Expanding the polymer science toolbox

*High-throughput experimentation, microwave irradiation and grid-like metal complexes*

**PROEFSCHRIFT**

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Chapter 1

An introduction to high-throughput experimentation, microwave irradiation and metal complexation in polymer science

Abstract

Polymer science is a field that provides a seemingly inexhaustible playground to polymer chemists due to the large parameter space such as monomers, polymer chain length, polymer architectures and their combinations. Especially, the use of living/controlled polymerization techniques is extensively applied to create novel polymeric architectures. On the contrary, new experimentation techniques and the introduction of metal coordinating units into polymer chains are less commonly studied. This chapter provides an overview on high-throughput experimentation, microwave irradiation and metallo-supramolecular initiators with a focus on their application to living/controlled polymerization techniques. The limited number of available examples in these fields created the desire to further expand the polymer science toolbox with high-throughput experimentation, microwave irradiation and other metallo-supramolecular initiators (besides the commonly used bipyridine and terpyridine ligands). Based on the literature studies, the aim and scope of this thesis are formulated.

1.1 Polymer science, a conservative or an intricate field?

Nowadays, a world without polymers would be unimaginable. Polymers are used in numerous examples like packaging, casings and many less obvious applications such as diapers, hairspray and ink-jet inks. However, most of these applications are fulfilled with a limited number of bulk polymers. On the other hand, current (academic) research on polymer science focuses much more on the design and synthesis of new well-defined polymer structures. To do so, various living and controlled polymerization techniques have been developed. These living/controlled polymerization techniques allow the synthesis of block, gradient and random copolymers with a narrow molecular weight distribution. Moreover, a variety of architectures like star-shaped, graft or comb copolymers can be prepared. Figure 1.1 provides an overview of different (co)polymer structures that are attainable. An additional advantage of living/controlled polymerization techniques is the ability to synthesize end-functionalized polymers by using functional initiators or terminating agents.

![Figure 1.1. Schematic overview of different (co)polymer architectures.](image)

Even though, the number of (living/controlled) polymerization techniques has been expanded in the last decades, the research equipment has remained rather the same. This in large contrast to the field of organic and medicinal chemistry, where high-throughput experimentation and microwave irradiation are common tools nowadays. So the question remains, why polymer chemists were reluctant to explore these novel experimentation methods as well. One reason can be found in the complexity of polymer science when compared to organic synthesis: Small organic molecules can be synthesized and characterized in a straightforward manner, whereas a variety of parameters has to be chosen in polymer synthesis like monomers, initiator and monomer to initiator ratio and, additionally, many parameters have to be investigated to know the exact structure of the resulting polymers. The absence of the necessary high-throughput characterization methods for polymer science has delayed the introduction of high-throughput experimentation as well. Moreover, the availability of a wide range of possible variations in polymer science, like copolymers, terpolymers and a variety of architectures (Figure 1.1), seems to have discouraged polymer chemists to explore novel experimentation techniques that would further broaden the scope of
An introduction to high-throughput experimentation, microwave irradiation and metal complexation research. Therefore, it might be concluded that both the complex character of polymer science and the reticence of polymer chemists have contributed to the slow introduction of high-throughput experimentation and microwave irradiation techniques in polymer science. Sections 1.2 and 1.3 provide an introduction to the efforts that have been made to adopt high-throughput experimentation and microwave-irradiation for living/controlled polymerization techniques. Besides using high-throughput experimentation and microwave irradiation, the scope of polymer chemistry can be further expanded by the introduction of supramolecular moieties into polymer chains. The resulting supramolecular interactions might be explored to prepare ‘smart’ materials in which the polymer properties can be changed by selectively addressing the supramolecular units. Especially, the introduction of metal coordinating moieties seems to be promising since the mechanical and optical properties of the resulting material can be fine-tuned by changing the applied metal ions. Section 1.4 provides an overview of the field of metallo-supramolecular polymers with a focus on the synthesis of these materials via living/controlled polymerization techniques.

1.2 High-throughput experimentation in polymer science

The development and design of new (polymeric) materials are based on the synthesis of new compounds and the optimization of existing materials. Therefore, researchers have to synthesize a large amount of (co)polymers and screen many reaction conditions by varying, e.g., monomers, catalysts, molecular weights, reaction times, reaction temperatures, which represents a very time-consuming process. In order to speed up this research, combinatorial techniques, parallel experimentation as well as high-throughput methods represent a very promising approach: Many different parameters can be screened (simultaneously or in fast serial mode) and the results can be easily compared, which can result in new structure-property relationships.

1.2.1 Historical overview of combinatorial and high-throughput experimentation

Combinatorial and high-throughput methods in pharmaceuticals research have been very successful. The adaptation of combinatorial and high-throughput techniques can, in principle, decrease the time-to-market for new drugs tremendously, because hundred to thousand times more compounds can be synthesized and screened in the initial phase compared to traditional approaches. The success of combinatorial methods in pharmaceutical research is closely related to the fact that it is relatively easy to rapidly screen the new libraries of compounds on purity (LC/MS) and to identify bioactive materials by standard binding assays. This success in pharmaceutical research resulted in an increased attention in parallel and combinatorial approaches for the synthesis and discovery of new inorganic materials, catalysts and organic polymers. Therefore, a short overview of the history and development of combinatorial techniques that led to the emergence of combinatorial and high-throughput research in the field of polymer chemistry is provided. The first examples of combinatorial approaches in material research can be addressed to Edison and Ciamician. Thomas A. Edison already applied parallel and combinatorial methods in material research as early as 1878. To discover suitable filament materials for the incandescent lamp, he tested over 1600 different earths, minerals and ores. Finally, he discovered that carbonized cotton thread in a vacuum light bulb was the optimal material. This discovery led to electrical lighting, as it is known in present days. In 1912, the Italian photochemist Ciamician...
investigated the possibility of using a photochemical process for batteries by exposing hundreds of flasks with potentially photoactive materials to the sun at the roof of the University of Bologna (see Figure 1.2 left).\textsuperscript{11} In these first parallel approaches, the experiments were set-up manually and screened in parallel. The first examples of parallel equipment also date back about a century.\textsuperscript{12,13} In Figure 1.2 right, a historical parallel shaker for six flasks is depicted. The first example of automated preparation and screening of inorganic materials was reported by Hanak in 1970.\textsuperscript{14,15} The use of a radio-frequency co-sputtering technique allowed the synthesis of nearly complete binary or ternary solid alloy systems in one experiment. For rapid screening, 50 gold contacts were evaporated on top of the library to investigate superconducting transition temperatures and resistivity at regular composition intervals of 2\%. 

![Figure 1.2. Left: This photograph shows photochemist Ciamician testing hundreds of flasks in parallel for photosynthesis on the roof of his laboratory at the university of Bologna (Photo courtesy of the university of Bologna). Right: Historical parallel shaking device for 6 flasks (from ref. 12).](image)

In materials research, parallel and combinatorial techniques are only being used intensively during the last decade\textsuperscript{16} since only then the first high-throughput screening techniques for materials became available.\textsuperscript{9} A combination of thin-film deposition and physical masking steps allowed the synthesis of libraries of inorganic compounds. Novel superconducting materials\textsuperscript{17} and inorganic phosphorus compounds\textsuperscript{18-21} have been discovered using this technique. Systematic variation of composition and processing conditions is particularly well-suited to ternary and higher-order inorganic materials, for which predictions of basic properties have been unsuccessful.\textsuperscript{18} In the area of catalysis, parallel combinatorial techniques have also been introduced.\textsuperscript{22-29} High-throughput screening of catalyst activities were reported by utilizing e.g. laser-induced resonance-enhanced multiphoton ionization,\textsuperscript{22} thermographic techniques\textsuperscript{23} and fluorescence spectroscopy.\textsuperscript{26} Furthermore, parallel synthesis and high throughput screening have been proven to be successful for faster discovery of novel catalysts.\textsuperscript{22,28}

On the contrary, combinatorial (bio)polymer research was nearly completely unexplored until eleven years ago,\textsuperscript{30} because of the absence of the essential high-throughput screening techniques for, e.g., molecular weight, polydispersity index, viscosity, hardness, stiffness and other application specific properties. In the last few years several reviews and feature articles on combinatorial materials research were published,\textsuperscript{8,16,31-36} mainly covering inorganic materials and catalysis. Therefore, this section provides an overview of the present status of combinatorial and parallel polymer synthesis focusing on living/controlled polymerizations techniques.
1.2.2 High-throughput experimentation applied to controlled polymerization techniques

Free radical polymerization is a widely used technique in industry for the production of numerous bulk materials, like e.g. poly(styrene) and poly(methyl methacrylate). The main drawback of the free radical polymerization technique is the poor control of the molecular weights and polydispersity indices. Therefore, controlled free radical techniques have been introduced during the last decades. Controlled radical polymerizations, including reversible addition fragmentation transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP) and nitroxide-mediated polymerizations (NMP), were performed successfully in a high-throughput manner.

The RAFT polymerization technique was used to prepare graft copolymers with controlled length and spacing of the grafted chains in a 96-well, parallel batch, reactor equipped with a liquid dispensing robot. Therefore, backbones with varying molecular weight were chemically modified in order to attach RAFT control agents with different degrees-of-modification. These modified polymers were polymerized with different monomers to prepare a library of graft-copolymers. Fluorescence labeling of the polymers was utilized to quantify the absorption to a substrate (Figure 1.3 left). This procedure is capable of producing 200 to 300 materials per day. A similar automated controlled radical polymerization (MADIX) was reported by Chapon and coworkers. MADIX differs from RAFT in the nature of chain-transfer agent: MADIX is performed with xanthates (RS(C=S)OZ), whereas RAFT may be performed with all kinds of thiocarbonylthio (RS(C=S)Z) compounds. Both homopolymers and diblock copolymers were automatically synthesized with two different xanthates in a reproducible way. GPC characterization demonstrated that the automatically synthesized polymers were highly comparable with polymers obtained from ‘classical’ polymerizations. More recently, Schubert and coworkers also reported the application of high-throughput synthesis robots for the automated parallel optimization of the RAFT process. The polymerization temperature and the RAFT to initiator ratio were optimized for four acrylate and four methacrylate monomers. Moreover, the reproducibility in between different synthesis robots, including a mini-plant robot, was demonstrated, whereby a slightly lower polymerization rate was observed at larger scale in the mini-plant scale. Furthermore, a systematical library of random and block copolymers consisting of methyl methacrylate and dimethylaminoethyl methacrylate was successfully synthesized utilizing the robot systems (see Figure 1.3 right for a schematic representation of the synthesized library).

![Figure 1.3](image_url)
Furthermore, the RAFT polymerization of 1-ethoxyethyl acrylate (EEA) was investigated utilizing high-throughput experimentation. The EEA monomer can be converted into acrylic acid by thermal deprotection. Therefore, the polymerization temperature was optimized to prevent significant decomposition during the polymerization. In addition, a series of EEA containing block copolymers was prepared, which resulted in a series of amphiphilic block copolymers after deprotection of the EEA.

Symyx demonstrated that it is possible to polymerize styrene and butyl acrylate in parallel and fully automated by ATRP. They mention the possibility to create libraries in sizes from 48 to 140 members with volumes of 0.1 to 20 mL per reaction vessel. Robotic systems were used to dispense all reagents and to prepare samples for high-throughput characterization. Schubert and coworkers have also reported the utilization of an automated synthesizer for ATRP. Both reproducibility and comparability with ‘classical’ ATRP were demonstrated and in addition a method for automated GPC sample preparation by online column chromatography (to remove the catalyst) was reported. Moreover, automated parallel investigations of new reaction conditions and catalysts for ATRP were performed. The homogeneous ATRP of MMA mediated by copper(I) bromide and n-hexyl-2-pyridylmethanimine was investigated regarding influence of both initiator and solvent as depicted in Figure 1.4. Linear first order kinetics with similar polymerization rates were obtained using ethyl 2-bromoisobutyrate, (1-bromoethyl)benzene, and p-toluenesulfonyl chloride as initiators. On the contrary, the molecular weight and PDI of the obtained polymers were significantly influenced by the specific initiators used. Moreover, it was found that the polymerization rate increased dramatically when changing the solvent from toluene or p-xylene to n-butylbenzene resulting in increased radical termination reactions.

![Figure 1.4. Schematic representation of the different ATRP systems that were investigated utilizing an automated synthesizer (from ref. 52).](image-url)

More recently, combinations of four different copper(I) and iron(II) salts with differently substituted bipyridines were screened for the ATRP of methyl methacrylate. 4,4'-Dihexylbipyridine provided the best control over the polymerization from a series of linearly 4,4'-substituted bipyridines. In addition, 4,5'-dimethylbipyridine provide better control over the ATRP than symmetrically substituted dimethylbipyridines.
A manual parallel approach towards new soluble supports for organic synthesis has been described by Janda et al. in which both free radical polymerization and NMP were combined. Bifunctional initiators with both a \(\alpha\)-nitrile diazene (-N=N-) and a 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) group were utilized to synthesize block copolymers, whereby five different monomers were utilized. The \(\alpha\)-nitrile diazene was first polymerized at 70 °C with different monomers. After work-up, the polymers were split and used, as macro-initiators to polymerize the different second blocks with the TEMPO groups at 130 °C. Furthermore, a TEMPO-methacrylate initiator was synthesized and polymerized first with different monomers using AIBN at 60 °C. These polymers were again split and further polymerized with different monomers at 130 °C to result in different graft copolymers. Hawker et al. evaluated the usage of NMP macro-initiators for the preparation of star-shaped polymers utilizing high-throughput experimentation. A library of 96 members with different ratios of macro-initiator to styrene monomer and different ratios of macro-initiator to 1,1’-(methylenedi-4,1-phenylene)-bismaleimide or divinylbenzene cross-linking agent was designed (Figure 1.5). As a result, optimized conditions for the formation of star polymers were obtained. In a next step, a 168 membered library was generated around the ‘hits’ from the initial library. This provided further insight into the reaction conditions that are required in order to form well-defined star polymers.

Besides the controlled radical polymerizations, the controlled ring-opening polymerizations of lactones and lactides were also performed utilizing high-throughput experimentation. Hedrick and coworkers reported the automated parallel (up to 20) controlled ring-opening polymerizations of lactides and lactones. The organocatalytic behavior of 4-(dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) for the polymerization of lactides was studied using ethanol, as initiator, with 0.1 to 4 equivalents of amine to initiating alcohol and varying monomer-to-initiator ratios ([M]/[I]). DMAP and PPY showed comparable catalytic activity, whereby polymers with narrow polydispersity indices and molecular weights closely tacking the [M]/[I] ratios were obtained. The automated synthesizer was also utilized for rapid screening and optimization of catalyst-initiator systems and the associated polymerization conditions for the controlled ring-opening polymerization of \(\varepsilon\)-caprolactone as shown in Figure 1.6. During these investigations, the polymerizations were initiated with mono-, bi-, tri- and tetrafunctional alcohols, whereby both tin(II)triflate and tin(II)ethylhexanoate were examined as catalyst.

\[\text{Figure 1.5. General synthesis of star-shaped polystyrene, whereby the synthesis of the star-shaped polymers was optimized utilizing an automated synthesizer (from ref. 55).}\]
Chapter 1

Figure 1.6. Library of initiators and catalysts that were screened for the controlled ring-opening polymerization of \( \varepsilon \)-caprolactone (from ref. 58).

More recently, high-throughput experimentation was successfully applied to the anionic polymerization technique.\(^5^9\) The apparent polymerization rates for the anionic polymerization of styrene were determined in an automated parallel fashion at two different concentrations of monomer and initiator at temperature ranging from 10 to 60 °C. Furthermore, the automated parallel synthesis of block copolymers of poly(styrene) and poly(isoprene) or poly(methyl methacrylate) were successfully demonstrated.

1.3 Microwave irradiation in polymer science

Microwave irradiation is a well-known method for heating and drying materials and is utilized in many private households or industrial applications for this purpose. It offers a bundle of advantages over conventional heating, such as non-contact heating (circumventing the decomposition of molecules close to the walls of the reaction vessel), instantaneous and rapid heating (resulting in a uniform heating of the reaction liquor) and highly specific heating (with the material selectivity emerging from the wavelength of microwave irradiation that intrinsically excites dipolar oscillation and induces ionic conduction).\(^6^0-6^2\) Microwave reactors have resulted in accelerated synthesis and improved yields in organic chemistry\(^6^3-6^6\) and solid phase synthesis,\(^6^7-7^0\) overcoming the long reaction times previously associated to these fields. During the last decades, also polymer chemists have started to investigate the use of microwave irradiation. Especially in the last few years, the number of publications on microwave-assisted polymerizations has increased almost exponentially (Figure 1.7).\(^7^1\) Most of the reported investigations on microwave-assisted polymerizations focused on step-growth or free radical polymerization reactions. However, microwave irradiation seems to be a promising tool for controlled polymerization techniques as well since these polymerization techniques proceed generally in slow manner to prevent chain transfer and termination reactions resulting in the controlled character. This section will provide an introduction to the field of microwave-assisted living/controlled polymerizations.
With a few exceptions only, it is mainly the group of Zhu who has transferred controlled radical polymerizations to microwave irradiation. Zhu et al. described the homogeneous atom transfer radical polymerizations (ATRP) as well as the reverse atom transfer radical (solution) polymerizations (RATRP) of methyl methacrylate (MMA) with a variety of combinations of initiator, catalyst and solvent. The applied polymerization temperatures were controlled by the boiling points of the solvents in an open reflux system or by placing the reactors into a thermostat bath. Especially for low concentrations of the corresponding initiators and catalysts, the (modified) domestic microwave reactor resulted in a 5-fold increase in polymerization rates and better control over the polymerizations. The stereoregularities of the resulting poly(methyl methacrylate)s were not influenced by microwave heating. The good control over the polymerizations of MMA was further illustrated by the observed linear first order kinetics. Similar enhancements were also obtained for the microwave-assisted ATRP of \( n \)-octyl acrylate using ethyl-2-bromo-isobutyrate (EBIB) as initiator and copper(I) chloride [Cu(I)Cl] with bipyridine as catalyst in tetrachloromethane. In a more recent publication, Zhu et al. performed ATRP of MMA in \( n \)-hexane, with \( \alpha,\alpha' \)-dichloroethylene as initiator and [Cu(I)Cl] and PMDETA as catalytic system. In the course of this polymerization, additional investigations were performed to determine the nature of the acceleration under microwave irradiation. It was observed that the dissociation of [Cu(I)Cl] and consequently the concentration of copper ions in solution were enhanced when the polymerization was performed in a microwave reactor. The authors attributed the increase in reaction speed observable for all the ATRP-reactions under microwave-assistance to this finding. In contrast to these reports, Zhang and Schubert observed no acceleration for the ATRP of MMA initiated by EBIB with [Cu(I)Cl] and \( n \)-hexyl-2-pyridylmethanimine in \( p \)-xylene and \( N,N \)-dimethylformamide using a monomodal microwave reactor (Emrys Liberator, Biotage). Furthermore, it was shown that for reaction temperatures higher than 110 °C, the molecular weight distributions became significantly broader (PDI > 1.4), exhibiting severe deviations from an ideally controlled radical polymerization and thereby limiting the use of microwave reactors for the reaction conditions employed.
Besides ATRP, NMP was also performed under microwave-irradiation. Wisnoski et al. have prepared novel Rasta-Merrifield resins in a monomodal microwave reactor (SmithSynthesizer, Biotage). A TEMPO-methyl resin was reacted with various functionalized styrene monomers or 4-vinylpyridine at 185 °C for 10 minutes under microwave irradiation. The resin beads grew from ~ 200 µM to 550 µm upon polymerization, whereby the spherical shape was retained (Figure 1.8). The authors strongly assumed a controlled radical mechanism (involving the TEMPO-radical) in the course of the polymerization since the beads grew in a uniform manner. The successful synthesis of these rasta-resins represents a 150-fold increase in reaction speed when compared to conventional heating. Furthermore, conventional heating (at an identical temperature of 185 °C) failed to yield resins of similar size, loading or uniform shape.

![Figure 1.8. Photographs of the TEMPO-methyl resin before (left) and after the loading with p-bromostyrene (middle) and a mixture of m- and p-chloromethylstyrene (right). Reprinted from reference [83].](image)

To the best of our knowledge, other controlled polymerization techniques have not been investigated under microwave-irradiation. Although the microwave-assisted, ring-opening polymerization of \( \varepsilon \)-caprolactone and lactides has been investigated extensively, none of the studies focused on the controlled ring-opening polymerization.

### 1.4 The use of metallo-supramolecular initiators for living/controlled polymerization techniques

The previous two sections described the utilization of high-throughput experimentation and microwave irradiation in the field of polymer science. The current section does not deal with a novel experimentation technique, but with a novel concept that has been introduced in polymer science, namely supramolecular chemistry. The combination of supramolecular interactions and polymer chains can lead to novel ‘smart’ materials that exhibit both the reversible binding of the supramolecular interactions and the mechanical properties of the polymer materials. Moreover, the introduction of directional supramolecular interactions like hydrogen bonding and metal coordination into a polymer structure allows the construction of well-defined supramolecular assemblies. In this work, we have chosen to work with metal coordination rather than hydrogen bonding, because of the easy variation of binding strength and optical properties by varying the metal ions. Moreover, our interest in living/controlled polymerization techniques also favored metal coordinating units due to their better compatibility with the various living/controlled polymerization techniques. Polymers with metal coordinating end-groups can be (reversibly) assembled into coupled polymers, block copolymers, star-shaped polymers or chain-extended polymers by the addition of metal ions as depicted in Figure 1.9.
Telechelic functionalized polymers can be synthesized via end-group functionalization or via living/controlled polymerization techniques utilizing metallo-supramolecular initiators. Both strategies are schematically depicted in Figure 1.10. The end-group modification route has been applied for the synthesis of a variety of pyridine,\textsuperscript{94} bipyridine\textsuperscript{95-97} and terpyridine\textsuperscript{98-101} functionalized polymers that were subsequently used for metal coordination. However, the metallo-supramolecular initiator approach seems to be more promising since all polymer chains contain a connected metal coordinating unit after simple purification of the polymer by precipitation. Furthermore, the nature of the resulting polymers can be fine-tuned by utilizing different (combinations of) monomers. By introducing more initiating groups onto the central metal complex, a wide variety of linear and star-shaped polymers is accessible.
The metal coordinating polymers and corresponding metal complexes that were synthesized using living/controlled polymerization techniques will be reviewed in this section (for previous overviews on metallo-supramolecular initiators, see refs. 96 and 102).

1.4.1 Cationic ring-opening polymerizations using metallo-supramolecular initiators

The first polymerization method that was explored utilizing metallo-supramolecular initiators was the cationic ring-opening polymerization of 2-oxazolines. This living polymerization method can be initiated by electrophiles resulting in a cationic oxazolinium propagating species. A variety of bromomethyl functionalized bipyridines and terpyridines has been prepared as initiator for this polymerization method. However, the direct polymerization of 2-oxazolines with these metal coordinating ligands cannot be performed since attack of the propagating species on the nitrogen atom of the pyridyls will result in loss of control over the polymerization. Therefore, metal complexes had to be applied as initiating species: The metal ions block the nitrogen atoms of the ligand and thus prevent chain termination reactions.

Fraser and coworkers reported the cationic ring-opening polymerization of 2-ethyl-2-oxazoline with di-, tetra-, and hexafunctional tris(bipyridine) iron(II)\textsuperscript{103} and ruthenium(II)\textsuperscript{103,104} complexes as initiators resulting in well-defined star-shaped polymers (Figure 1.11 top). Moreover, the successful decomplexation of the iron complexes was performed by reaction with potassium carbonate resulting in the free poly(2-ethyl-2-oxazoline) bipyridine macroligands. In addition, it was mentioned that decoloring of the polymer films was observed at 210 °C indicative of decomplexation, whereby the violet color of the iron(II) complex returned upon cooling. Besides the polymerization of 2-ethyl-2-oxazoline, 2-methyl-2-oxazoline, 2-phenyl-2-oxazoline and 2-undecyl-2-oxazoline were also polymerized in a living manner utilizing these bipyridine complex initiators.\textsuperscript{105} Furthermore, the synthesis of an iron bipyridine centered six-arm star poly(2-ethyl-2-oxazoline-\textit{b}-2-undecyl-2-oxazoline) and its decomplexation into bipyridine centered BAB triblock copolymers was reported.\textsuperscript{106} A cylindrical morphology was observed by small angle X-ray scattering (SAXS) and transmission electron microscopy (TEM) for thin films of both this metallo-supramolecular polymer and the metal-free macroligand.\textsuperscript{107}

![Figure 1.11. Different approaches for the bipyridine initiated polymerization of 2-ethyl-2-oxazoline.](image-url)
An introduction to high-throughput experimentation, microwave irradiation and metal complexation...

Next to the work of the group of Fraser, also Schubert and coworkers reported the cationic ring-opening polymerization of 2-ethyl-2-oxazoline utilizing bipyridine initiators. In contrast to the hexafunctional iron(II) and ruthenium(II) complexes used by Fraser, Schubert et al. explored the use of tetrafunctional copper(I) complexes (Figure 1.11 bottom). The livingness of the polymerizations was demonstrated by a linear dependence of the obtained polymer molecular weight on the initial monomer to initiator ratio. Amphiphilic poly(2-ethyl-2-oxazoline-\textit{b}-2-nonyl-2-oxazoline) block copolymers were also prepared in a similar manner with the copper(I) bipyridine initiators.

In addition, Schubert and coworkers investigated the cationic ring-opening polymerization of 2-ethyl-2-oxazoline utilizing iron(II) or cobalt(II) \textit{bis}(terpyridine) complexes as initiators. Both bromomethyl- and di(bromomethyl)-functionalized terpyridines were prepared for this purpose resulting in two- or four-armed poly(2-ethyl-2-oxazoline) metallo-supramolecular polymers, respectively. Decomplexation of both the iron(II) and cobalt(II) containing polymers could be achieved by refluxing the polymer with potassium carbonate in acetonitrile. The resulting free macroligands could be recomplexed up to 94% according to UV-vis titration experiments. Moreover, an increase in viscosity was observed upon recomplexation due to the coupling of the polymer chains by the metal complexation.

1.4.2 Incorporation of metal binding sites into polyesters via controlled ring-opening polymerization of lactones and lactides

The controlled ring-opening polymerization of cyclic monomers (e.g. \textit{\varepsilon}-caprolactone, glycolide or \textit{DL}-lactide) has often been applied for the synthesis of metallo-supramolecular polymers and macroligands. The controlled ring-opening polymerization techniques can be performed utilizing a hydroxyfunctional (co)initiator resulting in end-functionalized polymers.

The stannous octoate-catalyzed, ring-opening polymerization of \textit{\varepsilon}-caprolactone and \textit{DL}-lactide utilizing a \textit{bis}hydroxyfunctional bipyridine ligand was reported by Fraser and coworkers. A range of homo- and block copolymer macroligands was synthesized based on a \textit{bis}(hydroxymethyl)bipyridine initiator. The resulting macroligands were assembled into star-shaped polymeric complexes by the addition of iron(II) ions. Moreover, the preparation of ruthenium(II) complexes bearing two or six polymer chains was reported. Similarly, Schubert et al. have reported the application of a monohydroxyfunctional bipyridine ligand as initiator for the stannous octoate catalyzed ring-opening polymerization of \textit{\varepsilon}-caprolactone. Complexation of the poly(\textit{\varepsilon}-caprolactone) bipyridine was performed utilizing both iridium(III) and ruthenium(II) precursors resulting in the corresponding polymeric metal complexes as was demonstrated by MALDI-TOF-MS analysis. In addition, it was confirmed that the polymer side-chain did not influence the optical and electrochemical properties of the metal complexes while it improved the solubility and provided film forming properties. Farah and Pietro also reported the application of monohydroxyfunctional bipyridine ligands as initiator for the Sn(Oct)$_2$ catalyzed controlled ring-opening polymerization of \textit{\varepsilon}-caprolactone. Additionally, the polymerization of \textit{\varepsilon}-caprolactone utilizing a preformed ruthenium(II) bipyridine complex with two hydroxy groups was demonstrated as well. Correspondingly, Fraser demonstrated the direct application of a hexahydroxyfunctional ruthenium(II) bipyridine complex as initiator for the ring-opening polymerization of \textit{DL}-lactide utilizing dimethylaminopyridine as organic catalyst.
Schubert and Hochwimmer applied the aluminum alkoxide mediated controlled ring-opening polymerization technique for the synthesis of metallo-supramolecular polyesters. An aluminum alkoxide was generated from both mono- and bifunctional hydroxymethyl bipyridines by reaction with triethylaluminum. The resulting aluminum alkoxides were applied for the polymerization of ε-caprolactone and DL-lactide. Furthermore, the application of a bipyridine copper(I) complex based aluminum alkoxide also resulted in well-defined metallo-supramolecular polymers. A similar synthetic approach was used for the synthesis of a poly(L-lactide) terpyridine macroligands as depicted in Figure 1.12. The resulting macroligands were successfully dimerized with iron(II) ions as demonstrated by GPC utilizing a photodiode array detector and by MALDI-TOF-MS. The resulting polymeric iron(II) terpyridine complex could be decomplexed by changes in temperature or pH and by UV-irradiation. The thermal decomplexation was found to be reversible.

![Figure 1.12. Synthesis and complexation of a terpyridine poly(L-lactide) macroligand.](image)

More recently, Schubert used a hydroxypropylterpyridine as initiator for the stannous octoate catalyzed ring-opening polymerization of ε-caprolactone. The mechanical properties of this polymer were significantly improved upon the addition of iron(II) ions and only slightly improved upon complexation with zinc(II) ions (due to the lower binding strength) as was shown by rheometry. Moreover, the resulting polymer properties also depended on the utilized counterions. In a next step, the terminal hydroxy group of the α-terpyridine-ω-hydroxy-poly(ε-caprolactone) was coupled to an ureidopyrimidinone quadruple hydrogen bonding unit resulting in a polymer with both a metal-coordinating end-group and a hydrogen bonding end-group. The addition of iron(II) ions to this polymer resulted in the formation of high-molecular weight supramolecular polymers as shown by viscometry and rheometry. Moreover, the solution viscosity of this metallo-supramolecular polymer was strongly dependent on temperature due to the hydrogen bonding interactions.

A different type of metallo-supramolecular polymers was reported by Fraser. Mono- and bis-hydroxy-functionalized dibenzoylmethanes were synthesized and applied as initiator for the stannous octoate-catalyzed ring-opening polymerization of ε-caprolactone. Although the polymerizations did not follow first order kinetics, macroligands with narrow molecular weight distributions were obtained. The dibenzoylmethane macroligands were successfully complexed with europium(III), iron(III), nickel(II) and copper(II) ions. Moreover, a miktoarm metallo-supramolecular star-shaped copolymer was prepared consisting of an europium(III) complex bearing three poly(ε-caprolactone) dibenzoylmethane ligands and one poly(DL-lactide) bipyridine ligand. This metallo-supramolecular polymer exhibited a lamellar morphology in thin films with the europium(II) ions on the phase boundary.
1.4.3 Controlled radical polymerizations using metallo-supramolecular initiators

Another promising route towards well-defined metallo-supramolecular polymers is the utilization of controlled radical polymerization techniques that allow the polymerization of a wide variety of styrene and (meth)acrylate monomers and thus expand the scope of accessible polymers. All three most common controlled polymerization techniques (ATRP, RAFT and NMP) have been applied for the synthesis of metallo-supramolecular polymers.

ATRP is the most commonly used controlled radical polymerization technique for the synthesis of metallo-supramolecular polymers. Fraser and coworkers have performed most of the pioneering work in this direction. Already in 1998, the ATRP of styrene was reported utilizing bis(chloromethyl)bipyridine and corresponding di-, tetra- and hexachloro-functionalized ruthenium(II) complexes, as initiators. Well-defined polystyrene metallo-supramolecular polymers were obtained demonstrating the compatibility of the ATRP with the cationic ruthenium initiators. Moreover, it was reported that replacing one or two of the bipyridine ligands for alkyl-substituted bipyridines resulted in improved initiation efficiencies of the polymerization due to the better solubility of the complexes. The ATRP of methyl (meth)acrylate was performed utilizing a ruthenium bipyridine complex bearing six \( \alpha \)-bromoester initiating groups. Well-defined polymers were obtained for both monomers, although only methyl methacrylate revealed linear first order kinetics. In addition, the ATRP of \( t \)-butyl acrylate was performed with the ruthenium(II) bipyridine complexes as well. Hydrolysis of the poly(\( t \)-butyl acrylate) side chains resulted in the formation of metallo-supramolecular poly(acrylic acid). The ATRP of methyl methacrylate utilizing \( trist(\text{dialkylaminostyrylbipyridine}) \) iron(II) and zinc(II) metallo-initiators was reported by Haddleton and Le Bozec (Figure 1.13). Both metal complexes with six \( \alpha \)-bromoesters resulted in the controlled polymerization of methyl methacrylate. The good film-forming properties of the resulting polymers were illustrated by scanning electron microscopy images. The film formation together with the UV-spectra of the polymer film clearly revealed that both the properties of the polymer and the metal complexes were combined in the novel materials.

![Figure 1.13. Synthesis of metallo-supramolecular star-shaped poly(methyl methacrylate).](image-url)
Sequential ATRP of styrene and methyl methacrylate was performed by Fraser to synthesize a bipyridine ligand bearing both a polystyrene and a poly(methyl methacrylate) polymer side chain.\textsuperscript{126} First ATRP of styrene was performed using a bipyridine initiator bearing both hydroxy- and chloromethyl-groups. Subsequently, the resulting halide chain-end of the polystyrene was removed and the hydroxyl group was converted into a $\alpha$-bromoester group. This $\alpha$-bromoester was applied as initiator for the ATRP of MMA resulting in the mixed polymer bipyridine macroligand. The same bifunctional bipyridine initiator was applied as dual initiator for sequential ATRP of styrene and controlled ring-opening polymerization of $\varepsilon$-caprolactone.\textsuperscript{127} The resulting two-armed bipyridine was used for the complexation with a bisbipyridine ruthenium(II) precursor, with an iron(II) salt and with a platinum(II) salt. The complexation with platinum(II) ions led to the formation of bipyridine platinum(II) monocomplexes that might be used in the formation of mixed ligand metal complexes. Based on the previous investigations, Fraser et al. further expanded the concept of connecting different polymeric arms to one bipyridine ligand to combinations of poly(methyl methacrylate) and poly(ethylene glycol), poly($DL$-lactide) and poly(ethylene glycol), poly($\varepsilon$-caprolactone) and poly(ethylene glycol) and, finally, the combination of poly($\varepsilon$-caprolactone) and poly(methyl methacrylate) side chains.\textsuperscript{128} The scope of available polymeric bipyridine ligands was further enlarged by the synthesis of bipyridine ligands with two identical block copolymers attached.\textsuperscript{129} Sequential ring-opening polymerization and ATRP or two-step ATRP were performed utilizing bifunctional bipyridine initiators. To be able to combine all the prepared bipyridine ligands in supramolecular miktoarm star (block)copolymers, a stepwise ruthenium complexation method was developed as depicted in Figure 1.14.\textsuperscript{130} Ruthenium(II) precursors with two polymeric bipyridines were successfully prepared using elevated reaction temperatures and elongated reaction times to overcome the steric hindrance of the polymer chains. In a next step, the polymeric ruthenium(II) bipyridine precursors were coupled to a third polymeric bipyridine ligand resulting in ruthenium(II) complexes with two identical and one different bipyridine ligands.

