<td>13</td>
<td>78</td>
<td>24</td>
<td>35</td>
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</tbody>
</table>

1 Uncertainty in absolute intensities is 5% and in $R_g$ is ± 2 Å.

3.2.4 Thermal properties

In Chapter 2 the thermal properties of 2 p-R-BuEtOx were described and it was found that this polymer has a glass transition temperature ($T_g$) followed by cold crystallization ($T_{cc}$) and a double melting peak ($T_{m1}$ and $T_{m2}$) due to melt-recrystallization. Since the racemic polymer was completely amorphous, the crystallinity must at least partially be the result of its chirality, allowing regular packing of the polymer chains. To investigate the effect of the side-chain length on the thermal properties, also the other chiral poly(2-alkyl-4-ethyl-2-oxazoline)s were analyzed by differential scanning calorimetry (DSC) to determine their thermal properties.
When the side-chain length was decreased to ethyl in 1 p-R-EtEtOx an endotherm was observed in the first heating run, while the second heating run only revealed a $T_g$ at 92 °C with a heat capacity ($\Delta C_p$) of 0.38 J/(g K) (Figure 3.1). The endotherm on top of the $T_g$ in the first heating run is most probably due to aging or enthalpic relaxation of the polymer sample, which means that during annealing, i.e. storage, below the $T_g$, the polymer chains relax towards an equilibrium state which results in a decrease of thermodynamic parameters such as enthalpy and specific volume.\textsuperscript{21} This structural rearrangement causes an endotherm in the first heating run. No melting endotherm ($T_m$) could be observed up to a temperature of 250 °C, also annealing above the $T_g$ at 120 °C for 24 hours did not result into crystallization demonstrating that this polymer is completely amorphous like poly-2-ethyl-2-oxazoline (pEtOx). The ethyl side-chains are too short to crystallize and also the main-chain does not crystallize.
Table 3.3 Thermal properties of 3 p-R-OctEtOx after annealing (T_a = 60 °C: 10 °C/min and t_a = 33 h: 20 °C/min).

<table>
<thead>
<tr>
<th>T_a (h)</th>
<th>T_m (°C)</th>
<th>ΔH (J/g)</th>
<th>T_a (°C)</th>
<th>T_m (°C)</th>
<th>ΔH (J/g)</th>
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</thead>
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<td>12</td>
<td>112</td>
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<tr>
<td>15</td>
<td>112</td>
<td>0.5</td>
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<td>2</td>
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<td>113</td>
<td>15</td>
<td>100</td>
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</table>

When the side-chain length is increased to octyl in 3 p-R-OctEtOx, a melting endotherm is observed in the first heating run at 115 °C with a small peak at 75 °C and a melting enthalpy (ΔH_m) of 27 J/g. However, in the second heating run the T_m did not appear anymore (Figure 3.13a) indicating that the polymer does not crystallize either from the melt during cooling or from the rubbery state during heating. The T_g appeared around −10 °C (Figure 3.13b). The polymer needed to be annealed for at least 12 hours at 60 °C to obtain a small amount of crystals with a T_m of 112 °C (Figure 3.13c). The heating rate was decreased from 20 to 10 °C/min, in order to enable a better detection of the T_m. The amount of crystals increased with increasing annealing time (t_a) and this increase starts to level off after 30 hours (Table 3.3). A second unclear annealing effect is also observed, namely the appearance of a hump in front of the melting endotherm which increases with increasing annealing time. When the polymer is annealed for 33 h at different temperatures, it can be concluded that an annealing temperature (T_a) between 60 and 70 °C results in the highest fraction of crystals and that the T_m increases from 115 to 122 °C when the T_a is increased from 60 to 80 °C, indicating the formation of more perfect crystals at higher T_a (Table 3.4 and Figure 3.13d). Compared to 2 p-R-BuEtOx the T_m of 3 p-R-OctEtOx is much lower and a long annealing time is necessary in order to form crystals. The crystallinity of 3 p-R-OctEtOx is probably due to side-chain crystallization, since the melting endotherm is close to the melting temperature of achiral semi-crystalline
poly(2-alkyl-2-oxazoline)s, which have a $T_m$ of $\sim 150 \, ^\circ C$.\textsuperscript{16} Due to the more rigid and bulky chiral main-chain it takes a long time before the octyl side-chains crystallize, making long annealing times necessary. Moreover, the presence of the ethyl main-chain substituents and the chiral organization results in less stable crystals leading to a lower $T_m$. It might be speculated that besides side-chain crystallization also main-chain crystallization occurs in 2 p-R-BuEtOx, which could explain the much higher $T_m$ at 210 °C.

Figure 3.12 DSC traces of 3 p-R-OctEtOx of (a) the first and second heating run (20 °C/min), (b) second heating run at lower temperatures to detect the $T_g$ (20 °C/min), (c) after annealing at 60 °C for different annealing times (10 °C/min) and after annealing for 33 h at different annealing temperatures (20 °C/min).

For 4 p-R-NonEtOx a double melting peak with $T_{m1} = 79 \, ^\circ C$ and $T_{m2} = 93 \, ^\circ C$ and a total $\Delta H_m$ of 57 J/g is observed in the first heating run (Figure 3.13a) while no $T_g$ could be detected. In the second heating run the melting peak is completely disappeared like in 3 p-R-OctEtOx. Also 5 p-R-UndeEtOx reveals a double $T_m$ with
3. Library of chiral main-chain poly(2-oxazoline)s

\[ T_{m1} = 83 \, ^\circ C \] and \[ T_{m2} = 100 \, ^\circ C \] and a total \[ \Delta H_m \] of 51 J/g in the first heating run (Figure 3.14a). However, annealing \( 4 \) p-R-NonEtOx for 2 hours at 20 \(^\circ\)C already resulted in the formation of some crystals (Figure 3.13b) and \( 5 \) p-R-UndeEtOx crystallizes already during heating (\( T_{cc} = 40 \, ^\circ C \), \( \Delta H_{cc} = -39 \, J/g \)) in the second heating run. From these results it can be concluded that the crystallization rate of the chiral polymer increases when the side-chain length is increased from octyl side-chains to nonyl and undecyl side-chains, indicating that these polymers indeed undergo side-chain crystallization. Parts further away from the backbone have more flexibility to adopt ideal packing conformation. Upon annealing \( 4 \) p-R-NonEtOx for 2 hours at 20 \(^\circ\)C a double melting endotherm in the temperature range between 85 and 105 \(^\circ\)C was observed. The double melting endotherm is due to melt-recrystallization since \( \Delta H_{m2} \) decreases and \( \Delta H_{m1} \) increases and \( T_m \) moves to higher temperature with increasing \( T_a \) (Table 3.4; Figure 3.13b). No melting endotherm in the temperature range between 60 and 85 \(^\circ\)C is observed like in the first heating run. However, when the annealing time is increased, also a double melting endotherm (\( T_{m3} \) and \( T_{m4} \)) is visible in this temperature range (Table 3.4; Figure 3.13c). Similar thermal behavior as \( 4 \) p-R-NonEtOx is observed for \( 5 \) p-R-UndeEtOx. Annealing the polymer for 1 hour at 30 \(^\circ\)C resulted in the formation of a double melting endotherm between 85 and 110 \(^\circ\)C due to melt-recrystallization and no melting endotherm could be detected between 60 and 85 \(^\circ\)C as in the first heating run (Table 3.5; Figure 3.14b). By increasing the annealing time, a third melting endotherm (\( T_{m3} \)) appeared in the temperature range from 60 to 80 \(^\circ\)C (Table 3.5; Figure 3.14c). The origin of the additional melting endotherm was investigated by DSC measurements with increasing heating rate of \( 5 \) p-R-UndeEtOx which were annealed for 4 hours at 40 \(^\circ\)C (Table 3.5; Figure 3.14d) and by annealing \( 5 \) p-R-UndeEtOx for 4 hours with increasing \( T_a \) (Table 3.5; Figure 3.14e). Again \( T_{m1} \) and \( T_{m2} \) merge into one melting peak by increasing the heating rate or annealing temperature, confirming that \( T_{m1} \) and \( T_{m2} \) are the result of melt-recrystallization. However, \( T_{m3} \) only slightly increases to higher temperature with increasing heating rate or annealing time, indicating that these crystals are not part of the melt-recrystallization mechanism. Only when \( T_a \) comes close to \( T_{m3} \), a shoulder in front of \( T_{m1} \) is observed instead of \( T_{m3} \). Since the melting peaks (\( T_{m1} \) and \( T_{m2} \)) at the higher temperature appear before the melting endotherm (\( T_{m3} \)) at lower temperature, this indicates that the melting peaks are possibly caused by a dual crystal size population at which the crystal sizes are smaller at the lower
3. Library of chiral main-chain poly(2-oxazoline)s

melting temperature. Another explanation could be the presence of a second chirally ordered structure. If another secondary structure is formed, this might be detected by CD measurements of the polymer film.

Table 3.4 Thermal properties of 4p-R-NonEtOx after annealing (20 °C/min).

<table>
<thead>
<tr>
<th>T_a (°C)</th>
<th>T_m1 (°C)</th>
<th>T_m2 (°C)</th>
<th>ΔH_m (J/g)</th>
<th>t_a (h)</th>
<th>T_m1 (°C)</th>
<th>T_m2 (°C)</th>
<th>ΔH_m (J/g)</th>
<th>T_m3 (°C)</th>
<th>T_m4 (°C)</th>
<th>ΔH_m (J/g)</th>
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</table>
3. Library of chiral main-chain poly(2-oxazoline)s

Figure 3.13 DSC traces of 4 p-R-NonEtOx of (a) the first and second heating run, (b) after annealing for 2 h at different annealing temperatures (20 °C/min) and (c) after annealing at 40 °C for different annealing times (20 °C/min).
3. Library of chiral main-chain poly(2-oxazoline)s

Figure 3.14 DSC traces of 5 p-R-UndeEtOx of (a) the first and second heating run (10 °C/min), (b) after annealing for 1 hour at different annealing temperatures (20 °C/min), (c) after annealing at 40 °C for different annealing times (20 °C/min), (d) after annealing at 40 °C for 4 h with different heating rate and (e) after annealing for 4 hours at different temperatures.
3. Library of chiral main-chain poly(2-oxazoline)s

Table 3.5a *Thermal properties of 5 p-R-UndEtOx after annealing (20 °C/min).*

<table>
<thead>
<tr>
<th>$T_a$ (°C)</th>
<th>$T_{m1}$ (°C)</th>
<th>$T_{m2}$ (°C)</th>
<th>$T_{m3}$ (°C)</th>
<th>$\Delta H_m$ (J/g)</th>
<th>$t_a$ (h)</th>
<th>$T_{m1}$ (°C)</th>
<th>$T_{m2}$ (°C)</th>
<th>$T_{m3}$ (°C)</th>
<th>$\Delta H_m$ (J/g)</th>
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<td>75</td>
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</table>

Table 3.5b *Continued.*

<table>
<thead>
<tr>
<th>$T_a$ = 40 °C, $t_a$ = 4 hours</th>
<th>$T_a$ = 4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>$hr$ (°C/min)</td>
<td>$T_{m1}$ (°C)</td>
</tr>
<tr>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>20</td>
<td>93</td>
</tr>
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<td>50</td>
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</tr>
<tr>
<td>60</td>
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</tbody>
</table>

When the thermal results of the chiral poly(2-oxazoline)s are compared, it can be concluded that the alkyl side-chains require a certain length before side-chain crystallization can occur, since 1 p-R-EtEtOx is completely amorphous. 2 P-R-BuEtOx has a relatively high melting temperature, probably due to a close packing of the main-chain induced by the side-chain crystallization. By increasing the side-chain length from butyl chains to octyl chains, a significant drop in the melting temperature is observed, which corresponds to side-chain crystallization, and the crystallization rate of the side-chain crystallization is decreased due to the more bulky, chiral backbone. Further increasing the side-chain length results in an increase in crystallization rate and the presence of a dual crystal population.
3. Library of chiral main-chain poly(2-oxazoline)s

3.2.5 Formation of chiral crystals

CD measurements of spin coated polymer films were performed to investigate if the crystalline structures of the chiral poly-2-oxazolines are chirally ordered and whether different chiral structures are formed during the different melt-transitions. 2 P-R-BuEtOx crystallizes upon heating around 100 °C and also the Cotton effect at 198 nm increased significantly in size at this temperature, indicating that the crystals formed in 2 p-R-BuEtOx are chirally ordered, as discussed in Chapter 2.

1 P-R-EtEtOx is amorphous and reveals weak dichroic Cotton effects at all temperatures (Figure 3.15). The Cotton effect caused by the n-π* transition decreases in strength with increasing temperature. This indicates that still some chiral order is present in the amorphous polymer, which is reduced with increasing temperature.

![Temperature dependent CD spectra of 1 p-R-EtEtOx film.](image)

The initially present crystals in 3 p-R-OctEtOx, as seen in the first DSC heating run, probably disappear upon solvation in chloroform, since the polymer film only reveals weak dichroic Cotton effects which decrease in strength with the increase in temperature, indicating that the persistence length decreases with increasing temperature like in solution (Figure 3.16a). No sudden drop in Cotton effects is observed around the melting temperature of 115 °C, indicating that the spincoated film was indeed amorphous. The CD results of the annealed 3 p-R-OctEtOx film reveal that chiral crystals have formed since the Cotton effect due to the n-π* transition became positive, resulting in two positive Cotton effects (Figure 3.16b). At 100 °C the crystals start to melt and the positive Cotton effect around 224.5 nm decreases in intensity until all crystals are molten and a negative Cotton effect is observed again at 220 nm. Only a thin annealed polymer film could be measured,
3. Library of chiral main-chain poly(2-oxazoline)s

since most polymer films turned completely opaque upon annealing due to the crystal formation, making it impossible to pass enough light through the sample to be measured. The high tension (HT) of this annealed polymer film just went through the maximum of 600 V below 205 nm (634 V max.). When 3 p-R-OctEtOx crystallizes this mainly influences the Cotton effect caused by the n-π* transition, while the Cotton effect caused by the π-π* transition is mainly changed when 2 p-R-BuEtOx crystallizes. This difference in the CD spectra might be due to the difference in crystallinity as speculated before; the main-chain of 2 p-R-BuEtOx is probably closely packed, while in the polymers with longer side-chains, only side-chain crystallization occurs.

Figure 3.16 (a) CD spectra of a 3 p-R-OctEtOx film and (b) CD spectra of 3 p-R-OctEtOx film annealed at 70 °C for 16 hours at increasing temperature.

4 P-R-NonEtOx also reveals weak dichroic Cotton effects, just like 3 p-R-OctEtOx (Figure 3.17). At 50 °C this does not change, however, after annealing the polymer at 50 °C for 1 hour, both Cotton effects increase in strength (Figure 3.17a). By annealing the polymer for longer times at 50 °C, chiral crystals form which results in the formation of a strong positive Cotton effect which shifts to higher wavelengths and increases in intensity with increasing annealing time. The CD spectrum of 4 p-R-NonEtOx after annealing is different compared to the annealed 2 p-R-BuEtOx due to the side-chain crystallization that occurs in 4 p-R-NonEtOx, which most likely forces the amide moieties in a different chiral orientation. By increasing the temperature the Cotton effect decreases, until weak positive and negative dichroic Cotton effects
appear again after the crystals have melted (Figure 3.17b). At 80 ºC the crystals responsible for \( T_{m3} \) have melted (Figure 3.13c), however, no change in the CD spectra occurs at this temperature indicating that \( T_{m3} \) is probably not the result of the presence of another secondary structure, but is related to different crystal sizes. In another polymer film, the same small dichroic Cotton effects are observed after spin coating (Figure 3.17c). However, when the temperature reaches 50 ºC the Cotton effects do not increase in intensity, but the dichroic Cotton effects almost completely disappeared. Measuring the polymer film again at 50 ºC resulted in a strong positive Cotton effect like the first polymer film, but now at a higher wavelength together with a negative Cotton effect. The second polymer film also needed to be heated to higher temperature in order to melt the chiral crystals (Figure 3.17d). The polymer film intended for annealing prior to the measurement was spin-coated from chloroform with a lower concentration of 5 instead of 20 mg/mL to assure that enough light could pass through the final polymer film. After annealing the thin polymer film for 4 hours at 50 ºC, strong dichroic Cotton effects are measured, although the signs were not inverted (Figure 3.17e). Upon heating the strength of the Cotton effects decrease with a stronger decrease at 80 ºC indicating that the crystals start to melt until hardly any Cotton effects are observed anymore at 90 ºC. The different results indicate that the thickness of the polymer film has a large effect on the obtained CD spectra. However, the side-chain length also plays a role since different films of 2 p-\textit{R}-BuEtOx always resulted in the same CD spectra. Presumably, the side-chain crystallization influences the orientation of the main-chain in different ways depending on the crystal thickness, resulting in different CD spectra.
Figure 3.17 CD and spectra of (a) a 4-p-R-NonEtOx film and (b) a 4-p-R-NontEtOx film annealed at 50 °C for 4 hours with increasing temperature (20 mg/mL). CD spectra of (c) and (d) another 4-p-R-NonEtOx film with increasing temperature (20 mg/mL) and (e) a 4-p-R-NonEtOx film annealed at 40 °C for 2 hours (5 mg/mL).
Figure 3.18 CD and spectra of (a) a 5 p-R-UndeEtOx film and (b) a 5 p-R-UndeEtOx film annealed at 40 °C for 1.5 hours followed by annealing at 50 °C for 1.5 hours with increasing temperature. CD spectra of (c) and (d) another 5 p-R-UndeEtOx film with increasing temperature and (e) a 5 p-R-UndeEtOx film annealed at 50 °C for 4 hours.
Small dichroic Cotton effects were also observed when 5 p-R-UndEtOx was spin coated (Figure 3.18). At 40 °C the Cotton effects decrease in strength followed by the appearance of a strong negative Cotton effect at 50 °C (Figure 3.18a), while the positive Cotton effect remained small. When the temperature was set back to 40 °C, the negative Cotton effect was increased even more, indicating that chiral crystals have formed during heating. Leaving the polymer for longer times at 50 °C does not result in a stronger Cotton effect. When the temperature is further increased, the negative Cotton effect decreases in strength until almost no Cotton effects are observed anymore at 120 °C when the crystals have melted (Figure 3.18b).

Different results were obtained for a second polymer film which is ascribed to the difference in film thickness resulting in differences in crystallization. This second polymer film resulted in the formation of a strong positive Cotton effect instead of a strong negative Cotton effect at 50 °C (Figure 3.18c). At 110 °C the crystals melted and again a weak dichroic Cotton effect was observed (Figure 3.18d). The annealed polymer film hardly revealed any Cotton effects, indicating that the film spin coated from 5 mg/mL was too thin to form crystals (Figure 3.18e).

In general, crystallization has mainly an effect on the Cotton effect caused by the n-π* transition for 3 p-R-OctEtOx, 4 p-R-NonEtOx and 5 p-R-UndEtOx, while the Cotton effect caused by the π-π* transition is mainly increased in strength when 2 p-R-BuEtOx crystallizes. This difference might be explained by a difference in crystallinity; the crystals of 2 p-R-BuEtOx are proposed to be due to a combination of side-chain and main-chain crystallization, while longer side-chains prevent the close packing of the main-chains resulting in only side-chain crystallization, which could also explain the large difference in the melting temperatures. Furthermore, the film thickness of 4 p-R-NonEtOx and 5 p-R-UndEtOx effects the crystallization resulting in different CD spectra. It is commonly observed that the crystallization rate as well as the morphology of polymer crystals are changed in confined space like ultrathin films.23

### 3.3 Influence bulky side-chains

Besides alkyl side-chains, also phenyl or benzyl groups were incorporated in the chiral main-chain poly(2-oxazoline)s to investigate if the chiral structure is better stabilized in solution by more bulky side-chains. For this purpose the monomers R-2-phenyl-4-ethyl-2-oxazoline (R-PhEtOx)24 and R-2-benzyl-4-ethyl-2-oxazoline (R-
BnEtOx) were synthesized and polymerized under microwave-assisted conditions using methyl tosylate as initiator and acetonitrile as solvent. Due to the bulky side-chains that hinder the polymerization, 6 p-R-PhEtOx and 7 p-R-BnEtOx were obtained with a low molar mass ($M_n$) of 1,870 g/mol and a PDI of 1.41 for 6 p-R-PhEtOx and a $M_n$ of 1,150 g/mol and a PDI of 1.22 for 7 p-R-BnEtOx, as measured by SEC (Figure 3.19). Changing the initiator to methyl triflate or changing the solvent to benzonitrile did not result in improved polymerization behavior.