![Figure 1.14. Synthesis of hetero-arm metallo-supramolecular polymers from bipyridine ligands.\textsuperscript{130}](image)

Metal-complexes based on a $\alpha$-bromoester functionalized diimine ligand were applied as initiator for ATRP as well.\textsuperscript{131} Both rhenium(I) tricarbonyl diimine and bis(bipyridine) ruthenium(II) diimine complexes resulted in the controlled polymerization of styrene and methyl methacrylate as demonstrated by linear first order kinetics and a linear increase of the molecular weight with conversion. The photoconducting properties of the resulting polymers were studied demonstrating that the metal complexes mainly act as photosensitizers and not as charge carriers.
The previous part of this section dealt with ATRP utilizing metallo-supramolecular initiators. However, ATRP is catalyzed by metal salts and thus the used metal salts could also be complexed by free ligand initiators. Therefore, the utilization of other metal-free controlled radical polymerization techniques seems to be promising for the synthesis of metallo-supramolecular polymers. Nevertheless, only in the last few years some examples of RAFT and NMP utilizing metallo-supramolecular RAFT agents or NMP initiators have been reported. The slower introduction of RAFT and NMP for the synthesis of metallo-supramolecular polymers might be due to the higher complexity of the RAFT agents and the NMP initiators compared to ATRP initiators.

RAFT-agents coupled to bipyridine ligands were first reported by Ghiggino and coworkers. A bis(hydroxymethyl)bipyridine and corresponding di-, tetra- and hexahydroxy-functional ruthenium(II) complexes were coupled to an preformed acid functionalized RAFT agent using dicyclohexylcarbodiimide as coupling agent. The resulting RAFT-agents were successfully applied for the controlled polymerization of a styrene functionalized coumarin monomer. The resulting metallo-supramolecular poly(styrene-coumarin)s exhibited energy transfer efficiencies up to 60% between the light-absorbing coumarin chromophores and the ruthenium bipyridine complexes. Zhou and Hurruna synthesized a bipyridine ligand bearing two RAFT-agents directly on the 5 and 5’ positions of the bipyridine (Figure 1.15) This novel bipyridine RAFT-agent proved to be a good control agent for the polymerization of styrene resulting in linear first order kinetics and a linear increase of molecular weight with conversion. The resulting bipyridines with two polystyrene chains were successfully complexed with a bisbipyridine ruthenium(II) precursor to form the corresponding metallo-supramolecular polymers. A similar synthetic procedure was applied for the synthesis of a terpyridine with one RAFT-agent connected. It was demonstrated that this RAFT-agent can be used for the controlled polymerization of styrene and n-isopropylacrylamide resulting in terpyridine end-functionalized polymers. The terpyridine functional polystyrene was treated with ruthenium(III) trichloride to form the ruthenium(III) monocomplex. This monocomplex was further reacted with both the terpyridine functionalized polystyrene and poly(n-isopropylacrylamide) to form the dimerized polystyrene and the poly(styrene-\(b\)-(n-isopropylacrylamide)) metallo-supramolecular polymers.

![Figure 1.15. RAFT polymerization of styrene utilizing a bipyridine with two coupled RAFT-agents and the subsequent formation of the metallo-supramolecular polymer.](image)

A terpyridine functionalized initiator for NMP has been reported by Lohmeijer and Schubert. A preformed benzyl chloride functionalized initiator was coupled to 2,6-di(2-pyridyl)-4-pyridone in the presence of potassium carbonate. This initiator was successfully applied for the controlled bulk polymerization of styrene resulting in the formation of a polystyrene macroligand. Moreover, the remaining nitroxide group at the end of the polystyrene could be successfully substituted by a terpyridine modified maleimide resulting in bisterpyridine telechelic polystyrene as was demonstrated by MALDI-TOF-MS.
1.5 Aim of the thesis

High-throughput experimentation and microwave irradiation are only flourishing in polymer science since the last decade. Moreover, the majority of these studies focused on less demanding uncontrolled polymerization techniques. The limited number of reported examples in which high-throughput experimentation and microwave irradiation have been applied for controlled polymerization techniques, are summarized in sections 1.3 and 1.4, respectively. From this literature study, it was clear that mainly controlled radical polymerization techniques have been investigated. In addition, most of the reported studies focused on screening polymerization parameters or polymer properties; whereas, the application of high-throughput experimentation would allow simultaneous screening of both polymerization kinetics and resulting polymer properties. Therefore, the aim of the first part of the thesis was to further expand the scope of polymer science with high-throughput experimentation and microwave irradiation. The introduction and adaptation of suitable high-throughput experimentation (both synthesis and screening) and microwave irradiation equipment for polymer science was investigated. Besides expanding the scope of applicable experimentation techniques, the aim of the investigations was to demonstrate the added value of these novel experimentation techniques for polymer science by demonstrating their feasibility for fast and accurate screening of polymerization conditions and for the preparation of systematical libraries of copolymers. In addition, the ability to prepare systematical libraries of (block) copolymers could lead to a better understanding of the structure-property-relationships in polymer science. Next to the use of novel experimentation techniques, the scope of polymer science can also be expanded by the introduction of non-covalent interactions to tune the polymer properties. The overview on metallo-supramolecular initiators for controlled polymerization techniques (section 1.4) clearly demonstrated that this field has been successfully introduced and explored during the last decade. Even though a large variety of controlled polymerization techniques has been already explored, the number of applied metal coordinating ligands is almost completely limited to bipyridines and terpyridines. Therefore, the aim of the second part of the thesis was to enlarge the range of available metal-coordinating units by the incorporation of larger well-defined metallo-supramolecular structures via the use of grid-forming metal coordinating ligands.

The different parts of the thesis are aimed at expanding the polymer science toolbox: The described high-throughput experimentation and microwave irradiation techniques as well as the introduction of other metal coordinating ligands will enlarge the scope and possibilities in polymer science.

1.6 Outline of the thesis

The high-throughput experimentation equipment that was adapted and used for polymer science during the course of these studies is described in chapter 2. Moreover, the applicability of the automated parallel synthesis and screening equipment to polymer science was demonstrated on the basis of feasibility studies. Chapter 3 illustrates the added value of high-throughput experimentation for polymer science on the basis of in depth studies of the cationic ring-opening polymerization of 2-oxazolines. Both the optimization of the polymerization process as well as the preparation of systematical copolymer libraries are described in this chapter. The cationic ring-opening polymerization of 2-oxazolines was further investigated under microwave irradiation to demonstrate the applicability of
microwave irradiation techniques to polymer science. The microwave-assisted homopolymerizations of a range of 2-oxazoline monomers are discussed in chapter 4. Besides the acceleration of the cationic polymerization, the (non)-existence of non-thermal microwave effects was also investigated. Chapter 5 describes the application of microwave heating for the synthesis poly(2-oxazoline) copolymer libraries. Diblock, triblock and random copolymers and their properties are discussed in detail. A different approach to broaden the scope of polymer science is discussed in the last two chapters of this thesis: The incorporation of grid-forming metal coordinating ligands into polymers. The utilized 3,6-di(2-pyridyl)pyridazine ligand self-assembles into [2×2] grid-like complexes with copper(I) or silver(I) ions. Chapter 6 describes the efforts made to incorporate functional groups into the 3,6-di(2-pyridyl)pyridazine ligand via the inverse-electron demand Diels-Alder reaction under both thermal and microwave heating. The incorporation of the resulting functional ligands into polymer chains and the subsequent self-assembly into polymeric [2×2] copper(I) grids is described in chapter 7.

1.7 References and notes


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Chapter 2

High-throughput experimentation in polymer science

Abstract

Polymer chemistry is a diverse area of research in which many parameters can be varied to optimize and change the resulting polymers and the corresponding polymer properties. Therefore, high-throughput experimentation seems to be perfectly suited to polymer research: Different parameters can be screened and optimized in a fast, comparable and automated manner; however, few examples of high-throughput experimentation have been reported in polymer science due to difficulties in the synthesis like high viscosities and due to the absence of required high-throughput characterization techniques. In this chapter, the synthesis robots that were applied for polymer synthesis in our laboratories are described. The applicability of these robot systems to polymer research is demonstrated on the basis of feasibility studies on the cationic ring-opening polymerization of 2-ethyl-2-oxazoline and on the RAFT polymerization of methyl methacrylate. Moreover, gas chromatography and gel permeation chromatography were connected to the synthesis robots allowing online monitoring of monomer conversion and polymer molecular weight, which is required to investigate polymerization kinetics. The results obtained utilizing online characterization techniques were validated by comparison with offline characterization.


2.1 Introduction

Combinatorial and high-throughput experimentation methods have revolutionized pharmaceutical research in the last decades.\(^1\)\(^-\)\(^6\) In pharmaceutical research, the synthesized libraries of (new) organic compounds can be easily screened on purity (e.g. by LC/MS) and the identification of bioactive materials can be performed by standard binding assays.\(^7\) In materials research, libraries of inorganic materials can be prepared by a combination of thin-film deposition and physical masking and subsequent screening can be performed by fluorescence spectroscopy\(^8,\)\(^9\) or (super)conductivity measurements\(^10,\)\(^11\) after deposition of electrodes. In combinatorial catalyst research, the activity of catalyst libraries could be easily screened by utilizing e.g. microelectrode arrays,\(^12\) IR cameras\(^13\) and mass spectrometry.\(^14\)

In contrast to the above mentioned fields, high-throughput polymer research is rather difficult. Polymerization mixtures often get viscous and difficult to handle. In addition, polymer libraries have to be screened on numerous important parameters, like molecular weight, polydispersity index, glass transition temperature, melting temperature, viscosity, hardness, stiffness and other specific properties related to certain applications. On the other hand, the field of polymer research seems to be perfectly suited for parallel and combinatorial experiments due to the fact that many parameters can be varied during synthesis (e.g. monomers, initiators, and many reaction conditions), processing, blending and compounding. The main advantages of utilizing automated parallel synthesis are the possibility to screen desired parameters systematically in a fast manner and the high comparability of the obtained results: All reactors are loaded from the same stock solutions with the same high accuracy and very similar reaction conditions are applied to the reactions (e.g. inert atmosphere and temperature). Besides applying and screening systematical changes during synthesis, diverse combinatorial libraries can also be designed by blending different polymers and/or by the addition of multiple additives. High-throughput screening of such libraries followed by statistical evaluation of the obtained data with appropriate descriptors might result in the discovery of higher-order effects. To gain optimal productivity from high-throughput experimentation, the entire workflow should be optimized and accelerated. In our laboratory, the high-throughput workflow consists of the following steps (see also Figure 2.1):

- (1) Design of Experiments (DoE);
- (2) Automated polymer synthesis;
- (3) High-throughput screening and
- (4) data analysis. The current studies focused mainly on automated polymer synthesis (2) and, to a smaller extend, on high-throughput screening methods (3).

![Figure 2.1. Schematic representation of the high-throughput experimentation (HTE) cycle that starts with design of experiments (DoE), followed by automated polymer synthesis and characterization and ends with data analysis.](image-url)
This chapter describes our efforts to implement high-throughput methodologies in polymer research. In section 2.2, the utilized high-throughput synthesis robots are described. The applicability of these automated synthesizers to polymer research is demonstrated on the basis of feasibility studies (section 2.3). These feasibility studies include the cationic ring-opening polymerization of 2-ethyl-2-oxazoline and the controlled radical polymerization of methyl methacrylate. Besides high-throughput polymer synthesis, high-throughput screening techniques were developed for online monitoring of monomer conversion (gas chromatography) and polymer molecular weight determination (gel permeation chromatography; section 2.4). These online characterization techniques provide easy access to automated parallel investigations of polymerization kinetics. To demonstrate the reliability of the online characterization, the obtained results were validated against offline analysis.

### 2.2 Synthesis robots

The automated synthesis robots that were applied for polymer synthesis can be divided into two classes: (1) Synthesizers for small scale low viscous reactions with vortex agitation and (2) synthesizers with 100 mL tank reactors equipped with mechanical stirring. The first class of synthesis robots can be applied for screening of reaction parameters and for library synthesis, whereas the second class can be used to investigate up-scaling conditions and process development. Moreover, the process development robot is equipped with continuous feed pumps providing the possibility of performing semi-batch or continuous flow reactions. The different types of synthesizers that were applied for automated polymer synthesis during the course of these studies will be described in detail in the following sections.

#### 2.2.1 Chemspeed ASW2000 synthesis robot

The Chemspeed ASW2000 synthesis robot is an automated parallel synthesis platform. Figure 2.2 left shows a picture of the robot equipped with one reactor block and Figure 2.2 right depicts a schematic overview of the workspace of the synthesis robot as it is used in the programming software. The pictures demonstrate the modular approach of this robot with five positions for reactor arrays (bottom left of the scheme), two positions to place microtiter plates or custom racks (top left of the scheme; here a rack for 2 mL vials is programmed), one position for a large vial rack (here for 8 mL vials) and the stock solution rack (right of the scheme). Besides the shown sample vial racks, many custom-made racks and holders can be placed and programmed in the synthesizer providing a flexible platform for all kind of different polymerization reactions. Examples of custom-made racks and holders include various sample vial racks, a MALDI-target holder, an AFM wafer holder and a Teflon mold for the preparation of tensile-test specimen.

Moreover, the synthesizer is equipped with a xyz-liquid handling system with two sizes of syringes (1 mL or 10 mL) to accurately transport different volumes of e.g. stock solutions and samples. Agitation is achieved by a vortex movement of the reactors (up to 1400 rpm). During this vortex movement, the needle of the xyz-liquid handling can still reach the bottom of the reactors and thus samples can be taken during the polymerizations without interrupting the agitation. In addition, the synthesizer is covered with a glove box to retain an inert atmosphere, which is required for oxygen and moisture sensitive polymerizations. The glove box is flushed with argon during the polymerizations. In addition to this inert environment in the hood, a small argon flow is applied to the reactors and the stock solutions directly.
The automated parallel polymerizations can be performed in 13 mL reactors (maximum 80 parallel), 27 mL reactors (maximum 40 parallel), 75 mL or 100 mL reactors (both maximum 20 parallel). These reactors can be cooled or heated with a cryostat (−70 °C to 145 °C) that is connected to the double jacket heating mantles of the reactors. On top of the reactors an array of cold finger reflux condensers can be placed for reactions under reflux conditions. The temperature of these condensers (−5 °C to 50 °C) can be controlled via a second cryostat, whereby the possibility of heating the condensers is a valuable tool for evaporating solvents from the reactors. The final part in assembling the reaction arrays is the placement of a metal reaction block on top of the reflux condensers. This reaction block has a ceramic drawer inside that can switch between opening the reactors, opening the reactors under argon, closing the reactors under argon or vacuum and closing the reactors independently. To reduce solvent evaporation, the reactors are only opened when liquid handling is required in the reactors. The vacuum can be applied to the reactors for evaporation of solvents or to create an inert atmosphere by vacuum/argon cycles.

All described parts of the synthesis robots are controlled by the ASW2000 software implying that the polymerizations in the synthesis robot can be performed completely unattended in an automated parallel manner. Programming the synthesis robots requires a translation step from the standard laboratory procedure to a process suitable for the automated parallel robot system. Each (sometimes obvious) single operation performed during the polymerization process has to be recognized and listed in a flow scheme before programming the synthesis robot. In addition, some steps have to be translated into a suitable method for the synthesis robot. For example, weighing of solid compounds has to be translated into dispensing of stock solutions. A representative step-by-step polymerization procedure might contain tasks like ‘create inert atmosphere’ (set high temperature, apply vacuum, fill with argon), switch on reflux and stirring, dispensing reagents in the appropriate amounts, set reaction temperature followed by a waiting time for performing the actual reaction, sampling and shutting down all equipment when finished. Besides all steps that are required for the actual polymerization, it is important to program several additional rinsing steps to avoid cross-contamination via the needle or the tubings and to avoid small bubbles in the tubings, which might reduce the accuracy of dispensing.
2.2.2 Chemspeed Accelerator SLT100 synthesis robot

The Chemspeed Accelerator SLT100 automated synthesizer combines the flexibility of the ASW2000 synthesizer platform with more sophisticated tools for liquid and solid handling. The Accelerator is also designed for small scale synthesis and screening with vortex agitation (13 mL, 27 mL, 75 mL and 100 mL reactors). The Accelerator SLT100 automated synthesizer is depicted in Figure 2.3a. The reaction arrays and peripherals are similar to those of the ASW2000, but the working area of the accelerator is larger (up to 192 reactors of 13 mL can be placed in parallel). However, the main difference of the Accelerator is its overhead robot arm that can pick up different modules. In our laboratories we have both a four needle head (4-NH; Figure 2.3b) and a solid dosing unit (SDU; Figure 2.3c) available.

![Figure 2.3. Pictures of the Chemspeed Accelerator™ automated synthesizer: a) Synthesis robot; b) Close up of the four needle head; c) Close up of the solid dosing into the individual heater.](image)

The 4-NH has four needles in parallel that can be used simultaneously (or separately) to accelerate all liquid handling tasks. The sampling of 16 reactors could be accelerated by a factor of three if compared to the ASW2000. Even though the aspiration and dispensing are four times faster (4 needles compared to 1), picking up the 4-NH and the movement through the synthesizer are slower than moving the xyz-liquid handler of the ASW2000 resulting in three times faster sampling. The SDU is a module that can pick up containers of solids to dispense the solids directly into the reactors. The containers are equipped with microextruders inside and by rotating the containers solids are dispensed down to submilligram accuracy. An internal microbalance in the SDU measures the amount of dispensed solid. Solid dosing of readily flowing silica powder was successfully performed with submilligram accuracy. However, automated solid dosing of sodium iodide could only be performed within 4 mg accuracy. This relatively large error is due to the hygroscopic character and its bad flowability.

Next to the standard glass reactors as described in the ASW2000 section, individually heatable reactors and pressure reactors are available for the Accelerator (both special reactor arrays can also be installed on the ASW2000 robots). The individually heatable reactor array consists of 16 parallel 13 mL reactors that all have a ceramic heating mantle (Figure 2.3c). As a result, the separate reactors can be electrically heated from 25 to 230 ºC. In addition, all reactors have a PT100 temperature sensor and thus the reaction temperature can be controlled.
with an internal or external reference. The pressure reactors that are available for the Accelerator synthesis robot consist of steel reaction vessels (16 parallel 13 mL reactor) with glass inserts that can be operated with pressures up to 90 bar. The pressure is controlled by a separate gas cylinder that can be manually set to a certain pressure. When this pressure is available, the robot system can automatically apply this pressure to the reactors and release it again too.

2.2.3 Accelerator autoplant process development robot A100

The Chemspeed Accelerator Autoplant A100 is an up-scaling and process development synthesis robot on the basis of the Accelerator SLT100 platform meaning that all peripheral equipment and the overhead robot arm with the four needle head are similar. A schematic overview from the software (showing only half of the machine) is depicted in Figure 2.4 left. This overview shows the Autoplant A100 with two reactor modules.

Each module consists of two sets of two reaction vessels (100 mL), one stock solution vessel (50 mL) and two continuous feed pumps. Heating is performed electrically, whereby the temperature is controlled by a valve that opens the connection to the cooling liquid. This separate cooling circuit also allows for very fast cooling rates to be obtained. Moreover, the two reaction vessels can be heated and cooled individually from −70 °C to 300 °C and reflux is obtained by pumping cooling liquid through the reactor head. Agitation is performed by overhead anchor stirrers, which make the reactions more comparable to industrial scale processes. In addition, polymerizations up to 30 Pa·s can be effectively agitated with the overhead stirring. Other stirrer designs, e.g. propeller stirrers, are also available if different agitation profiles are required. The continuous feed pumps can be used in many different ways as depicted in Figure 2.4 right. If the feeds are not used or are only used to fill the reactions before heating, batch reactions can be performed; however, semi-batch (with one or two continuous feeds), continuously stirred tank reactions (CSTR) and cascade reactions can be performed with the same apparatus by only changing the connection of the tubings.
The application of the continuous feed pumps has been demonstrated for the free radical polymerization of methyl methacrylate, whereby the resulting molecular weight and, even more pronounced, the resulting molecular weight distribution could be tuned by continuously feeding of initiator and/or monomer during the polymerization.\textsuperscript{15,16}

The combination of electrical heating controlled by cooling liquid, mechanical stirred tank reactors and continuous feed possibilities, make the reactors in this synthesis robot comparable to a mini-pilot-plant. As a result, the robot system is very well-suited for process development and upscaling.

### 2.3 High-throughput polymer synthesis: Feasibility studies

In polymer chemistry, a broad range of parameters can be varied in order to design and synthesize (functional) polymers with the desired properties. A few examples of these parameters are e.g. solvent, temperature, initiator, endcapper, monomer(s) and architecture. These numerous variations make polymer chemistry an ideal field for the application of high-throughput experimentation techniques; however, before the automated synthesis robots can be applied for the screening of different reaction parameters and subsequent library synthesis, first the applicability and reproducibility of the polymerizations had to be investigated in detail. In this section, feasibility studies of the different robot systems for polymer synthesis are described.

#### 2.3.1 Automated parallel cationic ring-opening polymerization of 2-ethyl-2-oxazoline

The living cationic ring-opening polymerization of 2-ethyl-2-oxazoline (EtOx) was performed in a Chemspeed ASW2000 automated synthesizer in order to investigate the living character and the reproducibility of this polymerization technique in the robot system. Therefore, we studied a model polymerization of EtOx initiated with benzyl bromide and utilizing piperidine, as terminating agent in acetonitrile at 80 °C as depicted in Scheme 2.1 (the polymerization mechanism will be explained in detail in section 3.1).

![Scheme 2.1. Schematic representation of the mechanism of the living cationic ring-opening polymerization of 2-ethyl-2-oxazoline utilizing benzyl bromide, as initiator, and piperidine, as terminating agent.](image)

The molecular weight of the synthesized polymers was varied from 1,000 to 10,000 Dalton by varying the monomer to initiator ratio from 10 to 100. Eight parallel polymerizations at a 500 mg scale as well as 40 parallel polymerizations at a 150 mg scale (Figure 2.5a) were performed successfully including automated precipitation of the synthesized polymers in diethyl ether (Figure 2.5b). After precipitation and subsequent washing of the polymers, they were dissolved in dichloromethane and transferred into vials. Figure 2.5c shows the resulting poly(2-ethyl-2-oxazoline)s (pEtOx’s) after removal of the solvent.
The resulting pEtOx’s were obtained in yields ranging from 55% to 95% (Figure 2.6 left). Up to a monomer to initiator ratio ([M]/[I]) of 80 the yields are comparable to ‘classically’ synthesized polymers with a monomer/initiator ratio of 50. However, the yields of the automated polymerizations were decreasing towards higher molecular weight. GC measurements after 24 hours reaction time revealed complete conversion for the polymerizations with [M]/[I] ratios of both 50 and 100, thus showing that the lower yields are not due to insufficient reaction times. The gradual decrease in yield towards higher molecular weight polymers is probably due to loss of material during precipitation and the transfer procedures since the vessels were not rinsed to prevent loss of compound. Furthermore, Figure 2.6 left revealed that two out of the 48 pEtOx’s were obtained in low yields of around 30%. This discrepancy is most likely due to loss of polymer during work-up since further characterization of the polymers revealed no irregularities.

The parallel synthesized pEtOx’s were characterized with $^1$H-NMR spectroscopy in order to determine the number average molecular weight ($M_n$) by careful integration of the initiator protons ($\delta = 7.3$ ppm) and the backbone protons of the polymers ($\delta = 1.0$, 2.3 and 3.5). Since the resonances from the protons of the benzyl bromide initiator overlapped with the signal of the standard solvent CDCl$_3$, the spectra were recorded in CD$_2$Cl$_2$. The determined $M_n$ is plotted against the monomer to initiator ([M]/[I]) ratio in Figure 2.6 right illustrating the linear relationship between the number average molecular weight $M_n$ and the [M]/[I] ratio. The
observed $M_n$ values are within ten percent of the theoretical molecular weights of the polymers. These $^1$H-NMR spectroscopy results indicate that the polymers are synthesized in a living way. In order to further investigate the obtained polymers, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) and gel permeation chromatography (GPC) analyses were performed on the synthesized pEtOx’s to determine the $M_n$ and polydispersity indices (PDI’s) (Figure 2.6 right). For the MALDI-TOF-MS analysis, the polymerization mixtures were automatically spotted on the MALDI-target utilizing the synthesis robot. The pEtOx’s could be characterized up to a molecular weight of 7,000 dalton. The resulting MALDI spectra are depicted in Figure 2.7 left. The difference between the peaks was found to be 99 mass units, which corresponds to the mass of one EtOx unit. The PDI’s calculated from the MALDI-spectra range from 1.03 to 1.14.

**Figure 2.7.** MALDI-TOF-MS spectra (left) and GPC traces (right; THF with 1% NEt$_3$ as eluent) obtained for pEtOx’s with different [M]/[I] ratios that were synthesized in a high-throughput manner.

Endgroup analysis of the MALDI-TOF-MS spectra confirmed that the polymers were initiated with benzyl bromide and terminated with piperidine, which demonstrates the living character of the polymerizations in the automated synthesizer. In addition, GPC analysis was performed on the synthesized pEtOx’s (Figure 2.7 right). Up to a [M]/[I] ratio of 40, the obtained molecular weights corresponded with the theoretical values and narrow PDI’s were obtained. However, higher molecular weight polymers revealed significant tailing of the GPC signals utilizing THF with 1% triethylamine as eluent, which is caused by interactions of the nitrogen atoms in the backbone with the column material (see also ref. 22). Several attempts were performed to eliminate these interactions by changing eluent (tetrahydrofuran or chloroform with or without triethylamine), temperature of the column oven and flow speed. The best results were obtained with 4% triethylamine in chloroform as eluent, the column oven set to 40 ºC and a flow speed of 2 mL/min; however, optimizing the GPC conditions could reduce the tailing but not eliminate it completely. The PDI’s obtained for the parallel synthesized pEtOx’s increased from 1.11 (1,000 dalton) to 1.37 (10,000 dalton), which is higher than the values obtained from MALDI-TOF-MS due to the remaining column interactions of the pEtOx’s on the GPC. When these column interactions are taken into account, the GPC results also indicate a living polymerization mechanism as was already demonstrated by $^1$H-NMR spectroscopy and MALDI-TOF-MS.
2.2.3 Comparability/reproducibility studies of the different automated synthesizers for the RAFT polymerization of methyl methacrylate

The comparison and reproducibility of the different automated synthesizer robots were investigated for the reversible addition-fragmentation chain transfer (RAFT) polymerization of methyl methacrylate (MMA), as model polymerization. The RAFT polymerizations in the ASW2000 and the Accelerator SLT100 were performed under similar conditions. The application of the Autoplant A100 for up-scaling was investigated by multiplying the same reaction recipe by a factor of ten. The RAFT polymerizations of MMA were performed in toluene with azoisobutyronitrile (AIBN) as initiator and 2-cyano-2-butyl dithiobenzoate (CBDB) as RAFT agent (Scheme 2.2 top). The control over the radical polymerization is achieved by establishing an equilibrium between the dormant polymeric RAFT agent and the free polymeric radicals as depicted in Scheme 2.2 (bottom). This equilibrium controls the amount of free radicals present and thus determines the polymerization speed and, even more importantly, it determines the probability of chain termination and chain transfer reactions. When appropriate reaction conditions are applied, chain termination is reduced to a minimum resulting in a controlled radical polymerization in which all polymer chains have a (dormant) radical chain end. As a result, all polymer chains will grow with similar rates resulting in a narrow molecular weight distribution. Moreover, the controlled polymerization method allows the synthesis of well-defined random, gradient and block copolymers.17-19

![Reagents (top) and mechanism (bottom) for the investigated RAFT polymerization of methyl methacrylate (MMA) with azobisisobutyronitrile (AIBN) as initiator and 2-cyano-2-butyl dithiobenzoate (CBDB) as RAFT agent.](image)

The RAFT polymerizations of MMA were performed with RAFT to initiator ratios of 1:1, 1:0.25, 1:0.10 and 1:0.05 on the different synthesizers. After 10 hours heating to 70 ºC, the resulting polymerization mixtures were analyzed by GPC. The GPC analyses revealed similar molecular weights and molecular weight distributions for the polymerizations on the different synthesizer platforms as demonstrated by the GPC traces of the pMMA’s that were synthesized with a RAFT to initiator ratio of 1:0.25 (Figure 2.8 left). All GPC results are summarized in Figure 2.8 right. The standard deviations on the molecular weights and PDI’s within one synthesizer are within 5% proving the good reproducibility of the RAFT polymerization on the different automated synthesizers.
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Figure 2.8. Left: GPC traces obtained for pMMA synthesized with a RAFT to initiator ratio of 1:0.25 utilizing the Autoplant A100 (top), ASW2000 (middle) and Accelerator SLT100 (bottom) automated synthesizers. Right: Dependence of $M_n$ (closed symbols) and PDIs (open symbols) on the ratio of RAFT to initiator for the methyl methacrylate polymerizations that were performed in the Accelerator™ SLT100, ASW2000 and Autoplant A100 automated synthesizers together with a conventional polymerization.

The observed molecular weights decreased with lower initiator content due to insufficient reaction time. Therefore, the theoretical molecular weight of 10,000 Da was not reached. For the RAFT to initiator ratio of 1:1 high polydispersity indices were observed (PDI > 1.4) demonstrating less control over the polymerization process. By adding less initiator, the control of the polymerization increased due to the lower radical concentration, which resulted in narrower molecular weight distributions. A RAFT to initiator ratio of 1:0.25 was found to be the optimal ratio providing good control over the polymerization and high polymerization rates. The up-scaling experiments on the Autoplant A100 revealed lower molecular weights and slightly higher PDI values compared to the small-scale polymerizations in the ASW2000 and the Accelerator SLT100 (Figure 2.8 right). A reference polymerization was also performed at this larger scale with a RAFT to initiator ratio of 1:0.25 in the laboratory (‘Lab reaction’ in Figure 2.8 right). This lab reaction resulted in the same molecular weight and PDI-value as the polymerization in the A100 demonstrating that the observed differences with the small-scale polymerization reactions probably resulted from insufficient heat- and mass-transfer as it is commonly observed for up-scaling of polymerization processes.²⁰

2.4 High-throughput screening of polymerization kinetics

For fast and comparable studies of polymerization kinetics, automated parallel polymerization equipment seems to be highly suitable because of the high comparability of the various experiments. This good comparability results from loading the reactors with high accuracy from the same stock solutions and, secondly, from the very similar reaction conditions (e.g. inert atmosphere and temperature). In addition, the automated synthesizer provides the possibility of continuous investigation of the polymerization kinetics throughout the complete reaction time (16-20 hours), whereas conventional manual experimentation usually results in long intervals during nights or weekends. Moreover, direct monitoring of GPC and GC during a polymerization reaction can speed up high-throughput experimentation. Normally, samples from the reaction mixtures are taken to sample vials and they are measured when the
polymerization is finished. By coupling the GPC and GC to the synthesis robot, the results are ready as soon as the polymerization is finished and thus the next experiment can be started directly. In addition, the direct monitoring provides direct feedback from the polymerization. This feedback offers the opportunity to adjust the reaction conditions during a polymerization run (e.g. reaction time or temperature).

However, most described automated characterization techniques for the determination of monomer conversion and molecular weight were applied to final polymer samples only and thus no data were obtained on the polymerization kinetics. Although it has been shown that IR spectroscopy\textsuperscript{21-24} and Raman spectroscopy\textsuperscript{25,26} are promising tools for the online monitoring of monomer conversion, they have never been applied in a high-throughput workflow to the best of our knowledge. In addition, fast molecular weight screening and conversion determination\textsuperscript{31} by gel permeation chromatography (GPC) were also mainly applied to final polymer products.\textsuperscript{32-34} Nevertheless, for kinetic investigations it is important to monitor during the polymerization instead of characterizing only end samples. Though, with most automated synthesizers it is not possible to take samples during the reactions due to too small-scale reactions\textsuperscript{29} or due to separate dispensing and reaction platforms.\textsuperscript{35} The Chemspeed robot systems do allow online sampling providing the possibility for online monitoring. In this section, the experimental set-up for online GPC characterization is described together with a method for online GC characterization of polymerization mixtures. The applicability and limitations of such online GPC and GC analysis were evaluated utilizing polystyrene standards and by monitoring the cationic ring-opening-polymerization (CROP) of 2-ethyl-2-oxazoline at different concentrations, respectively.

2.4.1 Online GPC monitoring

The integration of a GPC system into a high-throughput workflow for direct monitoring is relatively easy since GPC’s work with a closed-loop liquid system. Therefore, in our laboratory the tubings from the closed loop were extended into the robot system and an injection port was integrated into the synthesizer platform to connect the GPC with the automated synthesizer as demonstrated in Figure 2.10. Moreover, a trigger signal to start the measurement is sent to the GPC as soon as the sample is injected. To further increase the speed of analysis, a commercially available high-speed column was installed on the online GPC system (Figure 2.10 right).

![Figure 2.9. Schematic representation of the utilized online GPC characterization method.](image)
Especially for fast polymerizations it might be necessary to have a short analysis time (compared to the standard 15 minutes analysis time), because otherwise not enough samples can be measured to gain insight into the polymerization kinetics. However, by installing a high-speed column, some loss in resolution will occur as demonstrated in Figure 2.11. For polymers with a molecular weight lower than 3,500 Dalton, the GPC signal of the polymer overlapped with the solvent signal making it impossible to calculate molecular weight distributions. The large solvent signal for the high-speed GPC is caused by the fact that the samples were dissolved in another solvent than the eluent. However, this would also be the usual case for online sampling since most polymerizations will not be performed in THF. An additional problem that was encountered utilizing the online GPC system was clogging of the injection port by the injection of polystyrene standards with a molecular weight over 200,000 Dalton. In our opinion, this might be overcome by the injection of less concentrated samples, but that would make the RI-signal too weak. As a result, for the monitoring of slow controlled polymerization reactions, it is best to use a standard column on the online GPC apparatus and for fast polymerizations that do not exceed molecular weights of 200,000 Dalton, a high-speed column might be the best choice.