![SEC traces of 6 p-R-PhEtOx and 7 p-R-BnEtOx](image)

**Figure 3.19** SEC traces of 6 p-R-PhEtOx and 7 p-R-BnEtOx obtained under microwave-assisted conditions at 180 °C for 1 h using MeOTs as initiator ($M/I = 60$) and acetonitrile as solvent ($M_0 = 3 \text{ M}$).

Since the molar masses were quite low, only 6 p-R-PhEtOx was analysed by DSC and CD to investigate the influence of the bulky side-chain. In the first heating run, a peak was observed at 94 °C which was due to the glass transition as can be seen from the second heating run (Figure 3.20). No melting peak was observed up to a temperature of 200 °C, indicating that the polymer is amorphous.
3. Library of chiral main-chain poly(2-oxazoline)s

Figure 3.20 DSC traces of 6 p-R-PhEtOx of the first and second heating run (heating rate = 20 °C/min).

In solution 6 p-R-PhEtOx reveals a dichroic Cotton effect due to the amide chromophore with an isosbestic point around the wavelength where the absorption is maximal (Figure 3.21). The phenyl side-chain causes a second UV absorption around 230 nm and, therefore, another Cotton effect is observed around this wavelength due to the \( \pi-\pi^* \) transition of the phenyl groups which are located in a chirally perturbed environment.\(^{25} \) In TFE and HFIP approximately the same CD results are obtained, indicating that the bulky side-chains prevent the inversion of the dichroic Cotton effect with increasing temperature. Also the Cotton effects do not decrease with increasing temperature when dissolved in HFIP, like 5 p-R-UndeEtOx, indicating that the bulky side-chains prevent the formation of a second conformation caused by hydrogen bond formation between the solvent and the polymer amide group due to sterical hindrance of the phenyl groups. Both in TFE and HFIP the Cotton effects decrease slightly in intensity with the increase in temperature, indicating that the persistence length slightly decreases with increasing temperature. Compared to the chiral poly(2-oxazoline)s with an alkyl side-chain the UV absorption as well as the dichroic Cotton effects caused by the amide chromophore shifted to lower wavelengths, which indicates that the type of secondary structure changes when the side-chains are changed from alkyl groups to bulky phenyl groups. Furthermore, the intensities of the dichroic Cotton effects caused by the amide chromophore have not increased in intensity compared to the poly(2-alkyl-4-ethyl-2-oxazoline)s, indicating that the secondary structure is not further stabilized by the bulky aromatic rings nor by \( \pi-\pi \) interactions.
3. Library of chiral main-chain poly(2-oxazoline)s

Figure 3.21 (a) UV absorption and (b) CD spectra of \(6 \text{P-R-PhEtOx}\) in TFE and (c) UV absorption and (b) CD spectra of \(6 \text{P-R-PhEtOx}\) in HFIP with increasing temperature.

3.4 Conclusion

Five different chiral 2-oxazoline monomers with varying alkyl side-chain lengths could be prepared and polymerized in a living manner. \(1 \text{P-R-EtEtOx}\) is soluble in polar solvents due to the accessibility of the polar amide group, while polymers with a long alkyl side-chain of eight carbon atoms or more become soluble in apolar solvents. The CD results of the polymers dissolved in TFE and HFIP indicate that the chiral conformation changes when the side-chain length is elongated from octyl to nonyl chains probably due to a decrease in solubility of the longer apolar side-chains in the polar solvents. In HFIP the chiral conformation is thermo-responsive due to the presence of two chiral conformations which exist in different ratios at different temperatures. Conformation I has the same conformation as formed in TFE and conformation II is caused by the hydrogen bond formation between the polymer
amide group and the solvent, which becomes stronger at lower temperatures. Conformation II is suppressed when the alkyl side-chain length is increased to nonyl or undecyl chains possibly due to the steric hindrance of the long alkyl side-chains that decrease the hydrogen bonding ability of the polymer amide groups. The long-range structure of 2 p-R-BuEtOx in HFIP-d2 measured with SANS is not responsive to temperature indicating that both chiral structures are present in each dynamic and flexible chain at all temperatures. Furthermore, the polarity of the solvent influences both the short-range structure as well as the long-range structure of 5 p-R-UndeEtOx due to a change in solvation. In apolar solvents a more pronounced secondary structure is formed since the backbone amide groups are not soluble in apolar solvents. In polar solvents, on the other hand, the polymer backbone is completely stretched.

The crystallinity of the polymers changes when the side-chains are altered. 1 P-R-EtEtOx is amorphous while the polymers with longer alkyl side-chains are semicrystalline due to side-chain crystallization. However, 2 p-R-BuEtOx most likely also reveals main-chain crystallization resulting in a significant higher melting temperature. Furthermore, the crystallization rate depends on the alkyl side-chain length; while 2 p-R-BuEtOx still reveals melting endotherms in the second heating run, 3 p-R-OctEtOx has to be annealed extensively in order to form crystals, while 4 p-R-NonEtOx and 5 p-R-UndeEtOx form crystals after a short annealing period or directly in the second heating run, respectively. After annealing 4 p-R-NonEtOx and 5 p-R-UndeEtOx for a longer period, a third endotherm at lower temperature appears besides a double melting peak due to melt-recrystallization, most likely due to a dual crystal population.

Since 1 p-R-EtEtOx is amorphous, it only reveals dichroic Cotton effects in bulk, which are similar as in solution. The formation of crystals mainly affects the π-π* transition of the amide chromophore of 2 p-R-BuEtOx, while the n-π* transition is mainly changed for the chiral polymers with longer alkyl side-chains, which indicates that the type of chiral crystals formed are different as also indicated by the difference in melting temperature. The film thickness of 4 p-R-NonEtOx and 5 p-R-UndeEtOx also has a large influence on the CD spectra, due to differences in the crystal thickness.

By changing the alkyl-side chains into bulky benzyl or phenyl groups, the polymerization does not reach completion due to sterical hindrance. 6 P-R-PhEtOx
was found to be completely amorphous. The sterical hindrance of the phenyl group prevented the formation of hydrogen bonds between HFIP and the amide group of the polymer since the Cotton effects did not inverse in sign with the decrease in temperature. Another Cotton effect was observed due to the $\pi-\pi^*$ transition of the phenyl group indicating that the chirality of the main-chain is transferred to the side-chains.

These results indicate that the side-chains have a significant influence on the properties of the chiral polymers. The most significant change in optical properties in solution occurs when the side-chain length is increased from octyl chains to nonyl chains. The thermal properties vary a lot with the increase in side-chain length, from completely amorphous for 1 p-R-EtEtOx to a close packing of the main-chain for 2 p-R-BuEtOx to solely side-chain crystallization for 3 p-R-OctEtOx, 4 p-R-NonEtOx and 5 p-R-UndEtOx. Changing the side-chains from alkyl groups to bulky phenyl groups resulted in more sterical hindrance preventing hydrogen bond formation between the polymer and HFIP.

### 3.5 Experimental

**Materials and Instrumentation**

$n$-Propionitrile (Aldrich), $n$-valeronitrile (Aldrich), $n$-nonanenitrile (Aldrich), $n$-undecanenitrile (Aldrich), $n$-dodecanenitrile (Aldrich), benzonitrile (Aldrich) benzylcyanide (Aldrich) and $R$-2-amino-1-butanol (ee 96%, Aldrich) were used as received. Acetonitrile (Aldrich) was dried in a solvent purification system (Pure Solv EN, Innovative Technology) before use as a polymerization solvent. Methyl tosylate (Aldrich) was distilled over barium oxide and stored under argon.

Small-scale reactions of 1 mL were carried out in capped reaction vials in a Biotage Initiator Sixty microwave system equipped with an IR temperature sensor. The vials were dried in an oven at 105 °C and cooled under argon to room temperature before usage.

$^1H$ NMR and $^{13}C$ NMR spectra were recorded in CDCl$_3$ using a Bruker Advance 250 or 400 MHz spectrometer. Chemical shifts are given in ppm relative to TMS.

GC measurements were performed on a Schimadzu GC-2010 equipped with a Restek Rtx-5 column, a FID detector and a PAL autosampler.
3. Library of chiral main-chain poly(2-oxazoline)s

ESI-Q-TOF-MS measurements were performed with a microTOF Q-II (Bruker Daltonics) mass spectrometer equipped with an automatic syringe pump from KD Scientific for sample injection.

GC-MS measurements were performed using a Shimadzu GC-17A (Column: DB-SMS, 5% phenyl-/95% dimethylpolysiloxane, length = 30 m, inner diameter = 0.25 mm, film thickness = 0.1 μm) connected to an AOC-20i autoinjector and a GCMS-QP5050A mass spectrometer. Ionization was performed by EI (electron impact 70 eV).

Size exclusion chromatography (SEC) was measured on a Shimadzu system equipped with a LC-10AD pump, a RID-10A refractive index detector, a SCL-10A VP system controller, and a PSS SDV pre/lin S column utilizing chloroform:triethylamine:isopropanol (93:5:2) mixture as eluent at a flow rate of 1 mL/min and a column temperature of 40 °C (polystyrene calibration).

Solubility tests were performed using a Crystal 16 from Avantium Technologies at a concentration of 5 mg/mL. The transmittance was measured at a temperature range from –15 to 65 °C using methanol, ethanol, n-butanol, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, n-heptane and cyclohexane as solvents.

UV and CD absorption spectra were measured simultaneously on a Jasco J815 spectropolarimeter equipped with a PTC-348WI temperature controller for temperatures ranging from –10 to 110 °C. Measurements were performed in a 1 mm quartz cell using sample concentrations of 0.25 mg/mL. The following scanning conditions were used: 50 nm/min scanning rate, 1 nm bandwidth, 0.1 nm datapitch, 0.5 s response time, and 10 accumulations. For measurements in bulk the samples were spin coated from chloroform (5-40 mg/mL) onto a quartz slide for 2 minutes with 2,000 rpm. The following scanning conditions were used: 50 nm/min scanning rate, 1 nm bandwidth; 0.1 nm datapitch, 0.5 s response time, and 10 accumulations.

SANS experiments were conducted on the time-of-flight LOQ diffractometer at the ISIS neutron facility. The incident wavelength range of 2.2 – 10 Å resulted in a Q-range of 0.009 – 0.249 Å⁻¹. Absolute intensities for I (Q) (cm⁻¹) were determined within 5% by measuring the scattering from a partially deuterated polymer standard. Standard procedures for data treatment were employed. The measurements were performed in a 2 mm quartz cell using sample concentrations of 5.29 mg/mL in HFIP-d₂, 4.50 mg/mL in cyclohexane-d₁₂, 4.33 mg/mL n-hexane-d₁₄ and 2 mg/mL in butanol-d₁₀. Heating was necessary to dissolve the polymer in butanol-d₁₀. The
solutions were filtered over 200 nm filters before the measurements. Solvent-scattering profiles were subtracted for background correction. The FISH analysis program\textsuperscript{27} was used for data modeling. Either an ellipsoid form factor, a rod/disc form factor or a Gaussian coil model were employed depending on the conformation of the chain being studied. There are two structural dimensions in both the ellipsoidal and rod/disc form factor models; for the ellipsoidal model there is the primary and secondary radii $R_1$ and $R_3$ with the aspect ratio $X = R_3/R_1$. The value of $X$ is unity for a spherical, $<1$ for an oblate and $>1$ for a prolate structure. For the rod/disc model there is the length ($L$) and radius ($R$). If $L > R$ then the structure is a rod and $R > L$ then the structure is a disc. Although estimates of all of these values can be made from the length and the structure of the polymer, all parameters were allowed to float during the fitting process. Values for $I(0)$, flat background and radius of gyration are obtained from the Gaussian coil model and again these were allowed to adjust freely during the modeling process. In all cases absolute intensity and scale factor checks were made to ensure the values obtained were physically realistic. Further detail on the models used can be found in the FISH manual.\textsuperscript{28} The radii of gyration were also determined by Guinier analysis. More information about the SANS measurements can be found in the experimental part of Chapter 2.

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netsch under nitrogen atmosphere with cooling rates of 20 °C/min and heating rates of 20 °C/min, unless stated differently.

**Monomer synthesis**

All monomers have been synthesized in a similar way by reacting $R$-2-amino-1-butanol with the corresponding nitrile using zinkacetate dihydrate as the catalyst, resulting in $R$-2,4-ethyl-2-oxazoline ($R$-EtEtOx), $R$-2-buty1-4-ethyl-2-oxazoline ($R$-BuEtOx) (see Chapter 2), $R$-2-octyl-4-ethyl-2-oxazoline ($R$-OctEtOx), $R$-2-nonyl-4-ethyl-2-oxazoline ($R$-NonEtOx), $R$-2-undecyl-4-ethyl-2-oxazoline ($R$-UndeEtOx), $R$-2-phenyl-2-ethyl-2-oxazoline ($R$-PhEtOx) and $R$-2-benzyl-2-ethyl-2-oxazoline. The monomers were characterized with $^1$H NMR spectroscopy, $^{13}$C NMR spectroscopy, GC-MS and HR-MS (ESI-TOF) to prove their structure and purity.

$R$-EtEtOx: $^1$H NMR (400 MHz, $\delta$ in ppm, CDCl$_3$): 4.18 (t, $J = 8.74$ Hz, CH$_3$O, 1H), 3.92 (q, $J = 7.41$ Hz, CHN, 1H), 3.74 (t, $J = 7.74$ Hz, CH$_2$O, 1H), 2.20 (t, $J = 7.59$ Hz, OCCH$_2$CH$_3$, 2H), 1.2-1.7 (br, $J = 6.75$-7.01 Hz, NCHCH$_2$CH$_3$, 2H and OCCH$_2$CH$_3$,
3. Library of chiral main-chain poly(2-oxazoline)s

2H), 0.82 (t, J = 7.58 Hz, OCCH₂CH₃, 3H) and 0.86 (t, J = 7.44 Hz, NCHCH₂CH₃, 3H). ¹³C NMR (400 MHz, δ in ppm, CDCl₃): 168.3 (NCO, 1C), 71.7 (CH₂OC, 1C), 67.5 (NCHCH₂, 1C), 28.4 (CH₂, 1C), 21.4 (CH₂, 1C), 10.3 (CH₃, 1C), 9.7 (CH₃, 1C). HR-MS (ESI-TOF): calculated for C₁₉H₁₃NO + H⁺ = 212.2075, found = 212.2076. GC-MS: 127 [M⁺], 112 [M⁺-CH₃], 98 [M⁺-C₃H₅], 82 [M⁺-C₆H₁₂], 70 [M⁺-C₄H₁₁], 56 [M⁺-C₅H₁₃] 41 [M⁺-C₆H₁₄].

R-OctEtOx: ¹H NMR (400 MHz, δ in ppm, CDCl₃): 4.21 (t, J = 8.76 Hz, CH₂O, 1H), 3.96 (q, J = 7.41 Hz, CH₂N, 1H), 3.79 (t, J = 7.82 Hz, CH₂O, 1H), 2.22 (t, J = 7.66 Hz, OCCH₂(CH₂)₆CH₃, 2H), 1.2-1.7 (br, J = 7.01-7.24 Hz, OCCH₂(CH₂)₆CH₃ and NCHCH₂CH₃, 14H), 0.8-1.0 (br, J = 6.80-7.44 Hz, OCCH₂(CH₂)₆CH₃ and NCHCH₂CH₃, 6H). ¹³C NMR (400 MHz, δ in ppm, CDCl₃): 167.55 (NCO, 1C), 71.69 (CH₂OC, 1C), 67.34 (NCHCH₂, 1C), 31.75 (CH₂, 1C), 29.17 (CH₂, 1C), 29.14 (CH₂, 1C), 29.07 (CH₂, 1C), 28.06 (CH₂, 1C), 26.08 (CH₂, 1C), 22.57 (CH₂, 1C), 13.99 (CH₃, 1C), 9.77 (CH₃, 1C). HR-MS (ESI-TOF): calculated for C₁₃H₂₅NO + H⁺ = 212.209, found = 212.2075. GC-MS: 210 [M⁺], 196 [M⁺-CH₃], 182 [M⁺-C₃H₅], 168 [M⁺-C₆H₁₂], 154 [M⁺-C₄H₁₁], 140 [M⁺-C₇H₁₅], 126 [M⁺-C₅H₁₃], 113 [M⁺-C₈H₁₈], 96 [M⁺-C₉H₂₀], 72 [M⁺-C₁₀H₂₂], 55 [M⁺-C₁₁H₂₃] 41 [M⁺-C₁₂H₂₄].

R-NonEtOx: ¹H NMR (400 MHz, δ in ppm, CDCl₃): 4.15 (t, J = 8.76 Hz, CH₂O, 1H), 3.90 (q, J = 7.42 Hz, CH₂N, 1H), 3.72 (t, J = 7.82 Hz, CH₂O, 1H), 2.16 (t, J = 7.66 Hz, OCCH₂(CH₂)₆CH₃, 2H), 1.2-1.7 (br, J = 7.00 Hz, OCCH₂(CH₂)₆CH₃ and J = 7.01 Hz, NCHCH₂CH₃, 16H), 0.8-1.0 (br, J = 7.42 Hz, OCCH₂(CH₂)₆CH₃ and J = 6.74 Hz, NCHCH₂CH₃, 6H). ¹³C NMR (400 MHz, δ in ppm, CDCl₃): 167.48 (NCO, 1C), 71.60 (CH₂OC, 1C), 67.27 (NCHCH₂, 1C), 31.75 (CH₂, 1C), 29.31 (CH₂, 1C), 29.13 (CH₂, 1C), 29.09 (CH₂, 1C), 28.46 (CH₂, 1C), 27.97 (CH₂, 1C), 26.01 (CH₂, 1C), 22.53 (CH₂, 1C), 13.91 (CH₃, 1C), 9.68 (CH₃, 1C). HR-MS (ESI-TOF): calculated for C₁₄H₂₇NO + H⁺ = 226.2165, found = 226.2209. GC-MS: 224 [M⁺], 210 [M⁺-CH₃], 196 [M⁺-C₂H₅], 182 [M⁺-C₃H₇], 168 [M⁺-C₆H₁₂], 154 [M⁺-C₇H₁₅], 140 [M⁺-C₅H₁₃], 126 [M⁺-C₈H₁₈], 113 [M⁺-C₉H₂₀], 96 [M⁺-C₁₀H₂₂], 72 [M⁺-C₁₁H₂₃], 55 [M⁺-C₁₂H₂₄] 41 [M⁺-C₁₃H₂₆].

R-UndeEtOx: ¹H NMR (400 MHz, δ in ppm, CDCl₃): 4.25 (t, J = 8.76 Hz, CH₂O, 1H), 4.00 (q, J = 7.4 Hz, CH₂N, 1H), 3.82 (t, J = 7.84 Hz, CH₂O, 1H), 2.25 (t, J = 7.66 Hz, OCCH₂(CH₂)₆CH₃, 2H), 1.2-1.7 (br, J = 7.02-7.65 Hz, OCCH₂(CH₂)₆CH₃ and NCHCH₂CH₃, 20H), 0.8-1.0 (br, J = 6.74-7.44 Hz, OCCH₂(CH₂)₆CH₃ and NCHCH₂CH₃, 6H). ¹³C NMR (400 MHz, δ in ppm, CDCl₃): 167.47 (NCO, 1C), 71.62
(CH$_2$OC, 1C), 67.32 (NCHCH$_2$, 1C), 31.81 (CH$_2$, 1C), 29.50 (CH$_2$, 1C), 29.37 (CH$_2$, 1C), 29.23 (CH$_2$, 1C), 29.14 (CH$_2$, 1C), 29.12 (CH$_2$, 1C), 28.49 (CH$_2$, 1C), 27.99 (CH$_2$, 1C), 26.03 (CH$_2$, 1C), 22.57 (CH$_2$, 1C), 13.91 (CH$_3$, 1C), 9.68 (CH$_3$, 1C). HR-MS (ESI-TOF): calculated for C$_{16}$H$_{31}$NO + H$^+$ = 254.2478, found = 254.2500. GC-MS: 252 [M$^+$], 238 [M$^+$-CH$_3$], 224 [M$^+$-C$_3$H$_5$], 210 [M$^+$-C$_7$H$_7$], 196 [M$^+$-C$_9$H$_9$], 182 [M$^+$-C$_{5}$H$_{11}$], 168 [M$^+$-C$_6$H$_{13}$], 154 [M$^+$-C$_7$H$_{15}$], 140 [M$^+$-C$_8$H$_{17}$], 126 [M$^+$-C$_9$H$_{19}$], 113 [M$^+$-C$_{10}$H$_{21}$], 98 [M$^+$-C$_{11}$H$_{24}$], 84 [M$^+$-C$_{12}$H$_{26}$], 72 [M$^+$-C$_{13}$H$_{28}$], 55 [M$^+$-C$_{12}$H$_{25}$], 41 [M$^+$-C$_{13}$H$_{26}$].

**R-PhEtOx:** $^1$H NMR (250 MHz, δ in ppm, CDCl$_3$): 7.93 (d, J = 6.45 Hz, CH$_2$C$_6$H$_5$, 2H), 7.38 (br, CH$_2$C$_6$H$_5$, 3H), 4.41 (t, J = 8.65 Hz, CH$_2$O, 1H), 4.19 (q, J = 7.4 Hz, CH$_2$N, 1H), 3.98 (t, J = 7.78 Hz, CH$_3$O, 1H), 1.91-1.4 (br, J = 7.00-7.08 Hz, NCHCH$_2$CH$_3$, 2H) and 0.98 (t, J = 7.43 Hz NCHCH$_2$CH$_3$, 3H). $^{13}$C NMR (250 MHz, δ in ppm, CDCl$_3$): 163.4 (NCO, 1C), 132.1 (C$_6$H$_5$, 1C), 128.2 (C$_6$H$_5$, 4C), 72.1 (CH$_2$OC, 1C), 68.0 (NCHCH$_2$, 1C), 28.6 (CH$_2$, 1C), 9.95 (CH$_3$, 1C).

**R-BnEtOx:** $^1$H NMR (400 MHz, δ in ppm, CDCl$_3$): 7.25 (br, CH$_2$C$_6$H$_5$, 5H), 4.23 (t, J = 8.16 Hz, CH$_2$O, 1H), 4.01 (q, J = 7.22 Hz, CH$_2$N, 1H), 3.81 (t, J = 7.88 Hz, CH$_3$O, 1H), 3.60 (s, CH$_2$C$_6$H$_5$, 2H), 1.4-1.7 (br, J = 7.03 Hz, NCHCH$_2$CH$_3$, 2H) and 0.92 (t, J = 7.44 Hz, NCHCH$_2$CH$_3$, 3H). $^{13}$C NMR (400 MHz, δ in ppm, CDCl$_3$): 165.6 (NCO, 1C), 135.3 (C$_6$H$_5$, 1C), 128.9 (C$_6$H$_5$, 4C), 72.2 (CH$_2$OC, 1C), 67.5 (NCHCH$_2$, 1C), 34.9 (CH$_2$, 1C) 28.5 (CH$_2$, 1C), 9.9 (CH$_3$, 1C).

### Kinetic investigation of the microwave-assisted polymerization

A kinetic investigation of the polymerization of R-EtEtOx was performed under microwave-assisted conditions at 180 °C, with an initial monomer concentration of 4.5 M in acetonitrile and a monomer to initiator ratio ([M]/[I]) of 60 using methyl tosylate (MeOTs) as initiator. These conditions are similar to the reaction conditions used for R-BuEtOx, as described in Chapter 2.

### Polymer synthesis

All chiral polymers were synthesized under similar conditions. The initial monomer concentration varied between 2.0 and 4.5 M in acetonitrile to keep the monomer concentration around 40%. The [M]/[I] (I = MeOTs) ratio varied between 50-60. These polymerization mixtures were heated to 180 °C under microwave irradiation.
for 60-90 min, depending on the initial monomer concentration. After the polymerizations, the mixtures were quenched by the addition of water. After drying under reduced pressure at 40 °C, the polymers were redissolved in tetrahydrofuran and precipitated in demineralized water. Subsequently, they were dried again under reduced pressure at 40 °C before further characterization.

3.6 References and notes

3. Library of chiral main-chain poly(2-oxazoline)s


(27) R. K. Heenan, FISH Data Analysis Program; Rutherford Appleton Laboratory, Report RAL-89-129; CCLRC, Didcot, UK, **1989**.

(28) The FISH manual can be downloaded from: http://www.small-angle.ac.uk/small-angle/Software.html (last accessed: June 2010).
Chapter 4

Chiral copolymers

Abstract

Chiral poly(2-oxazoline)s can be regarded as pseudopolypeptides, although, not much is known about their secondary structure formation. In the current chapter the chiral structure formation of main-chain chiral copoly(2-oxazoline)s with controlled ratio of S-2-butyl-4-ethyl-2-oxazoline (S-BuEtOx) and R-BuEtOx are addressed. No chiral amplification was found in solution or in the solid state, clearly indicating that the polymers adopt a dynamic secondary structure that is easily disrupted by incorporation of the second monomer. Nonetheless, the properties of these main-chain chiral copoly(2-oxazoline)s, such as the optical rotation, solubility and crystallinity, can be tuned by controlling the enantiomeric excess (ee) as was demonstrated by optical rotation measurements, turbidimetry and differential scanning calorimetry (DSC) investigations, respectively. In the second part of this chapter the self-assembly of chiral amphiphilic copolymers into chiral nanostructures was investigated. Such chiral micelles have a high potential in targeted drug delivery or chiral separation applications. Gradient copolymers could be obtained by statistically copolymerizing the hydrophilic 2-ethyl-2-oxazoline (EtOx) with the hydrophobic chiral R-BuEtOx or the racemic RS-BuEtOx monomers. Self-assembly of the gradient enantiopure copolymer was studied by both cryogenic transmission electron spectroscopy (cryo-TEM) and dynamic light scattering (DLS) revealing the formation of spherical micelles in aqueous solution. Additionally, amphiphilic block copolymers were synthesized by sequential monomer addition. The type of self-assembled structure could be controlled from spherical and cylindrical micelles to sheets and vesicles by varying the hydrophobic to hydrophilic ratio within the block copolymer. When the enantiopure block was replaced by the corresponding racemic block, only spherical micelles could be observed, while the chiral block copolymers with similar hydrophobic content revealed cylindrical micelles indicating the importance of secondary structure formation.

4. Chiral copolymers

4.1 Introduction

Chiral helical polymers can be divided into two groups: helical polymers with high helix inversion barriers, the so called static helical polymers, and helical polymers with low helix inversion barriers, known as dynamic helical polymers.\(^1\)\(^{-4}\) Static helical polymers have in general bulky or interacting side groups that lock the preferred handed secondary structure during polymerization under kinetic control, dynamic helical polymers usually have a chiral pendant group.\(^4\) Chiral amplification in polymer systems has been first reported for polyisocyanates by Green \textit{et al.}.\(^1\),\(^5\) A copolymer of achiral and chiral isocyanates was demonstrated to form a helical structure with only a small amount of chiral monomer, which is the so-called “sergeant and soldiers” effect.\(^1\),\(^3\),\(^5\) In addition, a small enantiomeric excess (ee) in a polymer chain comprising both isocyanate enantiomers resulted in an almost perfect one-handed helical structure, which is called the ‘majority rule’.\(^4\)\(^\text{-}^6\)

2-Oxazolines can be polymerized in a living manner via the cationic ring-opening polymerization (CROP) under microwave-assisted conditions.\(^7\) Poly(2-oxazoline)\(^8\)\(^\text{-}^10\) with a substituent on the 4\(^\text{th}\) or 5\(^\text{th}\) position are main-chain chiral polymers\(^11\)\(^\text{-}^15\) that, according to a model published by Oh \textit{et al.},\(^16\) can form a helical structure. In the previous chapters it was already observed that the chiral main-chain poly-\(R\)-2-butyl-4-ethyl-2-oxazoline (p-\(R\)-BuEtOx) forms a chiral secondary structure in the solid phase and in solution. Copolymerizing \(R\)-BuEtOx with \(S\)-BuEtOx could lead to the “majority rule” as observed for chiral poly(isocyanate) when the enantiomeric excess of the copolymer forms a rigid secondary structure that forces the minority to fold into the same direction.

![Scheme 4.1](attachment:image.png)

\textbf{Scheme 4.1} Schematic representation of the reaction scheme for the copolymerization of \(R\)-BuEtOx and \(S\)-BuEtOx initiated with methyltosylate (MeOTs).
Besides copolymerizing two enantiomers, a hydrophilic polymer segment can be combined with a hydrophobic block, creating an amphiphilic block copolymer that can undergo self-assembly in aqueous solution. The type of nanostructure that is formed depends on the hydrophobic to hydrophilic ratio, the block lengths as well as the chemical composition. Spherical micelles, wormlike micelles and vesicles are widely reported self-assembled structures. Such architectures can be used as detergents and stabilizers as well as for the inclusion of organic molecules for drug delivery applications. Since both hydrophobic and hydrophilic poly(2-oxazoline)s can be synthesized, depending on the substituent on the 2-position of the 2-oxazoline ring, amphiphilic gradient or block copolymers can be prepared that self-assemble in water. The synthesis and self-assembly of both hydrophilic/lipophilic and hydrophilic/fluoro-philic poly(2-oxazoline)s are reported in literature. When the hydrophobic chiral p-R-BuEtOx is combined with a hydrophilic polymer into an amphiphilic structure, micelles with a chiral hydrophobic core could be obtained in water. Such optically active micelles would be interesting given their potential application in chiral amplification, molecular recognition and catalysis.

In this chapter the copolymerization of R-BuEtOx or S-BuEtOx with RS-BuEtOx (Scheme 4.1) is described and the effect of an enantiomeric excess (ee) is discussed for the secondary structure formation in solution, the solubility, thermal properties and the formation of chiral crystals based on optical rotation and circular dichroism (CD), turbidimetry, differential scanning calorimetry (DSC) and CD measurements of polymer films, respectively (section 4.1). In section 4.2 the kinetics of the statistical copolymerization of the hydrophilic 2-ethyl-2-oxazoline (EtOx) with the chiral R(S)-BuEtOx is described as well as the self-assembly of these copolymers investigated with cryogenic transmission electron microscopy (cryo-TEM) and dynamic light scattering (DLS). The self-assembly of block copolymers based on EtOx and R-BuEtOx with different hydrophilic to hydrophobic ratios is described in section 4.3 together with the influence of chirality by studying also the self-assembly of the block copolymer that contains the racemic RS-BuEtOx as the hydrophobic block.

4.2 Statistical copolymers of R-BuEtOx with S-BuEtOx

To investigate how the presence of the second enantiomer in the polymer chain influences the polymer properties, the enantiopure and racemic BuEtOx monomers
4. Chiral copolymers

were (co)polymerized under the optimized microwave assisted conditions, namely 60 minutes at 180 °C, resulting in more than 80% conversion for all copolymers.\textsuperscript{7,30,31} Size exclusion chromatography (SEC) revealed the formation of relatively well-defined copolymers with polydispersity indices (PDI) ranging from 1.24 to 1.43 (Table 4.1). Figure 4.1a shows representative SEC traces demonstrating the monomodality of the molar mass distributions.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>ee R-BuEtOx (%)</th>
<th>$M_n$ (g/mol)\textsuperscript{1}</th>
<th>PDI\textsuperscript{1}</th>
<th>$\alpha_D^{RT}$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>4,100\textsuperscript{2}</td>
<td>1.24\textsuperscript{2}</td>
<td>–26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6,090\textsuperscript{3}</td>
<td>1.29\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>4,960</td>
<td>1.37</td>
<td>–22</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>5,390</td>
<td>1.37</td>
<td>–20</td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>5,670</td>
<td>1.43</td>
<td>–16</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>4,490</td>
<td>1.31</td>
<td>–15</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>7,810</td>
<td>1.37</td>
<td>n.m.</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>5,670</td>
<td>1.39</td>
<td>–11</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>5,630</td>
<td>1.43</td>
<td>n.m.</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>5,820</td>
<td>1.38</td>
<td>–6.9</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>5,580</td>
<td>1.36</td>
<td>–2.7</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>5,100</td>
<td>1.25</td>
<td>–0.2</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>5,060</td>
<td>1.25</td>
<td>+8.2</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>4,960</td>
<td>1.27</td>
<td>+16</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>4,950</td>
<td>1.27</td>
<td>+26</td>
</tr>
</tbody>
</table>

\textsuperscript{1}PS calibration and DMA as solvent, \textsuperscript{2}Used for DSC measurements, \textsuperscript{3}Used for CD measurements, n.m.: not measured.

The observed differences in the number average molar mass ($M_n$) of the copolymers are due to small differences in the actual monomer to initiator ([M]/[I]) ratios as well as variations in the extent of chain-transfer side reactions caused by protic impurities such as water. The PDI values of the $R$-rich
copolymers are somewhat higher, most likely due to the use of dichloromethane as polymerization solvent instead of acetonitrile, which was used for the $S$-rich polymers. Dichloromethane can act as a very poor initiator too leading to broadening of the molar mass due to slow initiation (Figure 4.1a). Nonetheless, in the second part of this project, dichloromethane was utilized as polymerization solvent since it is a better solvent for the p-BuEtOx polymers resulting in higher monomer conversions (~90%) compared to acetonitrile (~80%).

4.2.1 Solution properties of the copolymers

The solution properties of the synthesized BuEtOx copolymers with varying ee were investigated by polarimetry, turbidimetry and circular dichroism (CD) spectrometry. The optical rotation of the copolymers was determined in chloroform solution and was found to linearly decrease with theoretical ee from $\alpha_0^{RT} = +26 \times 10^{-1}$ deg cm$^2$ g$^{-1}$ (30 mg/mL in CHCl$_3$) for p-$S$-BuEtOx to $\alpha_0^{RT} = -26 \times 10^{-1}$ deg cm$^2$ g$^{-1}$ (30 mg/mL in CHCl$_3$) for p-$R$-BuEtOx and $\alpha_0^{RT} = 0$ deg cm$^2$ g$^{-1}$ (30 mg/mL in CHCl$_3$) for the racemic polymer (p-$RS$-BuEtOx) (Figure 4.1b). This linear dependence in optical rotation with ee indirectly proofs that the copolymers have indeed the desired ee.

![Figure 4.1](image-url)  
**Figure 4.1** (a) Representative SEC traces (in DMA) of the copolymers synthesized in dichloromethane (polymer 2, 95% R-BuEtOx) and acetonitrile (polymer 13, 83% S-BuEtOx). (b) Optical rotation as a function of the amount of R-BuEtOx present in the copolymer. The solid line is a linear fit through the data.
The solubility of the homopolymers as well as the copolymers was investigated by turbidity measurements in a range of solvents at a concentration of 5 mg/mL (Table 4.2). Both homopolymers are only soluble in tetrahydrofuran (THF) and n-butanol, whereby heating was required to disrupt the crystalline fractions. When the ee decreased to 95%, the solubility did not significantly change. However, when the ee was decreased to 90%, the polymer became well-soluble in all investigated solvents indicating that the secondary structure is disturbed with the addition of the second enantiomer resulting in an improved solubility. As such, the solubility of the main-chain chiral poly(2-oxazoline)s can be enhanced maintaining their chirality to a large extent (90% ee).

### Table 4.2 Solubility of the (co)polymers measured at 5 mg/mL and the dielectric constants and dipole moments of the solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>100% ee</th>
<th>95% ee</th>
<th>90% ee</th>
<th>(\varepsilon^1)</th>
<th>(\mu^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)-Heptane</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>7.5</td>
<td>1.63</td>
</tr>
<tr>
<td>(n)-Butanol</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>17.8</td>
<td>1.66</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>25.3</td>
<td>1.69</td>
</tr>
<tr>
<td>Methanol</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>33.0</td>
<td>1.70</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>36.6</td>
<td>3.92</td>
</tr>
<tr>
<td>(N,N)-Dimethylformamide</td>
<td>Insoluble</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>38.3</td>
<td>3.82</td>
</tr>
</tbody>
</table>

\(^1\) Dielectric constant \((\varepsilon)\) and dipole moment \((\mu)\) taken from the CRC handbook of chemistry and physics 86th edition.

The chiroptical properties of the copolymers were further investigated with CD (Figures 4.2a and 4.2b). The double Cotton effect in CD retains the same shape and decreases in intensity with decreasing ee (Figure 4.2a). The Cotton effects disappear for the racemic p-RS-BuEtOx and (co)polymers with an ee of R-BuEtOx.
are opposite in sign compared to the polymers with an ee of S-BuEtOx. Like the optical rotation, also the Cotton effects decrease linearly with the reduction in ee (Figure 4.2b). These results demonstrate a decrease in persistence length of the chiral regimes in the copolymers with decreasing ee and the absence of the majority rule principle in solution for which a S-shaped relation of both optical rotation and the Cotton effects would be expected as function of ee.\textsuperscript{5,32,33}

**Figure 4.2**  (a) CD spectra of the chiral poly(2-oxazoline)s with different ee. The legend indicates the amount of R-BuEtOx present in the polymer. (b) CD maxima as a function of the amount of R-BuEtOx present in the copolymer. Solid lines are linear fits through the data.

### 4.2.2 Solid state properties of the BuEtOx copolymers

The solid state properties of the main-chain chiral BuEtOx copolymers were studied by differential scanning calorimetry (DSC) and CD of thin polymer films to investigate the effect of ee on the crystallization and the formation of ordered chiral structures. In the first heating run (Table 4.3 and Figure 4.3a), only the enantiopure polymers and the copolymers with an ee of 90% or higher revealed a single or double melting peak ($T_{m1}$ and $T_{m2}$), indicating that they are semi-crystalline. The difference in enthalpy ($\Delta H_m$) is small between p-R-BuEtOx and the copolymer with an ee of 95% of p-R-BuEtOx. However, when the ee decreases to 90%, $\Delta H_m$ decreases to approximately 1/3 of the crystallinity of the enantiopure polymer and no crystallinity is observed for the copolymers with an ee of 85% or less. In fact, this decrease in crystallinity explains the observed increase in solubility as discussed in the previous part, i.e. there is no competition between
4. Chiral copolymers

crystallization and solvation of the polymer chains, which is similar to chiral vinyl polymers for which the solubility decreases with increasing isotacticity due to the higher crystallinity.\(^5\)

In the second heating run (Table 4.3, Figure 4.3b), a glass transition temperature \(T_g\) was observed around 50 °C with a heat capacity \(\Delta C_p\) of approximately 0.3 J/(g K) for all investigated BuEtOx copolymers. The crystals initially present in the copolymers with 95% or 90% ee \(R\)-BuEtOx are not capable of crystallizing again from the melt or from the glassy state after melting during the DSC measurement and only the enantiopure polymer revealed a \(T_m\) in the second heating run.