![Figure 2.10. Comparison of fast online GPC (high-speed column, tetrahydrofuran) with the optimized standard offline GPC characterization (chloroform:triethylamine:isopropanol ratio of 94:4:2) of polystyrene standards.](image-url)

### 2.4.2 Online GC monitoring

The integration of a GC apparatus into an automated synthesizer is more difficult than the integration of a GPC, because there is no closed-loop system. Additionally, it is not possible to place the GC inside the robotic system, because it is too large and the liquid handling system of the robot is not suitable for GC injection. Therefore, we have connected a flow cell, which is positioned in the working area of the GC autosampler, to an injection port inside the robot system. A sample is taken from the polymerization mixture and it is dispensed in this injection port. Subsequently, the sample is eluted to the flow cell by additional solvent and the GC autosampler will inject the sample after it got a trigger from the synthesizer (Figure 2.12 left). To inject the polymerization samples directly in the GC, a special liner had to be installed to prevent contamination of the column with precipitated polymer. This liner, with additional glass wool, was designed to trap all precipitated material.
The reliability and comparability of the online GC were investigated by monitoring the cationic ring-opening-polymerization of EtOx at different concentrations. This polymerization system was chosen because its successful application in automated parallel synthesis was already demonstrated in section 2.3.1. After dispensing the EtOx (monomer), benzyl bromide (initiator) and \(N,N\)-dimethylacetamide (DMAc, solvent) into the 13 mL reactors, polymerization mixtures with a \([M]/[I]\) ratio of 60 were obtained at ten different concentrations. Figure 2.12 right shows the obtained ratios of the integrals from the EtOx signal divided by the DMAc signal for the different concentrations at time zero from both online and offline GC. This graph clearly shows the good correspondence between online and offline GC and in addition it demonstrates that, as expected, the ratio EtOx/DMAc becomes larger at higher concentrations. The polymerizations were then performed at 100 °C and after half an hour polymerization time, samples were taken for online and offline measurements. After another 60 minutes polymerization time, samples were taken from the reactors without waiting intervals other than the GC analysis time. Sampling was performed by taking samples from the reaction mixture and injecting them into the flow cell and subsequently into the GC. During the GC analysis time (± 8 minutes including cooling), a sample was taken from the same reactor to a vial prefilled with chloroform for offline GC characterization. This procedure was finished after 9 minutes and subsequently an online sample was taken from the next reactor. After 500 minutes polymerization time, the reactions were stopped because the high concentration polymerizations became solid polymer and thus sampling was not possible anymore. From Figure 2.13, it can be concluded that the polymerizations at all different concentrations follow linear first order kinetics (ln\([M]/[M_0]\) versus time), which is expected for a living polymerization. Moreover, for the complete kinetic investigations exactly the same (general within 5 percent difference) signals and polymerization kinetics were obtained utilizing both online and offline GC. However, at higher concentrations (more than 5 M) the time in between sampling (60 minutes waiting time after the second sampling) was too long to elucidate the polymerization rates since full conversion was already reached before the third sampling. For the evaluation of very fast polymerizations, omission of the waiting times or performing fewer reactions in parallel might still result in too slow monitoring. In that case, the monitoring speed could still be increased by installing a faster GC or by connecting several parallel GC’s to the automated synthesizer since the GC analysis time is currently the limiting factor.
2.5 Conclusions

Different automated synthesizers that seem to be well-suited for polymer synthesis became commercially available in the last few years. The different synthesis robots that are suitable for screening of polymerization conditions, library synthesis, up-scaling and/or process development were described in detail.

The feasibility of such synthesis robots for polymer chemistry was demonstrated on the basis of the cationic polymerization of 2-ethyl-2-oxazoline. The cationic ring-opening polymerization of 2-ethyl-2-oxazoline could be performed in a reproducible manner utilizing the ASW2000 synthesis robot. Up to 40 pEtOx’s (five times eight different [M]/[I] ratios) were synthesized and purified in one single polymerization run. Characterization of the resulting pEtOx’s with $^1$H-NMR spectroscopy, MALDI-TOF-MS and GPC revealed that the polymerization proceeded via a living mechanism as it was expected. Moreover, it was demonstrated that the RAFT polymerization of methyl methacrylate could be performed in a reproducible manner in the different automated synthesizers. The results obtained using the ASW2000 and the Accelerator SLT100 were directly comparable, whereas the Autoplant A100 yielded slightly lower molecular weights and higher PDI values due insufficient heat- and mass-transfer processes associated with the 10-fold up-scaling of the polymerization. To accelerate investigations on polymerization kinetics, both GPC and GC characterization methods were introduced into an automated workflow for online monitoring. The online GPC could be performed in 4 minutes per sample by using a high-throughput column. However, some loss of resolution occurred when compared to a standard GPC (15 minutes per sample). The online GC was evaluated by both online and offline monitoring of the cationic ring-opening-polymerization of 2-ethyl-2-oxazoline at different concentrations. The results revealed the same initial concentrations and the same polymerization kinetics, whereby the errors were usually within 5%. Even though the characterization time for both online and offline GC is the same, the advantage of online characterization is that the samples are all measured during the polymerization run instead of after the polymerization run.
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In conclusion, we have demonstrated that the commercial synthesis robots are very well suited to perform polymerization reactions providing a valuable tool to accelerate polymer research. The online characterization methods reported here provide a high-throughput platform for the direct kinetic monitoring of parallel polymerization reactions. This platform will be very well suited for the fast optimization of polymerization conditions and for the fast discovery of new controlled polymerization systems.

2.6 Experimental part

Materials
Solvents were purchased from Biosolve Ltd. except for N,N-dimethylacetamide (DMAc; Aldrich). Acetonitrile (size 3 Å) and DMAc (size 4 Å) were dried over molecular sieves. All other solvents were used without further purification. 2-Ethyl-2-oxazoline (Aldrich), benzyl bromide (Acros Organics), and piperidine (Merck-Schuchardt) were distilled over barium oxide and stored under argon. NaI (Aldrich was used as received. For the controlled radical polymerizations, methyl methacrylate (MMA, Aldrich) was purified by passing over basic alumina and azoisobutyronitrile (AIBN, Aldrich) was recrystallized from methanol.

Instrumentation
$^1$H-NMR spectra were recorded on a Varian AM-400 spectrometer or a Varian Gemini 300 spectrometer.
MALDI-TOF-MS was performed on a Voyager-DE™ PRO Biospectrometry™ Workstation (Applied Biosystems) time-of-flight mass spectrometer using linear mode for operation. All spectra were obtained in the positive ion mode and ionization was performed with a 337 nm pulsed nitrogen laser. All data were processed using the Data Explorer™ software package (Applied Biosystems).
Gel Permeation Chromatography (GPC) was measured on a Shimadzu system with a SCL-10A system controller, a LC-10AD pump, a RID-6A refractive index detector and a PLgel 5 µm Mixed-D column, whereby 1% triethylamine in THF was used as eluent at a flow rate of 1 mL/min and the molecular weights were calculated against PMMA standards. Optimized GPC traces were obtained on a Waters system with a 1515 pump, a 2414 refractive index detector and a Waters Styragel HT4 column utilizing 4% triethylamine in chloroform as eluent (flow rate of 2 mL/min) with the column oven set to 50 °C. The molecular weights were determined against polystyrene standards. Online Gel Permeation Chromatography (GPC) was measured on the above mentioned Shimadzu system utilizing a PSS gram linear M column, whereby THF was used as eluent at a flow rate of 4 mL/min. Offline GPC of the polystyrene standards was measured on a similar system with a PLgel 5 µm Mixed-D column utilizing a chloroform:triethylamine:2-propanol (94:4:2) mixture as eluent at a flow rate of 1 mL/min with the column oven at 50°C.
Online and offline GC measurements were performed on an Interscience Trace GC with a Trace Column RTX-5 connected to a PAL autosampler. For the injection of polymerization mixtures, a special Interscience liner with additional glass wool was used.

Automated parallel cationic ring-opening polymerization of 2-ethyl-2-oxazoline
Reactions were carried out on a Chemspeed ASW2000 automated synthesizer. Two different polymerization set-ups were used: (A) Eight parallel reactions utilizing one reactor block with 16 reactor vessels of 13 mL for the polymerizations and two reactor blocks containing 4 reaction vessels of 75 mL for the precipitation step; (B) 40 parallel reactions utilizing five reactor blocks with 16 reaction vessels of 13 mL (40 polymerizations and 40 precipitation vessels). All reaction vessels were equipped with a heating jacket and a cold-finger reflux condenser. The ASW2000 was connected to a Huber Unistat 390W cryostat.
Prior to the reaction, the reaction vessels were heated to 120 °C, evacuated at 10 mbar for 15 minutes and subsequently filled with argon. This procedure was repeated four times to create an inert atmosphere. In addition, 1.1 bar argon pressure was applied to the reaction blocks and 1.5 bar argon pressure was applied to flush the glove-box of the automated synthesizer. Subsequently, a stock solution of 2-ethyl-2-oxazoline (A: 500 mg EtOx (5.03 mmol) in 3 mL acetonitrile; B: 150 mg EtOx (1.51 mmol) in 1 mL acetonitrile) and a stock solution of benzyl bromide (varying amounts resulting
in different \([\text{M}]/[\text{I}]\) ratios) were transferred into the 13 mL reaction vessels while vortexing at 600 rpm. These mixtures were heated to 80 °C and vortexed at 600 rpm for 24 hours with the reflux condensers set to –5 °C. The polymerizations were terminated by the addition of piperidine (5 eq. to initiator) followed by another 4 hours heating to 80 °C. After these four hours, the solvents were removed at 40 °C under reduced pressure (10 mbar) and 2.0 mL dichloromethane was dispensed into the reaction vessels at room temperature. To completely dissolve the polymers, the reactors were vortexed (600 rpm) for 10 minutes. These polymer solutions were then precipitated by adding them dropwise to diethyl ether (Et₂O; A: 50 mL; B: 7.0 mL). For this precipitation the reaction vessels were cooled to –20 °C while vortexing with 400 rpm. After sedimentation of the polymers (vortex off), 80 percent of the Et₂O was removed from each vessel by the needle and the remaining Et₂O was evaporated under reduced pressure (40 °C, 10 mbar, 400 rpm). The polymers were washed two times by adding another portion of Et₂O into each reaction vessels. This Et₂O was removed as described previously. The purified polymers were dissolved in 3.5 mL dichloromethane by vortexing (400 rpm) the solvents 10 minutes in the reaction vessels and these solutions were transferred into 8 mL vials. These vials were taken out of the automated synthesizer and the solvent was evaporated under a stream of air and finally the poly(2-ethyl-2-oxazoline)s were dried in a vacuum oven (40 °C, 10⁻² mbar) to yield white solids.

\(^1\)H-NMR poly(2-ethyl-2-oxazoline) \([\text{M}]/[\text{I}] = 20\) (CD₂Cl₂): \(\delta\) (ppm) 7.35-7.15 (m, Ar, 7H), 4.42 (m, Ar-CH₂, 2H), 3.40 (br, N-CH₂-CH₂-N, 87H), 3.09 (t, CH₂-N(CH₃)₂, 4H), 2.30 (br, N-CO-CH₂, 50H), 1.82 (quintet, CH₂-N(CH₃)₂-CH₂, 4H), 1.65 (quintet, N-CH₂-CH₂-CH₂, 2H), 1.03 (br, CH₃, 65H).

**RAFT polymerizations of methyl methacrylate (MMA)**

Small-scale polymerizations were performed on ASW2000 and Accelerator SLT100 automated synthesizers. The robot systems were fitted with an array of 16 parallel 13 mL reactors with additional cold-finger reflux condensers. The large scale polymerizations were performed in an Autoplant A100. The Autoplant A100 was equipped with three modules consisting of four 100 mL steel reaction vessels, one 50 mL feed vessel and four continuous feed pumps. The reaction vessels were equipped with anchor stirrers. All reaction mixtures and stock solutions were bubbled with argon (30 minutes) before starting the experiment.

Stock solutions of MMA (monomer), AIBN (initiator) and dithiobenzoic acid 1-cyano-1-methyl-propyl ester (RAFT-agent) in toluene and pure toluene were transferred into the reaction vessels resulting in 4.2 mL reaction mixtures for the ASW2000 and Accelerator SLT100 and 42 mL reaction mixtures for the Autoplant A100 with different RAFT to initiator ratios. All polymerization were performed with 2.21 M monomer concentration. The polymerization mixtures were heated to 70 °C and vortexed at 600 rpm for 10 hours on the ASW2000 and the Accelerator SLT100, whereas the polymerizations on the Chemspeed Autoplant A100 were performed for 10 hours at 70 °C with mechanical stirring at 200 rpm. The cold finger reflux (Chemspeed ASW2000 and Chemspeed Accelerator™ SLT100) and the reflux of the Chemspeed Autoplant A100 were set to –5 °C. After the 10 hours polymerization time, 100 µL samples were taken to 1 mL vials that were prefiled with 900 µL chloroform. These samples were used for GPC analysis.

**Parallel polymerizations of EtOx with different monomer concentrations**

Reactions were carried out on a Chemspeed ASW2000 automated synthesizer. The polymerizations at different concentrations were performed utilizing a reactor block with 16 reaction vessels of 13 mL. Reaction vessels were heated to 120 °C, evacuated at 10 mbar for 15 minutes and subsequently filled with argon. This procedure was repeated four times to perform the reactions in an inert atmosphere. 2-Ethyl-2-oxazoline (pure, varying amounts), N,N-dimethylacetamide (varying amounts) and a solution of benzyl bromide in N,N-dimethylacetamide (0.166 mg/mL, varying amounts) were transferred into the 13 mL reaction vessels resulting in 3.2 mL reaction mixtures with different concentrations, but with the same \([\text{M}]/[\text{I}]\) ratio of 60. The mixtures were heated to 100 °C and vortexed at 600 rpm with the reflux condensers set at –5 °C. At suitable time intervals, samples were injected into the flow cell connected to the GC autosampler for online measurements. During the analysis time of the online GC, another sample was taken from the same reaction vessel to a 2 mL vial (prefilled with chloroform saturated with water to quench the polymerization) for the offline measurements.
2.7 References and notes


The effect of concentration on the living cationic ring-opening polymerization of 2-ethyl-2-oxazoline will be discussed in detail in section 3.5.
Chapter 3

Parallel investigations on the cationic ring-opening polymerization of 2-oxazolines

Abstract

The cationic ring-opening polymerization of 2-oxazolines is known since the late sixties. Many kinetic studies have been performed to gain understanding in the polymerization mechanism. In addition, the resulting polymers have been applied in various applications facilitated by the easy fine-tuning of the polymer properties by changing the monomer substituents. Despite all these previous studies, the polymerization of 2-oxazolines remains a slow process that can last from several hours to several days. Moreover, statistical copolymerizations of 2-oxazolines have not often been studied in contrast to block copoly(2-oxazoline)s. To accelerate the cationic polymerization of 2-oxazolines, the polymerization temperature was optimized utilizing the automated synthesizers equipped with individually heatable reactors. To gain further insight in the cationic polymerization of 2-oxazolines, an automated parallel kinetic screening was performed using combinations of four 2-oxazolines, four initiators, four \([M]/[I]\) ratios and two temperatures. Based on these insights, a library of statistical copolymers was synthesized resulting in truly random copolymers and gradient copoly(2-oxazoline)s. These polymers were applied to investigate the effect of monomer distribution on the polymer properties. In addition to the temperature optimization, concentration effects were also studied: Higher concentrations result in faster polymerizations. This concentration optimization led to an optimal monomer concentration window in which the polymerizations were living. The observed concentration effects were studied in detail by NMR monitoring of the polymerization processes. In the last part of this chapter, the cationic ring-opening polymerization of 2-oxazolines was studied under pressure conditions. The pressure allows superheating of the polymerization mixtures in acetonitrile leading to faster polymerizations. Besides kinetic studies of the polymerizations under pressure, a series of amphiphilic block copolymers was synthesized utilizing these pressure conditions.

3.1 Introduction

The living cationic ring opening polymerization of 2-substituted-2-oxazolines was first described in 1966.\textsuperscript{1-4} Ever since, the biocompatible poly(2-oxazoline)s have been widely used for a broad range of specific applications.\textsuperscript{5,6} The polymer properties can be fine-tuned by changing the side-groups of the 2-oxazoline monomers.\textsuperscript{4,7} When a methyl side-group is used, the structure of the resulting poly(2-methyl-2-oxazoline) is comparable with the structure of \(N,N\)-dimethylacetamide (DMAc). DMAc is mixable with water and is capable of dissolving many organic polymers that are insoluble in other common organic solvents.\textsuperscript{5} Similarly, poly(2-methyl-2-oxazoline) is water soluble and it can be utilized as compatibilizing agent for polymeric blends.\textsuperscript{8} The living character of the polymerization provides easy access to block copolymers by the sequential addition of different monomers and to polymers with functional end-groups by the utilization of functional initiators and/or terminating agents.\textsuperscript{9} Moreover, the hydrophilicity of poly(2-methyl-2-oxazoline) and poly(2-ethyl-2-oxazoline) along with the hydrophobicity of other poly(oxazoline)s provides an easy access to amphiphilic structures,\textsuperscript{10,11} which have been used e.g. in micellar catalysis\textsuperscript{12,13} and for modifying enzymes resulting in similar or even better activity than the original enzyme, whereby the good biocompatibility of the poly(oxazoline)s is favorable.\textsuperscript{14,15} Furthermore, hydrogels have been fabricated from cross-linked poly(2-methyl-2-oxazoline), whereby both covalent cross-links\textsuperscript{16} as well as metallo-supramolecular cross-links\textsuperscript{17} have been used. In the last few years, poly(oxazoline)s have also been synthesized utilizing metallo-supramolecular initiators to construct well-defined supramolecular architectures.\textsuperscript{18-20}

\[
\begin{align*}
\text{Initiation} & \quad \text{Propagation} & \quad \text{Termination}
\end{align*}
\]

\textbf{Scheme 3.1. Overall reaction scheme for the cationic ring-opening polymerization of 2-oxazolines.}

The overall reaction mechanism for the cationic ring-opening polymerization of 2-oxazolines is depicted in Scheme 3.1. The polymerization can be initiated by a strong electrophile (initiator) resulting in the formation of a cationic oxazolinium ring. The C-O bond in this oxazolinium ring is weakened and propagation occurs by the nucleophilic attack of the next monomer onto this carbon atom. Recently, it was demonstrated that even though both ionic and covalent active species can be present during the polymerization of 2-oxazolines (the equilibrium depends on monomer, solvent and initiator), the polymerization process proceeds almost exclusively via the present cationic species.\textsuperscript{21}
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When all monomer is consumed, a second monomer can be added to synthesize block copolymers or a nucleophile (terminating agent) can be added to terminate the polymerization reaction. Functional end-groups can be introduced in the polymer chains by utilizing functionalized initiators and/or terminating agents. When the initiation process is fast and side reactions, like chain transfer or chain termination, are excluded, the polymerization proceeds in a living manner. As a result, the amount of propagating species is constant and the polymerization should proceed via first order kinetics.

Consequently, the rate of polymerization \( k_p \) (assuming that all initiator molecules reacted instantaneously upon heating) can be expressed by equation 3.1, where \([M]\) and \([P^*]\) are the concentrations of monomer and propagating species:

\[
-\frac{d[M]}{dt} = k_p \cdot [P^*] \cdot [M]
\]

Integration of eq 1 results in the velocity equation 3.2 when it is assumed that \([P^*]\) is equal to the initial initiator concentration \([I]_0\):

\[
\ln \frac{[M]_0}{[M]_t} = k_p \cdot [I]_0 \cdot t
\]

The temperature dependence of the rate of polymerization is expressed in the Arrhenius equation 3.3 in which \(A\) is the frequency factor and \(E_a\) is the activation energy:

\[
k_p = A \cdot e^{\frac{-E_a}{RT}}
\]

A serious disadvantage of the cationic ring-opening polymerization of 2-oxazolines is the long reaction times from several hours up to several weeks\(^22\) to reach full conversion.

The high-throughput experimentation workflow that was described in chapter 2 was applied to investigate and screen a range of reaction conditions to accelerate this polymerization procedure. This chapter describes the temperature (section 3.2) and concentration (section 3.5) optimization of the cationic polymerization of 2-oxazolines. In addition, combinations of four initiators with four monomers were screened to identify the best suitable initiators and to determine the polymerization rates of the different combinations (section 3.3). The resulting kinetic insights in the 2-oxazoline polymerizations were exploited for the directed synthesis of random and gradient copolymers (section 3.4). The effect of pressure and superheated conditions on the cationic polymerization of 2-oxazolines is described in section 3.6.

### 3.2 Temperature optimization of the cationic polymerization of 2-oxazolines

Many kinetic investigations on 2-oxazole polymerizations have been already described in literature utilizing a wide range of different solvents, initiators, monomers and temperatures\(^21,23-27\). Those kinetic investigations of 2-oxazoline polymerizations were mainly based on \(^1\)H-NMR spectroscopic investigations: The polymerizations were performed at a certain temperature in a NMR-tube and by measuring spectra at suitable time-intervals the conversion and number average molecular weight were determined. However, performing these \(^1\)H-NMR spectroscopic investigations is very time-consuming and only one polymerization can be performed at the time. Moreover, the reported studies regarding the effect of temperature on the cationic ring-opening polymerization of 2-oxazolines only included up to three different temperatures. Therefore, we have investigated and optimized
the polymerization temperature for the cationic ring-opening polymerizations of 2-ethyl-2-oxazoline and 2-phenyl-2-oxazoline over a broad range of temperatures utilizing the high-throughput workflow. These two monomers were chosen since they exhibit completely different reactivities. For these investigations, the automated synthesizers were equipped with individually heatable reactors to be able to investigate a wide range of polymerization temperatures in parallel. The polymerization kinetics were monitored by automated sampling from the reaction mixtures at suitable time intervals. These samples were analyzed by online or offline gel permeation chromatography (GPC) and gas chromatography (GC).

3.2.1 Polymerization of 2-ethyl-2-oxazoline

The cationic ring opening polymerization of 2-ethyl-2-oxazoline (EtOx) in \( N,N \)-dimethylacetamide (DMAc) was investigated to optimize the polymerization temperature and to determine the activation energy of the polymerization. Although, acetonitrile is more commonly used for this polymerization, DMAc was chosen due to its broader applicability as solvent and the wider possible temperature range. By utilizing ‘classical’ polymerization techniques, the temperature optimization and activation energy determination for the EtOx polymerization would have required six to seven weeks, whereby sampling during night would have been required in order to obtain optimal results. With the automated synthesizer, the optimization and activation energy determination were done within 3 days.

The polymerization of EtOx initiated with benzyl bromide was investigated at temperatures ranging from 50 to 130 °C utilizing the ASW2000 automated synthesizer equipped with the individually heatable reactors (see also section 2.2.2). This temperature range was chosen around the common polymerization temperature (80 °C), whereby the upper limit was dictated by the boiling point of 2-ethyl-2-oxazoline (128.4 °C). The individually heatable reactors (16 parallel) can be heated separately by a ceramic heating mantel and thus 16 different polymerization temperatures could be investigated simultaneously. During the polymerizations, samples were taken automatically by the synthesis robot. These samples were collected in 1 mL vials that were prefilled with tetrahydrofuran containing 1% of water. The water was present to terminate the living polymer chains and thus to stop the polymerization. These samples were characterized with both online GPC and offline GC, whereby the DMAc was utilized, as an internal standard. After the polymerization at different temperatures, the appearance of the resulting polymerization mixtures already indicated whether the polymerization was successful or not (Figure 3.1): The polymerization at 50 °C remained colorless indicating no polymerization, whereas the polymerizations at high temperatures (T > 110 °C) turned orange (gray in the figure) indicative of side reactions.

![Figure 3.1. Picture of the EtOx polymerization mixtures after 16 hours heating at various temperatures utilizing the individually heatable reactors.](image-url)
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The monomer conversion (obtained from GC; represented by \( \ln \left[ \frac{[M]}{[M_0]} \right] \)) in time of the polymerizations at different temperatures is shown in Figure 3.2 left. Linear first order kinetic plots were obtained for all investigated temperatures. The first order kinetics demonstrate that the concentration of propagating species was constant during the polymerizations and thus that termination reactions were absent. However, chain-transfer reactions can not be distinguished by the monomer consumption. The polymerizations at 90 °C, 100 °C, 120 °C in DMAc and 80 °C in acetonitrile were performed twice to check the reproducibility. The obtained results clearly demonstrated the high reproducibility of the different experiments with the individually heatable reactor block (Figure 3.2 left). Moreover, it was observed that the reaction rate (\( k_p \)) increased with temperature as expected. The \( k_p \) of the commonly used temperature of 80 °C in acetonitrile is higher than the \( k_p \) in DMAc at 90 °C but lower than the \( k_p \) of the polymerization in DMAc at 100 °C. This higher \( k_p \) in acetonitrile can be explained by the slightly higher dipole moment of acetonitrile (3.92 D against 3.81 D for DMAc),28 which leads to a better solvation of the propagating oxazolinium ring and the corresponding bromide counterion.29 As a result, in DMAc the counterion will be in closer proximity of the oxazolinium species making it less reactive.

From the slopes of the regression lines of the conversion against time plot in Figure 3.2 left, the value of \( k_p \) at different temperatures was determined. The Arrhenius plot (equation 3.3) for the benzyl bromide initiated EtOx polymerization in DMAc is shown in Figure 3.2 right. From this Arrhenius plot, the activation energy was determined to be 68.7 kJ/mol. This obtained value for the activation energy of the polymerization of EtOx in DMAc is similar to the values reported for the polymerization of 2-methyl-2-oxazoline (MeOx) in acetonitrile with both methyl iodide \( (E_a = 72.9 \text{ kJ/mol})^{30} \) and methyl tosylate \( (E_a = 80.0 \text{ kJ/mol})^{31} \) as initiators. Up to now, the activation energy for the cationic ring opening polymerization of EtOx was not reported. Kinetic studies of the bulk polymerizations of MeOx and EtOx initiated by the carboxyl groups of carbon black resulted in an activation energy of 45.6 kJ/mol for MeOx and uncontrolled polymerization of EtOx.32

GPC characterization of the samples taken in time was performed utilizing a standard (15 minutes characterization time) offline GPC with THF as eluent (primary screening tool). Although high-speed GPC columns are available (see also section 2.4.1),33,34 the characterization was performed utilizing a standard column since it was not the bottleneck in the workflow (GPC injections were performed over the weekend). Furthermore, the standard
GPC column provides better resolution and it allows the characterization of low molecular weight polymers (see also section 2.4.1). The progress of the weight average molecular weight ($M_w$) in time for the different temperatures is shown in Figure 3.3 (left). The obtained final molecular weights of the polymers ($M_w = 4000$ Dalton; $M_n = 2500$ Dalton; polydispersity index (PDI) around 1.5) were quite broad and lower than the targeted molecular weight ($M_n = 6200$). This discrepancy can be ascribed to the utilized GPC with THF as eluent. The pEtOx’s are known to interact with the column material resulting in lower molecular weights and higher polydispersity indices (PDI’s). The polymerizations in DMAc below 90 °C did not show significant polymerization in 16 hours.

![Figure 3.3](image)

**Figure 3.3.** Left: Increase of $M_w$ in time for the EtOx polymerizations at different temperatures (solid lines: DMAc; dashed lines: acetonitrile). Right: $M_n$ against monomer conversion plotted for selected temperatures including the measurements utilizing the optimized GPC eluent.

To determine the livingness of the polymerizations, the number average molecular weights ($M_n$, from the primary GPC screening) were examined against conversion for the temperatures that showed significant polymerization ($T = 80–120$ °C; Figure 3.3 right). The polymerizations in DMAc at 90 °C, 100 °C and in acetonitrile at 80 °C show a similar linear relationship (see dotted line), although they are far off the theoretical curve (solid line) due to the previously discussed interactions with the column material. Polymerizations in DMAc performed above 100 °C revealed a non-linear increase of $M_n$ with conversion. In addition, the found $M_n$’s were lower than for the other polymerizations. These results indicate loss of control over the polymerization when the polymerization temperature exceeds 100 °C. This loss of control might be due to side reactions like chain-transfer or spontaneous initiation by small traces of impurities. The occurrence of side reactions is also suggested by the orange appearance of the reaction mixtures from the polymerizations that were performed above 100 °C (Figure 3.1). To demonstrate the reliability of the utilized primary screening GPC where tailing occurred, the $M_n$ and PDI of the samples from the EtOx polymerization at 100 °C in DMAc were also determined with an optimized GPC (4% triethylamine in chloroform as eluent with the column oven set to 40 °C and a flow rate of 2 mL/min). The obtained $M_n$ (PDI from 1.04 to 1.24) against conversion (see Figure 3.3 right) still revealed a linear relationship. In addition, values within 10% of the theoretical values were obtained, demonstrating the living character of the polymerization.

The results from GC and GPC characterization demonstrated that 100 °C is the optimal temperature for the cationic ring opening polymerization of EtOx in DMAc since at this temperature the fastest living polymerization was obtained. To verify this optimal...
polymerization temperature, a series of eight pEtOx’s with molecular weights ranging from 1000 to 8000 Dalton were synthesized utilizing the automated synthesis robot equipped with standard glass reactors. The molecular weight of the resulting pEtOx’s was determined with the optimized GPC and $^1$H-NMR spectroscopy (Figure 3.4). GPC characterization showed a linear increase of $M_n$ with increasing monomer to initiator ratio with PDI’s ranging from 1.09 to 1.26 up to a $[M]/[I]$ of 50. The longer pEtOx’s still revealed broad molecular weight distributions probably due to remaining column interactions and have been omitted from Figure 3.4. $^1$H-NMR spectroscopy was measured in CD$_2$Cl$_2$ to prevent overlap of the solvent signal with the initiator signal. The $M_n$ was calculated from the integrals of the backbone and the initiator. The $M_n$’s obtained with both GPC and $^1$H-NMR spectroscopy closely matched the theoretical values demonstrating that the optimized temperature is indeed applicable for the synthesis of well-defined pEtOx.

![Figure 3.4. Characterization of the polymers synthesized with the optimal polymerization temperature. $M_n$ from GPC; $\ominus$ PDI from GPC; $\blacksquare$ $M_n$ from $^1$H-NMR spectroscopy (in CD$_2$Cl$_2$).](image)

### 3.2.2 Polymerization of 2-phenyl-2-oxazoline

In the previous section, the temperature optimization and activation energy determination of the cationic ring-opening polymerization of EtOx initiated with benzyl bromide in DMAc were described. This section deals with the temperature optimization of the polymerization of the less reactive 2-phenyl-2-oxazoline (PhOx). Even though various kinetic studies on the cationic polymerization of PhOx were reported, the temperature dependency of PhOx polymerization and the corresponding reaction kinetics have not been studied in detail. Utilizing the Accelerator SLT100 synthesis robot equipped with individually heatable reactors, parallel polymerizations of PhOx initiated with benzyl bromide in DMAc were performed at temperatures ranging from 80 to 150 °C. This higher temperature range (compared to EtOx) was chosen, because of the lower reactivity of PhOx. Moreover, the investigated range covered the common polymerization temperatures (from 110 to 130 °C). At suitable time intervals, samples were taken to vials prefilled with water saturated chloroform. GC characterization revealed that no significant polymerization occurred with this combination of monomer and initiator at the investigated temperatures. Only little polymerization, up to 45% conversion, was observed at 140 and 150 °C. In a next step, the polymerization of PhOx initiated with the more reactive methyl tosylate (MeOTs) initiator was investigated at temperatures ranging from 80 to 150 °C. Both the appearance of the reaction mixtures after the polymerization (left) and the first order kinetic plot of the PhOx polymerizations at the investigated temperatures (right) are depicted in Figure 3.5.
Figure 3.5. Left: The picture shows the final polymerization mixtures from the different temperature runs. Right: First order kinetic plot obtained for the PhOx polymerizations at different temperatures.

The picture (Figure 3.5 left) shows the resulting polymerization mixtures after 980 minutes, whereby the effect of temperature can be clearly observed. At low temperatures, colorless mixtures are obtained indicating no polymerization and with increasing temperature more yellowish mixtures are obtained representing polymer formation. At high temperatures, orange polymerization mixtures indicative of side reactions are obtained. For this combination of monomer and initiator, significant polymerization was obtained for temperatures of 100 ºC and higher. Figure 2 right plots \( \ln([M]_0/[M]_t) \) against time, which should be linear for the living cationic ring-opening polymerization of 2-oxazolines because it is known to follow first order kinetics. From Figure 3.5 right, it can be concluded that linear first order kinetics are obtained for all temperatures that show polymerization indicating a constant concentration of living chain ends. From the slopes of the regression lines of the \( \ln([M]_0/[M]_t) \) plots, the value of \( k_p \) at different temperatures was determined. The Arrhenius plot for the polymerization of PhOx initiated with methyl tosylate in DMAc is shown in Figure 3.6 left. From this Arrhenius plot, an activation energy of 81.3 ± 2.1 kJ/mol was derived. This value is in the same range as the so far reported values for the activation energy (71.1-113 kJ/mol) of the PhOx polymerization in various solvents.29,38

Figure 3.6. Left: Arrhenius plot for the polymerization of PhOx initiated with MeOTs in DMAc. Right: GPC traces of the resulting pPhOx’s after 980 minutes polymerization time at different temperatures.
The final polymer samples taken after 980 minutes polymerization time were also used for GPC characterization (Figure 3.6 right). High polydispersity indices (PDI ≥ 1.40) were obtained for polymerizations performed at 120 °C or lower. This is probably due to slow initiating and thus not all polymer chains start growing at the same time resulting in a broader distribution. This effect is visible in the GPC traces as a lower molecular weight shoulder, which is decreasing with increasing temperature. At polymerization temperatures of 140 or 150 °C, the PDI is increasing again, which is most likely due to the occurrence of chain transfer reactions. During the chain transfer, the active cationic site is transferred to a monomer by α-hydrogen subtraction, whereby the propagating chain-end is converted into a hindered enamine and the new oxazolinium species can form a new polymer chain. At the end of the polymerization when (almost) all monomer is consumed, the chain transferred polymeric enamines can react with cationic polymeric end-groups resulting in coupled polymers (Scheme 3.2). These chain transfer reactions can be observed as both low and high molecular weight shoulders in the GPC traces, which is most pronounced for the polymerization at 150 °C.