<table>
<thead>
<tr>
<th>(R)-BuEtOx (%)</th>
<th>First heating run</th>
<th>Second heating run</th>
<th>Third heating run(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T_m1) (°C)</td>
<td>(T_m2) (°C)</td>
<td>(\Delta H_m)(^3) (J/g)</td>
</tr>
<tr>
<td>100</td>
<td>-</td>
<td>220</td>
<td>31</td>
</tr>
<tr>
<td>95</td>
<td>-</td>
<td>205</td>
<td>27</td>
</tr>
<tr>
<td>90</td>
<td>184</td>
<td>198</td>
<td>8</td>
</tr>
<tr>
<td>85</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>218</td>
<td>36</td>
</tr>
</tbody>
</table>

\(^1\) Heating rate of 20 °C /min. \(^2\) After 24 h annealing at 140 °C. \(^3\) Cumulative \(\Delta H_m\) of both observed melting transitions. \(^4\) Midpoint of the observed transition. \(^5\) \(\Delta C_p\) and \(\Delta H_m\) of polymer 6 with 75% ee of \(R\)-BuEtOx could not be determined, because the pan was not fully in contact with the oven.

The polymer samples were subsequently annealed to induce crystallization. After
4. Chiral copolymers

annealing the polymers for 24 h at 140 °C, the copolymers with an ee up to 80% partially crystallized as indicated by the melting transitions (Table 4.3 and Figure 4.3c). Therefore, it can be concluded that these copolymers can crystallize when they are heated for some time above the $T_g$, which increases the chain mobility allowing reorganization of the chains.

Upon annealing a second melting peak at a lower temperature could be determined for the enantiopure polymer and the copolymer with 95% $R$-BuEtOx and the first melting peak in the copolymer containing 90% $R$-BuEtOx increased (Figure 4.3c). It appeared that these crystals partially melt-recrystallize into more perfect crystals resulting in the second melting peak at a higher temperature, like observed for the homopolymers as discussed in Chapter 2. Upon annealing it was also possible to induce crystal formation in copolymers containing 85%, 80% and 17% $R$-BuEtOx, while these polymers were initially amorphous after polymerization and purification. However, for these polymers no melt-recrystallization into more perfect crystals is observed. Since the ratio between $\Delta H_{m1}$ and $\Delta H_{m2}$ decreases with the decrease in ee, it seems that the extent of imperfect crystals increases and the amount of crystals that recrystallize into more perfect crystals during melting is reduced. With the decrease in ee, the total $\Delta H_m$ and $T_m$ are decreased (Figure 4.3d), indicating a reduction in the amount and quality of the crystals formed. Therefore, it can be concluded that the chiral crystalline structure is interrupted by the incorporation of the other enantiomer. A similar behavior was observed for polypropylene (PP). When the syndiotacticity decreases to below 90% a double melting endotherm due to melt-recrystallization instead of a single melting peak occurs and the crystallinity decreases.\textsuperscript{34} The crystalline structures were further investigated by CD measurements of the polymer films.
Figure 4.3 DSC traces of the enantiopure polymers and copolymers (a) First heating run (20 °C/min), (b) second heating run (20 °C/min) and (c) after annealing for 24 h at 140 °C (20 °C/min). The legend indicates the amount of R-BuEtOx present in the polymer. (d) Melting enthalpy and melt temperatures as a function of the enantiomeric excess (ee) after annealing the polymers.

The CD measurements of spin coated polymer films revealed similar Cotton effects as in solution except that the peak maxima slightly shifted to higher wavelengths (Figure 4.4a). Since the strength of the Cotton effects are strongly influenced by the film thickness, the ratio between the maximum Cotton effects before and after annealing will be compared instead of the absolute intensities (Figure 4.4b). Annealing the enantiopure polymer films for 24 h at 140 °C resulted in a change of the chiral structure, since the ratio between the maximum Cotton effects significantly changed. Before annealing both Cotton effects have approximately the same strength, while after annealing the Cotton effect at ~202 nm is strongly enhanced while the Cotton effect at ~218 nm remains small.
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The ordered chiral structure formed during annealing is similar to the chiral structure present in the crystals formed during cold crystallization as observed previously in Chapter 2 for the homopolymers. This observed change in chiral structure in the solid state is unusual, since in most chiral polymers the Cotton effects only increase in intensity upon annealing, indicating an increase in persistence length of the chiral structure. This was also observed for the copolymers containing 90% or 95% \( R \)-BuEtOx, in which an increase in Cotton effects is observed without a change in the ratio between the maximum Cotton effects after annealing (Figure 4.4b). The maximum Cotton effects for the copolymers containing 80% or 17% \( R \)-BuEtOx hardly increased upon annealing (not shown), even though a melting peak is observed after annealing these copolymers. The formation of less perfect crystals, as observed with DSC, is probably the reason why the Cotton effects of these copolymers do not strongly increase upon annealing. When the ee is further decreased, no change in CD spectra could be observed after annealing since these polymers are amorphous and, thus, no chiral crystals are formed.

**Figure 4.4** Normalized (by setting the maximum UV absorption at 1 A) (a) CD spectra of the (co)polymers after annealing for 24 h at 140 °C. The legend indicates the amount of \( R \)-BuEtOx present in the (co)polymer. (b) Ratio of the maximum Cotton effects before and after annealing for 24 h at 140 °C.
4.3 Amphiphilic chiral copolymers

Besides the copolymerization of two enantiomers, also other 2-oxazoline monomers can be statistically or, due to the living nature of the cationic ring-opening polymerization (CROP), block copolymerized with BuEtOx. By combining the chiral hydrophobic monomers with the hydrophilic 2-ethyl-2-oxazoline (EtOx), amphiphilic chiral copolymers can be obtained. The synthesized amphiphilic copolymers are expected to self-assemble in water. In this section the self-assembly behavior in aqueous solution with varying hydrophobic to hydrophilic ratio and monomer distribution is described in this section.

4.3.1 Statistical copolymers

The polymerization kinetics of the statistical copolymerization of EtOx and R-BuEtOx or RS-BuEtOx in an one-step-one-pot system was determined at 140 °C, utilizing a monomodal microwave-synthesizer with an initial monomer concentration (M₀) of 4 M and a monomer to initiator ratio ([M]/[I]) of 100 ([M]/[I] = 70 for EtOx and [M]/[I] = 30 for R-BuEtOx or RS-BuEtOx) with MeOTs as initiator and acetonitrile as solvent. Separate polymerizations were performed for different reaction times and the resulting mixtures were analyzed by gas chromatography (GC) and size exclusion chromatography (SEC) to determine the monomer conversion and molar mass distribution, respectively. A linear first order kinetic plot could be obtained for EtOx, R-BuEtOx and RS-BuEtOx up to at least 80% conversion, indicating a constant concentration of propagating species (Figure 4.5a). It was already observed that the polymerization of R-BuEtOx and RS-BuEtOx does not reach full conversion even after prolonged heating, as described in Chapter 2. Together with the linear increase of molar mass with conversion, the linear first order kinetics confirms a living copolymerization (Figure 4.5b). The similar kinetic plots of R-BuEtOx and RS-BuEtOx demonstrate that the chirality of the monomers has no influence on the kinetics of the copolymerization. The SEC traces (Figure 4.6) reveal monomodal shapes and the PDI values stay below 1.4. The observed lower Mₙ compared to the theoretical Mₙ is most likely related to the compact structure of p-R(S)-BuEtOx leading to a smaller hydrodynamic volume compared to the utilized polystyrene SEC standards. From the first order kinetic plots, the polymerization rate constants (k_p) were calculated assuming complete initiation and absence of termination. The k_p of
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EtOx \((52 \pm 8 \times 10^{-3} \ L/(\text{mol s}))\) is reduced by a factor 2 in the presence of the second monomer,\(^{35}\) while the \(k_p\) of \(R\text{-BuEtOx}\) and \(RS\text{-BuEtOx}\) \((11 \pm 3 \times 10^{-3} \ L/(\text{mol s}))\) increases with almost a factor 10. During the non-ideal EtOx – BuEtOx copolymerization, the EtOx propagating species are better accessible than the BuEtOx propagating species, which is responsible for the faster incorporation of BuEtOx while the sterical hindrance of the BuEtOx propagating species slows down the polymerization of EtOx.\(^{36}\)

![Figure 4.5](image1)

**Figure 4.5** (a) Kinetic plots for the copolymerization of EtOx and \(R\text{-BuEtOx}\) or \(RS\text{-BuEtOx}\) initiated with methyl tosylate \(([\text{EtOx}]:[\text{BuEtOx}]:[\text{MeOTs}] = 70:30:1)\) in acetonitrile \(([M] = 4 \ M)\) at 140 °C. (b) Corresponding molar masses \((M_n)\) against conversion plot, including polydispersity indices (PDI). The black line indicates the theoretical molar mass.

![Figure 4.6](image2)

**Figure 4.6** SEC traces \((\text{CHCl}_3)\) of the statistical copolymerization of EtOx with a) \(R\text{-BuEtOx}\) and b) \(RS\text{-BuEtOx}\), \((M/I = 100, \text{EtOx}:R(S)\text{-BuEtOx} = 70:30; M_0 = 4 \ M)\).
After the full conversion of EtOx in ~30 minutes, ~62% R-BuEtOx or R5-BuEtOx is polymerized, indicating that after full conversion of EtOx still ~20% of the chiral monomer polymerizes into a pure pBuEtOx hydrophobic block. When the monomer distribution along the chains of p-EtOx-stat-R(S)-BuEtOx is calculated from the copolymerization kinetics by averaging the composition of each five consecutive monomers and fitting with a sigmoidal shape, it can be seen that at the beginning of the polymerization mainly EtOx is incorporated and the amount of R-BuEtOx or R5-BuEtOx in the polymer chain increases with increasing polymerization time until the EtOx monomer is fully converted and only R-BuEtOx or R5-BuEtOx is left to polymerize (Figure 4.7). As such, these polymers display an amphiphilic gradient monomer distribution going from rich in EtOx to pure BuEtOx.

Figure 4.7 Structural and schematic representations (top) as well as calculated monomer distributions (bottom) of the investigated (a) p-EtOx69-stat-R(S)-BuEtOx29 and (b) p-EtOx68-stat-R-BuEtOx31.

In a next step, a gradient copolymer pEtOx70-stat-R-BuEtOx30 was synthesized in a larger amount. The SEC trace revealed a monomodal shape with a molar mass (Mn) of 10,100 g/mol and a PDI value of 1.23. From turbidity measurements it can be observed that the statistical copolymer has a cloud point temperature (TcP) of 66 °C when dissolved in water at a concentration of 5 mg/mL, which is similar to block
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copolymers that contain EtOx. This $T_{CP}$ is also similar to high molar mass pEtOx at high concentrated solutions indicating close proximity of the chains as is also the case in micellar structures. The polymer solution was further investigated with cryo-TEM and DLS to determine if supramolecular aggregates have formed. Cryo-TEM indeed revealed the presence of spherical micelles with a core diameter of ~7 nm together with some larger aggregates (Figure 4.8a) and DLS confirmed this result by demonstrating the presence of self-assembled structures with a hydrodynamic radius ($R_h$) of 12 nm. Moreover, the DLS signal was not angular dependent, proving the spherical nature of the formed micelles (Figure 4.8b). Also the low polydispersity (PD) of 0.03 measured with DLS is in agreement with the formation of well-defined spherical micelles for this statistical copolymer. This result is indeed expected from the hydrophilic/hydrophobic ratio of the pEtOx$_{70}$-stat-R-BuEtOx$_{30}$ copolymer. These results support the assumption that an amphiphilic gradient copolymer is formed, which was able to form well-defined spherical micelles in water.

![Spherical micelle formation of pEtOx$_{70}$-stat-R-BuEtOx$_{30}$ indicated by (a) cryo-TEM (5 mg/mL in water) and (b) DLS (5 mg/mL in water at 25 °C at an angle of 90°) revealing a single distribution with a $R_h$ of 12 nm (PD 0.03).](image)

4.3.3 Block copolymers

Besides the gradient copolymers, pure diblock copolymers were prepared using the sequential monomer addition method. To investigate the influence of the ratio between the hydrophilic and hydrophobic blocks on the self-assembled structure in water, six block copolymers with varying ratios of EtOx:R-BuEtOx were synthesized (Table 4.4, I-VI) under microwave-assisted conditions using MeOTs as initiator and acetonitrile as solvent. The hydrophilic monomer EtOx was first polymerized at 140 °C (SEC traces are presented in Figure 4.9a), followed by the addition of the
second hydrophobic monomer, \( R\)-BuEtOx, which was polymerized at 180 °C to shorten the required polymerization time (SEC traces are presented in Figure 4.9b).

To investigate the influence of the chiral structure on the formation of the self-assembled structures, block copolymers based on EtOx and the racemic \( R\)-BuEtOx have been synthesized as well (Table 4.4, VII-VIII-RS); the self-assembled structures have also been investigated with cryo-TEM and DLS.

**Table 4.4 Selected molecular characterization data of the synthesized copolymers.**

<table>
<thead>
<tr>
<th>PEtOx- ( b)-R(S)-BuEtOX</th>
<th>( M_n^{i} ) EtOx (g/mol)</th>
<th>PDI (^{i} )</th>
<th>( M_n^{i} ) copolymer (g/mol)</th>
<th>PDI (^{i} ) copolymer</th>
<th>DP (^{i} ) EtOx</th>
<th>DP (^{i} ) BuEtOx</th>
<th>DP (^{i} ) copolymer</th>
<th>Wt% (^{i} ) BuEtOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6,600</td>
<td>1.06</td>
<td>8,500</td>
<td>1.07</td>
<td>67</td>
<td>12</td>
<td>79</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>6,100</td>
<td>1.13</td>
<td>8,600</td>
<td>1.16</td>
<td>62</td>
<td>16</td>
<td>80</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>6,400</td>
<td>1.06</td>
<td>11,000</td>
<td>1.12</td>
<td>64</td>
<td>30</td>
<td>94</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>5,900</td>
<td>1.06</td>
<td>10,700</td>
<td>1.11</td>
<td>59</td>
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<td>10,700</td>
<td>1.20</td>
<td>54</td>
<td>34</td>
<td>88</td>
<td>50</td>
</tr>
<tr>
<td>7-RS</td>
<td>4,500</td>
<td>1.14</td>
<td>7,000</td>
<td>1.12</td>
<td>45</td>
<td>16</td>
<td>61</td>
<td>36</td>
</tr>
<tr>
<td>8-RS</td>
<td>4,100</td>
<td>1.09</td>
<td>7,000</td>
<td>1.18</td>
<td>41</td>
<td>19</td>
<td>60</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^{i}\) Determined by SEC in CHCl\(_3\) using PS standards. The calculated DP and Wt\% represents a rough estimation based on SEC.

The resulting block copolymers still contain some pEtOx homopolymer, which could be removed to a large extend by precipitating the block copolymer in cold \( n\)-heptane or cold \( n\)-hexane. However, still some pEtOx homopolymers were left for most copolymers. Purifying the block copolymer for a second time did not significantly reduce the amount of unreacted pEtOx. Nonetheless, the presence of some pEtOx homopolymers will not interfere with the self-assembly studies since it will fully dissolve in water.
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**Figure 4.9** SEC traces (CHCl₃) of (a) the first block, pEtOx and (b) the block copolymers after purification.

**Figure 4.10** Transmittance curves of the second heating run from turbidity measurements revealing \( T_{CP} \)'s between 60 and 70 °C for the gradient and block copolymers.

Turbidimetry revealed that the transmittance before the \( T_{CP} \) strongly varies with the composition of the copolymers. In general, the transmittance is lower for polymers with a higher hydrophobic content indicating the presence of larger self-assembled structures that scatter away part of the light, which is also evident from the translucent appearance of the solutions. The \( T_{CP} \) obtained from turbidity measurements of the block copolymers are similar to the \( T_{CP} \) of the statistical copolymer and varied between 60 and 70 °C (Figure 4.10) indicative for a self-assembly behavior as explained for the gradient copolymer. Most polymer solutions turned translucent upon
heating, also indicating the presence of self-assembled structures which was investigated in further detail using cryo-TEM and DLS.

All the synthesized block copolymers contain a major fraction of hydrophilic pEtOx component and should be, therefore, prone to form spherical micelles. However, preliminary investigations revealed that the formed structures were clearly dependent on the micelle preparation method used. This observation indicated that non-equilibrium micelles are formed in the present study and that kinetically trapped transient morphologies could be therefore expected. In order to allow a comparison of the obtained results, a standard sample preparation protocol has been validated (see experimental section) and further used for all the investigated block copolymer solutions. Using this preparation protocol, some spherical micelles with a mean diameter of ~25 nm together with large vesicular structures which can reach sizes of several hundreds of nanometers were observed for the pEtOx-\(b\-\)R-BuEtOx-1 copolymer (Figure 4.11a). Moreover, the vesicles deviate significantly from the usually found perfectly round shape and exhibited characteristic protrusions, which could indicate the abstraction of smaller vesicles or micelles or may be related to fusion processes. Those vesicles could be considered as transient structures trapped during the sample preparation process, while the ultimate structures being small spherical micelles in agreement with the composition of the copolymer.

When the hydrophobic content of the chiral block copolymer is increased, large structures are always observed with cryo-TEM. PEtOx-\(b\-\)R-BuEtOx-2 mainly resulted in the formation of spherical micelles and thin sheet structures (Figure 4.11b). Again, it might be that the sheet structures are transient morphologies caused by the sample preparation method. Indeed, a second sample was prepared revealing only the presence of spherical micelles with a core diameter of ~7 nm (Figure 4.11c). It might be speculated that sheets, fused micelles and vesicles are non-equilibrium morphologies due to nonergodicity effect, which are formed depending on the sample preparation.\(^{38}\) By further increasing the hydrophobic content, the formation of sheet-like structures is clearly favored (pEtOx-\(b\-\)R-BuEtOx-3 in Figure 4.11d). For the copolymers with higher hydrophobic content discussed in the following, it might be assumed that spherical micelles are no longer the final equilibrium morphology but that rod-like micelles and vesicles or other morphologies now represent the most stable state for the system. This is in particular evident if the ‘fiber-like’ aggregates in Figure 4.11c are analyzed. They show an internal structure which can be attributed to
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the formation of a layered structure in a presumably bilayer-like fashion. The hydrophobic part of the molecules is thereby centered in the middle of the sheet’s cross-section whereas the hydrophilic EtOx blocks are facing towards the liquid interface (Figure 4.12). In this sample hardly any residual spherical micelles are observed. The tendency to form layered sheet structures is also revealed by analyzing pEtOx-b-R-BuEtOx-4 (Figure 4.12) where a comparable internal layered structure of vertically aligned sheets is observed. It has to be mentioned here that the orientation of the sheets significantly influences the resolution capabilities of the TEM investigations as only perfectly aligned sheets result in a good contrast, where the different layers can be clearly resolved. PEtOx-b-R-BuEtOx-5 (Figure 4.11f) and -VI (Figure 4.11g) have the highest hydrophobic content and in these polymer solutions also extended structures were observed. However, it could be revealed that the formed supramolecular aggregates are fiber-like objects with a diameter of ~12 nm, rather than 2-dimensional sheets as could be confirmed by a cryo-TEM tilting series that were acquired to investigate the three dimensional structure of the objects (Figure 4.12c). Since pEtOx-b-R-BuEtOx-5 and -6 provide a comparable hydrophobic content, which resulted in similar structures, the reproducibility of the structure formation could be demonstrated. It is commonly observed that with the increase of the hydrophobic content spherical micelles, wormlike micelles and eventually sheets and/or vesicles are obtained. However, the formation of fiber-like structures is less common. It has been reported that when EtOx is copolymerized with a peptide, also fibrous structures can be observed when this block copolymer with a relatively high hydrophobic content is dissolved in a helicogenic solvent. 39 As a consequence, the formation of a fiber-like structure might be ascribed to the formation of an ordered chiral structure of the core, resulting in a rod-coil amphiphilic block copolymer which can aggregate in diverse less common morphologies. Also other rod-coil block copolymers can form tubular-like structures in a selective solvent. 40

To further evaluate the effect of the chiral block on the self-assembly process and to validate this hypothesis, pEtOx-b-RS-BuEtOx-7 and -8 were also investigated. The cryo-TEM images in Figures 4.11h and 4.11i reveal that both block copolymers form spherical micelles with a core diameter of ~13.5 nm. Since the micelles of pEtOx-b-RS-BuEtOx-8 are hexagonally packed, also the length of the hydrophilic part can be estimated. The average distance between the micelles is ~22 nm, indicating that the
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length of the pEtOx corona of one micelle is ~11 nm, suggesting that the size of one micelle is approximately 36 nm in diameter.
The obtained spherical micelles formed by the racemic block copolymers and the enantiopure block copolymers have a comparable size. However, in contrast to pEtOx-\textit{b}-R-BuEtOx-3 no sheets are obtained for pEtOx-\textit{b}-RS-BuEtOx-8, while they have a similar hydrophobic content. Therefore, it seems that the enantiopure block does have an influence on the supramolecular structure formed indicating the importance of the chiral block as schematically depicted in Figure 12b.
Figure 4.11 Variation of the hydrophobic content of the copolymer and influence on the resulting supramolecular aggregates. (a) $\text{PEtOx-b-R-BuEtOx-1}$ forms micelles and vesicles, (b) $\text{pEtOx-b-R-BuEtOx-2}$ results in the formation of micelles and two dimensional sheet structures or (c) in spherical micelles depending on the sample preparation. (d) With further increasing the hydrophobic content ($\text{pEtOx-b-R-BuEtOx-3}$) the tendency to form two dimensional sheets is more pronounced and hardly spherical micelles are found. (e) $\text{PEtOx-b-R-BuEtOx-4}$ shows vertically aligned sheets as evidenced by the clearly resolved internal structures of the aggregates. Even higher hydrophobic contents of (f) $\text{pEtOx-b-R-BuEtOx-5}$ and g) $\text{pEtOx-b-R-BuEtOx-6}$ yield in the formation of worm-like micellar structures, where no internal structure can be resolved. (h) $\text{PEtOx-b-RS-BuEtOx-7}$ and (i) $\text{pEtOx-b-RS-BuEtOx-8}$ are block copolymers containing the racemic block which both form spherical micelles.
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**Figure 4.12** (a) Zoom in of Fig. 6d, revealing the bilayer sheet structure of pEtOx-b-R-BuEtOx-III and (b) schematic presentation of the bilayer sheets wherein the internal red helices represent the R-BuEtOx segment and the blue chains the EtOx segment sticking into the aqueous solution. (c) Assembly of five tilted cryo-TEM images of pEtOx-b-R-BuEtOx-V that proves the formation of a three dimensional fiber-like structure.

The polymer solutions have been characterized by DLS as well. Since only a minor influence of the concentration has been noted, all measurements have been collected at 5 mg/mL in water. To ascertain the diffusive behavior of the species in solution, DLS data have been collected at different angles. In contrast to the cryo-TEM results, DLS suggested the presence of spherical micelles for pEtOx-b-R-BuEtOx-I with a hydrodynamic radius ($R_h$) of 13 nm (Table 4.5). Also the narrow PD associated to these structures is in agreement with the formation of well-defined spherical micelles. As such, the presence of large vesicles was not detected by DLS for this sample. This might be due to the filtration step that has been used for sample preparation in DLS experiments or to aggregation due to the cryo-TEM sample preparation method. The large vesicles could have been retained on the filter or transformed into spherical micelles due to the high shear operating during filtration. This observation further indicates the hypothesis that spherical micelles are indeed the final equilibrium structures expected for this sample. Also spherical micelles are suggested by DLS for pEtOx-b-R-BuEtOx-II with a $R_h$ of 19 nm and a narrow PD of 0.06 which corresponds to the second cryo-TEM sample.

For the next samples with a higher hydrophobic content, DLS results confirm in all cases the formation of non-spherical large structures as ascertained by the angular dependence of the DLS measurements. Moreover, the average sizes associated to these samples are much larger than for the previously discussed polymer solutions.
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(Table 4.5) and fall in the 100 nm range. PD’s associated to the aggregates formed by these polymer solutions are much broader and CONTIN histograms (not shown) reveal large, sometimes bimodal, distributions. All these observations point toward the formation of non-spherical aggregates for pEtOx-\(b\)-R-BuEtOx-3, -4, -5 and -6 as also observed by cryo-TEM.

### Table 4.5 Characteristic DLS data obtained from the investigated samples.

<table>
<thead>
<tr>
<th>PEtOx-(b)-RS-BuEtOx</th>
<th>Wt% BuEtOx</th>
<th>Angular dependence</th>
<th>PD</th>
<th>(R_h) (nm, at 90°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>No</td>
<td>0.11</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>No</td>
<td>0.06</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Yes</td>
<td>0.25</td>
<td>86</td>
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<tr>
<td>4</td>
<td>45</td>
<td>Yes</td>
<td>0.30</td>
<td>116</td>
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<td>5</td>
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<td>95</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Yes</td>
<td>0.21</td>
<td>116</td>
</tr>
<tr>
<td>7-RS</td>
<td>36</td>
<td>uncertain</td>
<td>n.m.</td>
<td>15 and 85</td>
</tr>
<tr>
<td>8-RS</td>
<td>41</td>
<td>No</td>
<td>0.08</td>
<td>17</td>
</tr>
</tbody>
</table>

\(n.m. = \text{not measured.}\)

DLS confirmed the formation of spherical micelles found in pEtOx-\(b\)-RS-BuEtOx-7 and -8 and that micelles formed by both polymers have approximately the same size. Also the \(R_h\) of 17.5 nm measured for pEtOx-\(b\)-RS-BuEtOx-8 corresponds to the diameter of \(~36\) nm measured with cryo-TEM. However, DLS revealed two distributions for pEtOx-\(b\)-RS-BuEtOx-VII, which indicates that, besides the formation of spherical micelles, also larger, non-spherical aggregates are present in solution, although such aggregates have not been observed with cryo-TEM. These larger aggregates are presumably dynamic clusters of micelles which have frequently been observed for poly(2-oxazoline) micelles.\(^{37}\)
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4.4 Conclusion

Well-defined pBuEtOx copolymers with controlled ee ranging from pure $S$-BuEtOx to pure $R$-BuEtOx were successfully prepared with polydispersity indices ranging from 1.24 to 1.43. The linear dependence of the optical rotation and the Cotton effects on the ee demonstrates the absence of the “majority rules” principle in solution indicating that these main-chain chiral poly(2-oxazoline)s adopt a dynamic flexible secondary structure, presumably due to the high flexibility of the polymer chains and the absence of stabilizing interactions within the formed secondary structures. Furthermore, the DSC results indicate that, upon annealing, polymers with an ee of 80% or higher can form crystalline structures. The amount and quality of the crystals depend on the ee and decrease with decreasing ee, indicating that the crystal structure becomes less perfect by the incorporation of the second monomer. This decreased crystallinity also explains the better solubility of the copolymers with decreasing ee. The CD measurements of the annealed polymer films revealed that the crystals have an ordered chiral structure and confirmed that the incorporation of the second enantiomer disrupts the crystalline chiral structure. The type of chiral structure changed for the enantiopure polymers upon annealing and not for the copolymers. In addition, the persistence length of the chiral structure increased upon annealing for all the semi-crystalline copolymers.

The statistical copolymerization of EtOx with $R$-BuEtOx in a 70:30 ratio resulted in the formation of an amphiphilic gradient copolymer that self-assembles into spherical micelles based on cryo-TEM and DLS investigations. During the non-ideal copolymerization, the EtOx propagating species are better accessible, which increased the polymerization rate of BuEtOx, while the sterical hindrance of the BuEtOx propagating species slowed down the polymerization of EtOx. The polymerization kinetics revealed similar copolymerization behavior of EtOx with $R$-BuEtOx or $RS$-BuEtOx and the monomer composition gradient goes from an EtOx rich part to a pure BuEtOx segment.

Block copolymers with varying compositions of EtOx and $R$-BuEtOx were prepared in a two-step-one-pot reaction under microwave-assisted conditions. These thermo-responsive block copolymers form different types of self-assembled structures, depending on the hydrophobic to hydrophilic ratio. Block copolymers with a higher
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A hydrophobic content resulted in more stable non-spherical structures, while for low hydrophobic contents spherical micelles coexists with other morphologies. The multiple self-assembled structures found in some cryo-TEM samples might represent nonequilibrium morphologies due to nonergodicity effects, possibly due to the formation of an ordered chiral hydrophobic core, which results in an amphiphilic rod-coil block copolymer. DLS investigations confirmed the formation of spherical micelles at relatively low hydrophobic content and non-spherical aggregates at higher hydrophobic/hydrophilic ratio. Block copolymers based on EtOx and the racemic RS-BuEtOx only formed spherical micelles in aqueous solution with a similar size compared to the block copolymers containing the enantiopure chiral block, indicating the importance of the chiral block for the self-assembly process.

All together, it is demonstrated that the optical activity, solubility and thermal properties of the BuEtOx main-chain chiral copolymers can be controlled by the ee. The type of self-assembled structures that are formed depends on the hydrophobic to hydrophilic ratio as well as the chirality and such amphiphilic chiral block copolymers might be useful for separating enantiomeric mixtures in aqueous solution or for drug delivery applications.

4.5 Experimental

**Materials and Instrumentation**

Acetonitrile (Aldrich) was dried in a solvent purification system (Pure Solv EN, Innovative Technology) before use as a polymerization solvent. Methyl tosylate (MeOTs, Aldrich) and 2-ethyl-2-oxazoline (EtOx, Aldrich) were distilled over barium oxide and stored under argon.

Reactions were carried out in capped reaction vials designed for the Emrys Liberator microwave system (Biotage) equipped with an IR temperature sensor. The vials were dried in an oven at 105 °C and cooled under argon to room temperature before use.

GC measurements were performed on a Schimadzu GC-2010 equipped with a Restek Rtx-5 column, a FID detector and a PAL autosampler.

Size exclusion chromatography (SEC) was measured on a Shimadzu system equipped with a LC-10AD pump, a RID-10A refractive index detector, a SCL-10A VP system controller, and a PSS SDV pre/lin S column utilizing chloroform:triethylamine:isopropanol (93:5:2) mixture as eluent at a flow rate of 1 mL/min and a column
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temperature of 40 °C. Alternatively, on a Shimadzu system with a LC-10AD pump, a
RID-10A refractive index detector, a system controller SCL-10A, degasser DGU-14A
and a CTO-10A column oven was utilized including two PSS GRAM 10 µm, 8 mm ×
300 mm, 1000/30 Å columns and N,N-dimethylacetamide (DMA) with ~2 g/L LiCl as
the eluent at a flow rate of 0.5 mL/min (the column oven set to 50 °C). A polystyrene
calibration was used to calculate the molar mass values.

Solubility tests and turbidity measurements were performed using a Crystal 16 from
Avantium Technologies at a concentration of 5 mg/mL and a heating or cooling rate
of 1 °C/min. The transmittance was measured in a temperature range from −15 to
65 °C using methanol, ethanol, n-butanol, acetonitrile, tetrahydrofuran, N,N-
dimethylformamide, n-heptane and cyclohexane as solvent and in a temperature range
of 0 to 100 °C in water to determine the cloud point temperature where the
transmittance goes trough 5%.

Optical rotation at the Na-D line was measured with a sample concentration of
30 mg/mL in chloroform at room temperature with a polarimeter using a quartz cell
with a path length of 10 cm.

UV and CD absorption spectra were measured simultaneously on a Jasco J815
spectropolarimeter equipped with a PTC-348WI temperature controller for
temperatures ranging from −10 to 110 °C. Measurements were performed in a 0.1 cm
quartz cell using sample concentrations of 0.25 mg/mL. The following scanning
conditions were used: 50 nm/min scanning rate, 1 nm bandwidth, 0.1 nm datapitch,
0.5 s response time and 10 accumulations. CD spectra in the solid state were
measured on a Jasco J815 spectropolarimeter equipped with a Linkam temperature
controller. The samples were spin coated from chloroform (20 mg/mL) on a quartz
slide for 2 minutes with 2,000 rpm and annealed at 140 °C for 24 h after measuring
the as spin coated sample. The following scanning conditions were used: 50 nm/min
scanning rate, 1 nm bandwidth, 0.1 nm datapitch, 0.5 s response time and
10 accumulations.

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netsch under a
nitrogen atmosphere with cooling rates of 40 °C/min and heating rates of 20 °C/min.
Cryogenic transmission electron microscopy (cryo-TEM) measurements were
performed using a Philips CM120 operating at an acceleration voltage of 120 kV.
Images were recorded with a bottom mounted 1k×1k CCD camera. The polymer
solution was prepared at a concentration of 5 mg/mL in water and heated to 100 °C

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and cooled back to room temperature. A drop of the polymer solution was placed on a perforated carbon grid in an in-house-built controlled environment vitrification system (CEVS), blotted and rapidly plunged into a cryogen reservoir containing liquid ethane. After preparation the samples were stored and measured at a temperature of \( \sim 180 \, ^\circ C \) to avoid the formation of crystalline ice layers.

DLS experiments were performed on a Malvern CGS-3 apparatus equipped with a He-Ne laser with a wavelength of 633 nm. The micellar solutions were prepared by dissolving 5 mg of sample in 1 mL of ultrapure water and heating them to 100 \( ^\circ C \) followed by cooling back to room temperature. Before the experiments the solutions were filtrated over a 0.2 \( \mu \)m syringe filter. The measurements were performed in water at 25 \( ^\circ C \), at different angles and at different concentrations. The data were analyzed using the Cumulants method and the CONTIN method, which is based on an inverse-Laplace transformation of the data and provides access to a size distribution histogram for the analyzed micellar solutions. The polydispersity (PD) of the micelles was estimated from the \( \Gamma_2/\Gamma_1^2 \) ratio in which \( \Gamma_1 \) and \( \Gamma_2 \) represent the first and second cumulant, respectively. Hydrodynamic radii (\( R_h \)) were calculated from the diffusion coefficients by using the Stokes-Einstein approximation.

**Monomer synthesis**

\( R-2\)-Butyl-4-ethyl-2-oxazoline (\( R\)-BuEtOx), \( S\)-BuEtOx and \( RS\)-BuEtOx were synthesized as described in Chapter 2.

**Kinetic investigation of the microwave-assisted copolymerization**

Two stock solutions with an initial total monomer concentration (\( M_0 \)) of 4 M of EtOx and \( R\)-BuEtOx or \( RS\)-BuEtOx together with the initiator MeOTs with a [EtOx]:[BuEtOx]:[MeOTs] ratio of 70:30:1 were prepared in acetonitrile. The stock solution was divided over eight microwave vials (1 mL each), heated in the microwave to 140 \( ^\circ C \) for different times, cooled by compressed nitrogen and quenched by the addition of water after the desired polymerization time. The resulting mixtures were analyzed by GC and SEC to determine the monomer conversion and polymer molar mass (distribution), respectively.
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**Polymer synthesis**

The copolymers p-R-BuEtOx-stat-S-BuEtOx were prepared in a similar way as the homopolymers (Chapter 2) by weighing in the desired amount of R-BuEtOx or S-BuEtOx together with RS-BuEtOx. A typical polymerization procedure was as follows: for the R-rich polymers a mixture of R-BuEtOx and RS-BuEtOx with an initial monomer concentration of 4 M in dichloromethane and a [M]/[I] (I = methyl tosylate) ratio of 60 was used. The S-rich polymers were prepared by mixing S-BuEtOx with RS-BuEtOx with an initial monomer concentration of 4.5 M in acetonitrile and a [M]/[I] (I = methyl tosylate) ratio of 50. The polymerization mixtures were heated to 180 °C under microwave irradiation for 60 min. After cooling the mixtures to <40 °C, the polymerizations were quenched by the addition of water. The polymers were dried, precipitated from tetrahydrofuran into demineralized water and again thoroughly dried at 40 °C under reduced pressure before further characterization.

The block copolymers p-EtOx-b-R(S)-BuEtOx were synthesized in a two-step-one-pot protocol using a M₀ of 4 M in acetonitrile and a total [M]/[I] (I = MeOTs) ratio of 100. The ratio EtOx:R-BuEtOx was varied to investigate the self-assembled structure dependence on the hydrophobic content. In the first step EtOx was polymerized at 140 °C under microwave irradiation for 6 to 9 min, depending on the [M]/[I] ratio. After the polymerization, a small sample of pEtOx was taken with a syringe to determine the molar mass and polydispersity index (PDI) using SEC. Subsequently, the second monomer, R(S)-BuEtOx, was added with a syringe. After the second polymerization stage at 180 °C for 10 to 40 min, depending on the [M]/[I] ratio, the mixtures were quenched by the addition of water. A small sample was taken with a syringe to determine the molar mass and PDI values of the block copolymer using SEC. After drying, the polymers were redissolved in chloroform and precipitated in cold n-hexane or n-heptane before further characterization. Solubility tests were carried out to determine if the block copolymers revealed LCST behavior in water and the formation of micelles was determined by DLS and cryo-TEM.
4.6 References and notes


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Chapter 5

Thermo-responsive poly(cyclic imino ether)s

Polymers that reveal lower critical solution temperature (LCST) behavior represent an interesting class of stimuli-responsive polymers that are soluble in water at low temperature and phase separate at elevated temperatures. To be able to tune the temperature at which the polymer precipitates, the influence of Hofmeister salts on thermoresponsive poly(2-oxazoline)s with different side chains have been investigated. It was found that the effect of the Hofmeister ions on the cloud point temperature ($T_{CP}$) of the poly(2-oxazoline)s strongly depends on their hydrophilicity. Furthermore, the group of poly(2-oxazoline)s that reveal a $T_{CP}$ has been extended by the synthesis of the new poly(2-cyclopropyl-2-oxazoline) (pCPropOx). Due to the electron withdrawing effect of the cyclopropyl groups, the polymerization rate was much higher compared to other 2-oxazolines. Detailed evaluation of the $T_{CP}$ of the amorphous pCPropOx by turbidimetry, dynamic light scattering (DLS) and viscosity measurements revealed a $T_{CP}$ just below body temperature. Furthermore, the influence of the addition of another methylene group in the backbone of the polymer on the LCST behavior was investigated by determining the $T_{CP}$ of poly(2-oxazine)s. The polymerization rate constants ($k_p$) of the 2-oxazines were about four times lower compared to the $k_p$ of the corresponding 2-oxazolines due to the lower ring-tension and non-planar ring conformation. Their $T_{CP}$ are lower compared to poly(2-oxazoline)s with similar side-chains. However, the side-chain has a stronger impact on the polymer solubility than the main-chain when comparing the poly(2-oxazoline) with the poly(2-oxazine) isomers. Altogether, by the addition of Hofmeister salts or changing the hydrophobic to hydrophilic ratio of the polymer by altering the side-chain or elongating the main-chain, the $T_{CP}$ of poly(cyclic imino ether)s can be tuned.