Scheme 3.2. Mechanism of the chain-transfer and the subsequent chain-coupling side reactions.

From the combination of both GC and GPC characterization, it can be concluded that the optimal polymerization temperature for PhOx initiated with MeOTs is 130 °C. At this temperature, the lowest PDI and the most symmetrical GPC signal is obtained although the PDI of 1.31 is still quite high for a living polymerization. Moreover, the Mₙ obtained for the polymerization at 130 °C (7,600 Dalton) is matching best (from all different temperatures) with the theoretical molecular weight (8,840 Dalton), whereby the lower value is due to the tailing of the signal. The tailing of the signal and the broad distribution probably result from slow initiation whereby kᵢ < kₚ.

3.3 Screening monomer/initiator combinations for the cationic ring-opening polymerization of 2-oxazoline monomers

Kinetic investigations (mainly based on ¹H-NMR spectroscopy) of the cationic ring-opening polymerization of MeOx, EtOx and PhOx utilizing a wide variation of different initiators (e.g. benzyl bromide, methyl tosylate and methyl iodide) in varying solvents (e.g. acetonitrile, chlorobenzene, and nitrobenzene) have been described in literature. In addition, the effect of solvents with different functional groups on the polymerization of 2-pentyl-2-oxazoline and the effect of solvent on the polymerization rate and activation energy on the
polymerization of PhOx were studied in detail. All these separate studies focused on the polymerization kinetics of only one monomer in a certain solvents with at most three different initiators, which makes it rather difficult to compare all results reported in literature. To be able to compare the reactivity of the different monomers with different initiators, we have investigated combinations of four 2-oxazoline monomers with four initiators in DMAc.

This section describes a systematical kinetic screening of the cationic 2-oxazoline polymerization utilizing combinations of four frequently used monomers (MeOx, EtOx, 2-nonyl-2-oxazoline (NonOx) and PhOx) with four well-known initiators (benzyl bromide (BB), methyl triflate (MeOTf), methyl tosylate (MeOTs) and methyl iodide (MeI)) in DMAc (Figure 3.7), which has a similar structure as the backbone of the poly(2-oxazoline)s. Up to now, no kinetic investigations of 2-oxazoline polymerizations in this solvent have been reported even though it is often used and it is widely applicable for e.g. functional initiators. For each of these 16 combinations of monomer and initiator, four different [M]/[I] ratios ([M]/[I] = 20, 40, 60 and 80) were investigated at both 80 and 100 ºC, resulting in 128 polymerizations in total. In order to screen this large parameter space an automated parallel approach was utilized (see also chapter 2), whereby 16 polymerizations (one monomer, four initiators, four [M]/[I] ratios and one temperature) were performed in parallel. The main advantages of utilizing robot systems for such a screening are the increased speed (up to 80 reactions in parallel), the high reproducibility and comparability of the results and as a final point the possibility of continuous sampling over longer time periods (e.g. over nights or weekends). Figure 3.7 depicts the layout of a reactor block used for 16 parallel polymerizations. During the polymerizations, samples were taken automatically from each reaction vessel at suitable time intervals for GC analysis. These samples were collected in vials, which were prefilled with chloroform saturated with water. The water was present to terminate the living polymer chains and thus to stop the polymerization.

![Figure 3.7](image)

**Figure 3.7.** Layout of a 16 vessel reactor block as used for the kinetic screening together with an overview of total investigated parameter space.

The following sections will describe the screening results obtained for the different monomers with the four initiators, four [M]/[I] ratios and two temperatures. Moreover, all resulting polymerization rates for the different monomers and initiators were calculated to evaluate the reactivities of the monomers and the initiators.
3.3.1 Initiator screening for the polymerization of 2-methyl-2-oxazoline

The monomer conversion in time obtained from GC for the polymerization of MeOx initiated with BB, MeOTf, MeOTs and MeI at both 80 and 100 °C is depicted in Figure 3.8, whereby the [M]/[I] ratios 20, 40, 60 and 80 are positioned at the top left, top right, bottom left and bottom right, respectively. From these graphs, it can be immediately seen that the polymerizations at 100 °C (solid lines) are faster than the polymerizations at 80 °C (dashed lines), which is obvious because more energy is brought into the system. Moreover, the polymerization speed decreases with increasing [M]/[I] ratios, which can be explained by the decreasing initiator concentration since the monomer concentration was kept constant. These first order kinetic plots of ln([M]₀/|M|) against time revealed a linear relationship for most combinations demonstrating a constant concentration of propagating species, which suggests a living polymerization mechanism. However, for the polymerizations of MeOx initiated with methyl tosylate (80 °C, [M]/[I]=80) and initiated with methyl triflate (80 °C, [M]/[I]=60 and 100 °C, [M]/[I]=60 and 80), a curved behavior was observed in the first order kinetic plot, which indicates that the amount of living species decreases during the polymerization. This loss of the living character is due to side reactions, like chain transfer or chain termination. Chain termination might be caused by traces of impurities in the reagents or reactors.

![Figure 3.8](image)
3.3.2 Initiator screening for the polymerization of 2-ethyl-2-oxazoline

For the kinetic screening of EtOx with the four different initiators (Figure 3.9) similar results were obtained as for the MeOx screening. Again the expected influence of polymerization temperature and of the initiator concentration was observed. Moreover, also for this monomer the polymerization kinetics revealed a linear first order behavior for most of the different experiments, whereby it is noteworthy that five out of eight polymerizations initiated with MeOTf are not living and one of the polymerizations initiated with MeOTs was not living either. The loss of control over the polymerizations initiated with MeOTf or MeOTs might be explained by the lower nucleophilicity of the tosylate and triflate counterions: The lower nucleophilicity results in a further distance between the oxazolinium and the counterion making the oxazolinium species more reactive and, secondly, the lower nucleophilicity of the counterion pushes the equilibrium between covalent and cationic propagating species towards the cationic species. As a result, the higher reactivity of the system will result in higher sensitivity to traces of impurities resulting in termination reactions. On the contrary, polymerizations initiated with benzyl bromide and methyl iodide show more often living polymerizations than those initiated with methyl triflate and methyl tosylate, because more (‘dormant’) covalent active centers are present.

![Figure 3.9. Kinetic plots for the cationic ring-opening polymerization of EtOx initiated with BB, MeOTf, MeOTs and MeI at both 80 and 100 °C with [M]/[I] ratios of 20 (top left), 40 (top right), 60 (bottom left) and 80 (bottom right). All polymerizations were performed with 1.25 M monomer concentration in DMAc.](image-url)
3.3.3 Initiator screening for the polymerization of 2-nonyl-2-oxazoline

The polymerization kinetics of NonOx with the different initiators was investigated in the same manner as for the two previously described monomers. However, the polymerizations at 100 °C did not reveal linear first order kinetics during repeated experiments, whereas for most of the NonOx polymerizations at 80 °C (dashed lines, Figure 3.10) a living polymerization behavior was observed. The loss of control at 100 °C might be due to the larger amount of monomer present (all polymerizations were performed with 1.25 M monomer concentration; 25% monomer and 75% solvent in the case of NonOx) in combination with the higher temperature leading to side reactions. However, the exact reason for the loss of control over the polymerizations and the nature of the side-reactions could not be cleared during this high-throughput kinetic screening. Nevertheless, when the monomer concentration was decreased from 1.25 to 0.625 M, linear first order kinetics were obtained for most polymerizations at 100 °C as well (Figure 3.10 solid lines). Due to the different concentration, the polymerizations at 80 and 100 °C show very similar polymerization rates. Also for the NonOx polymerizations, several polymerizations initiated with MeOTf or MeOTs revealed non-linear first order kinetics indicating the loss of propagating species during the polymerization.

![Figure 3.10. Kinetic plots for the polymerization of NonOx initiated with BB, MeOTf, MeOTs and Mel at both 80 and 100 °C with [M]/[I] ratios of 20 (top left), 40 (top right), 60 (bottom left) and 80 (bottom right). The polymerizations at 80 °C were performed with 1.25 M monomer concentration (dashed lines) and the polymerizations at 100 °C were performed with 0.625 M monomer concentration (solid lines) in DMAc.](image-url)
The polymers resulting from the NonOx screening at 80 °C were also characterized with gel permeation chromatography (Figure 3.11). The poly(2-nonyl-2-oxazoline) samples were chosen for GPC analysis since they exhibit the least interactions with the column material from all investigated 2-oxazoline monomers due to the long alkyl chains that shield the nitrogen containing polymer backbone. The obtained molecular weights are close to the theoretical values and the polydispersity indices are lower than 1.20 demonstrating that the polymers were synthesized in a living manner. Moreover, the number average molecular weight increased linearly with increasing [M]/[I] ratio proving the livingness of the polymerizations. The plotted [M]/[I] ratios were calculated from the initial concentration of reagents and the conversion obtained with GC. The polymer that was synthesized with MeOTs as initiator at a [M]/[I] ratio of 80 revealed a molecular weight much lower than theoretically expected. This is in good agreement with the kinetic investigations (Figure 3.10), whereby only this polymerization did not show linear first order kinetics. These results demonstrate that the livingness of the NonOx polymerizations can be very well judged by the observed (non)-linearity during the kinetic screening. Therefore, it was assumed that also for the other investigated 2-oxazoline monomers, the linearity of the first order kinetic plot demonstrates the livingness of the polymerization. However, it is important to realize that the possibility of chain transfer is neglected in this assumption.

![Figure 3.11.](image)

**Figure 3.11.** $M_n$ values (GPC) obtained for the resulting polymers of the NonOx screening at 80 °C plotted against the [M]/[I] ratios. The NonOx polymerization with [M]/[MeOTs] = 80 revealed a too low $M_n$ value, which corresponds to the observed non-linear first order kinetics.

### 3.3.4 Initiator screening for the polymerization of 2-phenyl-2-oxazoline

The kinetic investigations of the PhOx polymerization with the four different initiators (Figure 3.12) demonstrated that these polymerizations are much slower than the previously investigated 2-alkyl-2-oxazoline polymerizations. This can be explained by the lower nucleophilicity of PhOx compared to the 2-alkyl-2-oxazolines resulting in more covalent active species as it is also reported in literature. At 80 °C, no significant polymerization was obtained at all and at 100 °C only initiation with MeOTf and MeOTs resulted in significant polymerization. This can be explained by the fact that the nucleophilicity of triflate and tosylate counterions is lower than the nucleophilicity of PhOx resulting in the presence of cationic active centers instead of covalent active centers, which increases the polymerization rate. These results are in agreement with the previous observations that PhOx could not be
Parallel investigations on the cationic ring-opening polymerization of 2-oxazolines polymerized with BB, as initiator, and that significant polymerization occurred with MeOTs, as initiator, above 100 ºC (section 3.2.1). For all successful PhOx polymerizations, two slopes were observed in the kinetic plots. This kinetic behavior is due to a combination of slow initiation of the PhOx polymerization and secondly by the different reactivities of very short chains, that are influenced by the initiating species, and longer chains.

![Kinetic plots for the polymerization of PhOx initiated with BB, MeOTf, MeOTs and Mel at both 80 and 100 ºC with [M]/[I] ratios of 20 (top left), 40 (top right), 60 (bottom left) and 80 (bottom right). The polymerizations were performed with 1.25 M monomer concentration in DMAc.](image)

**Figure 3.12.** Kinetic plots for the polymerization of PhOx initiated with BB, MeOTf, MeOTs and Mel at both 80 and 100 ºC with [M]/[I] ratios of 20 (top left), 40 (top right), 60 (bottom left) and 80 (bottom right). The polymerizations were performed with 1.25 M monomer concentration in DMAc.

### 3.3.5 Polymerization rates $k_p$ for the 2-oxazoline polymerizations with four initiators

The polymerization rates of the different polymerizations were calculated from the slopes of the linear kinetic plots, whereby it was assumed that the amount of propagating species was the same as the amount of utilized initiator. For the curved kinetic plots, no polymerization rates were calculated, because these polymerizations were not living. Figure 3.13 depicts the polymerization rates for all different polymerizations. This graph clearly demonstrates that the polymerizations at 100 ºC are much faster than the polymerizations at 80 ºC for all different monomers as it was expected. Moreover, the polymerizations of 2-alkyl-2-oxazolines are faster than the PhOx polymerizations due to the lower nucleophilicity of the PhOx. Figure 3.13 clearly revealed that only MeOTf and MeOTs can successfully initiate the polymerization of PhOx. Furthermore, the $k_p$ values found for the different [M]/[I] ratios are quite similar within each combination of monomer and initiator although they slightly decreased with higher [M]/[I] values. This observed decrease in $k_p$ values with higher [M]/[I] ratios can be explained by the lower concentration of initiator: The presence of the same amount of traces of impurities would lead to a larger decrease of $k_p$ when less propagating species (generated by the initiator) are present.
The average rate constants for the different combinations of monomer, initiator, and temperature are listed in Table 1 demonstrating the large influence of initiating species on the polymerization rates. The standard deviation of the polymerization rates is normally within 10% except for the polymerization of 2-phenyl-2-oxazolines. The absolute error in polymerization rate for the 2-phenyl-2-oxazoline is similar to the error in polymerization rate for the other monomers, but due to the much lower polymerization rates the relative error is much larger. The obtained order in polymerization rate constants for the different initiating species for all monomers is in total agreement with the general statement that the lower the nucleophilicity of the counterions the higher the polymerization rates: MeOTf > MeOTs > MeI > BB. However, polymerizations initiated with MeOTf or MeOTs were much more sensitive to residual moisture or other small contaminations resulting in loss of control over the polymerization, whereas the BB was identified as the most robust initiator. In addition, the average polymerization rate constants revealed fastest polymerizations for MeOx, a bit slower polymerization rates for EtOx and NonOx and slowest polymerizations for PhOx.

Table 3.1. Polymerization rates for the different monomer/initiator combinations (in \(10^{-4} \text{ L·mol}^{-1} \cdot \text{s}^{-1}\)).

<table>
<thead>
<tr>
<th>Initiator</th>
<th>MeOx 80 ºC</th>
<th>MeOx 100 ºC</th>
<th>EtOx 80 ºC</th>
<th>EtOx 100 ºC</th>
<th>NonOx 80 ºC</th>
<th>NonOx 100 ºC</th>
<th>PhOx 80 ºC</th>
<th>PhOx 100 ºC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>15.6 ± 1.4</td>
<td>32.4 ± 3.0</td>
<td>8.6 ± 1.0</td>
<td>27.5 ± 2.3</td>
<td>8.9 ± 1.1</td>
<td>21.8 ± 1.9</td>
<td>0</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>MeOTf</td>
<td>25.1 ± 3.9</td>
<td>98.5 ± 6.3</td>
<td>16.2 ± 4.2</td>
<td>68.1 ± 7.7</td>
<td>22.4 ± 0.9</td>
<td>55.7 ± 3.3</td>
<td>1.4 ± 0.6</td>
<td>8.2 ± 1.7</td>
</tr>
<tr>
<td>MeOTs</td>
<td>24.0 ± 1.4</td>
<td>79.2 ± 0.6</td>
<td>14.9 ± 0.7</td>
<td>64.7 ± 4.0</td>
<td>17.9 ± 3.0</td>
<td>55.5 ± 2.9</td>
<td>1.2 ± 0.4</td>
<td>6.8 ± 1.2</td>
</tr>
<tr>
<td>MeI</td>
<td>22.2 ± 2.4</td>
<td>66.6 ± 5.3</td>
<td>13.0 ± 0.7</td>
<td>55.5 ± 8.9</td>
<td>15.9 ± 1.7</td>
<td>50.2 ± 2.3</td>
<td>0.5 ± 0.1</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

3.4 High-throughput synthesis and screening of a library of random and gradient copoly(2-oxazoline)s

The living cationic ring opening polymerization mechanism provides easy access to block copolymer structures by the sequential polymerization of different monomers. Therefore, many examples of block copoly(2-oxazoline)s have been reported in literature. Unlike block copoly(2-oxazoline)s, random copoly(2-oxazoline)s have not been extensively
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investigated so far. The possibility of copolymerizing different 2-oxazolines has been demonstrated by several groups.\textsuperscript{49-51} However, reactivity ratios have only been determined for copolymerizations involving PhOx.\textsuperscript{52} Due to the low reactivity of PhOx, the copolymerizations resulted in quasi-block copolymer structures instead of random or gradient copolymers. Moreover, the properties of copoly(2-oxazoline)s have not been studied in detail.

Inspired by this lack of knowledge in literature, we decided to investigate the synthesis and properties of a library of random copolymers from MeOx, EtOx and NonOx utilizing the high-throughput workflow. Based on the kinetic screening (section 3.3), the copolymerization of EtOx and NonOx was expected to result in truly random copolymers since they exhibit similar polymerization rates, whereas the copolymerizations of MeOx and NonOx or EtOx were expected to yield gradient copolymers due to the higher reactivity of MeOx. This section describes the systematic copolymerization studies and the corresponding structure-property investigations on the library of copolymers. In polymer science, these investigations are the first examples of a high-throughput approach in which kinetic details, library synthesis and property screening were investigated simultaneously providing both fundamental and application directed insights.

3.4.1 High-throughput synthesis of copolymers with simultaneous copolymerization studies

The optimal conditions from the previously described kinetic screening (section 3.3; polymerization with the robust benzyl bromide initiator at 100 °C in DMAc) were applied to synthesize copolymers from combinations of MeOx, EtOx and NonOx utilizing a Chemspeed ASW2000 synthesis robot. For each combination of monomers, 9 copolymers were synthesized with 0-100 mol% (steps of 12.5 mol%) of the second monomer resulting in 27 parallel polymerizations. These steps were chosen to cover the full range of possible copolymer compositions. For each of the copolymerizations, the monomer conversion in time was investigated by automated sampling from the polymerization mixtures for GC analysis.\textsuperscript{53} The monomer to solvent ratios of the initial polymerization mixtures clearly demonstrated the gradual change in monomer composition for the different copolymerization series (Figure 3.14).

![Figure 3.14](image_url)

*Figure 3.14. Initial ratios of monomer to solvent ([M]/[DMAc] from GC) for the copolymerizations plotted against fraction of the second monomer (f): a. EtOx:NonOx; b. MeOx:NonOx and c. MeOx:EtOx.*
Figure 3.15 (top row) depicts the resulting kinetic plots in time for 50 mol% copolymerizations. Similar kinetic plots were obtained for all other copolymerizations (one of the polymerizations failed during the library synthesis or kinetic screening). The linearity of the first order kinetic plots confirmed a constant concentration of living polymer chains as expected for a living polymerization. Moreover, monomodal GPC traces with narrow molecular weight distributions (PDI < 1.3) were obtained for the endsamples, which is indicative for a living polymerization mechanism as well. The kinetic plots revealed a slightly higher reactivity for MeOx compared to EtOx and NonOx. To further elucidate the copolymer compositions, the reactivity ratios ($r_1$ and $r_2$) were determined from the relation between the fraction of monomer A in the monomer feed ($f_1$) and the incorporated fraction of monomer A in the polymer ($F_1$) at both ~20% and ~60% monomer conversion (Figure 3.15, bottom row). For living polymerizations, the reactivity ratios should be calculated at higher monomer conversions (20% or higher) since different reactivities during the initiation process are commonly observed.\textsuperscript{54,55} Also for the polymerization of 2-oxazolines, it is well known that the polymerization rate during initiation can be different from the final polymerization rate.\textsuperscript{56} In first instance, the reactivity ratios were determined using the classical Mayo-Lewis terminal model (MLTM) utilizing non-linear least square fitting of the data in Figure 3.15 bottom.\textsuperscript{57} However, the applied MLMT method is strictly only valid for 0% monomer conversion and, therefore, reliable reactivity ratios can only be determined from extrapolation of the data obtained at low monomer conversions up to ~10%.

\textbf{Figure 3.15.} Top row: Conversion ($\ln([M]_0/[M]_t)$) against time plots for 50 mol% copolymerizations (a, c and e); Bottom row: Relationship between the monomer feed ($f_1$) and the actual monomer incorporation ($F_1$) at the initial (~20% conversion) and final (>50% conversion) polymerization stages (b, d and f). Both conversion and monomer incorporation are shown for EtOx:NonOx (a and b), MeOx:NonOx (c and d) and MeOx:EtOx (e and f) copolymerizations.
To accurately determine the reactivity ratios at higher monomer conversion, the extended Kelen-Tüdös (KT) method can be applied. The resulting reactivity ratios from both the MLTM and KT methods are summarized in Table 3.2. As expected, the reactivity ratios obtained for low conversion (initial $r_1$ and $r_2$) are similar with both calculation methods. However, the reactivity ratios for high conversion (final $r_1$ and $r_2$) from the different calculation methods differ significantly for the MeOx:NonOx and MeOx:EtOx copolymerizations. The KT method revealed similar reactivity ratios at low and high conversion for the MeOx:EtOx copolymerizations; whereas, the MeOx:NonOx and EtOx:NonOx copolymerizations revealed a more pronounced difference in reactivity ratios (utilizing the KT method) at the initial stage of the polymerizations demonstrating a higher reactivity of the MeOx and EtOx compared to the NonOx during the initiation process. Furthermore, the reactivity ratios (KT method) revealed the formation of random copolymers for the EtOx:NonOx copolymerization (both final $r_1$ and $r_2 \approx 1$). Moreover, the copolymerizations of MeOx:NonOx and MeOx:EtOx resulted in the formation of gradient copolymers, whereby the gradient is slightly more pronounced for the MeOx:NonOx copolymers.

Table 3.2. Reactivity ratios determined for the 2-oxazoline copolymerizations utilizing both the Mayo-Lewis terminal model (MLTM) and extended Kelen-Tüdös (KT) method.

<table>
<thead>
<tr>
<th>M1:M2</th>
<th>method</th>
<th>initial $r_1$</th>
<th>initial $r_2$</th>
<th>final $r_1$</th>
<th>final $r_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOx:NonOx</td>
<td>MLTM</td>
<td>1.2 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>0.97 ± 0.01</td>
<td>0.99 ± 0.01</td>
</tr>
<tr>
<td>EtOx:NonOx</td>
<td>KT</td>
<td>1.23 ± 0.13</td>
<td>0.60 ± 0.05</td>
<td>0.91 ± 0.05</td>
<td>0.94 ± 0.03</td>
</tr>
<tr>
<td>MeOx:NonOx</td>
<td>MLTM</td>
<td>1.8 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>1.26 ± 0.05</td>
<td>0.66 ± 0.03</td>
</tr>
<tr>
<td>MeOx:NonOx</td>
<td>KT</td>
<td>1.94 ± 0.15</td>
<td>0.25 ± 0.04</td>
<td>1.83 ± 0.04</td>
<td>0.46 ± 0.02</td>
</tr>
<tr>
<td>MeOx:EtOx</td>
<td>MLTM</td>
<td>1.52 ± 0.1</td>
<td>0.54 ± 0.03</td>
<td>1.18 ± 0.04</td>
<td>0.65 ± 0.02</td>
</tr>
<tr>
<td>MeOx:EtOx</td>
<td>KT</td>
<td>1.67 ± 0.04</td>
<td>0.51 ± 0.04</td>
<td>1.63 ± 0.05</td>
<td>0.52 ± 0.04</td>
</tr>
</tbody>
</table>

3.4.2 Surface energies of the random and gradient copoly(2-oxazoline)

The resulting library of copolymers was utilized to investigate the differences between random and gradient copolymers regarding surface and thermal properties. More specifically, the series containing MeOx:NonOx and EtOx:NonOx were compared, because they have a gradient or random composition, respectively (Figure 3.16). In addition, the pMeOx and pEtOx homopolymers have very similar surface and thermal properties and, therefore, any observed differences between those two NonOx containing series might be assigned to their different compositions. Other gradient copolymers were already shown to exhibit interesting mechanical and thermal properties.59-61

![p(EtOx-r-NonOx)](image1)

![p(MeOx-r-NonOx)](image2)

Figure 3.16. Schematic representation of the random and gradient monomer distributions throughout the EtOx:NonOx and MeOx:NonOx copolymers, respectively.
Chapter 3

The synthesized library of copolymers was screened with regard to the surface energy in a high-throughput manner. Contact angles (CA) of spin cast polymer films were measured with two different test liquids (ethylene glycol and diiodomethane). These contact angle values were used as input parameters for the surface energy (SE) calculations. Neumann’s equation of state (3.4) was used, since it does not require further input parameters:

\[
\cos \theta = 2 \sqrt{\frac{\gamma_{sv}}{\gamma_{lv}}} e^{-\beta(\gamma_{sv} - \gamma_{lv})^2} - 1 \tag{3.4}
\]

\(\theta\) is the contact angle, and \(\gamma_{sv}\) and \(\gamma_{lv}\) stand for the SE of the polymer surface and the surface tension of the test liquid, respectively. \(\beta = 0.0001247 \text{ m}^2\text{N}^{-2}\) is an empirical constant. \(\gamma_{lv}\) values were taken from the literature (ethylene glycol: 48 mN·m\(^{-1}\); diiodomethane: 50.8 mN·m\(^{-1}\)). A similar approach to determine surface energies of poly(2-oxazoline)s via contact angle measurements was already reported in 1969.

Figure 3.17 depicts the resulting SE’s for the NonOx containing copolymers against the w% of NonOx present in the copolymers. The SE’s are plotted against w% NonOx, because w% closer resembles the volume fraction NonOx and thus the theoretical surface coverage in the absence of preferential orientation. Both copolymer series show similar trends, whereby the SE changes from ~ 42 mN·m\(^{-1}\) for the pMeOx and pEtOx to ~ 21 mN·m\(^{-1}\) for the pNonOx. The similar trends for both series can be explained by the fact that the contact angle measurements are performed on a macroscopic scale (droplet size) whereas the small difference in composition for the copolymer series is a microscopic effect that is averaged out on this macroscopic level. Surprisingly, the SE does not decrease gradually with increasing NonOx content, but the presence of NonOx only becomes visible at approximately 50 w% of NonOx. With lower NonOx contents, the SE is the same as for the pMeOx or pEtOx. The reason behind this peculiar behavior of the SE’s of the copolymers is not understood at the moment. Moreover, the copolymers have a significantly higher SE when compared to a block copolymer or a blend of homopolymers of EtOx:NonOx (both 50 mol%; open square in Figure 3.17). This difference can be explained by the fact that the nonyl side-chains cannot orient to the surface without exposing the second monomer (MeOx or EtOx) to the surface in the copolymers, resulting in intermediate SE’s; whereas, the NonOx segment can orient to the surface in the block copolymer or in the blend resulting in a low surface energy close to the SE of pNonOx.

![Figure 3.17. Surface energies for the copolymer series consisting of MeOx:NonOx and EtOx:NonOx.](image)
3.4.3 Thermal properties of the random and gradient copoly(2-oxazoline)s

The influence of gradient or random monomer distribution on the thermal properties of the copoly(2-oxazoline)s was investigated by differential scanning calorimetry (DSC; Figure 3.18). Figure 3.18 shows the change of glass transition temperature ($T_g$) and melting temperature ($T_m$) against the incorporation of w% NonOx. Upon incorporation of NonOx into pMeOx or pEtOx, the $T_g$ is decreasing due to the higher flexibility of the nonyl side-chains. At approximately 90 w% of NonOx, no $T_g$ is observed in DSC anymore. However, the observed $T_g$ for the pMeOx homopolymer is lower than the reported value (80 °C) due to the short chain length. In addition, the melting point of pNonOx decreases upon the incorporation of MeOx or EtOx since the crystallinity of the pNonOx is disturbed. The difference in $T_m$ between the two series could be ascribed to small differences in polymer length since different $T_m$'s were obtained for both pNonOx homopolymers. As a result, no conclusions on the effect of MeOx or EtOx incorporation on the crystallinity can be drawn except that the presence of a second monomer disturbs the crystallinity of the pNonOx side chains.

![Figure 3.18. Thermal properties ($T_g$ and $T_m$) obtained by DSC for the copolymers consisting of MeOx:NonOx and EtOx:NonOx.](image)

3.5 Concentration effects in the cationic ring-opening polymerization of 2-ethyl-2-oxazoline in N,N-dimethylacetamide

In the previous sections, a wide range of kinetic investigations on 2-oxazoline polymerizations utilizing automated parallel synthesis robots were described. Some of the investigations focused more on the automated synthesis equipment (chapter 2) since combinatorial and high-throughput techniques are just flourishing in polymer science, whereas the investigations described in this chapter led to improved reaction temperatures or more detailed kinetic insights into the polymerization of 2-oxazolines.

In this section, we report the automated parallel optimization of the polymerization of EtOx regarding the utilized monomer concentration in DMAc. Increasing the monomer concentration and thus the initiator concentration (with equal [M]/[I] ratio) is a straightforward way to accelerate the polymerization. In addition, for environmental reasons it is preferable to perform reactions at the highest concentration possible to reduce the amount of organic solvents as well. However, the effect of monomer concentration on the cationic ring-opening polymerization of EtOx has not been studied in detail up to this moment. $^1$H-NMR spectroscopic kinetic investigations were performed to gain more detailed insights into the polymerization mechanism of the different systems. Finally, the controlled synthesis of previously unattainable high molecular weight pEtOx’s will be reported.
3.5.1 High-throughput optimization of the monomer concentration for the polymerization of 2-ethyl-2-oxazoline

The current study focused on the living character of the cationic ring-opening polymerization of EtOx at different monomer concentrations. To accelerate the investigations, a first screening was performed utilizing the Chemspeed ASW2000 automated synthesis robot (section 2.2.1). By automatically dispensing of a BB stock solution in DMAc, EtOx and DMAc, polymerization mixtures with [M]/[I] ratios of 60 were obtained at 11 different concentrations. After taking zero time samples, the 13 mL reactors were heated to 100 ºC and samples were taken from the polymerization mixtures at suitable time intervals. The progress of $\ln([M]_0/[M])$, obtained from the monomer consumption (GC) in time for the different monomer concentrations, is depicted in Figure 3.19 (the same concentration series was used to validate the online GC characterization, section 2.4.2).

A close look at those first screening results revealed insufficient sampling times for the higher concentrated polymerizations ([M] > 5 M) resulting in full conversion already at the second sampling time. For all other concentration, linear first order kinetics were obtained with a different polymerization rate in the initial stage of the polymerizations. The two different slopes in the first order kinetic plot indicate different polymerization rates ($k_p$’s) for short polymer chains ($k_{p1}^{app}$) and longer polymer chains ($k_{pn}^{app}$) as was reported by Saegusa. 42

GPC characterization of the samples taken from the EtOx polymerizations at different monomer concentrations yielded the corresponding number average molecular weight (Mₙ) against monomer conversion plot (Figure 3.20). GPC characterization was not performed for the polymerizations below 1 M concentration, since no significant polymerization occurred at those concentrations. For all other concentrations, a linear increase of molecular weight with monomer conversion was obtained as it is expected for a living polymerization. However, the polymerization performed at 1.56 M and 2.38 M revealed a larger deviation from the theoretical molecular weight. In addition, the polydispersity index (PDI) values for those polymerizations were drastically higher than for the polymerizations performed at higher concentrations as depicted in the inset of Figure 3.20, that shows the Mₙ and PDI values of the final polymers obtained. Moreover, yellow polymerization mixtures were obtained at low concentrations ([M] < 3 M), indicating side reactions, and the final polymer obtained at 8.66 M revealed a significant shoulder at the high molecular weight region which might be due to the occurrence of chain transfer reactions followed by chain coupling at high monomer concentration.
Parallel investigations on the cationic ring-opening polymerization of 2-oxazolines

In conclusion, the automated concentration screening revealed an optimal polymerization window in between 4 and 7 M monomer concentration for the cationic ring-opening polymerization of EtOx in DMAc.

![Figure 3.20](image)

**Figure 3.20.** Development of $M_n$ against monomer conversion for the different concentration polymerizations; the inset shows the dependence of the final $M_n$ and PDI values on the monomer concentration (GPC eluent: chloroform:triethylamine:2-propanol = 94:4:2).

3.5.2 $^1$H-NMR spectroscopic investigations of 1 M and 8 M EtOx polymerizations

To further elucidate the polymerization mechanisms at the different concentrations, the EtOx polymerizations with benzyl bromide as initiator ([M]/[I] = 60 and T = 100 °C) were performed in a NMR-spectrometer in DMAc-$d_9$ at both 1 M (10 w%) and 8 M (80 w%) monomer concentration, respectively. A screw cap NMR tube containing the polymerization mixture was inserted into a preheated NMR-probe.

![Figure 3.21](image)

**Figure 3.21.** Reaction kinetics obtained from NMR-polymerizations at 1 M (circles) and 8 M (squares) EtOx concentration; the inset shows the GPC traces for the polymers obtained after 2 hours.

Tuning, locking and shimming of the NMR probe had to be performed after insertion of the polymerization mixture into the preheated (100 °C) spectrometer, since the settings differed significantly from the settings at ambient temperature. In addition, optimization of the probe had to be redone regularly during the polymerization because the sample with different amounts of polymer inside required different shims than the initial mixture. After the first measurement, $^1$H-NMR spectra were recorded at regular time intervals. The monomer conversion was calculated from the integral ratios of both monomer (4.15 or 3.68 ppm) and
polymer (3.5 or 2.3 ppm). The resulting plot of $\ln([M]_0/[M]_t)$ against time (Figure 3.21) clearly revealed two slopes for both concentrations. The calculated polymerization rates for the initial ($k_{p1}^{\text{app}}$) and final ($k_{pn}^{\text{app}}$) polymerization regions are depicted in Table 3.3. The initial polymerization rate was found to be higher for the lower concentration; whereas, the final polymerization rate was higher for the higher concentration polymerization. Moreover, the polymerization at 8 M EtOx concentration was finished within 2 hours. The macroscopic appearance of the polymerization mixtures after 120 minutes polymerization time was very different for the polymerizations at 1 M and 8 M. The polymerization mixture with 8 M monomer concentration appeared as a colorless gel and the 1 M mixture was a yellow solution. GPC traces of the two pEtOx’s end samples (120 minutes polymerization time) are depicted in the inset of Figure 3.20 demonstrating the good control over the polymerization at 8 M (PDI = 1.16) and the ill-controlled 1 M polymerization (PDI = 1.69). The signal at 9.4 minutes results from unreacted monomer.