5.1 Introduction

There is a high potential for thermo-responsive polymers to be used in various applications, such as drug delivery systems \(^1\)–\(^6\) and separation processes, \(^7\),\(^8\) and, therefore, these materials received significant attention over the last years. Polymers that become insoluble with the increase in temperature exhibit a ‘lower critical solution temperature’ (LCST) behavior, which is mostly observed in water: \(^4\),\(^8\),\(^9\) At low temperatures, the polymer is hydrated making it water-soluble; upon increasing the temperature the hydrogen bonds are weakened resulting in dehydration when the LCST is reached. This entropically driven phase transition, i.e. release of water molecules, leads to a collapse of the hydrophobic polymer chains and the formation of aggregates. These types of water-soluble polymers comprise both hydrophobic and hydrophilic moieties. Since the LCST depends on the delicate hydrophilic/hydrophobic balance of the polymer, the LCST can be tuned by, e.g., variation of the polymer side chain or by copolymerization with other monomers, as has been fully explored for the most frequently studied LCST polymer, poly(N-isopropylacrylamide) (PNIPAM).\(^4\),\(^5\),\(^10\),\(^11\)

It is known that salts from the Hofmeister series can influence the LCST of polymers; as a consequence the solubility and the LCST of the respective polymer in solution can be varied by the addition of salts. The mechanism of the salting-in and salting-out effect caused by the addition of chaotropes or kosmotropes, respectively, is described by Bergbreiter and Cremer who investigated the effect of these salts on the LCST of PNIPAM and elastin-like polypeptides.\(^12\)–\(^15\) In general, the majority of the studies concerning the effects of Hofmeister ions on thermo-responsive polymers focused on a single polymer with a transition temperature close to body temperature. For elastin-like peptides, a comparison of the effect of Hofmeister salts on the thermo-responsive behavior of two peptides having a difference in \(T_{\text{CP}}\) in water of 14 °C was also described.\(^15\) Nonetheless, to the best of our knowledge, it is still an open question how similar synthetic polymers with a different hydrophilicity, leading to \(T_{\text{CP}}\) which range from ambient temperature up to 100 °C, respond to the addition of Hofmeister ions. Poly(2-oxazoline)s with methyl, ethyl, \(n\)-propyl or \(i\)so propyl side-chains are water soluble and show LCST behavior in water, except for poly(2-methyl-2-oxazoline) which is highly hydrophilic.\(^16\)–\(^19\) The LCST of poly(2-oxazoline)s can be fine-tuned by changing the side-chain substituent, by varying the degree of polymerization (DP),
5. Thermo-responsive poly(cyclic imino ether)s

by altering the hydrophobic/hydrophilic ratio by the addition of comonomers or functional endgroups, or by the addition of a cosolvent or salt.\textsuperscript{20-32} However, even though it was reported that the LCST of poly(2-oxazoline)s changes with the addition of salt,\textsuperscript{20} no systematical investigation was performed on the influence of the Hofmeister series, despite the easy variation of the LCST of these compounds by variation of the side-chains.

Poly(2-ethyl-2-oxazoline) (pEtOx) is known to only reveal a $T_{CP}$ when the DP is above 100, since smaller polymer chains are soluble up to 100 °C.\textsuperscript{22} Poly(2-iso-propyl-2-oxazoline) (piPropOx) is an interesting thermo-responsive polymer, since its $T_{CP}$ is close to body-temperature, making it suitable for biomedical applications.\textsuperscript{33} However, due to its semi-crystallinity the thermo-responsiveness becomes irreversible after annealing above the LCST.\textsuperscript{34-36} Poly(2-n-propyl-2-oxazoline) (pnPropOx) is amorphous but has a lower LCST of \(~24 °C.\textsuperscript{22} In addition, the rather low $T_g$ of \(~40 °C, which decreases in the presence of water, makes it difficult to handle and to store the polymer at ambient temperature. Therefore, an alternative thermo-responsive poly(2-oxazoline) with a reversible critical temperature close to body temperature is desired (Scheme 5.2).

![Scheme 5.1 Schematic presentation of pEtOx, piPropOx and pnPropOx.](image)

The living/controlled cationic ring-opening polymerization (CROP) is not limited to 5-membered 2-oxazoline cyclic imino ethers, but also 6-membered 2-oxazine rings can be polymerized in a similar manner.\textsuperscript{37} Even though the first report on the CROP
of 2-oxazines appeared shortly after the first 2-oxazoline reports, the CROP of 2-oxazines received much less attention compared to the 2-oxazolines. The polymerization kinetics of unsubstituted 2-oxazine, 2-methyl-2-oxazine, 2-butyl-2-oxazine and 2-phenyl-2-oxazine are significantly slower than for the 2-oxazolines with the same side-chain, which can be ascribed to the increased ring-size, leading to less ring tension and more sterical hindrance due to the non-planarity of the 2-oxazine ring. However, it is expected that poly(2-oxazine)s with optimized side-chain length also reveal LCST behavior like the poly(2-oxazoline)s, broadening the number of polymers for the use as thermo-responsive materials. Moreover, comparison of the thermo-responsive behavior of poly(2-oxazine)s with poly(2-oxazoline)s will provide important insights in the structure-property relationships for thermo-responsive polymers.

![Scheme 5.3](image)

**Scheme 5.3 Schematic presentation of the CROP of 2-oxazine monomers.**

The investigation of the effect of Hofmeister ions on the \( T_{CP} \) of pEtOx, piPropOx and pnPropOx, which have decreasing hydrophilicity going from pEtOx via piPropOx to pnPropOx (Scheme 5.1) is described in section 5.2. In section 5.3 the synthesis of a new linear poly(2-oxazoline), namely poly(2-cyclopropyl-2-oxazoline) (pCPropOx), is described (Scheme 5.2). The thermal properties were determined by differential scanning calorimetry (DSC) and the \( T_{CP} \) was extensively studied by turbidimetry, dynamic light scattering (DLS) and viscosimetry. Furthermore, the polymerization kinetics of linear 2-oxazines, namely 2-methyl-2-oxazine (MeOZI), 2-ethyl-2-oxazine (EtOZI), and 2-\( n \)-propyl-2-oxazine (\( n \)PropOZI) under microwave-assisted conditions (Scheme 5.3) are described in section 5.4 and their thermo-responsiveness as measured with turbidimetry is discussed in relation to the corresponding poly(2-oxazoline)s.
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5.2 Hofmeister salts

To investigate the effect of the Hofmeister salts on the temperature-induced phase transitions of a series of poly(2-oxazoline)s with different hydrophilicity, the cloud point temperatures \( T_{CP} \) of well-defined pEtOx, pPropOx and pnPropOx with a degree of polymerization (DP) of 100 were determined by turbidimetry at a polymer concentration of 5 mg/mL. First the \( T_{CP} \) of these polymers were determined in aqueous solutions in the absence of salt, to evaluate the difference in hydrophilicity. Figure 5.1 depicts the transmittance versus temperature plots, which clearly indicate that the hydrophilicity of the four polymers decreases in the following order: pEtOx > pPropOx > pnPropOx, as indicated by the decreasing \( T_{CP} \) of 94 °C, 43 °C and 26 °C, respectively. It is obvious from Figure 5.1 that the LCST behavior is reversible. Upon heating the polymer precipitates, resulting in a drop in transmittance, and upon cooling the polymer dissolves again. The transmittance curves during heating and cooling are almost identical, indicating that no or only slight hysteresis took place.

![Transmittance curves during heating and cooling scans](image)

**Figure 5.1** Transmittance curves during heating and cooling scans (conc. = 5 mg/mL, temperature ramp: 1 °C/min.) There is a slow decrease in transmittance from 100% to 90% in the curve of pEtOx due to the temperature sensitivity of the sensor.

In a next step, the effect of adding a range of Hofmeister salts, namely NaSCN, NaClO₄, LiClO₄, NaI, LiI, NaCl, NaOAc, LiOAc, Na₂SO₄ and Li₂SO₄, to the aqueous polymer solutions was investigated. To evaluate the effect of the Hofmeister ions on the \( T_{CP} \) of the three poly(2-oxazoline)s, the concentration of salt was systematically
increased in steps of 0.1 M from 0 to 0.5 M. The results of this systematic screening of $T_{CP}$ are depicted in Figure 5.2.

Figure 5.2 Influence of the Hofmeister salts on the cloud point temperature ($T_{CP}$) of (a) $p$EtOx, (b) $p$nPropOx and (c) $p$iPropOx.

Figure 5.2 clearly demonstrates that SCN$^-$, ClO$_4^-$ and I$^-$ have a salting-in effect, i.e., the $T_{CP}$ increases with increasing salt concentration. The other anions studied, namely Cl$^-$, OAc$^-$ and SO$_4^{2-}$, cause a salting-out effect: the $T_{CP}$ decreases with increasing salt concentration. The order of salting-in to salting-out effect is SCN$^-$ > ClO$_4^-$ > I$^-$ > Cl$^-$ > OAc$^-$ > SO$_4^{2-}$, which nicely follows the Hofmeister series.$^{13}$ In general, the anion has a larger influence on the LCST behavior in comparison to the cation. The results also demonstrate that Na$^+$ has a somewhat larger influence than Li$^+$, which again follows the Hofmeister series.$^{42}$ According to Bergbreiter and Cremer,$^{12}$ the kosmotropes cause a salting out effect by destabilizing the H-bonds between water and the polar groups of the polymer (Scheme 5.4a) and by increasing the cost of hydration (Scheme 5.4b), resulting in a linear decrease in LCST with increasing salt concentration. In addition, chaotropes can also cause a slight salting-out effect by increasing the hydrophobic hydration. Nonetheless, the stronger salting-in effect of chaotropes is caused by direct interactions of the salts with the polymer (Scheme 5.4c), resulting in
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an overall salting-in behavior. In fact, binding of the anion to the amide group of the polymer increases the LCST with increasing salt concentration until a saturation effect is observed. This saturation effect can explain why the increase in $T_{CP}$ is largest when going from 0 M to 0.1 M salt concentration.

![Scheme 5.4](image)

**Scheme 5.4** (a) The anions polarizes water molecules which are hydrogen bonded to the amide group. (b) Salt increases the surface tension of the cavity surrounding the backbone and the n-propyl side-chains. (c) Direct binding of the anions to the polymer.

Based on these considerations, it is obvious that the effects of the different salts follow the same trends for all four polymers. However, the $T_{CP}$ of pEtOx can be tuned over almost the whole temperature range of liquid water at ambient pressure by the addition of salts. For pEtOx, a small amount of chaotrope increases the $T_{CP}$ above 100 °C while the strongest kosmotrope, Na$_2$SO$_4$, can decrease the $T_{CP}$ of pEtOx by almost 70 °C, bringing it near to ambient temperature. In contrast to pEtOx, the $T_{CP}$ of piPropOx and pnPropOx only vary in a limited range (piPropOx: 11 to 65 °C; pnPropOx: 10 to 43 °C) upon addition of the Hofmeister salts. This difference is most likely related to the difference in hydrophilicity of the investigated poly(2-oxazoline)s, which also influences the hydration of the collapsed polymer globules above the LCST transition, i.e., more water is present in the collapsed state for the more hydrophilic polymers as was previously demonstrated for poly(oligoethylene glycol methacrylate)s using a solvatochromic dye.\textsuperscript{43} Previously, Cremer and coworkers demonstrated that partitioning of ions from bulk solution to the aqueous/polymer interface is more favorable with the more hydrophilic polymers.\textsuperscript{15}
For a better comparison of the effect of ions on the $T_{CP}$ of the poly(2-oxazoline)s, the differential $T_{CP}$ are plotted as function of salt concentration in Figure 5.3 for NaClO$_4$, LiI, NaCl and Li$_2$SO$_4$.

**Figure 5.3** Increase and decrease of the cloud point temperatures ($T_{CP}$) due to the addition of the Hofmeister salt (a) NaClO$_4$, (b) LiI, (c) NaCl and (d) Li$_2$SO$_4$.

The steep increase or decrease in the $T_{CP}$ of pEtOx by the addition of salt confirms that the ionic response of the more hydrophilic poly(2-oxazoline) is larger compared to the less hydrophilic piPropOx and to the even lesser hydrophilic pnPropOx.

### 5.3 Poly(2-cyclopropyl-2-oxazoline)

To increase the diversity in thermo-responsive poly(2-oxazoline)s, a new monomer, 2-cyclopropyl-2-oxazoline (CPropOx), was synthesized by the reaction of cyclopropionitrile with 2-amino-1-ethanol using zinc acetate as the catalyst following standard synthetic procedures. The polymerization kinetics of CPropOx was determined at 140 °C, using an initial monomer concentration ($M_0$) of 4 M and a
monomer to initiator ratio ([M]/[I]) of 52, 107 and 155 using methyl tosylate (MeOTs) as initiator and acetonitrile as solvent. The first order kinetic plots (Figure 5.4) do not pass the origin of the plots, indicating that the first data points in Figure 5.4a correspond to the conversions after 1 s reaction time at 140 °C, i.e. the reaction already started while heating the reaction mixture to the reaction temperature of 140 °C.

**Figure 5.4** (a) Kinetic plots for CPropOx polymerizations initiated with methyl tosylate ([M]/[I] = 52, 107 and 155) in acetonitrile (M₀ = 4 M) at 140 °C. (b) Corresponding molar mass (Mₙ) against conversion plot, including polydispersity indices (PDI). The black lines indicate the linear fits.

All three polymerizations of CPropOx revealed linear first-order kinetics up to a conversion of approximately 80% as well as a linear increase of the molar mass with conversion, demonstrating a constant concentration of propagating species and that the polymerizations proceeded in a controlled manner. The polymerization rate constants (k_p) calculated from the linear fit up to 80% are 0.257 (± 0.006) L/(mol s), 0.255 (± 0.008) L/(mol s) and 0.214 (± 0.008) L/(mol s) for [M]/[I] = 52, [M]/[I] =107 and [M]/[I] = 155, respectively. These similar k_p values confirm that the polymerization proceeded in a controlled fashion. Compared to other 2-oxazolines, CPropOx polymerizes approximately two times faster under similar conditions; the k_p of nPropOx is 0.117 (± 0.004) L/(mol s), while in contrast iPropOx polymerizes slower than nPropOx. In fact, the k_p of CPropOx is the fastest reported so far for a 2-oxazoline with an aliphatic side chain; only 2-phenyl-2-oxazolines with electron withdrawing ortho-fluoro groups were slightly faster. The higher reactivity of
CPropOx is not yet completely understood, but might be related to the electron withdrawing effect of the cyclopropyl substituent caused by the small angle of 60° between the C-atoms resulting in partial $\pi$-character of the bonds making the remaining orbitals s-rich and, thus, electron withdrawing.\textsuperscript{47} Even though this electron withdrawing effect lowers the nucleophilicity of the monomer, it enhances the reactivity of the cationic propagating species apparently dominating the overall polymerization rate. The lower steric hindrance of cyclopropyl compared to $n$-propyl or $i$-propyl most likely does not influence the polymerization rate since it has been demonstrated that 2-oxazolines with ethyl to $n$-nonyl substituents all have similar polymerization rates.\textsuperscript{45} At higher conversion (>80%), the solution became very viscous explaining the observed decrease in polymerization rate due to limited diffusion. This can also explain the slightly lower polymerization rate at higher [M]/[I] ratios due to the higher viscosity resulting from longer polymer chains. In addition, characterization by size exclusion chromatography (SEC) revealed monomodal molar mass distributions for the polymers with polydispersity index (PDI) values below 1.3 when the [M]/[I] ratio is 52 or 107 demonstrating that the polymers were prepared in a controlled manner. At a higher [M]/[I] ratio, the PDI values start to increase indicating the occurrence of more chain transfer reactions. It is known that the control over the polymerization is lost for most poly(2-oxazoline)s when the [M]/[I] value is above 200.\textsuperscript{48}

Based on the kinetic investigations, six CPropOx polymers with different DP were synthesized under microwave-assisted conditions using MeOTs as initiator and acetonitrile as solvent. The DP values were calculated from the conversion measured by gas chromatography (GC), assuming the absence of chain transfer and termination reactions. After the polymerization, the polymers were precipitated in $n$-hexane resulting in white solid powders. Most polymers show some tailing in the SEC traces (Figure 5.5), indicating the occurrence of some chain transfer and/or termination reactions during the polymerization. When $M_n$ (determined with SEC) is plotted against DP (calculated from the GC results), it is observed that the values progressively deviate from the theoretical values with increasing DP. This increasing deviation is a direct consequence of the broadening of the molar mass distributions, ascribed to chain transfer reactions, causing a decrease in $M_n$. It should be noted that this effect might be overestimated by the used SEC calibration standards.
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**Figure 5.5** (a) SEC traces of all six synthesized polymers dissolved in chloroform. (b) Molar mass and polydispersity indices (PS calibration) plotted against the calculated degree of polymerization (DP). The dashed line represents the theoretical molar mass.

The MALDI-TOF MS (Figure 5.6) spectrum of pCPropOx with a DP of 20 revealed two main distributions corresponding to the methyl initiated pCPropOx \((\text{CH}_3[\text{C}_6\text{H}_9\text{NO}]_n\text{OH})\) and the proton initiated pCPropOx \((\text{H}[\text{C}_6\text{H}_9\text{NO}]_n\text{OH})\), confirming the expected polymer structure as well as indicating the occurrence of minor chain transfer reactions leading to the proton initiated chains (Figure 5.7).

**Figure 5.6** MALDI-TOF MS spectrum of pCPropOx with \(\text{DP} = 20\), using DCTB as matrix.
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Figure 5.7 Isotopic patterns of pCPropOx (a) the desired product and (b) the minor formation of proton initiated pCPropOx resulting from chain transfer reactions. Both structures are ionized with Na\(^+\).

Turbidity of the aqueous pCPropOx polymer solutions was measured as a function of temperature with a concentration of 5 mg/mL with heating and cooling rates of 1 °C/min in a temperature range between 0 and 100 °C. Upon heating, the polymer precipitates resulting in a drop in transmittance, and, upon cooling, the polymer dissolves again demonstrating the reversibility of the solubility transition. Most polymers show similar transmittance curves during heating and cooling indicating that no or only a slight hysteresis took place (Figure 5.8), except for pCPropOx with a DP of 20. The reason for this larger hysteresis is still unclear, but it might be related to the formation of smaller aggregates that cannot be detected by turbidimetry. The \(T_{CP}\) taken from the first heating run decreases in a non-linear way from 54 °C for pCPropOx with a DP of 20 to 30 °C for pCPropOx with a DP of 112 (Figure 5.9a). The steepest decrease occurs when the DP is increased from DP = 20 to 51, which is due to the endgroup effect which is more pronounced in short polymers. Since the -OH endgroup is more hydrophilic than the polymer chain, the endgroup will increase the \(T_{CP}\). With the increase in concentration, the \(T_{CP}\) decreases in a non-linear way and only a small decrease is observed when the concentration is increased from 10 to 30 mg/mL indicating that the \(T_{CP}\) at 30 mg/mL approaches the LCST value (Figure 5.9b). Both the DP and concentration dependence of the \(T_{CP}\) follow the same trend as for pnPropOx,\(^{22}\) which is a consequence of the Type I Flory-Huggins miscibility behavior that is characterized by a shift of the LCST towards lower polymer
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concentration when the polymer chain length is increased. The \( T_{CP} \) of pCPropOx (30 °C) lies in between the \( T_{CP} \) of pnPropOx (44 °C) and piPropOx (27 °C) (all 5 mg/mL and a DP of 100, Figure 5.8b). This can be explained by the difference in hydrophilicity; the polymer that is most hydrophilic (pEtOx) has the highest \( T_{CP} \) followed by piPropOx, pCPropOx, and pnPropOx.