**Table 3.3. Rate constants for the polymerization of EtOx at 100 °C initiated with benzyl bromide ([M]/[I] = 60) at both 1 M and 8 M monomer concentration in DMAc-d$_9$.**

<table>
<thead>
<tr>
<th>monomer concentration</th>
<th>$10^3 \cdot k_{p1}^{\text{app}}$ L·mol$^{-1}$·s$^{-1}$</th>
<th>$10^4 \cdot k_{pn}^{\text{app}}$ L·mol$^{-1}$·s$^{-1}$</th>
<th>$10^4 \cdot k_{pn}^{\text{cat}}$ L·mol$^{-1}$·s$^{-1}$</th>
<th>$10^4 \cdot k_i$ L·mol$^{-1}$·s$^{-1}$</th>
<th>$10^4 \cdot k_{i\rightarrow p}$ L·mol$^{-1}$·s$^{-1}$</th>
<th>oxazolinium %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>8.0</td>
<td>56.0</td>
<td>191.1*</td>
<td>90.0</td>
<td>–</td>
<td>29.3**</td>
</tr>
<tr>
<td>8 M</td>
<td>5.8</td>
<td>72.3</td>
<td>192.8*</td>
<td>&gt;16.7</td>
<td>1.7</td>
<td>37.5</td>
</tr>
</tbody>
</table>

* $k_{pn}^{\text{cat}}$ was calculated assuming that chain growth occurs exclusively at the cationic centers. 
** This final oxazolinium percentage was calculated using a sigmoidal fit to the progress of the oxazolinium percentage in Figure 3.22.

**Figure 3.22.** Selected NMR-spectra obtained during the kinetic studies at both 8 M and 1 M monomer concentration in DMAc-d$_9$. 
Besides the monomer and polymer signals, the $^1$H-NMR spectra obtained during the polymerizations at 1 M and 8 M concentration were surprisingly different. This difference is visualized in Figure 3.22 that depicts $^1$H-NMR spectra from the polymerizations at 4 or 5, 20 and 90 minutes. For the 8 M NMR polymerization, locking and shimming was difficult at 100 °C and, unfortunately, the first spectrum could only be taken after 5 minutes polymerization time. This $^1$H-NMR spectrum at 5 minutes from the 8 M polymerization did not show the initial BB signal at 7.4 ppm indicating complete initiation. Additionally, the signals at 4.63 and 2.8 ppm could be assigned to the covalent species resulting from BB with one monomer unit (Figure 3.22).

Figure 3.23. Kinetic details obtained from the NMR polymerizations at 1 M and 8 M: (1) Initiation rates ($k_i$; open symbols); (2) the initial polymerization rate ($k_i \rightarrow p$; only for the 8 M polymerization; crossed symbols) and (3) the percentage of cationic propagating species (closed symbols).

To estimate the initiation rate$^{66}$ ($k_i$; Table 3.3 and open squares in Figure 3.23), it was assumed that the conversion of benzyl bromide was 99% after 5 minutes. Moreover, the monomer conversion after 5 minutes was close to 1 unit per chain suggesting that indeed all BB initiator molecules coupled to one first monomer unit. The spectrum after 20 minutes showed a decrease in the signal at 4.63 ppm from the BB with one monomer unit and a new signal appeared at 4.60 ppm, which could be assigned to the benzyl CH$_2$ protons from the polymer (more than one monomer unit attached). The change in these benzyl protons was utilized to calculate the conversion rate from benzyl bromide with one coupled monomer ([I + 1 · EtOx]) to polymeric species$^{67}$ ($k_{i \rightarrow p}$; Table 3.3 and crossed squares in Figure 3.23).

The $^1$H-NMR spectrum after 90 minutes polymerization time revealed the presence of the cationic oxazolinium species at 4.58 and 4.9 ppm. After 120 minutes, a final level of 37.5% oxazolinium (percentage of initial initiator amount$^{68}$ was present in the polymerization mixture. Previously, the amount of oxazolinium species was reported to be 62% in nitrobenzene and < 3% in tetrachloromethane for the benzyl bromide initiated polymerization of MeOx.$^{21}$ The formation of oxazolinium species during the polymerization is shown in Figure 3.23 (closed squares). The different stages (from the $^1$H-NMR spectra) in the 8 M EtOx polymerization lead to the proposed polymerization mechanism as shown in Scheme 3.3. The previously observed initial polymerization rate $k_{p1}^{app}$ can be considered as a combination of the two different initiation steps $k_i$ and $k_i \rightarrow p$, whereby the actual initiation process ($k_i$) is fast. In addition, the change of slopes in Figure 3.21 corresponds with the appearance of oxazolinium species meaning that those cationic rings show much higher polymerization rates as it was also previously reported.$^{21,42}$
Scheme 3.3. Detailed reaction mechanism for the EtOx polymerization performed at 8 M monomer concentration in DMAc-\(d_9\) inside the NMR-spectrometer. The upper part shows the important steps during initiation (\(k_i\) and \(k_i \rightarrow p\)). The lower part shows the polymerization steps (\(k_{p1,\text{app}}\) and \(k_{pn,\text{app}}\)) and the equilibrium between cationic and covalent species.

The spectrum after 4 minutes of the polymerization at 1 M did show small residual benzyl bromide signals at 7.4 and 4.6 ppm (Figure 3.22). The initiation rate (\(k_i\); Table 3.3 and open circles Figure 3.23) was calculated from the disappearance of those BB signals. The initiation is again fast as it was for the 8 M polymerization. Upon complete initiation, the monomer conversion is close to 1 unit per BB; however, characteristic \(^1\)H-NMR signals for the conversion from one monomer to polymeric species could not be distinguished and thus \(k_{i \rightarrow p}\) could not be determined. The \(^1\)H-NMR spectrum after 90 minutes polymerization time revealed the presence of oxazolinium species and also for this polymerization the change in slope of the overall polymerization rate occurs at the moment the oxazolinium species appear (combination of Figures 3.21 and 3.23). The final oxazolinium percentage\(^{68}\) was calculated to be 29.3\% of the initial initiator amount utilizing a sigmoidal fit to the progress in oxazolinium percentage (Figure 3.23, solid circles). The final percentage of oxazolinium species was found to be lower for the 1 M polymerization, whereas, theoretically, the higher polarity of 20 w\% (1 M) monomer (\(\mu = 1.32\) D for the similar MeOx\(^{69}\) in DMAc (\(\mu = 3.81\) D) compared to 80 w\% (8 M) monomer in DMAc should shift the equilibrium towards the cationic species. This unexpected lower percentage of cationic species at 1 M concentration is not yet understood and might indicate the occurrence of side reactions that lead to termination of the living chain ends for the 1 M polymerization. When assuming exclusive chain growth at the cationic centers (as reported previously),\(^{21}\) the apparent polymerization rates \(k_{pn,\text{app}}\) can be recalculated to the polymerization rate of the cationic centers \(k_{pn}^{\text{cat}}\) resulting in equal \(k_{pn}^{\text{cat}}\)s for both the 1 M and 8 M polymerizations (see Table 3.3). The oxazolinium species are only
formed after about 20 minutes polymerization time. Apparently, for very small oligomeric species the influence of the initiating benzyl group forces the active chain ends to be present as covalent species. Only after a significant polymerization time, the polymer chains are no longer influenced by the initiating group resulting in a stable equilibrium between covalent and cationic species.

A closer look at the NMR spectra after 4, 20 and 90 minutes for the 1 M polymerization revealed many small signals that could not be assigned (e.g. 7.6, 3.8 and 2.8-2.4 ppm), which indicate the occurrence of side reactions. Therefore, it is assumed that the loss of control over the polymerization might result from chain transfer reactions since the amount of propagating species is constant (linear first order kinetics; Figure 3.21). Surprisingly, the spectrum after 20 minutes polymerization shows only a small signal at 4.6 ppm indicating a different initiation mechanism for the 2-ethyl-2-oxazoline polymerization at 1 M compared to that at 8 M monomer concentration. Moreover, the spectra at 4 and 20 minutes show a sharp singlet at 3.8 ppm that has disappeared after 90 minutes polymerization time. At 90 minutes the signal at ~4.6 ppm has reappeared too. This signal might result from an exo double bond resulting from chain transfer on the growing chain end. To further investigate the uncontrolled polymerization at 1 M monomer concentration in DMAc and the many 1H-NMR signals that could not be assigned, the 1 M end sample was analyzed with GC-MS (Figure 3.24, bottom). For comparison two low concentration model reactions with EtOx and benzyl bromide were performed in DMAc and o-dichlorobenzene (ODCB) (Figure 3.24, middle and top, respectively). The two model reactions in DMAc and ODCB show completely different GC-MS spectra after 1 hour reaction time at 100 °C, whereby the DMAc reaction shows a good resemblance with the 1 M polymerization sample. In ODCB, the expected species, resulting from the reaction of benzyl bromide with one monomer, could be assigned to the largest signal at 5.8 minutes. Strikingly, this signal is not present in the spectrum for the model reaction in DMAc.

The largest signal (7.2 minutes) in DMAc could not be assigned, but the fragmentation pattern points towards a species with a dibenzyl amine unit present. This dibenzyl amine unit might result from double benzyl bromide attack onto one monomer that results in the release of HBr.
The presence of HBr might also explain the presence of ring-opened monomer (2.4 minutes), the orange color of the mixture, and the occurrence of side reactions. This compound with two benzyl units attached could result from reaction with the monomer, since it is also present in the ODCB reaction and a test with only benzyl bromide in DMAC at 100 °C did not show any reaction. Unfortunately, the reason for the different reaction mechanism at 1 M monomer concentration could not be elucidated; however, it is clear that many more (chain transfer) side reactions are present compared to the 8 M polymerization. Apparently, a minimal monomer concentration ([M] > 4 M, from the automated screening) is required to obtain a living polymerization in DMAC and to reduce the possibility of those chain transfer reactions. In addition, the cationic polymerization of EtOx could be completed within 2 hours at 8 M.

3.5.3 Synthesis of higher molecular weight poly(2-ethyl-oxazoline)s

The new insights into the polymerization mechanism of the polymerization of EtOx in DMAC at 100 °C were applied for the automated synthesis of pEtOx’s with different chain lengths. Especially the synthesis of higher molecular weight (M_n > 10,000 Dalton) pEtOx’s was of interest since most studies on pEtOx’s focus on shorter oligomers. The polymerizations were performed at the lowest monomer concentration that provided good control (4 M) to prevent solidification of the polymerization mixture during the reaction (solidification had to be avoided since it would make sampling for kinetic investigations impossible in the automated synthesizer). Figure 3.25 left plots the monomer conversion [represented by \( \ln([M]/[M]_0) \)] during the polymerizations against time. Different slopes were obtained for the initial and the later stage of the polymerization. For all different monomer to initiator ([M]/[I]) ratios, the amount of propagating species was constant during the polymerization. In addition, the obtained number average molecular weights are linearly increasing with the [M]/[I] ratios (Figure 3.25 right).

![Figure 3.25. Left: Plot of \( \ln([M]/[M]_0) \) against time for the higher molecular weight pEtOx’s. Right: Dependence of M_n on the [M]/[I] ratio demonstrating the living character of the polymerizations (GPC eluent: DMF with 5 mM NH_4PF_6).](image)

The lower M_n values, with respect to the theoretical values, is most likely due to the poly(ethylene glycol) calibration of the GPC, since a similar linear trend with higher molecular weight than theoretical was observed utilizing a PMMA calibration (not shown). It is noteworthy to mention that DMF was required as GPC eluent for the higher molecular weight pEtOx’s (M_n > 10,000 Dalton) to suppress interactions with the column material.
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Figure 3.26 depicts selected GPC traces for the obtained pEtOx’s. Monomodal polymer distributions were obtained up to a [M]/[I] ratio of 100. At higher [M]/[I] ratios, a (small) shoulder was observed at the high molecular weight region. This shoulder originates from chain transfer reactions and subsequent chain coupling reactions.\textsuperscript{35} Despite these shoulders, polymers with reasonably low polydispersity indices (PDI < 1.3 for the crude polymers) were obtained up to [M]/[I] ratios of 250. From the linear first order kinetics, the linear dependence of $M_n$ on [M]/[I] ratio and the low PDI values, it can be concluded that pEtOx’s can be synthesized in a living manner up to a molecular weight of 25,000 Dalton utilizing the higher monomer concentration in DMAc although side-reactions occurred with [M]/[I] ratios exceeding 100.

![Figure 3.26. Selected GPC traces of pEtOx’s with different [M]/[I] ratios synthesized at 4 M monomer concentration utilizing the automated synthesizer (GPC eluent: DMF with 5 mM NH$_4$PF$_6$).](image)

3.6 Polymerization of 2-oxazolines under pressure conditions

In the previous sections, it was described that the cationic ring-opening polymerization of EtOx can be accelerated by increasing the monomer concentration. Moreover, it was demonstrated for EtOx (1.25 M) that the polymerization temperature could not be increased beyond 100 °C without losing the control over the polymerization when benzyl bromide was used as initiator in DMAc. In addition, the polymerization of PhOx (1.25 M) initiated with MeOTs in DMAc could be performed up to 130 °C with good control. Furthermore, the observed side-reactions during the concentration studies were more pronounced in DMAc than in o-dichlorobenzene. Based on these previous observations and inspired by the success of the microwave-assisted polymerizations (see chapters 4 and 5), we decided to investigate the cationic ring-opening polymerization of EtOx and PhOx with methyl tosylate as initiator in superheated acetonitrile (CH$_3$CN) at both 120 and 140 °C. To be able to reach these temperatures in acetonitrile, the polymerization were performed under 15 bar nitrogen pressure utilizing an automated synthesis robot equipped with pressure reactors. The kinetic results obtained for the pressure polymerizations are described in this chapter. Moreover, a series of amphiphilic block copoly(2-oxazoline)s was prepared under pressure with conventional heating utilizing the synthesis robot. The thermal and surface properties of these block copolymers will be discussed as well.
3.6.1 Pressure polymerization of 2-ethyl-2-oxazoline

The pressure polymerizations were performed in the Accelerator SLT100 synthesis robot (section 2.2.2) equipped with pressure reactors. First the cationic ring-opening polymerization of EtOx was investigated with 15 bar nitrogen pressure. In one experimental run, four parallel polymerizations were performed with four different reaction times resulting in 16 different polymerizations. For each polymerization time, the monomer and initiator stock solutions in acetonitrile were transferred into the reactors resulting in 3.2 mL solutions with 4 M EtOx concentration in acetonitrile and a monomer to initiator ratio of 60. Subsequently, 15 bar nitrogen pressure was applied to the reactors and the reactors were heated to the set temperature. After the predefined reaction time, the reactors were cooled to 60 ºC, pressure was released and the reaction mixtures were transferred into sample vials that were prefilled with chloroform saturated with water to quench the polymerizations. This procedure was repeated for four different reaction times to investigate the polymerization kinetics. The conversion of the polymerizations was determined with gas chromatography (GC) and the molecular weights of the resulting polymers were analyzed by gel permeation chromatography (GPC). The first order kinetic plot obtained for the polymerization of EtOx at both 120 and 140 ºC is depicted in Figure 3.26. To compensate for the delay in monomer conversion during the heating period at different heating rates, the zero times (t₀) of the polymerizations were taken when the temperature reached 90 ºC. The pressure polymerizations at 120 ºC revealed linear first order kinetics indicative of a constant concentration of growing polymer chains. In contrast, the polymerizations at 140 ºC showed curved first order kinetics. However, the lower conversion at shorter polymerization times might be due to slow heating of the polymerization mixture to 140 ºC. The polymerizations that were performed for five minutes (after it reached 90 ºC) required still ~3 minutes to heat further to 140 ºC and thus the effective polymerization time at 140 ºC is overestimated resulting in non-linear kinetics. However, the polymerization mixtures that were heated longest at 140 ºC (13 minutes polymerization time) revealed a higher polymerization rate than the polymerizations at 120 ºC. In addition, the effect of the heating rate on the polymerization was investigated. This effect is especially interesting for up-scaling since at a larger scale the heating rate will be limited. Therefore, the polymerization kinetics at 120 ºC were investigated with both 10 ºC / min (closed symbols) and 30 ºC / min (open symbols) heating rates. The polymerization kinetics plotted in Figure 3.27 left show the same trend for both heating rates (with t₀ set to 90 ºC). These results demonstrate the possibility of up-scaling the pressure polymerizations of EtOx, whereby the linear first order kinetics are retained.

Figure 3.27. Left: First order kinetic plot for the polymerization of EtOx in acetonitrile under pressure (●, ▲, ▼: 140 ºC (heating rate = 30 ºC / min); ●, ■, ▲, ▼: 120 ºC (10 ºC / min) and □, ○, △, ▶: 120 ºC (30 ºC / min)). Right: Corresponding molecular weight (Mₙ) against conversion plots.
Moreover, the cationic ring-opening polymerization of EtOx in superheated acetonitrile at different polymerization temperatures with different heating rates revealed a linear increase of $M_n$ with conversion demonstrating the living nature of the polymerization (Figure 3.27 right). In addition, narrow molecular weight distributions were obtained for all performed polymerizations (PDI < 1.20). The livingness of the polymerizations under pressure was further investigated by chain extension experiments. After polymerization of a first portion of EtOx, the reactors were cooled to 60 ºC and a second portion of EtOx was added. Figure 3.28 shows the GPC traces before and after chain extension. These traces and the corresponding $M_n$ and polydispersity indices (PDI) prove the livingness of the polymerization by successful chain extension. Moreover, the good reproducibility of the polymerizations is verified by the perfect overlap of the two traces of p(EtOx$_{30}$-b-EtOx$_{60}$).

![Figure 3.28. GPC traces obtained for chain-extension experiments with EtOx in acetonitrile at 120 ºC (GPC eluent:chloroform:triethylamine:2-propanol = 94:4:2).](image)

### 3.6.2 Pressure polymerization of 2-phenyl-2-oxazoline

In addition to the polymerization of EtOx, the polymerization PhOx was investigated under pressure with conventional heating. PhOx was chosen as second monomer to investigate since it normally shows different (slower) polymerization kinetics due to stabilization of the oxazolinium species by the phenyl ring and due to the lower nucleophilicity of this monomer. The polymerization kinetics of PhOx were investigated at 120 and 140 ºC in a similar manner as the polymerization of EtOx with 3 M PhOx concentration in acetonitrile and a monomer to MeOTs ratio of 60. However, the finished polymerizations were quenched with water instead of transferred to sample vials due to their high viscosity. As a result, the first quenched polymerization mixtures remained in the reactors and have been heated several times to 120 or 140 ºC (see also experimental part). Moreover, the polymerization temperature was controlled by a PT-100 probe in a reference cell, whereby the $t_0$ was set to the moment that desired polymerization temperature was reached. The first order kinetic plot (Figure 3.29 left) does not show an ideal linear behavior for both temperatures. The increase in $\ln([M]_0/[M])$ values levels off above three (corresponding to 95% conversion), which might be due to insufficient stirring of the viscous mixture by the vortex shaking. Also for the polymerization of PhOx, an increase of $M_n$ with conversion was observed with narrow molecular weight distributions (PDI < 1.20) demonstrating the livingness of the polymerizations, whereby it should be noted that the obtained $M_n$ values are below the theoretical molecular weight.
3.6.3 Synthesis of block copoly(2-oxazoline)s under pressure

In the previous two sections, it was demonstrated that both EtOx and PhOx can be successfully polymerized under pressure with conventional heating resulting in very fast living cationic ring-opening polymerizations; full conversion was reached within 15 minutes polymerization time for EtOx and within 50 minutes for PhOx. In a next step, the synthesis of a series of amphiphilic block copolymers with a large content (~ 70 w%) of a water-soluble MeOx or EtOx first block and a small content (~ 30 w%) of a hydrophobic NonOx or PhOx second block. For all these combinations both a long (~ 70 monomer units) and a short copolymer (~ 30 monomer units) were synthesized to investigated the effect of polymer length on the polymer properties.

The block copolymers were synthesized comparable to the chain extension experiments of EtOx. After polymerization of the first block, the reaction mixtures were cooled to 60 °C and the second monomer was added after which the temperature was increased again to 120 °C. For the longer copolymers (~ 70 monomer units) the second block was added as stock solution in acetonitrile to prevent too viscous solutions, whereas for the short block...
Parallel investigations on the cationic ring-opening polymerization of 2-oxazolines

copolymers the second monomer was added as pure liquid. Each block copolymerization was performed four times in parallel to check the reproducibility resulting in total in 10 grams of final product. Figure 3.30 depicts the GPC traces obtained for the first block and the block copolymers of p(EtOx<sub>60</sub>-b-NonOx<sub>15</sub>) 6 demonstrating the successful synthesis and the good reproducibility of the block copolymerizations. The Mn and PDI data obtained by GPC for all different block copolymerizations are depicted in Figure 3.31.

![Figure 3.30](image)

**Figure 3.30.** GPC traces obtained for the first block and the block copolymers of p(EtOx<sub>60</sub>-b-NonOx<sub>15</sub>) 6 demonstrating the successful synthesis and the good reproducibility of the block copolymerizations.

All GPC analyses were performed with chloroform as eluent, except for block copolymers 1 and 3 (DMF), because the longer pMeOx segments showed strong interactions with the column material. These interactions are also present for the shorter pMeOx first blocks of 2, 4 and 5 resulting in higher PDI values. However, for these short MeOx containing block copolymers the non-interacting second block is sufficient to overrule these interactions resulting in reliable GPC data with chloroform as eluent. For p(MeOx<sub>70</sub>-b-NonOx<sub>15</sub>) 1 the final molecular weight data are missing due to the column interactions in chloroform and bad solubility in DMF. Based on the good reproducibility of the GPC data obtained for the block copolymers, the four batches of each block copolymer were combined and the final products were solidified from hexane. The theoretical composition, the composition calculated from <sup>1</sup>H-NMR spectroscopy, the theoretical molecular weight and the obtained GPC data (M<sub>n</sub> and PDI) of the ten different block copolymers 1-10 are summarized in Table 3.4. GPC analysis of a low concentrated sample of the combined batches of block copolymer 1 in DMF also succeeded and the results are included in Table 3.4. The block copolymers 3, 4, 8 and 9 with PhOx as second block showed a low incorporation of PhOx at 120 °C, which is due to the low reactivity of PhOx in combination with insufficient polymerization time (15 minutes). Therefore, the block copolymerizations of the short PhOx containing polymers were repeated with a polymerization temperature of 140 °C for the second blocks resulting in full incorporation of the PhOx monomer (polymers 5 and 10). The measured GPC data show a similar trend as the theoretical molecular weights, but they are systematically lower due to the lower monomer incorporation (from <sup>1</sup>H-NMR spectroscopy). Moreover, the molecular weight of the MeOx containing polymers 2, 4 and 5 is underestimated due to column interactions.
Table 3.4. Structural characterization of the synthesized block copolymers.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Monomer A</th>
<th>Monomer B</th>
<th>DP_{A,th}</th>
<th>DP_{B,th}</th>
<th>DP_{A,NMR}</th>
<th>DP_{B,NMR}</th>
<th>M_{n,AB,th}</th>
<th>M_{n,AB,GPC}</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOx</td>
<td>NonOx</td>
<td>70</td>
<td>15</td>
<td>64</td>
<td>15</td>
<td>8950</td>
<td>4600 (^{a})</td>
<td>1.20</td>
</tr>
<tr>
<td>2</td>
<td>MeOx</td>
<td>NonOx</td>
<td>25</td>
<td>5</td>
<td>23</td>
<td>4</td>
<td>3150</td>
<td>1370 ± 60</td>
<td>1.29</td>
</tr>
<tr>
<td>3</td>
<td>MeOx</td>
<td>PhOx</td>
<td>70</td>
<td>15</td>
<td>64</td>
<td>2</td>
<td>8200</td>
<td>5710 ± 210 (^{a})</td>
<td>1.15</td>
</tr>
<tr>
<td>4</td>
<td>MeOx</td>
<td>PhOx</td>
<td>25</td>
<td>5</td>
<td>22</td>
<td>2</td>
<td>2900</td>
<td>1100 ± 10</td>
<td>1.27</td>
</tr>
<tr>
<td>5</td>
<td>MeOx</td>
<td>PhOx</td>
<td>25</td>
<td>5</td>
<td>21</td>
<td>5</td>
<td>2900</td>
<td>1900 ± 60</td>
<td>1.30</td>
</tr>
<tr>
<td>6</td>
<td>EtOx</td>
<td>NonOx</td>
<td>60</td>
<td>15</td>
<td>52</td>
<td>13</td>
<td>9000</td>
<td>6400 ± 160</td>
<td>1.10</td>
</tr>
<tr>
<td>7</td>
<td>EtOx</td>
<td>NonOx</td>
<td>25</td>
<td>5</td>
<td>27</td>
<td>4</td>
<td>3500</td>
<td>2950 ± 70</td>
<td>1.14</td>
</tr>
<tr>
<td>8</td>
<td>EtOx</td>
<td>PhOx</td>
<td>60</td>
<td>15</td>
<td>52</td>
<td>3</td>
<td>8250</td>
<td>5330 ± 190</td>
<td>1.13</td>
</tr>
<tr>
<td>9</td>
<td>EtOx</td>
<td>PhOx</td>
<td>25</td>
<td>5</td>
<td>21</td>
<td>1</td>
<td>3250</td>
<td>2400 ± 40</td>
<td>1.15</td>
</tr>
<tr>
<td>10</td>
<td>EtOx</td>
<td>PhOx</td>
<td>25</td>
<td>5</td>
<td>21</td>
<td>4</td>
<td>3250</td>
<td>3000 ± 40</td>
<td>1.15</td>
</tr>
</tbody>
</table>

\(^{a}\) Measured with DMF (with 5 mM NH\(_4\)PF\(_6\)) as eluent. All others with CHCl\(_3\):NEt\(_3\):2-PrOH (94:4:2) as eluent.

3.6.4 Properties of the synthesized block copolymers

The thermal properties (glass transition temperature \(T_g\) and melting temperature \(T_m\)) and the surface properties of the synthesized copolymers were determined to investigate the effect of the different monomers and the length of the polymer on the final properties. The thermal properties were measured by differential scanning calorimetry (DSC) and the surface energy was calculated from contact angle measurements (see experimental part). The obtained bulk \(T_g\)'s and \(T_m\)'s and the surface energies (SE's) of spincoast films (non-annealed) are summarized in Table 3.5 and, for comparison, the literature data for \(T_g\), \(T_m\)\(^{71}\) and SE\(^{62}\) of the four homopolymers pMeOx, pEtOx, pNonOx and pPhOx are also included. In addition, the polymer composition determined by \(^1\)H-NMR spectroscopy and the weight percent of hydrophobic monomer are also summarized (Table 3.5). The pNonOx shows rather different properties than the other three homopolymers; the pNonOx does not show a glass transition in DSC and it is the only polymer that exhibits a melting point. In addition, a significantly lower SE is observed for pNonOx when compared to the other three homopolymers due to preferential orientation of the nonyl chains towards the surface (cf. the discussion in section 3.4)\(^{62,64}\). Therefore, a large influence on thermal and surface properties is expected upon incorporation of NonOx as second block. Indeed, the two block copolymers 1 and 6 that contain a large NonOx segment are the only block copolymers that revealed a melting point. The melting point of the p(MeOx-b-NonOx) 1 (142 °C) is much closer to the pNonOx melting point (147 °C) than the p(EtOx-b-NonOx) 6 melting point (122 °C). This difference can be explained by more effective phase separation in the case of the p(MeOx-b-NonOx) resulting in larger crystalline pNonOx domains and partial mixing of the two blocks in the case of p(EtOx-b-NonOx). This hypothesis is further confirmed by the glass transition temperatures: The \(T_g\) of 1 is close to the \(T_g\) of pMeOx, whereas the \(T_g\) of 6 is lower than the \(T_g\) of pEtOx. Furthermore, the more effective phase separation for p(MeOx-b-NonOx) 1 when compared to p(EtOx-b-NonOx) 6 is also expressed in the surface energy of thin films: The MeOx containing block copolymer 1 revealed a significantly lower SE than the EtOx containing block copolymer 6; whereas, the pMeOx and pEtOx exhibit similar SE’s. The observed SE’s for the NonOx containing block copolymers are different from the literature values reported for similar block copolymers of 2-undecyl-2-oxazoline (40 w% and higher) and MeOx\(^{72}\) or EtOx\(^{73}\) which were all 22 mN/m. However, this difference can be explained by the fact that the literature data were recorded after annealing the block copolymer films and thus the undecyl chains could more easily orient towards the surface.
Table 3.5. Thermal properties and surface energies of the synthesized block copolymers.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Monomer A</th>
<th>Monomer B</th>
<th>DP&lt;sub&gt;A,NMR&lt;/sub&gt;</th>
<th>DP&lt;sub&gt;B,NMR&lt;/sub&gt;</th>
<th>w% B</th>
<th>T&lt;sub&gt;g,DSC&lt;/sub&gt;</th>
<th>T&lt;sub&gt;m,DSC&lt;/sub&gt;</th>
<th>Surface energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOx</td>
<td>NonOx</td>
<td>64</td>
<td>15</td>
<td>35.2</td>
<td>75 °C</td>
<td>142 °C</td>
<td>34.9 ± 0.3</td>
</tr>
<tr>
<td>2</td>
<td>MeOx</td>
<td>NonOx</td>
<td>23</td>
<td>4</td>
<td>28.7</td>
<td>71 °C</td>
<td>-</td>
<td>29.9 ± 0.4</td>
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<tr>
<td>3</td>
<td>MeOx</td>
<td>PhOx</td>
<td>64</td>
<td>2</td>
<td>5.1</td>
<td>76 °C</td>
<td>-</td>
<td>43.7 ± 0.5</td>
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<tr>
<td>4</td>
<td>MeOx</td>
<td>PhOx</td>
<td>22</td>
<td>2</td>
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<td>-</td>
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<td>5</td>
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<td>21</td>
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<td>-</td>
<td>42.3 ± 0.5</td>
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<td>13</td>
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<td>122 °C</td>
<td>43.3 ± 0.2</td>
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<td>27</td>
<td>4</td>
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<td>-</td>
<td>38.7 ± 0.5</td>
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<td>PhOx</td>
<td>52</td>
<td>3</td>
<td>9.1</td>
<td>58 °C</td>
<td>-</td>
<td>47.1 ± 0.2</td>
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<tr>
<td>9</td>
<td>EtOx</td>
<td>PhOx</td>
<td>21</td>
<td>1</td>
<td>7.6</td>
<td>58 °C</td>
<td>-</td>
<td>45.0 ± 0.4</td>
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<tr>
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<td>PhOx</td>
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<td>pMeOx&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>79 °C</td>
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<td>-</td>
<td>100</td>
<td>-</td>
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<td>-</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>107 °C</td>
<td>45.9</td>
</tr>
</tbody>
</table>

* The properties of the homopolymers will be discussed in chapter 5.

The different phase separation behavior of polymers 1 and 6 was further investigated by atomic force microscopy (AFM). Topography (left) and phase (right) images were recorded from spincoated polymer films in tapping mode as depicted in Figure 3.32. The p(MeOx-<em>b</em>-NonOx)<sub>1</sub> showed large features in the topography image and a more pronounced contrast in the phase image (Figure 3.32, top images) indicating phase separation. In contrast, the p(EtOx-<em>b</em>-pNonOx)<sub>6</sub> showed a smooth film with only little phase contrast demonstrating the absence of significant phase separation (Figure 3.32, bottom images). These results also emphasize the difference between these MeOx (1) and EtOx (2) containing block copolymers.

*Figure 3.32. AFM topography (left) and phase (right) images of the p(MeOx<sub>70</sub>-<em>b</em>-NonOx<sub>15</sub>) 1 (top) and p(EtOx<sub>60</sub>-<em>b</em>-NonOx<sub>15</sub>) 6 (bottom) block copolymers.*
Chapter 3

Apparently, the more flexible ethyl side-chains of the EtOx are better compatible with the long flexible nonyl side-chains than the short rigid methyl side-groups of the MeOx. When a shorter NonOx segment is built-in while retaining the 30 w% fraction of NonOx (polymers 2 and 7), amorphous polymers are obtained: The small number of NonOx units per chain cannot orient into a crystalline phase. However, the NonOx has a similar effect on the T\text{g} of the shorter polymers 2 (T\text{g} close to the T\text{g} of pMeOx) and 7 (T\text{g} lower than the T\text{g} of pEtOx) as it has on the T\text{g} of the longer block copolymers 1 and 6. Moreover, the shorter block copolymers 2 and 7 show lower SE’s than the longer copolymers 1 and 6 even though they have a lower NonOx content. This difference is most likely due to the higher mobility of the shorter polymers that facilitate the orientation of the NonOx side chains to the surface. The block copolymers with PhOx as second block (3-5 and 8-10) do not show such clear trends as the NonOx containing block copolymers. For all p(EtOx-b-PhOx) block copolymers 8-10 both T\text{g} and SE are comparable with pEtOx. However, due to the small differences between pEtOx and pPhOx and due to the low number of PhOx units these results cannot conclusively be interpreted as phase separation but they are a first indication in this direction. The p(MeOx-b-PhOx) block copolymers 3-5 show all similar SE’s, but the T\text{g}’s are lower for the shorter copolymers 4 and 5 as was also observed for the short p(MeOx-b-NonOx) 2. These lower T\text{g}’s are most likely due to the short pMeOx segment, which might be in the range where the T\text{g} depends on the molecular weight as it has been shown for polystyrene by Gibbs. However, this effect was not observed for the short EtOx containing block copolymers. As a result, no clear conclusions can be drawn about possible phase separation for the p(MeOx-b-PhOx) and the p(EtOx-b-PhOx) block copolymers on the basis of the obtained results.

3.7 Conclusions

The cationic ring-opening polymerization of 2-oxazolines is a well-known and understood polymerization process. This polymerization method can be applied for the synthesis of various well-defined (block) copolymers. However, the major drawback of the cationic polymerization of 2-oxazolines are the long reaction times.

To accelerate the polymerization of EtOx initiated by BB in DMAc, polymerization temperatures from 50 to 130 °C were screened utilizing an automated synthesizer equipped with individually heatable reactors. Linear first order kinetics were observed for all investigated temperatures indicating a constant concentration of growing species. The activation energy was determined to be 68.7 kJ/mol. However, GPC analysis revealed no significant polymerization below 90 °C, living polymerizations at 90 °C and 100 °C and the occurrence of side-reactions above 100 °C. The optimal polymerization temperature of 100 °C was successfully applied for the synthesis of well-defined pEtOx’s with different molecular weights. Subsequently, the cationic polymerization of the less reactive PhOx was also optimized with regard to the polymerization temperature. The BB initiated reactions did not show significant polymerization at temperatures from 80 to 150 °C. Therefore, the PhOx polymerizations were investigated with MeOTs as initiator in DMAc. Kinetic investigations of the polymerizations initiated with MeOTs revealed an optimal polymerization temperature of 130 °C and an activation energy of 81.3 kJ/mol.