Figure 5.8 a) Transmittance curves during heating (solid symbols) and cooling (open symbols) scans of pCPropOx with varying degrees of polymerization (DP) and a heating/cooling rate of 1 °C min\(^{-1}\). b) Determined \( T_{CP} \) of poly(2-oxazoline)s with varying hydrophilicity (DP = 100).

Figure 5.9 (a) Cloud point temperatures (\( T_{CP} \)) determined by turbidimetry as a function of the degree of polymerization (DP) of pCPropOx at a concentration of 5 mg/mL in water. (b) \( T_{CP} \) as a function of concentration for pCPropOx with various DP.
The formation of aggregates of pCPropOx with varying DP was investigated in further detail by dynamic light scattering (DLS) measurements at a concentration of 1 mg/mL at different temperatures. At a certain temperature the hydrodynamic radius \( R_h \) measured by DLS increases from the characteristic size of individual polymer chains (<10 nm) to the size of larger aggregates (>100 nm) (Figure 5.10a). The detection of the formation of aggregates takes place approximately 5 °C below the \( T_{CP} \) measured by turbidimetry (Figure 5.10b). The basis of this difference is threefold: 1) DLS detects the scattering of any form of aggregation while turbidimetry only detects large aggregates that can scatter visible light at 500 nm, 2) the \( T_{CP} \) from turbidimetry is defined as 50% transmittance while the onset of aggregates is taken as \( T_{CP} \) for the DLS measurements and 3) DLS is measured in steady state while turbidimetry is performed with a heating rate of 1 °C/min. The only exception is pCPropOx with a DP of 20; at 77 °C the \( R_h \) of the particles are still <10 nm, while according to the turbidity measurements the solution becomes turbid at this temperature. Nonetheless, at 80 °C two distributions are also found in the DLS for pCPropOx with a DP of 20, indicating that larger aggregates with a size of 360 nm are formed. This discrepancy might be due to inaccuracies in the temperature calibrations at higher temperatures.

**Figure 5.10** (a) Hydrodynamic radius \( R_h \) of the particles/aggregates against temperature measured with DLS of pCPropOx at a concentration of 1 mg/mL dissolved in water. (b) Comparison of the critical temperature measured with turbidity measurements and DLS.
When the critical temperature is approached, also the viscosity of the solution will change providing an additional possibility to investigate the thermo-responsive behavior. The measured values of intrinsic viscosities $[\eta]$ at ambient conditions ($T = 20 \, ^{\circ}\text{C}$) are: $[\eta] = 4.6$, 8.2 and 11.6 cm$^3$/g, for pCPropOx with a DP of 20, 59 and 101, respectively. The LCST behavior of the polymers was investigated at different highly diluted concentrations where the Debye parameter $c/[\eta]$, which characterizes the degree of dilution, was in the range of $(0.008 \pm 0.003) \leq c/[\eta] \leq (0.24 \pm 0.15)$. There are several regions that can be considered within the temperature dependence of the viscosity. At first, when the temperature starts to increase, the dynamic viscosity ($\eta$) of the solution decreases according to equation (1) (Figure 5.1). When the critical temperature is approached, the viscosity increases due to deterioration of the solvent quality and more favorable interactions between the polymer chains. As a result, intermolecular interactions occur leading to the formations of clusters, which then subsequently merge together into large aggregates. Increasing the temperature further leads to the collapse of the polymer chains resulting in precipitation of the polymer and, consequently, to a reduction of the viscosity values. This behavior is most pronounced in pCPropOx with a DP of 51 at a low concentration (1 mg/mL), since this polymer has an intermediate viscosity and a relatively low critical temperature.

The critical temperatures determined by viscosity measurements, identified as the midpoint on a tangent line to the straight section of the curve, compare well with the $T_{\text{CP}}$ measured by turbidity measurements for pCPropOx with a DP of 59 and 101. However, the viscosity measurements of pCPropOx with a DP of 20 indicated a higher critical temperature compared to turbidity measurements due to the low molar mass resulting in minimal viscosity changes, especially at these low concentrations. At 1 mg/mL, the viscosity measurements underestimated the critical temperature for all three investigated polymers due to the low concentration and, thus, minimal chain overlap in solution.
5. Thermo-responsive poly(cyclic imino ether)s

The previously discussed investigations clearly revealed the high potential of pCPropOx for biomedical applications based on the $T_{CP}$ in between body- and ambient temperature as well as the low hysteresis. The thermal properties of the polymers are also very important for the ease of storage, i.e. for pharmaceutical applications storage should be at least 40 °C below $T_g$, and for the reversibility of the phase-transition, i.e. absence of polymer crystallization upon annealing of the solution, as observed for piPropOx. The differential scanning calorimetry (DSC) data (Figure 5.12) demonstrate that pCPropOx is amorphous since it does not reveal a melting endotherm ($T_m$) up to 300 °C. A glass transition temperature ($T_g$) at 79 °C was observed with a heat capacity ($\Delta C_p$) of 0.4 J/(g K). The polymer with a relatively low molar mass (DP = 26) has a lower $T_g$ at 75 °C, due to the increased fraction of

Figure 5.11 Dynamic viscosity ($\eta$) against temperature for pCPropOx with a DP of (a) 20, (b) 51 and (c) 101. (d) Comparison of the critical temperature determined with turbidity and viscometry against the concentration.
flexible chain ends. This $T_g$ above room temperature makes storing of the polymer easier.

![DSC traces of the second heating run (20 °C/min) of pCPropOx with different molar masses.](image)

**Figure 5.12** DSC traces of the second heating run (20 °C/min) of pCPropOx with different molar masses.

### 5.4 Thermo-responsive poly(2-oxazine)s

To investigate the influence of an elongated main-chain on the thermo-responsive properties of poly(cyclic imino ether)s, three poly(2-oxazine)s were synthesized. The oxazine monomers, 2-methyl-2-oxazine (MeOZI), 2-ethyl-2-oxazine (EtOZI) and 2-$n$-propyl-2-oxazine ($n$PropOZI) were synthesized by the reaction of 3-amino-1-propanol with the corresponding nitriles using zinc acetate as the catalyst following standard synthetic procedures. The polymerization kinetics of the 2-oxazines were determined at 140 °C, using an initial monomer concentration ($M_0$) of 4 M and a monomer to initiator ratio ([M]/[I]) of 60 using methyl tosylate (MeOTs) as initiator and acetonitrile as solvent. The first order kinetic plots (Figure 5.13a) together with the linear increase of the molar mass with conversion (Figure 5.13b) demonstrates that the polymerizations proceeded in a controlled manner, although the relatively high PDI values indicate the occurrence of some chain transfer reactions during the polymerizations. The $k_p$ calculated from the linear fits are 0.035 (± 0.001) L/(mol s) for MeOZI, 0.023 (± 0.001) L/(mol s) for EtOZI and 0.029 (± 0.003) L/(mol s) for $n$PropOZI. The higher $k_p$ of MeOZI compared to the $k_p$ of EtOZI and $n$PropOZI can be explained by the lower inductive effect (+I) of the methyl group resulting in less stabilization of the cationic oxazonium species as was also reported for the corresponding poly(2-oxazoline)s. Compared to the $k_p$ of 2-oxazolines the $k_p$ of the
5. Thermo-responsive poly(cyclic imino ether)s

2-oxazines are approximately four times lower.\textsuperscript{45} This observed decrease in $k_p$ can be ascribed to the lower ring-tension of the 2-substituted-2-oxazines compared to 2-substituted-2-oxazolines. In addition, the conformation of the 2-substituted-2-oxazines are most likely non-planar as was reported for unsubstituted 2-oxazine,\textsuperscript{51} which causes steric hindrance when the next nucleophilic 2-oxazine monomer attacks the C-6 carbon atom of the electrophilic oxazinium species due to the staggered hydrogen attached to the C-5 carbon atom. In contrast, the propagating species of 2-oxazolines are planar resulting in less sterical hindrance due to the eclipsed conformation of C-4 and C-5.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure513.png}
\caption{(a) Kinetic plots for 2-oxazine polymerizations initiated with methyl tosylate ([M]/[I] = 60) in acetonitrile ($M_0 = 4$ M) at 140 °C. Black lines are the linear fits. (b) Corresponding molar mass ($M_n$) against conversion plot, including polydispersity indices (PDI). Black lines are the theoretical molar masses.}
\end{figure}

Based on the kinetic investigations, pMeOZI with a [M]/[I] value of 50, pEtOZI with [M]/[I] values of 50 and 100 and pnPropOZI with [M]/[I] values of 50, 100 and 150 were synthesized under similar microwave assisted conditions. After the polymerization, the polymers were precipitated in cold $n$-hexane resulting in white solid powders. The isolated polymers show some tailing in the SEC traces (Figure 5.14a), indicating the occurrence of some chain transfer and/or termination reactions during the polymerization.
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Figure 5.14 (a) SEC traces of the poly(2-oxazine)s and (b) turbidity curves of the second heating (solid symbols) and cooling (open symbol) run.

Turbidity of the aqueous poly(2-oxazine) solutions were measured as a function of temperature with a concentration of 5 mg/mL with heating and cooling rates of 1 °C/min in a temperature range between 0 and 100 °C (Figure 5.14b). There is a small difference between the T_CP measured during heating and cooling, indicating that some hysteresis takes place, in particular for pEtOZI_{100} (Table 5.1). PMeOZI with a [M]/[I] of 50 remains soluble over the entire temperature range, indicating that this polymer has no T_CP in water under ambient pressure. Therefore it can be concluded that pMeOZI is too hydrophilic, like poly(2-methyl-2-oxazoline) (pMeOx), to exhibit LCST behavior. Also pEtOZI with a [M]/[I] of 50 remains soluble in water upon heating. However, when the [M]/[I] is increased to 100, pEtOZI reveals a T_CP at a temperature of 56 °C during the second heating and dissolves again at 60 °C during cooling. Similarly, pEtOx with a [M]/[I] of 50 is also soluble in water between 0 and 100 °C, while pEtOx with a [M]/[I] of 100 has a T_CP of 94 °C under the same conditions, which is 38 °C higher compared to pEtOZI. 22 As such, it can be concluded that the additional CH₂ group in the backbone increases the hydrophobicity and, thus, decreases the aqueous solubility of pEtOZI compared to pEtOx. However, pEtOZI is actually a structural isomer of poly(n-2-propyl-2-oxazoline) (pnPropOx), which has a much lower T_CP of 25 °C clearly demonstrating that the side-chain has a much stronger effect on the solubility than the main-chain. This can be rationalized by the direct exposure of the side-chains to the surrounding medium while the backbone is shielded from the solvent by hydrophilic amide side-chains. Finally, pnPropOZI with
5. Thermo-responsive poly(cyclic imino ether)s

a [M]/[I] of 50 reveals a $T_{CP}$ of 13 °C upon heating and cooling; increasing the molar mass does not decrease the $T_{CP}$ significantly. In comparison, $p_{n}$PropOZI has a $T_{CP}$ that is about 12 °C below the $T_{CP}$ of $p_{n}$PropOx, confirming that the additional methylene group in the poly(2-oxazine) backbone causes a decrease in the $T_{CP}$. However, comparing $p_{n}$PropOZI with the water insoluble poly(2-n-butyl-2-oxazoline) ($p_{n}$BuOx) isomer confirms that the side chain has a stronger impact on the solubility than the main chain.

Table 5.1 SEC data and $T_{CP}$ of the investigated poly(2-oxazine)s.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>[M]/[I]</th>
<th>$M_n$ (g/mol)$^1$</th>
<th>PDI$^1$</th>
<th>$T_{CP}$ (°C)$^2$ heating</th>
<th>$T_{CP}$ (°C)$^2$ cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMeOZI</td>
<td>50</td>
<td>6,070</td>
<td>1.42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pEtOZI</td>
<td>50</td>
<td>4,940</td>
<td>1.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pEtOZI</td>
<td>100</td>
<td>7,430</td>
<td>1.24</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>$p_{n}$PropOZI</td>
<td>50</td>
<td>9,650</td>
<td>1.20</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>$p_{n}$PropOZI</td>
<td>100</td>
<td>17,140</td>
<td>1.37</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>$p_{n}$PropOZI</td>
<td>150</td>
<td>20,960</td>
<td>1.44</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

$^1$ Determined from SEC in DMA using PS standards. $^2$ Measured with turbidimetry during the second heating or cooling run at a concentration of 5 mg/mL in water and a heating or cooling rate of 1 °C/min. $T_{CP}$’s were taken at a transmittance of 50%.

5.5 Conclusion

In this study it was found that the ionic response of poly(2-oxazine)s to the addition of salts from the Hofmeister series depends on the hydrophilicity of the polymer. The $T_{CP}$ of the most hydrophilic polymer, pEtOx, can be tuned over almost the entire temperature range of liquid water under atmospheric pressure, while the $T_{CP}$ of $p_{i}$PropOx and $p_{n}$PropOx can be varied to a lesser extent. The $T_{CP}$ of these polymers are limited to the range between 10 and 43 °C and between 11 and 65 °C, respectively. CpropOx could be synthesized via the reaction of cyclopropionitrile with 1-amino-2-ethanol. A kinetic investigation on the CROP of CPropOx revealed that the
polymerization took place in a controlled fashion with a $k_p$ in the range of $0.214 \pm 0.008$ to $0.257 \pm 0.006$ L/(mol s), which is the highest reported value for an aliphatic substituted 2-oxazoline monomer so far. This observed rate acceleration is ascribed to the electron withdrawing effect of the cyclopropyl group. The formation of well-defined polymers was confirmed by SEC and MALDI-TOF MS investigations. The $T_{CP}$ of linear pCPropOx decreases with both increasing DP and increasing concentration, which is typical for type I Flory-Huggins miscibility behavior. With a $T_{CP}$ of 25 °C for pCPropOx with a DP >100 at 30 mg/mL, the $T_{CP}$ is slightly higher compared to pnPropOx. DLS results indicated the formation of aggregates approximately 5 °C below the $T_{CP}$ measured by turbidimetry due to its higher sensitivity, and the critical temperatures determined by viscometry compare well with the $T_{CP}$ from turbidimetry. Furthermore, DSC measurements revealed that the linear pCPropOx ($T_g \approx 80$ °C) is amorphous.

In addition, it was demonstrated that MeOZI, EtOZI and $n$PropOZI could be synthesized via the reaction of 3-amino-1-propanol with the corresponding nitrile. The kinetic investigation on the CROP of the 2-oxazines under microwave-assisted conditions revealed that the polymerization took place in a controlled way with a $k_p$ which is approximately four times lower compared to similar 2-oxazolines due to the increased ring-size. As expected, the $T_{CP}$ of the poly(2-oxazine)s decreased with decreasing hydrophilicity. PMeOZI is fully soluble in water at ambient pressure as well as pEtOZI with a DP of 50. However, pEtOZI with a DP of 100 revealed a $T_{CP}$ of 56 °C which is about 29 °C below the $T_{CP}$ of pEtOx and 30 °C above the $T_{CP}$ of the structural isomer pnPropOx. Similarly, pnPropOZI with a DP of 50 to 150 has a $T_{CP}$ between 11 and 13 °C, which is below the $T_{CP}$ of pnPropOx of ~24 °C, while the structural isomer pnBuOx is water insoluble. As such, it can be concluded that the additional methylene group in the backbone makes the poly(2-oxazine)s more hydrophobic compared to the poly(2-oxazole)s with the same side-chains while the isomeric poly(2-oxazole)s, i.e. with an additional CH$_2$ in the side-chain, are more hydrophobic. This latter observation demonstrates that the location of the hydrophilic and hydrophobic groups plays an important role for the thermo-responsive behavior in addition to the hydrophobic/hydrophilic balance.

All together, a series of poly(cyclic imino ether) homopolymers with tunable $T_{CP}$ based on minor structural variations or the addition of Hofmeister salts is introduced. These polymers will be potential interesting building blocks for applications requiring
easy control over $T_{CP}$. Furthermore, based on the amorphous nature and desirable high $T_g$, pCPropOx has a significant potential as material for biomedical applications.

5.6 Experimental Section

Materials and Instrumentation
All salts used (NaSCN, NaClO$_4$, LiClO$_4$, NaI, LiI, NaCl, NaOAc, LiOAc, Na$_2$SO$_4$ and Li$_2$SO$_4$) were obtained from Sigma-Aldrich and used without further purification. Acetonitrile (Aldrich), propionitrile (Aldrich), butyronitrile (Aldrich), 3-amino-1-propanol (Aldrich), cyclopropionitrile (Aldrich) and 2-aminoethanol (Aldrich) were used as received. Acetonitrile (Aldrich) was dried in a solvent purification system (Pure Solv EN, Innovative Technology) before use as a polymerization solvent. Methyl tosylate (Aldrich) was distilled over barium oxide and stored under argon.

Small-scale reactions of 1 mL were carried out in capped reaction vials designed for the Biotage Sixty microwave system equipped with an IR temperature sensor. The vials were dried in an oven at 105 °C and cooled under argon to room temperature before use.

GC measurements were performed on a Shimadzu GC-2010 equipped with a Restek Rtx-5 column, a FID detector and a PAL autosampler.

$^1$H NMR and $^{13}$C NMR spectra were recorded in CDCl$_3$ on a Bruker Avance 250 MHz spectrometer. Chemical shifts are given in ppm relative to TMS.

ESI-Q-TOF-MS measurements were performed with a microTOF Q-II (Bruker Daltonics) mass spectrometer equipped with an automatic syringe pump from KD Scientific for sample injection.

GC-MS measurements were performed on a Shimadzu GC-17A (Column: DB-SMS, 5% phenyl-/95% dimethylpolysiloxane, length = 30 m, inner diameter = 0.25 mm, film thickness = 0.1 μm) connected to an AOC-20i autoinjector and a GCMS-QP5050A mass spectrometer. Ionization was managed by EI (electron impact).

Size exclusion chromatography (SEC) was measured on a Shimadzu system equipped with a LC-10AD pump, a RID-10A refractive index detector, a SCL-10A VP system controller, and a PSS SDV pre/lin S column utilizing chloroform:triethylamine:$iso$-propanol (93:5:2) mixture as eluent at a flow rate of 1 mL/min and a column temperature of 40 °C. A polystyrene (PS, homopolymers) calibration was used to calculate the molar mass values.
5. Thermo-responsive poly(cyclic imino ether)s

MALDI-TOF spectra were recorded on an Ultraflex III TOF/TOF of Bruker Daltonics, Bremen, Germany equipped with a Nd:YAG laser and a collision cell. Cloud point temperatures ($T_{CP}$) were determined in a Crystal 16 from Avantium Technologies connected to a chiller (Julabo FP 40) at a wavelength of 500 nm. The concentration of pEtOx, p$i$PropOx and p$n$PropOx was systematically varied between 1 and 30 mg/mL in water. The concentration of the pCPropOx, pEtOZI and p$n$PropOZI was kept constant at 5 mg/mL for all investigated aqueous (salt) solutions. The solutions were heated and cooled at a rate of 1 °C/min. The $T_{CP}$ was defined as the temperature where the transmittance decreased to 50% in the second heating run or increased to 50 °C in the second cooling run.

Dynamic light scattering (DLS) was performed on a Zetasizer Nano ZS of Malvern instruments, Malvern, United Kingdom equipped with a 10 mW He–Ne laser with a wavelength of 633 nm, operating at an angle of 173°. The aqueous polymer solution with a concentration of 1 mg/mL was measured three times at different temperatures for 60 s. The hydrodynamic radius ($R_h$) and polydispersity index (PD) was determined by the Cumulants method, assuming a spherical shape. Furthermore, the particle size distribution was obtained by the multi narrow mode.