Moreover, a kinetic screening of combinations of four different monomers (MeOx, EtOx, NonOx and PhOx), four initiators (BB, MeOTf, MeOTs and MeI), four different [M]/[I] ratios (20, 40, 60 and 80) and two temperatures (80 and 100 °C) was performed. To cover this large parameter space (128 combinations), an ASW2000 synthesizer was applied to perform the
Parallel investigations on the cationic ring-opening polymerization of 2-oxazolines

reactions in parallel (16 per run), whereby samples were taken automatically from the reaction mixtures opening the way for continuous investigation of the polymerization kinetics throughout the complete reaction time (16-20 hours). The found order in polymerization rate for the different initiators was in agreement with the decreasing nucleophilicity: MeOTf > MeOTs > MeI > BB, whereby the MeI and BB appeared to be the more robust. In addition, it was demonstrated that the polymerizations were controlled at both temperatures (80 and 100 ºC). The order of polymerization rates for the different monomers was found to be: MeOx > EtOx ≅ NonOx >> PhOx. Based on these kinetic insights it was expected that the copolymerization of EtOx and NonOx would lead to truly random copolymers; whereas, the copolymerization of MeOx with EtOx or NonOx would lead to gradient copolymers.

To proof this hypothesis, three series of random copolymers consisting of MeOx:EtOx, MeOx:NonOx and EtOx:NonOx were synthesized in parallel. During these automated polymerizations, samples were withdrawn from the reaction mixtures to investigate the polymerization kinetics and the copolymerization parameters. The reactivity ratios could be determined for both the initial and final stages of the polymerizations revealing indeed the predicted formation of random (EtOx:NonOx) or gradient (MeOx:NonOx and MeOx:EtOx) copolymers. These results clearly demonstrate the added value of the automated kinetic screening for the prediction of copolymer compositions. Contact angle measurements on thin films of the synthesized MeOx:NonOx and MeOx:EtOx copolymers revealed similar trends for both random and gradient copolymers; however, these copolymers showed significant different surface energies compared to a block copolymer or a polymer blend. Moreover, the glass transition and melting temperatures changed in a similar manner within both MeOx:NonOx and MeOx:EtOx copolymer series. More importantly, it was demonstrated that the application of a high-throughput workflow for the synthesis and screening of a library of copolymers can result in both fundamental and application directed knowledge at the same time.

Another part of this study focused on the concentration optimization of the EtOx polymerization since higher concentrations would lead to shorter polymerization times. An optimal monomer concentration between 4 M and 7 M was established in a high-throughput manner for the living cationic ring-opening polymerization of EtOx initiated with BB in DMAc at 100 ºC. At 8 M, the polymerization was finished within two hours, which is a tremendous acceleration when compared to the 20 hours at 1 M. However, to further investigate the mechanistic details of the polymerizations at different concentrations additional ¹H-NMR spectroscopic investigations were required. It could be concluded that due to the occurrence of side reactions (chain transfer reactions) the control over the polymerizations was lost at low monomer concentration ([M] < 4 M). However, the exact mechanism could not be elucidated from the NMR monitoring nor from additional GC-MS studies. The resulting optimal concentration range was utilized for the preparation of higher molecular weight (> 10,000 Dalton) pEtOx’s. Polymers up to a molecular weight up to 25,000 Dalton were successfully synthesized in a controlled manner (PDI values below 1.3).

The living cationic ring-opening polymerization of EtOx (15 min to completion) and PhOx (45 min) in acetonitrile could also be accelerated using conventional heating under pressure conditions with MeOTs as initiator. Moreover, the pressure polymerizations proceeded in a living manner resulting in polymers with narrow molecular weight distributions. The livingness of the EtOx polymerization was further demonstrated by the possibility of chain extension. The pressure polymerization procedure was applied for the synthesis of a series of block copolymers with a pMeOx or pEtOx first block (~ 70 w%) and a pNonOx or pPhOx
second block (~ 30 w%). Ten different block copolymers were successfully synthesized in a reproducible manner (polymerizations were performed in quadruplicate in an automated synthesizer). The thermal ($T_g$ and $T_m$) and surface (surface energy) properties of these block copolymers were determined by DSC and contact angle measurements, respectively. From these analyses, it could be concluded that p(MeOx-$b$-NonOx) phase separates to a large extend, whereas p(EtOx-$b$-NonOx) does not exhibit such clear phase separation. This difference in phase separation was further confirmed by topography and phase images determined by AFM. For the PhOx containing block copolymers, no definite conclusions could be drawn about possible phase separation.

3.8 Experimental part

Materials and instrumentation

Solvents were purchased from Biosolve Ltd. except for $N,N$-dimethylacetamide (DMAc; Aldrich). Acetonitrile (size 3 Å), DMAc (size 4 Å) and DMAc-$d_9$ (Deutero GmbH) were dried over molecular sieves. All other solvents were used without further purification. MeOx, EtOx (Aldrich), PhOx and NonOx (donated by Henkel) were distilled over barium oxide (BaO) and stored under argon. Benzyl bromide (Acros Organics), methyl tosylate (Aldrich) and methyl iodide (Aldrich) were distilled over P$_2$O$_5$ and stored under argon. Methyl triflate (Acros Organics) was distilled without drying agent. $^1$H-NMR spectra were recorded on a Varian AM-400 spectrometer or a Varian Gemini 300 spectrometer. NMR monitoring of the polymerizations was performed on a Varian Inova 500 spectrometer, whereby the chemical shifts are given in ppm relative to TMS.

Gel Permeation Chromatography (GPC) was measured on a Shimadzu system with a SCL-10A system controller, a LC-10AD pump, a RID-6A refractive index detector and a PLgel 5 µm Mixed-D column, whereby 1% triethylamine in THF (or chloroform:triethylamine:2-propanol (94:4:2)) was used as eluent at a flow rate of 1 mL/min and the column oven set to 50 ºC. Molecular weights were calculated against PS or PMMA standards. Optimized GPC traces were obtained on a Waters system with a 1515 pump, a 2414 refractive index detector and a Waters Styragel HT4 column utilizing 4% triethylamine in chloroform as eluent (flow rate of 2 mL/min; column oven at 50 ºC. For the MeOx containing block copolymers and the higher molecular weight pEtOx’s, the eluent was changed to DMF (5 mM NH$_4$PF$_6$) at a flow rate of 0.5 mL/min. Molecular weights were calculated using PS or PEG standards.

GC measurements were performed on an Interscience Trace GC with a Trace Column RTX-5 connected to a PAL autosampler. For the injection of polymerization mixtures, a special Interscience liner with additional glass wool was used. GC-MS analysis was performed on a Shimadzu GC-MS-QP5000, the mass values are reported as mass/charge ratio ($m/z$).

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netzsch under a nitrogen atmosphere with heating and cooling rates of 40 K·min$^{-1}$ (three measurements per sample after an initial first heating run that was not considered for the subsequent calculations); melting points were measured with a heating rate of 10 K·min$^{-1}$ and a cooling rate of 40 K·min$^{-1}$.

Contact angle measurements were performed on polymer films that were prepared by spincoating of chloroform solutions (20 mg/mL) of the polymers on pre-cleaned microscopy slides at 1000 rpm during 90 seconds using a WS-400/500 series spin coater from Laurell Technologies Corporation. An OCA30 optical contact angle measuring instrument from Dataphysics was used to determine the contact angles of both diiodomethane and ethyleneglycol as apolar and polar testliquids, respectively. Prior to all the reactions, the reaction vessels were heated to 120 ºC, evacuated at 10 mbar for 15 minutes and subsequently filled with argon. This procedure was repeated four times to create an inert atmosphere. In addition, 1.1 bar argon pressure was applied to the reaction blocks and 1.5 bar argon pressure was applied to flush the glove-box of the automated synthesizer.

Automated parallel temperature optimization for the cationic ring-opening polymerization of EtOx

Reactions were performed on an ASW2000 synthesizer equipped with individually heatable reactors. Solutions of EtOx (1.00 g, 10.02 mmol) in 7.0 mL DMAc (14 times) as well as acetonitrile (2 times) and solutions of benzyl bromide (28.8 mg, 0.168 mmol) in 1 mL DMAc (14 times) as well as acetonitrile (2 times) were transferred into the 13 mL reaction vessels while vortexing at 600 rpm. The
mixtures were heated (130 °C, 2 × 120 °C, 110 °C, 2 × 100 °C, 2 × 90 °C, 2 × 80 °C, 70 °C, 60 °C or 50 °C in DMAc and 2 × 80 °C in acetonitrile) and vortexed at 600 rpm for 16 hours with the reflux condensers set to −5 °C. From each reaction vessel ten samples (250 µL at 0, 30, 60, 120, 240, 360, 480, 600, 780 and 960 minutes) were taken to 1 mL vials filled with a THF solution containing 1% water (750 µL). From these samples both GC (offline) and GPC (online) were measured.

Automated parallel polymerisations with different monomer/initiator ratios
Reactions were performed on an ASW2000 robot equipped with 16 parallel 13 mL glass reactors. Solutions of EtOx (150 mg, 1.52 mmol) in 370 µL DMAc and solutions of benzyl bromide (varying amounts) in 500 µL DMAc were transferred into the 13 mL reaction vessels while vortexing at 600 rpm. The mixtures were heated to 100 °C and vortexed at 600 rpm for 24 hours with the reflux condensers set to −5 °C. Subsequently, solutions of piperidine (5 eq. to initiator) in 129 µL DMAc were added to terminate the reactions and the mixtures were vortexed (600 rpm) another 4 hours at 80 ºC under reflux. The resulting polymer solutions were then precipitated by adding them dropwise to 8.8 mL diethyl ether, which was dispensed in 13 mL reaction vessels. For this precipitation the reaction vessels were cooled to −15 ºC and the vortex speed was set to 400 rpm. After vortexing for 30 minutes at −20 ºC, the vortex was switched off. Ten minutes later (after the sedimentation of the polymers), 7.0 mL of diethyl ether was removed from each vessel by the needle and the remaining diethyl ether was evaporated under reduced pressure (40 ºC, 10 mbar, 400 rpm). The polymers were washed two times by adding diethyl ether (9.5 mL) into each reaction vessel and removing it again by the needle (8 mL) as well as by evaporation. The obtained polymers were dissolved in 2.0 mL diethyl ether, which was dispensed in 13 mL reaction vessels to result in 8 mL reaction mixtures with a [M]/[I] ratio of 7.0. The vortex speed was set to 400 rpm. The mixtures were heated (130 ºC, 120 ºC, 110 ºC, 2 × 100 ºC, 2 × 90 ºC, 2 × 80 ºC, 70 ºC, 60 ºC or 50 ºC in DMAc and 2 × 80 ºC in acetonitrile) and vortexed at 600 rpm for 16 hours with the reflux condensers set to −5 ºC. From each reaction vessel ten samples (250 µL at 0, 30, 60, 120, 240, 360, 480, 600, 780 and 960 minutes) were taken to 1 mL vials filled with a THF solution containing 1% water (750 µL). From these samples both GC (offline) and GPC (online) were measured.

Automated parallel temperature optimization for the cationic ring-opening polymerization of PhOx
Reactions were performed on the Accelerator SLT100 robot with individually heatable reactors. PhOx (10.0 mmol in 7.0 mL DMAc and initiator (BB or MeOTs; 0.17 mmol in 1.0 mL DMAc) were transferred into the 13 mL reaction vessels resulting in 8 mL reaction mixtures with a [M]/[I] ratio of 60. After sampling 100 µL aliquots to 500 µL DMAc were transferred into the 13 mL reaction vessels while vortexing at 600 rpm for 16 hours with the reflux condensers set to −5 ºC. From each reaction vessel ten samples (250 µL at 0, 30, 50, 90, 150, 290, 410, 600, 790 and 980 minutes) were taken to 1 mL vials prefilled with a chloroform solution saturated with water (750 µL). These samples were used for GC analysis. Moreover, the final samples (taken after 980 minutes polymerization time) were also used for GPC investigations.

Automated parallel screening of monomer/initiator combinations
Reactions were performed on an ASW2000 robot equipped with 16 parallel 13 mL glass reactors. Solutions of 2-oxazoline monomer in DMAc and of the four different initiators (BB, MeI, MeOTs and MeOTf) in DMAc were transferred into the 13 mL reaction vessels at different ratios resulting in 3.2 mL polymerization mixtures with 1.25 M total monomer concentration and a monomer to initiator ratio of 60. After sampling 100 µL aliquots to 2 mL vials prefilled with 1.0 mL of chloroform saturated with water, the mixtures were heated to

Random copolymerizations of 2-oxazolines
Reactions were performed on an ASW2000 robot equipped with 16 parallel 13 mL glass reactors. During the polymerizations, the temperature of the cold-finger reflux condensers was set to −5 ºC. Stock solutions of the 2-oxazoline monomers and BB in DMAc and DMAc were transferred into the 13 mL reaction vessels at different ratios resulting in 3.2 mL polymerization mixtures with 1.25 M total monomer concentration and a monomer to initiator ratio of 60. After sampling 100 µL aliquots to 2 mL vials prefilled with 1.0 mL of chloroform saturated with water, the mixtures were heated to
100 ºC and vortexed at 600 rpm for 20 hours. During the 20 hours polymerization time, samples (100 µL aliquots) were taken in time to 2 mL vials prefilled with 1.0 mL chloroform saturated with water. Subsequently, water was added into the reaction vessels to terminate the reactions and the final polymerization mixtures were collected in sample vials.

**Concentration optimization for the polymerization of EtOx in DMAc**

Reactions were performed on an ASW2000 synthesizer with 16 parallel 13 mL glass reactors. EtOx (pure, varying amounts), DMAc (varying amounts) and a solution of BB in DMAc (0.166 mg/mL, varying amounts) were transferred into the 13 mL reaction vessels resulting in 3.2 mL reaction mixtures with different concentrations, but with the same [M]/[I] ratio of 60. The mixtures were heated to 100 ºC and vortexed at 600 rpm with the reflux condensers set to –5 ºC. At suitable time intervals, samples were taken from the reaction vessels into 2 mL vials (prefilled with chloroform saturated with water in order to quench the polymerization) for the subsequent GC and GPC characterization.

The experiments aiming for different molecular weight pEtOx’s were performed in a similar manner utilizing a 0.113 mg/mL stock solution of BB in DMAc and the resulting reaction mixtures were 5 mL in volume (with 4 M monomer concentration).

**Monitoring of the EtOx polymerizations at 1 M and 8 M in the NMR spectrometer**

BB (8 M: 22.8 mg; 1 M: 2.8 mg), EtOx (8 M: 792 mg; 1 M: 99.1 mg) and DMAc-d$_9$ (8 M: 200 µL; 1 M: 900 µL) were weighed in dried vials (5 mL). From those polymerization mixtures, 0.5 mL was transferred into the NMR tube. The polymerization was started by insertion into the NMR probe that was preheated to 100 ºC. At suitable time intervals, $^1$H-NMR spectra were recorded to monitor the polymerization process. The monomer conversion was calculated from the integrals of both the monomer and the polymer signals. The initiation process was monitored by integrating the benzyl bromide signals. The amount of cationic species was determined from the ratio between the CH$_2$ signals of the oxazolinium species and the aromatic initiator signals.

**GC-MS model reactions**

The model reactions in DMAc and ODCB were performed by heating 1 mL solvent with 5 drops of both EtOx and BB for 1 hour at 100 ºC. Samples of these mixtures were analyzed by GC-MS.

**Parallel EtOx and PhOx pressure polymerizations**

Reactions were performed on an Accelerator SLT100 robot system equipped with pressure reactors. EtOx: Four reactors were filled with EtOx (1.27 g, 12.8 mmol) and 1.9 mL of a MeOTs stock solution (0.11 M; 0.70 g MeOTs in 25.9 g acetonitrile), resulting in 3.2 mL reaction mixtures with 4 M EtOx (40 w%) and a monomer to initiator ratio of 60. From these reaction mixtures, zero time GC samples (75 µL aliquots) were taken and stored into 2 mL vials that were prefilled with chloroform saturated with water (1 mL). After applying a pressure of 15 bar to the reactors, the polymerization mixtures were heated to 120 ºC or 140 ºC for a predefined time. Subsequently, the reactors were cooled to 60 ºC, the pressure was released and GC samples were withdrawn from the reaction mixtures (75 µL aliquots). The final polymerization mixtures were transferred into 8 mL vials that were prefilled with chloroform saturated with water (1 mL). Four different reaction times were investigated for 120 ºC (10, 20, 30 and 40 minutes) and 140 ºC (4, 8, 12 and 16 minutes) utilizing this procedure. All final mixtures were analyzed by GC and GPC. The experiments at 120 ºC were performed with two different heating rates (10 ºC / min and 30 ºC /min), whereas the experiments at 140 ºC were performed with 30 ºC / min.

PhOx: Two reactors were filled with PhOx (1.1 g, 7.5 mmol) and 1.4 mL of a MeOTs stock solution (0.091 M; 0.41 g MeOTs in 19 g acetonitrile), resulting in 2.5 mL reaction mixtures with 3 M PhOx (45 w%) and a monomer to initiator ratio of 60. After applying a pressure of 15 bar to the reactors, the polymerization mixtures were heated to 120 ºC or 140 ºC for a predefined time (for these polymerizations the temperature was controlled via a PT-100 temperature probe in a reference cell filled with PhOx). Subsequently, the reactors were cooled to 60 ºC, the pressure was released and the polymerizations were quenched with water (100 µL). This procedure was repeated for four different reaction times (120 ºC: 15, 25, 95 and 155 minutes; 140 ºC: 15, 25, 35 and 50 minutes) after which all mixtures were characterized by $^1$H-NMR and GPC. As a consequence, the first quenched polymerization mixtures were heated three additional times to 120 ºC or 140 ºC before analysis.
Parallel chain-extension and block copolymerizations under pressure

The chain extension experiments and block copolymerizations were performed in a similar manner as the previously described homopolymerizations utilizing the Accelerator SLT100 synthesizer equipped with pressure reactors. The block copolymerizations are described in detail in this section. The chain extension experiments were performed in the same way with EtOx as both first and second monomer. Each block copolymerization was performed four times in parallel at a 2.5 gram scale. After polymerization of the first block with 4 M monomer concentration at 120 °C (1, 3, 6 and 8: 40 minutes; 2, 4, 5, 7, 9 and 10: 15 minutes), the reactors were cooled to 60 °C, samples (75 µL aliquots) were taken into 2 mL vials (prefilled with 1 mL chloroform saturated with water) and the second monomer was added. For the longer block copolymers 1, 3, 6 and 8, a stock solution of the second monomer in acetonitrile was added (NonOx: 2 M; PhOx: 3 M), whereas the second monomer was added without dilution for the other block copolymers. The second block was polymerized at 120 °C as well (1, 3, 6 and 8: 30 minutes; 2, 4, 7 and 9: 15 minutes), except for block copolymers 5 and 10 (140 °C; 15 minutes). For work-up, all four identical parallel polymerizations were added together and diluted with chloroform (50 mL). This chloroform solution was poured into n-hexane (250 mL) and the product was obtained as white solid upon evaporation to dryness.

3.9 References and notes

(20) J. E. McAlvin, S. B. Scott, C. L. Fraser, Macromolecules, 2000, 33, 6953-6964.
(47) The monomer conversion was calculated from the ratio of monomer to solvent, whereby the solvent was applied as internal standard.
(53) The monomer conversion was calculated using the equation:
\[ \text{ln}\{(\text{polymer integral + monomer integral}) / (\text{monomer integral})\}.\]
(54) The initiation rate (\(k_i\)) was calculated utilizing the following equation:
\[ t_M k_{i} = I_{i} \cdot [M] \cdot t \]
(55) The \(k_{i,p}\) was calculated utilizing the following equation:
\[ \text{ln}\{I_{i,p}\} = k_{i,p} \cdot [M] \cdot t \]
(56) The percentage of oxazolinium species was calculated from the integrals of the oxazolinium and the aromatic part of the initiator.
(58) Conversion was calculated from the difference between the \(t_0\) and \(t_{end}\) GC samples, whereby the acetonitrile was taken as internal standard.
(59) The thermal properties of the homopolymers will be further discussed in chapter 5.
Microwave-assisted polymerization of 2-oxazolines

Abstract
During the last few decades, microwave irradiation has been established as a well-known tool in organic synthesis. Microwave irradiation provides fast non-contact heating of reaction mixtures and has lead to higher yields and increased reaction rates in many synthetic processes. Moreover, the development of single-mode microwave synthesizers tailor-made for organic synthesis has lead to increased reproducibility and higher safety levels. Although many examples of microwave irradiation are known in organic synthesis, only few examples on microwave polymerizations have been reported. More specifically, the effect of microwave irradiation on living/controlled polymerization techniques is almost completely unexplored. Therefore, this chapter describes our investigations on the cationic ring-opening polymerization of 2-oxazolines under microwave irradiation, whereby it was attempted to accelerate the cationic polymerizations by going to superheated microwave conditions. Moreover, the presence or absence of so-called non-thermal microwave effects (specific absorption of microwave power by the ionic intermediates) was evaluated by comparison with conventionally (super)heated polymerizations. In addition, the effect of increasing the monomer concentration on the livingness of the microwave-assisted polymerizations was investigated and the maximum molecular weight that could be reached in a living manner was determined as well. Furthermore, the microwave-assisted polymerization of a series of linear 2-alkyl-2-oxazolines was investigated. The effect of side-chain length on the polymer properties will be discussed. The polymerization of a soy-based 2-oxazoline monomer (SoyOx) was also performed with microwave heating. This monomer provides access to green chemistry and the double bonds resulting from the soy fatty acids offer the possibility of cross-linking the resulting polymers. Besides polymerization of all these different 2-oxazoline monomers, the microwave polymerization of 2-ethyl-2-oxazoline utilizing a tetrafunctional porphyrin-based initiator will be reported. Both the synthesis of this initiator and the subsequent polymerization will be discussed.

Chapter 4

4.1 Introduction

The influence of microwave irradiation on chemical reactions is of great current interest in virtually every field of chemical synthesis. Microwave energy consists of an electric field and a magnetic field. The magnetic field does not interact with the molecules, whereas the electric field interacts with dipole moments or ions in a reaction mixture. The microwave energy is in the range of the rotational energy of a molecule. As a result, the dipole moment of the molecules will try to orient to the microwaves resulting in a rotation of the molecule which is nothing else than heat.\(^1\) Subsequently, the heat will be dissipated through the reaction mixture by collision with other molecules. The main advantage of microwave heating over ‘conventional’ (conductive) heating is the fast direct heating of the reaction mixture. Secondly, the heat differences through the reaction mixture are less prominent as with conductive heating where the walls of the reactions vessel will be warmer then the interior.

Prominent examples from organic and pharmaceutical research have successfully shown that the utilization of microwave heating can lead to improved reaction rates, higher yields and different selectivities compared to conventional heating.\(^2-5\) As an additional advantage, reactions can be performed in reduced solvent amounts (green chemistry). However, performing microwave-assisted reactions in domestic (as used in the kitchen) microwave ovens can be accompanied by hazardous explosions or fires. This is in particular true for exothermic reactions as well as reactions with an increasing volume (formation of gaseous by-products). These safety issues have been overcome by the recent introduction of commercially microwave synthesizers.\(^6-8\) Most of the commercial microwave ovens for chemical synthesis irradiate the sample with single-mode microwaves facilitating quick heating and good reproducibility. In multi-mode microwave ovens, the different modes can interact positively or negatively resulting in hot spots and cold spots. For chemical synthesis, multi-mode reactors are normally equipped with turning tables and multiple microwave sources to average out these hot spots and cold spots. In addition, the microwave synthesizers monitor the temperature and pressure inside the capped reaction vessels providing accurate control of the reaction conditions. The capped reaction vessels facilitate pressure (up to 20 bar) and high-temperature (up to 250 °C) synthesis. Recently, a microwave synthesizer that allows temperatures up to 300 °C and pressures up to 120 bar became available too.\(^9\)

Despite the fact that (single-mode) microwave-assisted synthesis is quite common in organic synthesis nowadays, its application in polymer chemistry is only in its infancy.\(^10,11\) The effect of microwave irradiation has been mainly investigated for step-growth polymerizations,\(^12,13\) ring-opening polymerizations,\(^14,15\) and for both free and controlled radical polymerizations.\(^16,17\) However, many of the reported investigations were performed utilizing domestic microwave ovens without full temperature and pressure control making the reproducibility doubtful.\(^11\) In addition, the investigations on controlled polymerization techniques are limited, which is surprising since these are normally the slow polymerization techniques that might benefit tremendously from the fast non-contact heating.

\[
\text{Scheme 4.1. Schematic representation of the living cationic polymerization of 2-oxazolines initiated with methyl tosylate and terminated with water.}
\]
In this chapter, our investigations on the effect of microwave irradiation on the living cationic ring-opening polymerization of 2-oxazolines are described (for an introduction to the polymerization of 2-oxazolines, see section 3.1). To accelerate these investigations the microwave synthesizer was incorporated in the high-throughput workflow (section 4.2). The polymerization of 2-oxazolines was investigated over a wide range of temperatures, whereby the livingness of the polymerization was examined (section 4.3). Moreover, the (non) existence of non-thermal microwave effects resulting from specific microwave absorption by the ionic intermediates was explored by comparison with ‘conventional’ model polymerizations. Besides these kinetic investigations, we also checked the limits of monomer concentration (section 4.4) and monomer to initiator ratio (section 4.5) that still resulted in a living polymerization under microwave irradiation. A series of novel monomers with linear aliphatic side-groups (section 4.6) and a ‘soy’-based side-group (section 4.7) were also polymerized under microwave irradiation. The effect of substituents on the polymer properties is described as well. Section 4.8 describes the utilization of a porphyrin-base tetrafunctional initiator for the polymerization of 2-ethyl-2-oxazoline.

4.2 Incorporation of microwave-assisted synthesis into a high-throughput workflow

Before discussing the results obtained for microwave-assisted polymer synthesis, first the incorporation of the microwave synthesizer into the high-throughput workflow is described. Even though the utilized microwave system comprises automated liquid handling, a more modular approach was needed to fulfill the different automated filling and sampling tasks that are required for high-throughput experimentation. In addition, for many reactions it is a prerequisite to handle the stock solutions under an inert atmosphere, which is not possible with the microwave synthesizer. Both the inert atmosphere and the flexible modular approach were found in an ASW2000 synthesis robot (section 2.2.1). The standard racks for the microwave synthesizer were programmed as customized rack in the ASW2000 software enabling the incorporation of the microwave vials into the previously established high-throughput workflow around the ASW2000 robot. The extended workflow with the microwave synthesizer is schematically depicted in Figure 4.1. All arrows going in or out the synthesis robot represent manual transportation of the racks to the appropriate equipment.

Figure 4.1. Schematic representation of the automated workflow including the microwave synthesizer and the peripheral characterization equipment. All arrows going outside or inside the ASW2000 synthesis robot (Synthesizer) represent manual steps.
The developed high-throughput workflow including microwave synthesis consists of three major steps as depicted by the numbers in Figure 4.1:

1. Automated preparation of the reaction mixtures by dispensing stock solutions with the ASW2000 (under inert atmosphere, if required);

2. Transportation of the microwave vials to the microwave synthesizer and subsequent polymerization of the reaction mixtures utilizing the microwave robot arm for automated sequential irradiation of the vials (quenching can also be done automatically if required). When all polymerizations are finished, the rack is placed back into the ASW200 robot.

3. Samples for e.g. gas chromatography (GC) and gel permeation chromatography (GPC) can be taken automatically from all polymerization mixtures. After manual transportation of the samples, the analyses are performed (most of the equipment operates with autosamplers).

In addition, the extended workflow provides the possibility to perform multi-step reactions utilizing combinations of microwave irradiation and conventional heating for the different reaction steps.

4.3 Kinetic investigations on the cationic polymerization of 2-oxazolines under microwave irradiation

Microwave irradiation is a quickly emerging tool in (organic) chemical synthesis.\textsuperscript{1-5} In the recent years, it has also been recognized by polymer chemists to accelerate and improve polymer synthesis. However, in the field of living/controlled polymerization techniques only a few examples, mainly dealing with controlled radical techniques, were reported. To extend the application of microwave irradiation to living ionic polymerization techniques, the cationic ring-opening polymerization of 2-oxazolines was investigated. In this section, the kinetic investigations on the cationic polymerization of 2-ethyl- (EtOx), 2-phenyl- (PhOx), 2-methyl- (MeOx) and 2-nonyl-2-oxazoline (NonOx) under microwave irradiation are described. All investigations were performed with a monomer to initiator ([M]/[I]) ratio of 60 and a monomer amount of around 40 w\%: [MeOx] = [EtOx] = 4 M; [PhOx] = 3 M and [NonOx] = 2 M. The resulting polymerization kinetics were evaluated in comparison with ‘conventionally’ heated polymerizations. For each of the monomers, the polymerization temperature was investigated. Moreover, the activation energies were determined and compared to the activation energies that have been reported for ‘conventional’ polymerizations to judge the (non) existence of non-thermal microwave effects.

4.3.1 Microwave polymerization of 2-ethyl-2-oxazoline

The microwave-assisted cationic ring opening polymerization of EtOx was first attempted in \(N,N\)-dimethylacetamide (DMAc) with benzyl bromide as initiator as shown in many of the studies described in chapter 3. However, when higher temperatures were applied under microwave irradiation, the polymerization was uncontrollable as it was also observed with ‘conventional’ heating (section 3.2.1). In a next step, polymerizations with methyl tosylate as initiator in acetonitrile (CH\textsubscript{3}CN) were attempted under microwave irradiation. To eliminate side-reactions and termination reactions, the EtOx was purified by distillation over barium
Microwave-assisted homopolymerizations of 2-oxazolines

oxide, CH₃CN was dried on molecular sieves and the methyl tosylate was distilled without drying agent. Even though the methyl tosylate (MeOTs) is supplied as viscous oil, it crystallized after distillation. From this bulk crystallization, single crystals suitable for X-ray analysis were obtained. The observed molecular structure (ORTEP-plot) and the packing diagram are displayed in Figure 4.2. The packing diagram shows that the molecules are packed in an optimal space filling order, without any π-stacking between the phenyl rings.

![Figure 4.2. ORTEP plot (50% probability, left) and packing diagram (right) of the structure of methyl tosylate. Hydrogen atoms are omitted for clarity.](image)

A first kinetic investigation on the cationic ring-opening polymerization of EtOx initiated with MeOTs demonstrated that, as expected, the speed of the polymerization increased with temperature. In contrast to conventional heating, the polymerization temperature is not limited to the boiling point of CH₃CN (82 °C) in the closed vessel microwave polymerizations. The polymerization was completed in 6 hours at 80 °C, which is the common polymerization temperature for ‘conventional’ heating. When performing the polymerization at 190 °C in the microwave synthesizer, the pressure inside the vial reached 11 bars and the reaction was completed within 1 minute. Consequently, the cationic polymerization of EtOx was accelerated by a factor of 350. Figure 4.3 depicts the polymerization mixtures after 10 minutes heating to different temperatures. The polymerizations at 80 to 100 °C and above 150 °C resulted in slightly yellowish mixtures (gray in Figure 4.3), whereas the temperature window in between resulted in perfectly colorless solutions. The yellow colors are indicative of some side-reactions. The polydispersity index (PDI) values were below 1.2 for all investigated reaction temperatures, but in the colorless window the PDI values were even lower, around 1.10. After the set polymerization temperature was reached, the microwave power remained constant throughout the polymerizations indicating that the microwave absorption of the monomer and the polymer is rather similar.

![Figure 4.3. Picture of the final polymerization mixtures after heating 10 minutes to different temperatures under microwave irradiation.](image)
Besides this first visual appearance of the polymerization mixtures, the polymerization kinetics were studied in detail at temperature from 80 to 180 °C as depicted in Figure 4.3. For each investigated temperature, six polymerizations were performed with different reaction times. After microwave heating the polymerization mixture for a certain time, the reaction vessel was cooled to 38 °C and water was automatically added to quench the polymerization. The monomer conversion was determined by GC and the polymer molecular weight (distribution) was determined by GPC with CHCl₃:NEt₃:2-PrOH (94:4:2) as eluent. The first order kinetic plot (Figure 4.4 left) revealed linear first order kinetics for all investigated temperatures indicating a constant amount of propagating species throughout the polymerization. In addition, the $M_n$ values increased linearly with monomer conversion and the obtained values were close to the theoretical molecular weights (Figure 4.4 right). In addition, the PDI’s remained below 1.20. Strikingly, the highest PDI’s and the largest deviation from the theoretical molecular weight were observed for the most common polymerization temperature of 80 °C. These kinetic investigations clearly demonstrate that the microwave-assisted cationic ring-opening polymerization of EtOx proceeds via a living mechanism at all investigated temperatures.

![Figure 4.4. Left: First order kinetic plot for the polymerization of EtOx in CH₃CN under microwave irradiation (closed symbols) and under conventional heating (pressure NMR-tube or refluxing BCN; open symbols). Right: Corresponding molecular weight ($M_n$) against conversion plot.](image)

To investigate whether the observed acceleration of the EtOx polymerization results from temperature effects or from non-thermal microwave effects, the polymerization was also investigated in a pressure NMR-tube at 140 °C in CD₃CN and in refluxing butyronitrile (BCN; boiling point of 117 °C as control experiment for the microwave polymerization at 120 °C) as depicted in Figure 4.4 left, open symbols. Both the pressurized and the non-pressurized control polymerizations with ‘conventional’ heating revealed polymerization rates very close to the observed microwave polymerization rates. In addition, the pressure polymerizations of EtOx (section 3.6.1) revealed polymerization rates similar to the polymerization rates observed under microwave irradiation. All these observations indicate that the acceleration of the EtOx polymerization results solely from thermal effects.

The reaction rates $k_p$ for the different temperatures were calculated from the slopes of the first order kinetic plot. The resulting Arrhenius plot (Figure 4.5 left) yields an activation energy of 73.4 kJ·mol⁻¹, which is in excellent agreement with literature values for the polymerization of EtOx that range from 68.7 to 80.0 kJ·mol⁻¹ (see also section 3.2.1). This similar value for the activation energy also indicates that for this polymerization system the microwave device only serves as an efficient heating device and that there are no intrinsic microwave effects.
Microwave-assisted homopolymerizations of 2-oxazolines

To further proof the living character of the microwave polymerization of EtOx and to demonstrate the possibility of synthesizing block copolymers, a chain extension experiment was performed (Figure 4.5 right). After the synthesis of a pEtOx with 10 monomer units, a second batch of 80 monomer units was added to demonstrate the presence of living chain ends. The resulting GPC traces indeed show that there is no dead polymer left and that the entire molecular weight distribution has been shifted to lower retention times corresponding to higher molecular weight. As a result, it will also be possible to synthesize block copolymers under microwave irradiation when a different monomer is added as second batch.

To identify the reactive species during the microwave-assisted polymerization of EtOx, the polymerization was performed in CD$_3$CN in the microwave synthesizer. The polymerization mixture was analyzed before heating (Figure 4.6 bottom), after 10 minutes microwave heating to 140 ºC and subsequent cooling to ambient temperature (Figure 4.6 middle) and after addition of a drop of water to the NMR-tube (Figure 4.6 top). The upper two spectra in Figure 4.6 are more expanded than the spectrum at the bottom to show the signals of the end-groups. The first spectrum (before heating) shows the presence of the monomer signals and MeOTs signals (very small). After heating 10 minutes under microwave irradiation, the monomer signals have almost disappeared and the backbone signals of the polymers appeared instead. In addition, the signals of the propagating oxazolinium species and the corresponding tosylate counterion appeared in the spectrum. The integral ratios revealed that all propagating species are present as oxazolinium salt for this polymerization system. This is in contrast with the previously described EtOx polymerization initiated with benzyl bromide in DMAc, where it was found that only 30-40% of the propagating species was present as cationic center. This difference results from the high stability (lower nucleophilicity) of the tosylate anion when compared to the bromide anion. After the addition of water to this living polymerization mixture, the cationic oxazolinium species disappeared before the NMR-spectrum was measured (~ 10 minutes). In addition, the signals of the tosylate remained at the same position indicating that it is still present as anion. The signal at ~ 4.2 ppm could be assigned to the product resulting from the addition of water to the 2-position of the oxazolinium ring (Scheme 4.1). This hydrolysis of the oxazolinium with water was previously reported in literature.$^{19-21}$ However, this termination reaction was reported to be very slow (< 5% in 22 hour), whereas we found that it occurred readily at ambient temperature.
4.3.2 Microwave polymerization of 2-phenyl-2-oxazoline

The cationic polymerization of the less reactive PhOx (see also section 3.2.2) was also investigated at different temperatures under microwave irradiation utilizing MeOTs as initiator. Reaction temperatures up to 200 °C allowed reliable kinetic measurements (reaction time for full conversion less than one minute). The resulting first order kinetic plot (from GC) is depicted in Figure 4.7 left. Again for all investigated temperatures, linear first order kinetics were obtained. The first order kinetics together with the linear increase of $M_n$ with conversion and the low PDI values (Figure 4.7 right; GPC with CHCl$_3$:NEt$_3$:2-PrOH) prove the livingness of the microwave-assisted PhOx polymerization at all investigated temperatures (100 to 200 °C). The polymerizations performed at 120 and 140 °C were as fast as the pressure polymerizations at these temperatures (section 3.6.2) and, in addition, a model polymerization in BCN reflux revealed the same polymerization rate as the polymerization at 120 °C under microwave irradiation (open symbols, Figure 4.7 left). The GPC traces obtained after different reaction times under both microwave irradiation and under reflux in BCN are depicted in Figure 4.8 left demonstrating that there is no difference in molecular weight (distribution). As a result, it can be concluded that the acceleration of the PhOx polymerization under microwave irradiation is solely a consequence of the higher reaction temperatures as it was also shown for the polymerization of EtOx (section 4.3.1).

Figure 4.6. $^1$H-NMR spectra obtained before polymerization in CD$_3$CN (bottom), after 10 minutes microwave ($\mu$W) irradiation at 140 °C (middle) and after quenching with water (top).

Figure 4.7. Left: First order kinetic plot for the polymerization of PhOx in CH$_3$CN under microwave irradiation and conventional heating (BCN reflux). Right: Corresponding $M_n$ against conversion plot.
The slopes of the monomer conversion in the first order kinetic plot (Figure 4.7 left) were used to determine the polymerization rates. The Arrhenius plot of these $k_p$'s for the polymerization of PhOx is depicted in Figure 4.8 right. From this Arrhenius plot an activation energy of 84.4 kJ/mol was calculated, which is in the same range as the reported literature values (71.1 to 113 kJ/mol; 81.3 kJ/mol was determined in section 3.2.2). \(^{22,23}\)

**Figure 4.8.** Left: GPC traces obtained at different reaction times for PhOx synthesized under both microwave irradiation (top) and under reflux in BCN (bottom) (GPC with CHCl$_3$:NEt$_3$:2-PrOH = 94:4:2). Right: Arrhenius plot for the microwave-assisted polymerization of PhOx.

### 4.3.3 Microwave polymerization of 2-methyl-2-oxazoline

Inspired by the successful acceleration of both the EtOx and PhOx polymerization, the MeOx polymerization was also performed under microwave irradiation. The results of the kinetic investigations (GC) are depicted in Figure 4.9. As for the other two monomers, linear first order kinetic plots (right) and a linear increase of $M_n$ (GPC) with conversion were obtained for all investigated polymerization temperatures. However, the GPC was measured with $N,N$-dimethylformamide (DMF containing 5 mM NH$_4$PF$_6$) as eluent, because measurements in CHCl$_3$ showed strong tailing due to interactions between the column material and the nitrogen atoms of the polymers. At 180 °C, the polymerization of MeOx was completed within one minute. The comparison experiments in refluxing BCN revealed a similar polymerization rate as the microwave polymerization at 120 °C. The Arrhenius plot for the polymerization of MeOx (Figure 4.9) yielded an activation energy of 75.4 kJ/mol, which is comparable with the literature values under ‘conventional’ heating (72.9 – 80.0 kJ.mol). \(^{24,25}\)

**Figure 4.9.** Left: First order kinetic plot for the polymerization of MeOx in CH$_3$CN under microwave irradiation and conventional heating (BCN reflux). Right: Corresponding $M_n$ against conversion plot.
4.3.4 Microwave polymerization of 2-nonyl-2-oxazoline

In contrast to the microwave polymerization of the other three monomers, the polymerization of NonOx revealed precipitation of the resulting polymers. A test polymerization at 140 ºC in a pressurized glass reactor under ‘conventional’ heating did not show precipitation during the polymerization. Therefore, it can be assumed that precipitation occurs upon cooling of the polymerization mixture. For industrial applications, the observed precipitation might be advantageous to collect the solid polymer after the polymerization without additional work-up procedures. On the other hand, for the preparation of block copolymers or for end-capping precipitation is generally undesirable. Based on our interest in 2-oxazoline copolymers, we would like to avoid the direct precipitation of pNonOx. Commonly, high boiling chlorinated solvents, like o-dichlorobenzene, are added to the 2-oxazoline polymerization mixtures in order to prevent precipitation of the resulting polymers.\textsuperscript{26,27} However, the use of high-boiling solvents disturbs the work-up procedure that normally comprises an evaporation step. The use of these high-boiling solvents can be circumvented by operating the microwave synthesizer under pressure conditions (up to 20 bar). As a result, high temperatures are not limited to high boiling solvents. Therefore, the microwave-assisted polymerization of NonOx was investigated in dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}).

The kinetics of the NonOx polymerization in dichloromethane under microwave irradiation were investigated in detail. 42 Polymerizations were performed at seven temperatures ranging from 100 to 180 ºC utilizing the expanded high-throughput workflow (cf. section 4.2).\textsuperscript{28} For each temperature, six polymerizations were performed for different times. After cooling to room temperature, the polymerizations were automatically quenched by the addition of water with the microwave liquid handling system. After all polymerizations were finished, the microwave rack was placed back in the ASW2000 synthesis robot and samples were taken automatically from the reaction mixtures to GC vials and GPC vials. In addition, samples for matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) were prepared by automated spotting of the polymerization mixtures onto a MALDI-target.\textsuperscript{29} GC analysis of the samples yielded the monomer conversion in time as depicted in Figure 4.11 left. For all investigated temperatures, linear first-order kinetics were obtained suggesting a living polymerization. The BCN reflux polymerization (open symbols Figure 4.11 left) showed the same polymerization rate as the microwave-assisted polymerization of NonOx in CH\textsubscript{2}Cl\textsubscript{2} at 120 ºC indicating the absence of non-thermal microwave effects.
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Figure 4.11. Left: First order kinetic plot for the microwave-assisted polymerization of NonOx in CH$_2$Cl$_2$ at different temperatures ([NonOx] = 2 M). BCN reflux represents the comparative polymerization under conventional heating in BCN. Right: Corresponding Arrhenius plot for the NonOx polymerization in CH$_2$Cl$_2$.

The slopes of the kinetic plots divided by the initiator concentration resulted in the polymerization rates $k_p$. The corresponding Arrhenius plot (Figure 4.11 right) yielded an activation energy of 74.2 kJ·mol$^{-1}$ for the NonOx polymerization in CH$_2$Cl$_2$, which is comparable with the $E_a$ values found for the other monomers.

Figure 4.12 left depicts the MALDI-TOF-MS spectra and GPC traces obtained at different reaction times for the microwave-assisted polymerization of NonOx in CH$_2$Cl$_2$ at 120 °C. Narrow monomodal distributions with polydispersity indices around 1.1 were obtained with both techniques demonstrating the livingness of the polymerization. Similar narrow distributions were obtained for all investigated reaction times at all different temperatures. Moreover, the development of the number average molecular weight ($M_n$ from both GPC and MALDI-TOF-MS) with monomer conversion is linear as depicted in Figure 4.12 right. Moreover, these $M_n$ values are close to the theoretical molecular weight (Figure 4.12 right, dotted line). The combination of linear first order kinetics and linear increase of molecular weight (close to the theoretical molecular weight) with monomer conversion clearly revealed that NonOx was polymerized in a living manner in CH$_2$Cl$_2$ at the investigated temperatures, ranging from 100 to 180 °C.

Figure 4.12. Left: Obtained MALDI-TOF-MS spectra and GPC traces in time for the polymerization of NonOx at 120 °C. Right: Increase in $M_n$ against conversion and PDI values obtained from both GPC (solid symbols) and MALDI-TOF-MS (open symbols).
In conclusion, the polymerizations of MeOx, EtOx, NonOx and PhOx could be successfully accelerated down to several minutes under microwave irradiation. It was demonstrated that the observed acceleration resulted from the increased reaction temperatures (far beyond the boiling point of CH$_3$CN) and not from so-called non-thermal microwave effects. Moreover, the calculated activation energy was in the range from 73.4 to 75.4 kJ/mol for the 2-alkyl-2-oxazolines and 84.4 kJ/mol for PhOx. The higher activation energy for the PhOx polymerization is due to the lower nucleophilicity of the PhOx that lowers the reactivity.

### 4.4 Bulk polymerization of 2-oxazolines under microwave irradiation

Further investigations aimed at performing the 2-oxazoline polymerizations in reduced solvent amounts. Besides the efficient microwave heating due to the good absorbance of microwave irradiation by the solvent and the monomers, also the reduced solvent amounts would contribute to a greener process. A series of polymerizations with an increasing concentration of the monomer in CD$_3$CN with a constant [M]/[I] ratio of 60 (I = MeOTs) was investigated under microwave irradiation. The highest concentrations represent solvent-free bulk polymerizations. The polymerization mixtures with different amounts of solvents were automatically prepared from stock solutions utilizing the expanded high-throughput workflow that is described in section 4.2. The reaction times for completion of the polymerizations were calculated from the determined $k_p$’s (section 4.3) and equation 3.2. The molecular weights and corresponding distributions of the final polymers were determined by GPC. The pEtOx’s, pPhOx’s and pNonOx’s were measured with CHCl$_3$:NEt$_3$:2-PrOH (94:4:2) as eluent, whereas the pMeOx’s were characterized utilizing DMF as eluent to suppress the interactions with the column material. The formation of polymers with the desired $M_n$ values was observed for all samples, although the obtained $M_n$ values for the pPhOx were slightly higher (Figure 4.13).

**Figure 4.13.** $M_n$’s and PDI values (obtained by GPC) obtained for the polymerization of four differently substituted 2-oxazolines ([M]/[I] = 60) at different monomer concentrations.
The PDI values, on the other hand, increased with the concentration of the monomer to a maximum for the bulk situation. However, EtOx and NonOx revealed still quite narrow molecular weight distributions in bulk (PDI ~ 1.20). On the other hand, the polymerizations of the most reactive monomer MeOx and the least reactive monomer PhOx were uncontrolled when going to bulk conditions. The higher PDI values for these two monomers resulted from broader distributions and not from the appearance of clear shoulders in the GPC traces. Therefore, the loss of control might be attributed to inhomogeneity of the high concentrated polymerization mixtures due to increased viscosity; however, it is not clear why this broadening is only observed in the case of MeOx and PhOx. In general, the range in between 30–70 w% monomer concentration resulted in the best control over the 2-oxazoline polymerizations with PDI’s as low as 1.10. The success in going to controlled bulk polymerizations for EtOx and NonOx might be an effect of the fast and non-contact heating by the microwave irradiation that could reduce side reactions.

4.5 Microwave synthesis of high molecular weight poly(2-oxazoline)s

The effect of microwave-assistance on the polymerization of 2-oxazolines was also investigated with regard to the synthesis of higher molecular weight polymers. For all four monomers (MeOx, EtOx, PhOx and NonOx), a series of microwave-assisted polymerizations was performed at 140 °C with varying [M]/[I] ratios (I = MeOTs) and a monomer concentration around 40 w% in CH$_3$CN (4 M for MeOx and EtOx, 3 M for PhOx and 2 M for NonOx). The polymerization mixtures were prepared automatically utilizing the expanded high-throughput workflow as described in section 4.2. The reaction times for completion were calculated according to equation 3.2. The GPC analysis of the pNonOx’s was performed with CHCl$_3$:NET$_3$:2-ProOH, whereas all other polymers were measured with DMF as eluent since tailing occurred on the CHCl$_3$ system for the higher molecular weight polymers ($M_n > 10,000$ Da). GPC traces of selected polymers are depicted in Figure 4.14.

![Figure 4.14. GPC traces of selected polymers aiming at higher [M]/[I] ratios.](image)

The resulting $M_n$ and PDI’s are plotted against the theoretical [M]/[I] ratio in Figure 4.15. From this figure, it can be concluded that MeOx and NonOx polymerizations remain controlled up to 150 monomer units (PDI < 1.30 and linear increase of $M_n$ with [M]/[I]) and up to 300 monomer units for the EtOx and PhOx polymerizations. The amount of EtOx units that could be polymerized in a living manner (up to 300) is comparable to the amount of monomer units that could be polymerized in a living way for the EtOx polymerization initiated with BB in DMAc using conventional heating (section 3.5.3).
The synthesis of even longer polymers with narrow average molecular weight distributions failed as the corresponding molecular weight distributions started to broaden and began to exhibit shoulders (Figure 4.14). As a result of this broadening, the observed $M_n$ values do not increase linearly with $[M]/[I]$ anymore. Both the low and high molecular weight shoulders (e.g. pNonOx with $[M]/[I] = 152$ or 507 and pEtOx with $[M]/[I] = 300$) originate from the subtraction of an $\alpha$-hydrogen atom of the oxazolinium propagating species by unreacted monomer as already discussed in section 3.2.\textsuperscript{30} As a consequence of the $\alpha$-hydrogen subtraction, a substituted enamine ether chain end on the polymer and a positively charged monomeric cation are formed. The monomeric cation can initiate the growth of a new polymer chain resulting in the low molecular weight fraction in the GPC. On the other hand, the enamine polymer chain end can react to a cationic polymer chain to form the high molecular weight fraction. When chain transfer occurs very often during the polymerization, the shoulders in the GPC will not be discernable any longer resulting in one broad distribution as it is the case for pEtOx with a $[M]/[I]$ of 1000.

In order to unambiguously prove the successful synthesis of polymers with the targeted $M_n$ values, the well-defined poly(2-oxazoline)s (PDI < 1.30) were investigated by MALDI-TOF-MS. Utilizing a multilayer sample preparation method\textsuperscript{31} with sodium iodide as salt and trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix, we were able to investigate poly(2-oxazoline)s with relatively high number average molecular weights up to 30 kDa. The $M_n$ values obtained by MALDI-TOF-MS showed a good agreement between theoretical and experimental data as depicted in Figure 4.16.
This close resemblance can be mainly attributed to the fact that MALDI-TOF-MS is an absolute analytical technique, whereas GPC is relative and requires calibration with well-suited polymer standards (not available for all polymers). In addition, GPC is sensitive to interactions between the poly(2-oxazoline)s and the column material. Therefore, it can be expected that the molecular weights obtained by MALDI-TOF-MS fit better to the expected values than the values obtained by GPC. Moreover, the MALDI spectra showed the expected signal spacings for the respective monomers of the investigated poly(2-oxazoline)s (85 Da for MeOx, 99 Da for EtOx, 147 Da for PhOx and 197 Da for NonOx). The MALDI spectra obtained for the pNonOx’s are depicted in Figure 4.17 showing the good resolution up to 30 kDa.

![MALDI-TOF-MS spectra obtained for the pNonOx’s obtained at different [M]/[I] ratios demonstrating the good resolution with monomer spacing up to 30 kDa.](image)

4.6 Microwave polymerization and properties of linear 2-alkyl-2-oxazolines

In the previous sections, the investigations were focused on the microwave polymerization of MeOx, EtOx, NonOx and PhOx. To further expand the scope of the microwave-assisted polymerization of 2-oxazolines, we have synthesized and polymerized a series of linear 2-alkyl-2-oxazolines, namely MeOx, EtOx, 2-propyl-2-oxazoline (PropOx), 2-pentyl-2-oxazoline (PentOx), 2-heptyl-2-oxazoline (HeptOx) and NonOx. Besides the polymerization of these monomers, the thermal and surface properties were investigated throughout this series to study the effect of the length of the side-groups on the polymer properties. The PropOx, PentOx and HeptOx were not present in our laboratories and had to be synthesized by reaction of the corresponding nitriles with ethanolamine using zinc acetate as catalyst (Scheme 4.2). The $^1$H-NMR spectra of the utilized 2-alkyl-2-oxazolines are depicted in Figure 4.18 left. The protons of the two CH$_2$ groups of the oxazoline ring appeared at 3.82 and 4.23 ppm for all monomers. The CH$_3$ protons of MeOx appeared at 1.98 ppm and shifted upfield with increasing chain length until the oxazoline influence was diminished with PentOx resulting in a chemical shift of 0.89 ppm.

![Scheme 4.2. Synthesis of 2-alkyl-2-oxazolines from the corresponding nitriles and ethanolamine.](image)
The kinetics of the microwave polymerization of the different monomers were investigated at 140 °C in CH$_3$CN (except NonOx in CH$_2$Cl$_2$ for solubility reasons; see section 4.3.4). The monomer concentration was varied for the different monomers to have about 40% of monomer in the polymerization mixtures. The resulting first order kinetic plots are depicted in Figure 4.18 right. From the slope of the linear first order kinetics, the $k_p$'s were determined as summarized in Table 4.1. Except for the higher polymerization rate of the MeOx, the $k_p$ values are all in the same range indicating that the length of the alkyl side groups does not influence the polymerization speed significantly. The higher nucleophilicity and thus the higher reactivity of MeOx compared to EtOx was also observed in section 3.3.5. Besides the first order kinetics, the $M_n$ values increased linearly with conversion (not shown) demonstrating the living character of the microwave polymerizations.

Table 4.1. Polymerization rates obtained for the microwave polymerization of the 2-alkyl-2-oxazolines at 140 °C in CH$_3$CN except for NonOx, which was polymerized in CH$_2$Cl$_2$ ($k_p$ in 10$^{-3}$ L·mol$^{-1}$·s$^{-1}$).

<table>
<thead>
<tr>
<th>monomer</th>
<th>$k_p$</th>
<th>monomer</th>
<th>$k_p$</th>
<th>monomer</th>
<th>$k_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOx</td>
<td>146 ± 3</td>
<td>PropOx</td>
<td>117 ± 4</td>
<td>HeptOx</td>
<td>127 ± 7</td>
</tr>
<tr>
<td>EtOx</td>
<td>105 ± 1</td>
<td>PentOx</td>
<td>120 ± 3</td>
<td>NonOx</td>
<td>111 ± 5</td>
</tr>
</tbody>
</table>

The thermal properties of the synthesized poly(2-alkyl-2-oxazoline)s were determined by differential scanning calorimetry (DSC). The third heating curves at 10 K/min are depicted in Figure 4.19 left. For the MeOx, EtOx, PropOx and PentOx polymers, a clear glass transition temperature can be seen, whereas for the pHeptOx and pNonOx no glass transition was observed with DSC. The glass transition temperature decreased linearly with increasing number of carbon atoms in the side chain (Figure 4.19 right). Thus it can be concluded that the increasing flexibility of the side-chains is the cause of this decreasing glass transition temperature. In addition, melting points around 150 °C were observed for the PentOx, HeptOx and NonOx polymers. Since the crystallinity is only present for the polymers with longer side-chains, it can be concluded that the observed melting point results from side-chain crystallinity. The pPentOx represents a border case in this series: It is the only polymer that...
exhibits both a glass transition temperature and a melting temperature. Moreover, the pPentOx is the only crystalline polymer that does not show a crystallization exotherm upon cooling with 40 °C/min (not shown). However, crystallization of the side-chains occurs upon heating as demonstrated by the endotherm at 58.7 °C in the heating trace (Figure 4.19 left).

![Graph showing DSC heating curves](image)

**Figure 4.19.** Left: DSC heating curves (10 K/min) for the poly(2-alkyl-2-oxazoline)s. Right: Glass transition and melting temperature subtracted from these DSC curves.

The surface properties of the synthesized poly(2-alkyl-2-oxazoline)s were determined by contact angle measurements. Contact angles of both ethylene glycol and diiodomethane were determined on spincoated polymer films. From the difference of these contact angles, the surface energy of the polymer film was calculated using the equation of state method (equation 3.2; section 3.4.2). Figure 4.20 depicts the resulting surface energies for the series of poly(2-alkyl-2-oxazoline)s. A clear difference between the polymers with short side-chains and longer side-chains was observed for the surface energies. With side-chains of 1, 2 or 3 carbon atoms (MeOx, EtOx and PropOx), surface energies above 40 mN/m were obtained indicating hydrophilic surfaces. On the other hand, the longer side chains of PentOx, HeptOx and NonOx yielded surface energies below 25 mN/m indicative of hydrophobic surfaces. The polymers made of PropOx and PentOx have surface energies that are approaching the transition regime.

In conclusion, it was demonstrated that microwave irradiation is a powerful tool for the cationic ring-opening polymerization of 2-alkyl-2-oxazolines. Moreover, by changing the length of the side-groups, both thermal and surface properties of the resulting poly(2-oxazoline)s can be varied.

![Graph showing surface energies](image)

**Figure 4.20.** Surface energies of the poly(2-alkyl-2-oxazoline)s.
Chapter 4

4.7 Microwave polymerization of a soy-based 2-oxazoline monomer

In this section, the microwave-assisted polymerization of a sustainable soy based 2-‘soy alkyl’-2-oxazoline (SoyOx) monomer is described. Besides the green character of using a monomer based on soy-beans, the unsaturated nature of the fatty acids are transferred into the SoyOx monomer providing cross-linking possibilities for the resulting polymers. The SoyOx was synthesized by coupling soy bean fatty acids with ethanolamine followed by ring-closure in the presence of a titanium catalyst as depicted in Scheme 4.3. The resulting SoyOx is a mixture of 2-oxazolines with different fatty acid side chains.

\[
\text{soy alkyl} \overset{\text{120-140 °C}}{\longrightarrow} \text{soy alkyl}
\]

\[
\text{Ti(OR')}_4 \quad 200 \text{ °C} \quad \text{vacuum}
\]

\[
\text{soy alkyl}
\]

Scheme 4.3. Synthesis of the soy based 2-oxazoline monomer SoyOx.

The SoyOx (donated by Henkel) had to be purified before the microwave-assisted cationic ring-opening polymerization could be investigated. Unlike the smaller 2-oxazoline monomers, this SoyOx could not easily be purified by distillation due to its high molecular weight. Therefore, a new purification method was developed in which a solution of the monomer in hexane was passed over an aluminum oxide filtration column. All impurities, such as ring-opened monomer and polymer, stick to the column, whereas the SoyOx can be flushed through. After removal of the hexane, the monomer was dried by passing over barium oxide and it was stored under argon in the dark. The appearance of the monomer before and after this purification is shown in Figure 4.21 left. Before purification the SoyOx was dark yellow containing a large amount of white solid. After purification, the SoyOx was obtained as a colorless liquid. Figure 4.21 right shows the GC spectrum of the purified monomer with the structures that could be assigned by the mass spectra from the GC-MS. The spectrum showed four signals, which could all be assigned to different 2-oxazoline species with 16 or 17 carbon atoms and 0 to 2 unsaturated bonds in the side chain. The average composition of the side chain is 17 carbon atoms and 1.5 double bonds.

Figure 4.21. Left: Picture before (a) and after (b) purification of the SoyOx by Al₂O₃ filtration column with hexane as eluent. Right: GC-MS spectrum of the purified SoyOx.
The microwave-assisted polymerization of the purified SoyOx was investigated in CH₃CN, in CH₂Cl₂ and in bulk at 140 °C with MeOTs as initiator ([M]/[I] = 60). The kinetics of the SoyOx polymerization were investigated by quenching the polymerization after different reaction times with water. The resulting polymerization mixtures were analyzed by GC (CH₃CN and CH₂Cl₂ polymerizations) and ¹H-NMR spectroscopy (CH₂Cl₂ and bulk polymerizations) to determine the monomer conversion and by GPC to obtain the molecular weight (distribution) of the resulting polymers. Figure 4.22 left depicts the ¹H-NMR spectra that were obtained after different polymerization times for the bulk polymerization. With increasing reaction time, the monomer signals at 3.8 and 4.2 ppm decrease and the polymer backbone signal at 3.4 ppm increases indicating that monomer is converted into polymer. Moreover, the signals of the double bonds at 5.4 ppm stay constant demonstrating that they are unaffected by the cationic polymerization and that the resulting polymers still contain a large amount of double bonds. The GPC traces obtained for the bulk polymerization of SoyOx in time are depicted in Figure 4.22 right. In these traces, both the polymer and the large monomer are separated from the solvent signal. With increasing reaction time, the monomer signal decreased and the polymer signal increased and moved to lower retention times indicating an increase in molecular weight. Moreover, the narrow single distributions of the molecular weight indicate that the polymers were made in a living fashion. From integration of both monomer and polymer signals in the GPC traces, the monomer conversion could be calculated, whereby it was assumed that both the monomer and the monomer incorporated in the polymer have the same effect on the refractive index of the solution.

Figure 4.22. ¹H-NMR spectra (left) and GPC traces (right) in time for the microwave-assisted bulk polymerization of SoyOx at 140 °C.

The first order kinetic plot of the SoyOx polymerizations under microwave irradiation is depicted in Figure 4.23 left. All three polymerization media (bulk, CH₃CN and CH₂Cl₂) result in linear first order kinetics suggesting a living polymerization mechanism. The faster polymerization in bulk is due to the higher monomer concentration (3.3 M) compared to the solution polymerizations (1.5 M corresponding to 45 w%). The different methods to determine the monomer conversion give similar results, whereby the GC yielded slightly lower conversions. The lower conversion by GC might be due to the four small monomer signals resulting in less accurate integration when compared to one large signal (in GPC and ¹H-NMR spectroscopy). Similar to the NonOx polymerization, the pSoyOx also precipitated from CH₃CN upon cooling. The polymerization mixture in CHCl₃ remained homogeneous upon cooling providing the possibility to synthesize block copolymers. The living character of the SoyOx polymerizations is further verified by the linear increase of Mₙ with conversion.
with low PDI values (Figure 4.23 right). However, the observed $M_n$’s are significantly lower than the theoretical molecular weight (dotted line in Figure 4.23 right), which is most likely due to the utilized polystyrene calibration of the GPC.

Figure 4.23. Left: First order kinetic plot for the microwave-assisted polymerization of SoyOx in bulk (squares), CH$_3$CN (triangles) and CH$_2$Cl$_2$ (circles) at 140 °C. Right: Corresponding $M_n$ against conversion plot.

To be certain that the SoyOx polymerization under microwave irradiation proceeds via a living mechanism, a chain extension experiment was performed. Figure 4.24 left depicts the GPC traces obtained before and after chain extension proving the livingness of the polymerization after full consumption of the first monomer as can be concluded from the absence of the monomer signal in the GPC traces. The cross-linking of the double bonds of pSoyOx was attempted by UV-curing of the solid polymer for 2 hours. After curing, the pSoyOx did not dissolve in CH$_2$Cl$_2$ anymore indicating successful cross-linking. The photographs in Figure 4.24 right show the solutions of pSoyOx in CH$_2$Cl$_2$ before and after cross-linking, whereby the swollen particles of pSoyOx are clearly visible (see arrows) after UV-curing. Next to this visual proof, GPC was measured from the (minor) soluble part of the UV-cured pSoyOx (Figure 4.24 right). The GPC-trace after UV-curing shows the presence of uncoupled polymer and a second small distribution of two polymers coupled together. Apparently, if more chains are cross-linked together, the resulting pSoyOx does not dissolve anymore and thus cannot be detected by GPC. $^1$H-NMR spectroscopy on the swollen cross-linked pSoyOx revealed that 16% of all present double bonds had disappeared after UV-curing.

Figure 4.24. Left: Chain extension experiment for the microwave-assisted polymerization of SoyOx in CH$_2$Cl$_2$. Right: GPC traces for pSoyOx before and after UV-curing (only soluble part). The inset pictures show the appearance of solutions of pSoyOx in CH$_2$Cl$_2$ before and after curing.
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In summary, the SoyOx monomer can be polymerized in a living manner under microwave-irradiation, whereby the high molar mass of the monomer allows conversion determination by GPC. The resulting pSoyOx can be successfully cross-linked as was demonstrated by the insolubility of the resulting pSoyOx and by GPC and $^1$H-NMR spectroscopy.

4.8 Synthesis of a four-armed star poly(2-ethyl-2-oxazoline) based on a porphyrin core

In the previous part of this chapter, all microwave-assisted 2-oxazoline polymerizations were initiated with MeOTs. It was shown that a wide variety of 2-oxazolines can be polymerized in a living manner under microwave irradiation. In this section, the utilization of a different multifunctional tosylate initiator is described. Scheme 4.4 depicts the schematic path that was followed to synthesize the four-armed star pEtOx 4. A tetakis(hydroxyphenyl)porphyrin (1) was used to synthesize a rigid star-shaped initiator with four tosylate groups by reaction with butane ditosylate (2). Subsequently, this tetrafunctional initiator was applied for the microwave-assisted cationic ring-opening polymerization of EtOx. The synthesis of star-shaped poly(2-oxazoline) block copolymers was previously reported utilizing tetakis-(iodomethyl phenyl)porphyrin as initiator, but these polymerizations took three days to go to completion. 33

**Scheme 4.4. Schematic overview of the synthesis of a porphyrin initiated four-armed star pEtOx 4 starting from tetakis(hydroxyphenyl)porphyrin (1).**

The butane ditosylate 2 that was used to functionalize the porphyrin, was synthesized from 1,4-butanediol and an excess of tosyl chloride via a modified literature procedure. 34 After 24 hours stirring at ambient temperature, ethanolamine was added to react with the excess of tosyl chloride. Purification of the product 2 was done by washing with 3 N hydrochloric acid and brine followed by recrystallization from ethanol. The obtained white platelet crystals were suitable for X-ray analysis. The observed molecular structure (ORTEP-plot) and the packing diagram are displayed in Figure 4.25 left. A symmetry point was observed in the molecules in between the middle carbon atoms of the butyl chain. The packing diagram shows that the molecules are packed in an optimal space filling order, without any π-stacking between the phenyl rings. The tetakis(hydroxyphenyl)porphyrin (1) was reacted with a 20-fold excess of butane ditosylate (2). The desired tetakis(4-hydroxybutyloxy tosylate)porphyrin (3) was
obtained pure (13% yield) after a silica column in CH$_2$Cl$_2$ and preparative size exclusion chromatography in CH$_2$Cl$_2$. Figure 4.25 right depicts the MALDI-TOF-MS spectrum of the tosylate-porphyrin 3. This spectrum clearly shows the presence of the tosylate-porphyrin 3 (mass 1582) and a minor fraction with only three tosylate groups and one methoxy (mass 1446) next to the utilized matrix dithranol (mass 226).

The polymerization of EtOx utilizing tosylate-porphyrin 3 as initiator was performed with 2 M monomer concentration in CH$_3$CN at 140 °C under microwave irradiation with a [M]/[I] ratio of 200 corresponding to 50 monomer units per tosylate group. After 20 minutes polymerization time, the resulting polymer was purified by preparative size exclusion chromatography in CH$_2$Cl$_2$. Figure 4.26 left depicts the $^1$H-NMR spectra of the tosylate-porphyrin 3 (bottom) and the pEtOx-porphyrin 4 (top). The porphyrin signals are still present in the pEtOx 4 spectrum indicating that indeed a four armed pEtOx with a porphyrin core is synthesized. Integration of both the polymer backbone signals (l and m) and the porphyrin signals (a and b) revealed that 188 EtOx units were incorporated in the polymer, which correspond to 47 monomers per arm. Moreover, the obtained [M]/[I] ratio is close to the aimed number of 200 monomer units.

Figure 4.25. Left: ORTEP plot (50% probability, top) and packing diagram (bottom) of the structure of 1,4-butanediol ditosylate (2). Right: MALDI-TOF-MS spectrum of tosylate-porphyrin 3.

Figure 4.26. Left: $^1$H-NMR spectra (in CDCl$_3$) of the porphyrin initiator 3 (bottom) and pEtOx-porphyrin 4 (top). Right: GPC traces for 3 and 4 (in CHCl$_3$:NEt$_3$:2-PrOH; UV-detector at 500 nm).
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GPC characterization of the porphyrin initiator 3 showed a negative signal in the RI-detector and a positive signal in the UV-detector at 500 nm, where the porphyrin has strong UV-absorption (Figure 4.26 right). The $M_n$ was calculated to be 1,580 Da with a PDI of 1.06 (against polystyrene standards). This PDI value results from diffusion of the organic compound on the column since it is almost monodisperse (see MALDI in Figure 4.25). The pEtOx-porphyrin 4 could not be characterized with the RI-detector due to the combination of a positive signal of the polymer and a negative signal of the porphyrin. However, detection with the UV-detector at 500 nm revealed a single distribution for the polymer 4 (Figure 4.26 right) proving that the porphyrin is incorporated into the polymer. Moreover, the specific porphyrin absorptions were detected by a GPC with photodiode array detector (Figure 4.27).

Figure 4.28. GPC spectrum obtained for pEtOx-porphyrin 4 utilizing a photodiode array detector (eluent: DMF containing 5 mM NH$_4$PF$_6$).