Viscosity measurements were conducted on an AMVn (Anton Paar, Graz, Austria) rolling ball viscometer with a manually filled capillary with an internal diameter of 0.8 mm. The viscosity of the solution, $\eta$, and of the solvent, $\eta_0$, were obtained from the rolling times of the steel ball, measured at three inclination angles (from 30 to 70°) of the capillary. The temperature dependence of the dynamic viscosity is described by the following equation:

$$\eta(T) = \eta_0 \exp \left( \frac{E}{RT} \right)$$

The intrinsic viscosities of the polymer solutions at 20 °C were estimated according to the Kraemer extrapolation procedure:

$$\frac{\ln \eta_r}{c} = [\eta] + k' [\eta]^2 c + \cdots$$

where $\eta_r$ is the relative viscosity, $c$ is the concentration and $k''$ is Kraemer’s dimensionless parameter. For studying the temperature dependence, the dynamic viscosity was used.
Monomer synthesis
The CPropOx and 2-oxazine monomers have been synthesized by a standard procedure\(^\text{51}\) in which the nitrile (1 eq.) and zincacetate dehydrate (catalyst, 0.02 eq.) were heated just above the boiling point of the nitrile under reflux conditions and 3-amino-1-propanol (1.1 eq.) was added dropwise. After a reaction time of \(\sim 20\) h, the reaction mixture was allowed to cool to room temperature, and dichloromethane was added. The organic phase was washed three times with water and once with brine. After removing the dichloromethane under reduced pressure, the monomer was further purified by distillation over barium oxide.

**CPropOx**: \(^1\)H NMR (250 MHz, \(\delta\) in ppm, CDCl\(_3\)): 4.06 (t, \(J = 9.3\) Hz, CH\(_2\)O, 2H), 3.66 (t, \(J = 9.36\) Hz, CH\(_2\)N, 2H), 1.52 (q, \(J = 4.12\) Hz, NCCH\(_3\), 1H), 0.76 (br, \(J = 4.39\) Hz, CCH\(_2\)CH\(_2\), 4H). \(^{13}\)C NMR (250 MHz, \(\delta\) in ppm, CDCl\(_3\)): 169.0 (NC=O, 1C), 66.9 (CH\(_2\)O=C, 1C), 54.1 (NCCH\(_2\), 1C), 8.2 (CCCH, 1C), 6.4 (CH(CH\(_2\)), 2C). HR-MS (ESI-TOF): calculated for C\(_6\)H\(_9\)NO + H\(^+\) = 112.0757, found = 112.0759. GC-MS: 110 [M\(^+\)], 96 [M\(^+\)-CH\(_2\)], 80 [M\(^+\)-C\(_3\)H\(_4\)], 68 [M\(^+\)-C\(_3\)H\(_5\)], 54 [M\(^+\)-C\(_4\)H\(_7\)], 41 [M\(^+\)-C\(_5\)H\(_9\)].

**nPropOZI**: \(^1\)H NMR (250 MHz, \(\delta\) in ppm, CDCl\(_3\)): 3.98 (t, \(J = 5.44\) Hz, CH\(_2\)O, 2H), 3.19 (t, \(J = 5.83\) Hz, CH\(_2\)N, 2H), 1.93 (t, \(J = 7.53\) Hz, OCCH\(_2\)CH\(_2\)CH\(_3\), 2H), 1.68 (t, \(J = 5.68\) Hz, OCH\(_2\)CH\(_2\), 2H), 1.41 (br, \(J = 7.48\) Hz, CCH\(_2\)CH\(_2\)CH\(_3\), 2H), 0.77 (br, \(J = 7.36\) Hz, OC(CH\(_2\))\(_2\)CH\(_3\), 3H).

Kinetic investigation of the microwave-assisted polymerization
Kinetic investigations of the polymerizations were performed under microwave irradiation at 140 °C with an initial monomer concentration of 4 M in acetonitrile, utilizing methyl tosylate as the initiator. Three monomer to initiator ([M]/[I]) ratios of 52, 107 and 155 were investigated for CPropOx and the [M]/[I] ratio was kept at 60 for the 2-oxazines. A stock solution was prepared and divided over separate reaction vials (1 mL each) that were heated to 140 °C for different reaction times.

**pCPropOx**: \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 3.8 – 3.1 (N-CH\(_2\); backbone); 3.2 – 3.0 (N-CH\(_3\); small initiator signals), 2.0 – 1.6 (C-CH-C; c-propyl), 1.1 – 0.7 (CH\(_2\)-CH\(_2\) c-propyl) ppm.
5. Thermo-responsive poly(cyclic imino ether)s

Polymer synthesis
The investigated polymers pEtOx, p\textit{n}PropOx and p\textit{i}PropOx, with a monomer to initiator ratio (M/I) of 100, were synthesized in a similar way as described previously.\textsuperscript{22}

All pCPropOx with varying [M]/[I] values were synthesized under similar conditions. The initial monomer concentration (M\textsubscript{0}) was 4 M for all polymerizations. The [M]/[I] (I = methyl tosylate) ratio was changed between 25 and 150 to obtain six polymers with varying degree of polymerization (DP). These polymerization mixtures were heated to 140 °C under microwave irradiation for 1 to 5 min, depending on the [M]/[I] value, to reach ~80% conversion. All poly(2-oxazine)s were synthesized under similar conditions. The initial monomer concentration (M\textsubscript{0}) was 4 M in acetonitrile and the [M]/[I] (I = methyl tosylate) ratio was 50 (all monomers), 100 (EtOZI and nPropOZI) and 150 (nPropOZI). The polymerization mixtures were heated to 140 °C under microwave irradiation to reach full conversion, whereby the reaction times were calculated to reach \(\ln[M\textsubscript{0}]/[M]_t = 4\) from the kinetic investigation. After cooling to <40 °C, both the pCPropOx and poly(2-oxazine) polymerization mixtures were quenched by the addition of water. After drying under reduced pressure, the polymers were redissolved in chloroform and precipitated in cold \textit{n}-hexane. The polymers were isolated by filtration followed by drying under reduced pressure, before further characterization.

5.7 References and notes


5. Thermo-responsive poly(cyclic imino ether)s

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(44) H. Witte, W. Seeliger, Annal. Liebig 1974, 6, 996-1009.
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Summary

In nature, most polymers are chiral and form a defined secondary structure like helices or sheets. However, synthetic chiral polymers that form such secondary structures are less common. 2-Oxazolines can be polymerized via a living cationic ring-opening polymerization process. Since this monomer can become chiral when the 4th or 5th position is substituted, the goal of this research was to evaluate whether polymerization of such monomers yield chiral polymers that form secondary structures. Chapter 2 describes the synthesis and living polymerization of chiral 2-butyl-4-ethyl-2-oxazolines (BuEtOx) under microwave-assisted conditions to decrease the polymerization time and to optimize the polymerization process. The difference in solution properties between the racemic and the enantiopure polymers was investigated by solubility tests, optical rotation, circular dichroism (CD) and small angle neutron scattering (SANS) measurements. The combined results revealed that the racemic poly-RS-2-butyl-4-ethyl-2-oxazoline (p-RS-BuEtOx) is optically inactive and forms a random coil in solution making the polymer soluble in most organic solvents while the enantiopure p-R-BuEtOx and p-S-BuEtOx are only soluble in a small range of solvents. The enantiopure polymers are optically active and form a flexible structure that fluctuates around an ordered secondary structure with only a part of the monomeric units in an ordered conformation at the same time like observed for natural polyproline II type helices. The solid state properties of the polymers were studied by differential scanning calorimetry (DSC), x-ray diffraction (XRD) and CD measurements of polymer films revealing that the enantiopure polymers form chiral crystalline structures while the racemic polymer is completely amorphous.

How the alkyl side-chain length on the 2-position of the chiral monomer influences the polymer properties was investigated in Chapter 3. P-R-2-ethyl-4-ethyl-2-oxazoline (p-R-EtEtOx) and poly-R-2-octyl-4-ethyl-2-oxazoline (p-R-OctEtOx) have approximately the same optical properties in solution as p-R-BuEtOx; however, when the side-chain length is increased further to nonyl-chains the secondary structure measured by CD changed significantly in the solid state. P-R-EtEtOx was completely amorphous while poly-R-2-nonyl-4-ethyl-2-oxazoline (p-R-NonEtOx), p-R-OctEtOx and poly-R-2-undecyl-4-ethyl-2-oxazoline (p-R-UndeEtOx) are semi-crystalline like p-R-BuEtOx, although with a much lower melting temperature. The crystals formed were found to be chirally ordered. The thermal properties and the CD results suggest that main-chain crystallization occurs in p-R-BuEtOx, while only side-chain crystallization takes place in the chiral polymers with longer alkyl side-chains.
In the first part of Chapter 4 the presence of the majority rule effect is investigated by copolymerizing \( R\)-BuEtOx with \( S\)-BuEtOx in different ratios. Optical rotation and CD measurements of the copolymers revealed that the chiral polymer is not rigid enough to force the enantiomer that is in the minority to rotate in the same direction as the major enantiomer. Nonetheless, the thermal properties of these copolymers could be controlled by the ratio of the monomers. In the second part of Chapter 4 amphiphilic statistical and block copolymers are discussed based on the hydrophilic 2-ethyl-2-oxazoline (EtOx) and the hydrophobic chiral \( R\)-BuEtOx or racemic \( RS\)-BuEtOx. The statistical copolymerization resulted in the formation of a gradient copolymer where the monomer composition gradually changed from EtOx rich to pure BuEtOx. These gradient copolymers as well as block copolymers with different block ratios self-assembled into water as determined by cryogenic transmission electron microscopy (cryo-TEM) and dynamic light scattering (DLS). It was found that the type of structure formed depends on whether the racemic block or the enantiopure block is used and on the \( R\)-BuEtOx to EtOx ratio. Besides chiral poly(2-oxazoline)s also a new thermo-responsive poly(2-oxazoline), namely poly-2-cyclopropyl-2-oxazoline was developed which revealed a significantly faster polymerization rate compared to other 2-oxazolines and a thermal response in aqueous solution at a slightly higher temperature compared to poly-2-\( n\)-propyl-2-oxazoline measured by turbidity measurements, viscometry and DLS. The obtained polymer is amorphous with a glass transition temperature (\( T_g \)) of 80 °C, desirable for potential biomedical applications. The influence of a series of Hofmeister salts was investigated on the cloud point temperatures of various thermo-responsive poly(2-oxazoline)s using turbidimetry. The ionic response decreased with the decrease in hydrohilicity of the poly(2-oxazoline). Furthermore, the influence of the monomer ring-size on the thermal response of the polymers was investigated by synthesizing and polymerizing a series of 2-oxazines. The obtained polymers have a lower cloud point temperature compared to the corresponding poly(2-oxazoline)s. The alkyl side-chain length had a stronger influence on the cloud point temperature than the number of methylene units in the backbone. These thermo-responsive polymers are described in Chapter 5.

In general it can be concluded that the enantiopure polymers are chirally ordered and form a more compact structure compared to the racemic polymer. Copolymerizing the enantiopure monomer with a hydrophilic comonomer results in amphiphilic self-assembled structures in water, which might be useful for separating enantiomeric mixtures in aqueous solution or for drug delivery applications. Furthermore, the synthesized thermo-responsive poly(2-
oxazoline)s and poly(2-oxazine)s will be potentially interesting building blocks for applications requiring easy control over the cloud point temperature. Due to the amorphous nature and desirable high $T_g$ of poly(2-cyclopropyl-2-oxazoline), this polymer has a significant potential as material for biomedical applications.
Samenvatting

De meeste natuurlijke polymeren zijn chiraal en vormen een gedefinieerde secundaire structuur, zoals helices of sheets. Synthetische chirale polymeren die een secundaire structuur vormen komen niet vaak voor. 2-Oxazolines kunnen gepolymeriseerd worden via een levend cationische ring-opening polymerisatie proces. Omdat dit monomeer chiraal wordt wanneer de 4e of 5e positie gesubsstitueerd wordt, was het doel van dit onderzoek om te evalueren of er na de polymerisatie een chiraal polymer ontstaat en of dit polymer secundaire structuren vormt. Hoofdstuk 2 beschrijft de synthese en levende polymerisatie van 2-butyl-4-ethyl-2-oxazoline (BuEtOx) in een microgolf reactor, welke is gebruikt om de polymerisatietijd te reduceren en om het polymerisatieproces te optimaliseren. Het verschil in eigenschappen tussen het racemische en enantiomeerzuivere polymer in oplossing werd onderzocht door middel van oplosbaarheidstesten, optische rotatie, circulair dichroïsme (CD) en neutronenverstrooing onder kleine hoek (SANS) metingen. Hieruit blijkt dat het racemische poly-RS-2-butyl-4-ethyl-2-oxazoline (p-RS-BuEtOx) optisch inactief is en een willekeurige kluwenvorm aanneemt in oplossing, waardoor het in de meeste oplosmiddelen goed oplost. De enantiomeerzuivere p-R-BuEtOx en p-S-BuEtOx daarentegen, zijn alleen oplosbaar in een relatief klein aantal oplosmiddelen, zijn optisch actief en vormen een dynamische, flexibele structuur die fluctueert rond een geordende secundaire structuur. Hierbij zijn slechts een gedeelte van de monomeereenheden geordend op hetzelfde moment, zoals ook beschreven is voor natuurlijke polyproline II type helices. De eigenschappen van deze polymeren in de vaste fase zijn gemeten met differentieel scanning calorimetrie (DSC), röntgendiffractie (XRD) en CD metingen van gespincoate polymer. De resultaten lieten zien dat de enantiomeerzuivere polymeren chirale kristallijne structuren vormt, terwijl het racemische polymer volledig amorf is.

Wat voor invloed de zijketenlengte op de 2e positie van het chirale monomeer heeft op de karaktereigenschappen van het polymer, werd onderzocht in Hoofdstuk 3. P-R-2-ethyl-4-ethyl-2-oxazoline (p-R-EtEtOx) en poly-R-2-octyl-4-ethyl-2-oxazoline (p-R-OctEtOx) hebben vergelijkbare optische eigenschappen als p-R-BuEtOx in oplossing. Echter, wanneer de zijketenlengte verder verlengd wordt naar nonyl-ketens, verandert de secundaire structuur in de oplossing significant, zoals bepaald werd met behulp van CD metingen. Als vaste stof is p-R-EtEtOx volledig amorf, terwijl poly-R-2-nonyl-4-ethyl-2-oxazoline (p-R-NonEtOx), p-R-OctEtOx en poly-R-2-undecyl-4-ethyl-2-oxazoline (p-R-UndeEtOx) semi-kristallijn zijn, net zoals p-R-BuEtOx, maar dan wel met een veel lagere smelttemperatuur. De gevormde
Samenvatting

kristallen bleken chiraal te zijn geordend. De thermische eigenschappen en de CD resultaten suggereren dat er hoofdknten kristallisatie plaats vindt in p-R-BuEtOx, terwijl alleen zijkentenkristallisatie voorkomt in de chirale polymeren met een langere zijketen. In het eerste deel van Hoofdstuk 4 werd het ‘majority rule effect’ onderzocht door R-BuEtOx met S-BuEtOx te copolymeriseren in verschillende verhoudingen. Optische rotatie en CD metingen lieten zien dat het chirale polymeer niet rigide genoeg is om het enantiomeer dat in de minderheid aanwezig is, in dezelfde rotatierichting te dwingen als het enantiomeer dat in de meerderheid aanwezig is. Desalniettemin, worden de thermische eigenschappen van deze copolymeren wel bepaald door de ratio van de enantiomeren. In het tweede deel van Hoofdstuk 4 worden amfifiele copolymeren opgebouwd uit de hydrofiele 2-ethyl-2-oxazoline (EtOx) en de hydrofobe, chirale R-BuEtOx of racemische RS-BuEtOx bediscusseerd. De statistische copolymerisatie resulteerde in de vorming van een gradiënt copolymeer, waarin de monomeercompositie langzaam veranderde van EtOx rijk naar puur BuEtOx. Deze gradiënt copolymeren, als ook de blok copolymeren met verschillende blok verhoudingen, vormen geassembleerde structuren in water, welke zijn gevisualiseerd met een cryogene transmissie electronenmicroscoop (cryo-TEM) en dynamische lichtverstrooing (DLS). Het type structuur dat wordt gevormd is afhankelijk van de chiraliteit van p-BuEtOx blokn en van de verhouding R-BuEtOx tot EtOx. Naast chirale poly(2-oxazoline)s is er ook een nieuwe thermoresponsieve poly(2-oxazoline)s, namelijk poly-2-cyclopropyl-2-oxazoline (pCPropOx), gesynthetiseerd. Dit nieuwe monomeer heeft een significant hogere polymerisatiesnelheid in vergelijking tot andere 2-oxazolines. Het polymeer heeft een thermische respons in waterige oplossing, het precipiteert namelijk tijdens verwarming boven de vertroebelingstemperatuur (Tv) bij een iets hogere temperatuur ter vergelijking met poly-2-n-propyl-2-oxazoline (pnPropOx). Dit was gemeten aan de hand van turbiditeit metingen, vicosimetrie en DLS. Het polymeer bleek amorf te zijn met een glasovergangstemperatuur (Tg) van 80 °C, waardoor het geschikt voor potentiële biomedische applicaties is. De invloed van Hofmeister zouten op Tv van verschillende poly(2-oxazoline)s, is onderzocht met behulp van turbiditeit metingen. De reactie op de ionen werd sterker naarmate het polymeer meer hydrofiel was. Daarnaast werd er onderzocht wat de invloed is van de ring-grootte van het monomeer op de thermische respons van het polymeer door verschillende 2-oxazines te polymeriseren. De gesynthetiseerde poly(2-oxazine)s precipiteren bij een lagere temperatuur in vergelijking tot de corresponderende poly(2-oxazoline)s met evenlange zijketens, waarbij bleek dat de zijketenlengte een grotere
invloed op de $T_v$ heeft dan het aantal methyleen groepen van de hoofdketen. Deze polymeren met een thermische respons staan beschreven in Hoofdstuk 5.

In het algemeen kan geconcludeerd worden dat de enantiomeerzuivere poly(2-oxazoline)s een chiraal geordende structuur vormen en compacter zijn in vergelijking tot het racemische polymer. Door het enantiomeerzuivere monomeer te copolymeriseren met een hydrofiel comonomeer, ontstaat er een amfifiel copolymer dat zelf-geordende structuren vormt in water, waardoor het gebruikt zou kunnen worden voor het scheiden van een racemisch mengsel in waterige oplossing of voor biomedische systemen die medicijnen afgeven. De gesynthetiseerde thermoresponsieve poly(2-oxazoline)s en poly(2-oxazine)s zijn mogelijk interessante bouwstenen voor toepassingen waarbij een eenvoudige controle over de $T_v$ nodig is. Vanwege de amorf natuur en gewenste hoge $T_g$ van poly(2-cyclopropyl-2-oxazoline), heeft dit polymer potentie om als materiaal gebruikt te worden in biomedische toepassingen.
Meta Bloksma was born in 1980 in Opeinde (Netherlands). She obtained her B.Sc. degree in 2003 at the Noordelijke hogeschool Leeuwarden after she did an internship at EFKA working on additives for inks and paints followed by an internship at Philips to investigate how the electrochemical process for the production of shaving heads was influenced by metals dissolved in the electrolyte. She continued her education by studying polymer chemistry at the University of Groningen. Her undergraduate research concerning the synthesis and analysis of biodegradable bone plates was performed in the group of Prof. Arend Jan Schouten. After she obtained her M.Sc. degree in 2006, she started with her Ph.D work as a member of the Dutch Polymer Institute (DPI) in 2007 under the supervision of Prof. Ulrich S. Schubert (coadvisor Dr. Richard Hoogenboom) at the Eindhoven University of Technology (parts of the work were executed from February 1, 2009 until December 1, 2011 at the Friedrich-Schiller-University Jena, Germany).
List of publications


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Meta