The photodiode array spectrum clearly revealed that the complete polymer distribution has the porphyrin incorporated and that no free initiator is left in the polymer. The GPC with UV-detector yielded a $M_n$ of 10,700 Da and a PDI of 1.18. The $M_n$ is lower than the theoretical molecular weight (~ 21,000 Da) due to calibration with linear standards. The hydrodynamic volume, that determines the retention time, will be very different for a star-shaped polymer when compared to a linear polymer. Moreover, the narrow molecular weight distribution indicates that the tetrakis(pEtOx)-porphyrin 4 was synthesized in a controlled manner.

4.9 Conclusions

In this chapter, the effect of microwave-irradiation on the cationic ring-opening polymerization of 2-oxazolines has been investigated. To accelerate these investigations, an expanded high-throughput workflow was developed in which the filling of microwave vials and sampling from these vials is performed automatically by the ASW2000 synthesis robot. The workflow includes manual transportation steps from the ASW2000 to the microwave synthesizer, but all other steps are performed automatically. This expanded high-throughput workflow was applied for many of the investigations described in this chapter.

In conclusion, it has been demonstrated that microwave irradiation is a powerful tool for the cationic ring-opening polymerization of 2-oxazolines. The characteristic long reaction times for this polymerization technique could be reduced by a factor of up to 350. However, it was
also demonstrated that this acceleration solely results from thermal effects and it can be reproduced by conventional pressure polymerizations or by reflux polymerizations in high boiling solvents. Kinetic investigations on the microwave polymerizations of MeOx, EtOx, PhOx and NonOx revealed that the polymerizations proceeded via a living mechanism at all investigated temperatures from 80 to 200 °C. However, pNonOx precipitated from the polymerization mixture in CH$_3$CN and, therefore, the kinetic investigations on the NonOx polymerization were performed in CH$_2$Cl$_2$.

The monomer concentration of the microwave-assisted polymerizations of MeOx, EtOx, PhOx and NonOx were varied to accelerate the polymerizations and to reduce the required solvent amounts leading to environmentally friendlier processes. The polymerizations of EtOx and NonOx could be performed in bulk without losing the control over the polymerization (PDI ~ 1.20), whereas the PDI values increased to 1.5 for the bulk polymerizations of MeOx and PhOx. Although this difference is not understood yet, an optimal concentration window of 30-70 w% monomer could be identified for all monomers resulted in the narrowest molecular weight distributions. Besides the concentration optimization, the synthesis of high molecular weight poly(2-oxazoline)s was attempted under microwave irradiation. The polymerizations of MeOx and NonOx stayed controlled up to a [M]/[I] ratio of 150 and the polymerizations of EtOx and PhOx were living up to 300 monomer units. Upon further increasing the [M]/[I] ratios, the occurrence of side-reactions was discernable. More specifically, the appearance of both high and low molecular weight shoulders in the GPC revealed the occurrence of chain transfer to monomer and subsequent chain coupling reactions. Nevertheless, MALDI-TOF-MS characterization was successful for all poly(2-oxazoline)s with PDI-values below 1.30 implying that pNonOx up to 30 kDa could be characterized. So far, successful MALDI-TOF-MS was not reported for these high molecular weight poly(2-oxazoline)s.

Furthermore, the microwave-assisted polymerization of a series of linear 2-alkyl-2-oxazolines was investigated. The MeOx revealed a slightly higher polymerization rate as it is known from literature and from the previous chapter. However, this means that the length of the alkyl side chain does not influence the polymerization rate of the 2-oxazoline monomers when it is longer than a methyl. The thermal and surface properties of the resulting poly(2-alkyl-2-oxazoline)s were investigated by DSC and contact angle measurements. The pMeOx until the pPentOx showed a glass transition temperature that decreased linearly with increasing carbon number in the side chain. Moreover, a melting transition was observed around 150 °C for the pPentOx and polymers with longer side-chains indicating that the pPentOx is a border case that shows both $T_g$ and $T_m$ in DSC. Moreover, a clear transition in the surface energy from 40 to 20 mN/m was observed in between the pPropOx and the pPentOx. The polymerization of a soy-bean-based 2-oxazoline monomer (SoyOx) was also demonstrated. The double bonds of the side-chains were unaffected by the cationic polymerization resulting in well-defined polymers. Moreover, it was demonstrated that the double bonds can be applied for cross-linking the pSoyOx under UV-irradiation. In the last part of this chapter, the synthesis of a porphyrin-based tetrafunctional tosylate initiator is described. This initiator was successfully applied for the cationic polymerization of EtOx resulting in the formation of well-defined star-shaped pEtOx.
### Materials

Solvents were purchased from Biosolve Ltd. except for \(N,N\)-dimethylacetamide and butyronitrile (Aldrich). Acetonitrile (size 3 Å), butyronitrile (size 4 Å) and DMAc (size 4 Å) were dried over molecular sieves when used in the polymerization. \(\text{CH}_2\text{Cl}_2\) was distilled over potassium. All other solvents were used without further purification. MeOx, EtOx (Aldrich), PhOx and NonOx (donated by Henkel) were distilled over barium oxide (BaO) and stored under argon. SoyOx (donated by Henkel) was purified over aluminum oxide with hexane as eluent. After drying over BaO it was stored under argon. Benzyl bromide (Acros Organics) and methyl tosylate (Aldrich) were distilled over \(\text{P}_2\text{O}_5\) and stored under argon. Butyronitrile, hexanenitrile, octanenitrile, ethanolamine, zinc acetate, tosyl chloride, butane-1,4-diol and 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (1) were all obtained from Aldrich and used without further purification.

### Instrumentation

Polymerizations were carried out in an Emrys Liberator (Biotage, formerly PersonalChemistry) utilizing capped reaction vials. These vials were heated to 105 ºC, allowed to cool to room temperature and filled with argon prior to use. All microwave polymerizations were performed with temperature control (IR sensor). A Chemspeed ASW2000 automated synthesizer was utilized for dispensing the stock solutions into the microwave vials and for automated sample preparation after the polymerizations. An inert atmosphere was maintained by applying 1.5 bar argon flow through the hood of the synthesizer.

\(^1\)H-NMR spectra were recorded on a Varian AM-400 spectrometer or a Varian Gemini 300 spectrometer. Chemical shifts are given in ppm relative to TMS or residual solvent signals.

Gel Permeation Chromatography (GPC) was measured on a Shimadzu system with a SCL-10A system controller, a LC-10AD pump, a RID-6A refractive index detector, a SPD-10A UV detector and a PLgel 5 µm Mixed-D column with chloroform:triethylamine:2-propanol (94:4:2) as eluent and the column oven set to 50 ºC (polystyrene calibration). GPC of the pMeOx’s and high molecular weight pEtOx’s and pPhOx was measured on a Waters system with a 1515 pump, a 2414 refractive index detector and a Waters Styragel HT4 column utilizing DMF containing 5 mM \(\text{NH}_4\text{PF}_6\) at a flow rate of 0.5 mL/min as eluent and the column oven set to 50 ºC (PEG calibration). MALDI-TOF-MS was performed on a Voyager-DE™ PRO Biospectrometry™ Workstation (Applied Biosystems) time-of-flight mass spectrometer using linear mode for operation (positive ion mode; ionization with a 337 nm pulsed nitrogen laser). Elemental analyses were performed on an EuroEA3000 Series EuroVector Elemental Analyzer for CHNS-O.

GC measurements were performed on an Interscience Trace GC with a Trace Column RTX-5 connected to a PAL autosampler. For the injection of polymerization mixtures, a special Interscience liner with additional glass wool was used. GC-MS analysis was performed on a Shimadzu GC-MS-QP5000, the mass values are reported as mass/charge ratio (m/z).

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netzsch under a nitrogen atmosphere with heating and cooling rates of 40 K·min\(^{-1}\) (three measurements per sample after an initial first heating run that was not considered for the subsequent calculations); melting points were measured with a heating rate of 10 K·min\(^{-1}\) and a cooling rate of 40 K·min\(^{-1}\).

Contact angle measurements were performed on polymer films that were prepared by spincoating of chloroform solutions (20 mg/mL) of the polymers on pre-cleaned microscopy slides at 1000 rpm during 90 seconds using a WS-400/500 series spin coater from Laurell Technologies Corporation. An OCA30 optical contact angle measuring instrument from Dataphysics was used to determine the contact angles of both diiodomethane and ethylene glycol as apolar and polar test liquids, respectively.

X-ray crystal structures were measured by mounting selected crystals on a Bruker-AXS APEX diffractometer with a CCD area detector. Graphite-monochromated Mo-K\(_\alpha\) radiation (71.073 pm) was used for the measurements. The nominal crystal-to-detector distance was 5.00 cm. A hemisphere of data was collected by a combination of three sets of exposures at 173 K. Each set had a different \(\phi\) angle for the crystal, and each exposure took 20 s and covered 0.3° in \(\omega\). The data were corrected for polarization and Lorentz effects, and an empirical absorption correction (SADABS) was applied.\(^{35}\) The cell dimensions were refined with all unique reflections. The structures were solved by direct methods (SHELXS97). Refinement was carried out with the full-matrix least-squares method based on \(F^2\) (SHELXL97)\(^{36}\) with anisotropic thermal parameters for all non-hydrogen atoms.
Kinetic investigations on the microwave-assisted polymerization of 2-oxazolines

Unless otherwise stated, solutions with the following polymerization conditions were used: [MeOx] = [EtOx] = [PropOx] = 4 M; [PhOx] = 3 M; [PentOx] = [HeptOx] = 2.5 M; [NonOx] = 2 M; [SoyOx] = 1.5 M. These different initial monomer concentrations were utilized in order to have comparable weight amounts of monomer present in the polymerization mixtures. The microwave polymerizations were initiated by MeOTs with a [M]/[I] ratio of 60.

For the kinetic investigations, a stock solution was prepared for each monomer/solvent combination. This stock solution was divided over different reaction vials (1 mL each) that were heated for different times to different temperatures. After heating, the polymerization mixture was cooled to 38 ºC and quenched by the addition of water. GC and GPC samples were prepared from the polymerization mixtures to determine the monomer conversion and the molecular weight (distribution) of the resulting polymers. Due to the insolubility of pNonOx and pSoyOx in CH₃CN, these polymerization mixtures were first homogenized by the addition of ODCB or CH₂Cl₂ before sampling.

Comparative kinetic investigations on the polymerization of 2-oxazoline in BCN reflux with conventional heating

Reactions were performed on the ASW2000 robot system equipped with 13 mL glass reactors. Prior to the reactions, the reaction vessels were heated to 120 ºC, evacuated at 10 mbar for 15 minutes and subsequently filled with argon. This procedure was repeated four times to create an inert atmosphere. In addition, 1.1 bar argon pressure was applied to the reaction blocks and 1.5 bar argon pressure was applied to flush the glove-box of the automated synthesizer.

Subsequently, the monomers, a solution of MeOTs in BCN and BCN were transferred into the 13 mL reaction vessels resulting in 4 mL reaction mixtures with a [M]/[I] ratio of 60 and the same monomer concentrations as described above for the different monomers. The reactors were heated to 130 ºC and vortexed at 600 rpm with the reflux condensers set to ~5 ºC. During these reflux polymerizations, samples were withdrawn from the polymerization mixtures automatically at predefined times. These samples were used for GC and GPC analysis to determine the polymerization kinetics.

¹H-NMR investigations on the microwave-assisted polymerization of EtOx

A solution of EtOx (1.2 g, 12.12 mmol) and methyl tosylate (40 mg, 0.214 mmol) in acetonitrile-d₃ (1.5 g, 1.8 mL) was prepared in a dried microwave vial. A sample of this solution was measured by ¹H-NMR spectroscopy. Subsequently, the remainder of the solution was heated to 140 ºC for 10 minutes under microwave irradiation. A sample from the resulting polymerization mixture was added into a dried NMR-tube and analyzed by ¹H-NMR spectroscopy. Afterward, a drop of water was added to this NMR-tube and the sample was remeasured after about ten minutes.

Concentration screening and high molecular weight poly(2-oxazoline)s of MeOx, EtOx, PhOx and NonOx under microwave irradiation

For the concentration investigations, the [M]/[I] ratio was kept at a value of 60; only the amount of solvent was varied. For the experiments that aimed at the preparation of polymers with high average molecular weights, on the other hand, the monomer concentration was kept constant, whereby the amount of initiator was varied. The solutions for both series were prepared in a Chemspeed synthesizer robot. All described polymerizations were performed with MeOTs as initiator and CH₃CN as solvent.

Synthesis of 2-alkyl-2-oxazoline monomers

The nitrile (1 equivalent) and ethanolamine (1.1 equivalents) were mixed together with Zn(OAc)₂ as catalyst (0.02 equivalents). The resulting yellow suspension was stirred at 130 ºC for 16 hours. After cooling to ambient temperature, CH₂Cl₂ was added and the resulting mixture was washed with water (2 times) and brine (1 time). The resulting organic layer was dried with magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The final products were obtained as colorless liquid after vacuum distillation.

PropOx: ¹H-NMR (CDCl₃): δ 4.15 (d, 9.5 Hz, 2H, OCH₂), 3.75 (d, 9.5 Hz, 2H, NCH₂), 2.18 (t, 8.1 Hz, 2H, CCH₂), 1.59 (sextet, 7.4 Hz, 2H, CCH₂CH₂), 0.90 (t, 7.4 Hz, 2H, CH₃). GC-MS retention time: 0.97 min (100%, M⁺ = 113).
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PentOx: $^1$H-NMR (CDCl$_3$): $\delta$ 4.22 (d, 9.4 Hz, 2H, OCH$_2$), 3.82 (d, 9.4 Hz, 2H, NCH$_2$), 2.26 (t, 7.7 Hz, 2H, CCH$_2$). 1.63 (quintet, 7.7 Hz, 2H, CCH$_2$CH$_2$CH$_2$). 0.91 (t, 7.0 Hz, 2H, CH$_3$). GC-MS retention time: 1.88 min (100%, $M^+$ = 141).

HeptOx: $^1$H-NMR (CDCl$_3$): $\delta$ 4.22 (d, 9.3 Hz, 2H, OCH$_2$), 3.85 (d, 9.3 Hz, 2H, NCH$_2$), 2.26 (t, 7.7 Hz, 2H, CCH$_2$). 1.63 (quintet, 7.7 Hz, 2H, CCH$_2$CH$_2$). 1.40-1.20 (m, 8H, CCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$). 0.88 (t, 6.9 Hz, 2H, CH$_3$). GC-MS retention time: 3.15 min (100%, $M^+$ = 169).

**Synthesis of 1,4-butanediol ditosylate (2)**

1,4-Butanediol ditosylate was synthesized via a modified literature procedure. To a solution of 1,4-butanediol (4.5 g, 50 mmol) in dried CH$_2$Cl$_2$ (100 mL), a solution of tosyl chloride (23.8 g, 125 mmol) in CH$_2$Cl$_2$ (100 mL) was added dropwise in 75 minutes. The resulting solution was stirred for 24 hours under argon and subsequently ethanolamine (6 mL) was added to react to the excess of tosyl chloride. The resulting mixture was poured into water (200 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic layers were washed with 3 N HCl (2 x 100 mL) and brine (150 mL). After drying with MgSO$_4$ and filtration, the solvent was evaporated under reduced pressure. Recrystallization of the product from ethanol yielded the desired 1,4-butanediol ditosylate as white platelet crystals in 58% yield (11.5 g, 28.9 mmol).

$^1$H-NMR (CDCl$_3$): $\delta$ 7.74 (d, 8.3 Hz, 4H, o-CH$_2$), 7.33 (d, 8.3 Hz, 4H, m-CH$_2$), 2.43 (s, 6H, CH$_3$), 1.68 (t, 5.5 Hz, 4H, OCH$_2$CH$_2$). $^{13}$C-NMR (CDCl$_3$): $\delta$ 144.8 (C$_{por}$), 132.7 (C$_{por}$), 129.8 (m-C), 127.7 (o-C), 69.2 (OCH$_2$), 24.9 (OCH$_2$CH$_2$), 21.5 (C$_{CH_3}$).

**Synthesis of 5,10,15,20-tetrakis(4-hydroxybutyloxy tosylate)-21H,23H-porphyrin (3)**

A mixture of 5,10,15,20-tetrakis (4-hydroxyphenyl)porphyrin 1 (170 mg, 0.25 mmol), 1,4-butanediol ditosylate 2 (2 g, 5 mmol) and potassium carbonate (190 mg, 1.37 mmol) in dry CH$_2$CN was refluxed for 75 hours. After this period, the solvent was evaporated under reduced pressure and the residue was redissolved in CHCl$_3$. This solution was washed with water (100 mL), a saturated sodium hydrogen carbonate solution (100 mL) and brine (100 mL). After drying with MgSO$_4$ and filtration the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography (SiO$_2$ with CH$_2$Cl$_2$) and preparative size exclusion chromatography (biobeads SX-1 in CH$_2$Cl$_2$) resulting in the title compound 3 (38 mg, 0.024 mmol, 10% yield).

$^1$H-NMR (CDCl$_3$): $\delta$ 12.3 (s, 2H, NH), 8.99 (s, 8H, CH$_2$por), 8.20 (d, 8.5 Hz, 8H, OCCHCH$_2$), 7.90 (d, 8.2 Hz, 8H, o-CH$_2$por), 7.42 (d, 8.2 Hz, 8H, m-CH$_2$por). 7.21 (d, 8.5 Hz, 8H, OCCH$_2$), 4.15 (t, 7.2 Hz, 8H, SOCH$_2$), 2.48 (s, 12H, CH$_3$), 2.03 (m, 16H, OCH$_2$CH$_2$CH$_2$). $^{13}$C-NMR (CDCl$_3$): $\delta$ 158.3, 144.5, 135.3, 134.4, 132.9, 129.6, 127.7, 119.4, 112.3, 70.0, 66.8, 25.6, 25.2, 21.3. Cs$_8$H$_{34}$Na$_2$O$_{10}$S$_2$: calcd. C 66.7, H 5.47, N 3.54, S 8.10; found C 66.2, H 5.4, N 3.67, S 7.7. GPC (CHCl$_3$:NEt$_3$:2-PrOH = 94:4:2; UV detector at 500 nm): $M_n = 1,580$ Da; PDI = 1.06. MALDI-TOF-MS: m/z [M$^+$] 1582, [M$^+$-tosyl] 1446.

**Microwave synthesis of 5,10,15,20-tetrakis(PEtOx)-21H,23H-porphyrin (4)**

A mixture of porphyrin tosylate 3 (7.92 mg, 0.005 mmol) and EtOx (100 mg, 1 mmol) in CH$_2$CN (0.4 mL) was heated to 140 °C for 20 minutes under microwave irradiation. After heating, the solvent and residual monomer were evaporated under vacuum and the resulting residue was purified by preparative size exclusion chromatography (biobeads SX-1 with CH$_2$Cl$_2$) resulting in 60 mg of polymer 4 (56% yield).

$^1$H-NMR (CDCl$_3$): $\delta$ 12.23 (s, 2H, NH), 8.85 (br, 8H, CH$_2$por), 8.10 (br, 8H, 8H, OCCHCH$_2$), 7.23 (br, 8H, OCCH$_2$), 4.35-4.17 (br, 16H, OCH$_2$ + SOCH$_2$), 3.75-3.20 (br, 752H, NCH$_2$), 2.57-2.05 (br, 395H, COCH$_2$ + OCH$_2$CH$_2$CH$_2$), 1.11-1.09 (br, 574H, CH$_3$). GPC (CHCl$_3$:NEt$_3$:2-PrOH = 94:4:2; UV detector at 500 nm): $M_n = 10,700$ Da; PDI = 1.18.
4.11 References and Notes

(1) B. L. Hayes, *Microwave synthesis: Chemistry at the speed of light*, CEM publishing, Matthews (NC), 2002.


(18) CCDC 277011 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].


Chapter 5

Microwave-assisted synthesis of 2-oxazoline copolymers

Abstract
The microwave-assisted synthesis of copoly(2-oxazoline)s is described in this chapter. Libraries of diblock and triblock copolymers were prepared by the sequential addition of monomers to the polymerization mixtures. The resulting copolymers were characterized with regard to their thermal and surface properties to investigate the influence of the different monomers. The morphology of the diblock copoly(2-oxazoline)s was examined by AFM. Moreover, the effect of monomer order in the triblock copolymers was investigated by solubility tests. Besides these block copolymers, four random copolymer series were synthesized with a systematic change in the monomer composition. The reactivity ratios for the different copolymerizations were determined to investigate the monomer distribution throughout the copolymer chains. Moreover, the thermal and surface properties of the resulting copolymer series were investigated to determine the mixing behavior of the different combinations of monomers. In addition, the influence of monomer (in)compatibilities on the resulting solubilities were studied as well. Random and block copoly(2-oxazoline)s including the soy-based 2-‘soy alkyl’-2-oxazoline monomer were also prepared under microwave irradiation. The resulting random copolymers were applied to investigate the effect of UV-cross-linking of the unsaturated fatty acid side chains on the thermal and surface properties of the copolymers. On the other hand, the soy-based diblock copolymers were used for the preparation of cross-linked micelles.

Chapter 5

5.1 Introduction

The living cationic ring-opening polymerization of 2-oxazolines is a well-established polymerization technique (see introduction chapter 3). The living character of the polymerization allows the synthesis of a wide variety of well-defined copolymers including random, gradient and block copolymers. Random and gradient copolymers can be synthesized utilizing an one-pot procedure, whereby the monomer distribution throughout the polymer chains is determined by the reactivity of the different monomers. Even though a wide variety of monomers is (commercially) available, only a limited number of studies were performed on random copoly(2-oxazoline)s and their properties. The synthesis of block copolymers on the other hand, is performed in a two-step procedure. After complete consumption of the first monomer, the ‘living’ cationic propagating species is still present. Therefore, the addition of a second monomer will result in the continuation of the polymerization process and the formation of a block copolymer as depicted in Scheme 5.1.

![Scheme 5.1. Schematic representation of the two-step synthesis of a diblock copoly(2-oxazoline).](image)

In principal, multiblock copolymers can be synthesized by the sequential addition of different monomers to the propagating species. The synthesis of BAB and star-block copolymers has been reported starting from bi-, tri-, tetra- and hexafunctional initiators in a two-step copolymerization procedure. However, up to this moment only one report on the synthesis of ABC-triblock copoly(2-oxazoline)s has appeared in literature. Three triblock copolymers with the same monomer order were synthesized in which segments shorter than 10 monomer units were incorporated. The resulting triblock copolymers revealed narrow molecular weight distributions on GPC. The synthesis of longer triblock copolymers has not been established to the best of our knowledge. The possibilities of chain-transfer and chain termination reactions upon addition of monomer obstructed the controlled synthesis of well-defined triblock and longer copolymers via the sequential addition method. Moreover, the livingness of the 2-oxazoline polymerizations is lost when increasing the monomer to initiator ([M]/[I]) ratio (section 3.5 for conventional heating and section 4.5 for microwave heating), which also prevents the synthesis of higher molecular weight copolymer structures. The microwave-assisted polymerization of 2-oxazolines under superheated conditions proceeded with less side-reactions than conventional polymerizations in acetonitrile at ambient pressure as was demonstrated by the truly colorless polymerization mixtures that were obtained under microwave irradiation (section 4.2). Therefore, the synthesis of higher molecular weight copolymer structures might be accessible under microwave irradiation.

This chapter describes the investigations on the microwave-assisted synthesis of copoly(2-oxazoline)s. Section 5.2 reports the preparation of a library of diblock copoly(2-oxazoline)s that was made from all possible combinations of 2-methyl- (MeOx), 2-ethyl- (EtOx), 2-nonyl- (NonOx) and 2-phenyl-2-oxazoline (PhOx) including the four chain-extended homopolymers. Moreover, the thermal and surface properties of this library were investigated to determine the influence of the different monomers. Inspired by the success of the diblock copolymer synthesis, a library of triblock copoly(2-oxazoline)s was prepared and characterized regarding
their thermal and surface properties as well (section 5.3). The synthesis of random and gradient copolymer libraries with systematical changes in compositions of EtOx:NonOx and MeOx:NonOx combinations is described in section 5.4. The effect of the monomer distribution (random or gradient) on the resulting polymer properties is discussed in detail. Section 5.5 deals with the synthesis and characterization of copolymers including the less reactive PhOx monomer. Moreover, random and block copolymers including the 2-‘soy alkyl’-2-oxazoline (see section 4.7) are discussed in section 5.6. Besides the synthesis, the effect of cross-linking on the 2-‘soy alkyl’-2-oxazoline copolymer properties is reported.

5.2 Synthesis and characterization of a 4x4 library of diblock copoly(2-oxazoline)s

Block copoly(2-oxazoline)s can be synthesized in a straightforward manner by the sequential addition of different monomers as described in the introduction. Moreover, sequential addition of MeOx or EtOx and a longer aliphatic or aromatic monomer will result in amphiphilic block copolymers. These (amphiphilic) diblock copoly(2-oxazoline)s are an interesting class of polymers for applications as compatibilizers, emulsifiers, or dispersants. Furthermore, block copoly(2-oxazoline)s have been used for micellar catalysis, the preparation of hollow nanotubes and for the modification of enzymes.

The microwave-assisted synthesis of a 16-membered library of chain-extended homo poly(2-oxazoline)s and diblock copoly(2-oxazolines) consisting of the MeOx, EtOx, NonOx and PhOx (Figure 5.1) is described in this section. This 4x4 library of diblock copoly(2-oxazoline)s was analyzed using GPC, $^1$H-NMR spectroscopy, thermal gravimetical analysis (TGA) and differential scanning calorimetry (DSC).

Figure 5.1. Schematic representation of the synthesized 4x4 library of chain-extended homo poly(2-oxazoline)s and diblock copoly(2-oxazoline)s.

5.2.1 Microwave synthesis of a library of diblock copoly(2-oxazoline)s

The synthesis of the 16-membered library of diblock copoly(2-oxazoline)s was performed utilizing the optimal polymerization conditions that resulted from the investigations on the homopolymerizations (section 4.3). The methyl tosylate (MeOTs) initiated polymerizations were performed at 140 °C in acetonitrile (CH$_3$CN) with 40 w% of monomer ([MeOx] = [EtOx] = 4 M, [PhOx] = 3 M and [NonOx] = 2 M). Furthermore, the homopolymerizations of the different monomers were found to be controlled up to a [M]/[I] ratio of at least 100. Accordingly, the block copolymers were prepared with a total number of 100 monomer units and thus the blocks were composed of 50 monomer units. The first segments of the polymers were prepared six times from one single stock solution containing monomer, solvent and initiator. The first and sixth polymerizations were used to test the reproducibility of the polymerization: If both the first and sixth vials resulted in equal molecular weight...
distributions (GPC) it was assumed that all polymerizations in between were identical too. This procedure was chosen to prevent contamination during sampling. The four polymerizations in between were used for the preparation of the actual block copolymers by the addition of the neat second monomer under an argon atmosphere after cooling the polymerization mixture to room temperature. Subsequently, the polymerization of the second block was performed at 140 °C under microwave irradiation. The synthesis of four diblock copoly(2-oxazoline)s (including chain extension) having the same first block is schematically depicted in Figure 5.2. Despite the insolubility of the pNonOx in CH$_3$CN at ambient temperature, the pNonOx-containing block copolymers were synthesized in CH$_3$CN as well.

![Figure 5.2. Synthesis of four diblock copolymers (including chain extension) with the same first block.](image1)

The polymerization times required for complete conversion (\(\ln ([M]_0/[M]_t) = 4\) corresponding to a monomer conversion of 98%) of both the first and the second monomer were calculated from the velocity equation 3.2 together with the previously determined kinetic parameters for the homopolymerizations (section 4.3). The total required polymerization time depends on the initial initiator concentration and the reactivity of the monomers (Table 2). The initiator concentration scales directly with the monomer concentration since the [M]/[I] ratio remains constant. The polymerization times lie in the range from 13.3 min (p(MeOx$_{50}$-b-MeOx$_{50}$) and p(MeOx$_{50}$-b-NonOx$_{50}$)) to 80 min (for the chain-extended p(Phe$_{50}$-b-Phe$_{50}$)). More generally, reaction times of less than 30 minutes were required for the block copolymers that did not contain a pPhOx block, whereas the polymers that contain a pPhOx block require reaction times of more than 30 minutes due to the lower nucleophilicity of the PhOx monomer (see also section 3.3.4). Nevertheless, the synthesis of the entire 4×4 library of diblock copoly(2-oxazoline)s took less than one day (20.4 hours) net polymerization time.

<table>
<thead>
<tr>
<th>2(^{nd}) block</th>
<th>1(^{st}) block</th>
<th>MeOx</th>
<th>EtOx</th>
<th>NonOx</th>
<th>PhOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOx</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
</tr>
<tr>
<td></td>
<td>400 s + 400 s</td>
<td>400 s + 500 s</td>
<td>400 s + 400 s</td>
<td>400 s + 1800 s</td>
<td></td>
</tr>
<tr>
<td>EtOx</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
<td>4 M</td>
</tr>
<tr>
<td></td>
<td>500 s + 400 s</td>
<td>500 s + 500 s</td>
<td>500 s + 400 s</td>
<td>500 s + 1800 s</td>
<td></td>
</tr>
<tr>
<td>NonOx</td>
<td>2 M</td>
<td>2 M</td>
<td>2 M</td>
<td>2 M</td>
<td>2 M</td>
</tr>
<tr>
<td></td>
<td>800 s + 800 s</td>
<td>800 s + 1000 s</td>
<td>800 s + 800 s</td>
<td>800 s + 3600 s</td>
<td></td>
</tr>
<tr>
<td>PhOx</td>
<td>3 M</td>
<td>3 M</td>
<td>3 M</td>
<td>3 M</td>
<td>3 M</td>
</tr>
<tr>
<td></td>
<td>2400 s + 600 s</td>
<td>2400 s + 800 s</td>
<td>2400 s + 600 s</td>
<td>2400 s + 2400 s</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.1.** Reaction times for the preparation of the diblock copolymers. Each cell depicts the initial monomer concentration (top) and the polymerization times for the first and the second block (bottom).
5.2.2 Structural characterization of the 4×4 diblock copoly(2-oxazoline) library

The obtained copoly(2-oxazoline)s were characterized with GPC to determine the molecular weight (distribution) and $^1$H-NMR spectroscopy to elucidate the number of incorporated monomer units.

The GPC analysis of the diblock copoly(2-oxazoline)s had to be performed utilizing two different eluents, namely chloroform:triethylamine:2-propanol (94:4:2) and N,N-dimethylformamide (DMF) containing 5 mM ammonium hexafluorophosphate. Polymers that contained a pMeOx segment revealed strong interactions with the column material (cross-linked polystyrene) when using the chloroform mixture as eluent and had to be analyzed with DMF as eluent. On the other hand, pNonOx-containing polymers were insoluble in DMF and had to be measured with chloroform as eluent. As a consequence, Me$_{50}$Non$_{30}$ and Non$_{50}$Me$_{50}$ diblock copolymers could not be characterized with these eluents. However, changing the ratio of the solvent mixture to chloroform:triethylamine:2-propanol (from 94:4:2 to 80:10:10) could suppress the interactions of the pMeOx segment with column material almost completely resulting in GPC traces of which the PDI-values could be estimated. The polymers that did not contain a pNonOx or a pMeOx segment were analyzed using both eluents. Figure 5.3 depicts selected GPC traces from the 4×4 library of diblock copoly(2-oxazoline)s.

Figure 5.3. Selected GPC-traces of the set of 16 chain-extended and diblock copoly(2-oxazoline)s having pMeOx (top left; eluent DMF), pEtOx (top right; DMF), pNonOx (bottom left, CHCl$_3$) or pPhOx (bottom right, DMF) as first blocks.
Table 5.2. Theoretical and determined (GPC) number average molecular weights and polydispersity indices for the first blocks and chain-extended homopoly(2-oxazoline)s.

<table>
<thead>
<tr>
<th>polymer</th>
<th>( M_{n,th} ) (kDa)</th>
<th>( M_{n,GPC} ) (kDa)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMeOx(_{50})^a</td>
<td>4.3</td>
<td>4.0</td>
<td>1.10</td>
</tr>
<tr>
<td>p(MeOx(<em>{50}-b)-MeOx(</em>{50}))^a</td>
<td>8.5</td>
<td>6.3</td>
<td>1.16</td>
</tr>
<tr>
<td>pEtOx(_{50})^b</td>
<td>5.0</td>
<td>4.8</td>
<td>1.08</td>
</tr>
<tr>
<td>p(EtOx(<em>{50}-b)-EtOx(</em>{50}))^b</td>
<td>10.0</td>
<td>9.5</td>
<td>1.12</td>
</tr>
<tr>
<td>pNonOx(_{50})^b</td>
<td>9.9</td>
<td>9.2</td>
<td>1.10</td>
</tr>
<tr>
<td>p(NonOx(<em>{50}-b)-NonOx(</em>{50}))^b</td>
<td>19.8</td>
<td>16.1</td>
<td>1.14</td>
</tr>
<tr>
<td>pPhOx(_{50})^b</td>
<td>7.4</td>
<td>7.2</td>
<td>1.13</td>
</tr>
<tr>
<td>P(PhOx(<em>{50}-b)-PhOx(</em>{50}))^b</td>
<td>14.7</td>
<td>12.0</td>
<td>1.27</td>
</tr>
</tbody>
</table>

\(^a\) Measurements performed with DMF containing 5 mM \( \text{NH}_4\text{PF}_6\) as eluent (PEG calibration).

\(^b\) Measurements performed with \( \text{CHCl}_3\):\( \text{NEt}_3\):2-PrOH (94:4:2) as eluent (PS calibration).

The molecular weights of the first blocks and the chain-extended homopolymers could be calculated from the GPC results using a polystyrene (PS) calibration on the chloroform system and a poly(ethylene glycol) (PEG) calibration on the DMF system. The resulting number average molecular weights and polydispersity indices (PDI’s) are summarized in Table 5.2. The observed molecular weights are (slightly) lower than the theoretical value due to the applied calibrations as was also shown in section 4.5 by MALDI-TOF-MS comparison experiments. In contrast to the homo poly(2-oxazoline)s, the molecular weights calculated from the GPC traces of the diblock copoly(2-oxazoline)s did not correspond to the theoretical molecular weights. This discrepancy is attributed to the different folding behavior of the different diblock copolymers resulting in other hydrodynamic volumes and thus resulting in inaccurate molecular weights. Nevertheless, the resulting PDI values were considered to demonstrate the success of the block copolymerizations. Table 5.3 depicts the theoretical molecular weights of the diblock copolymers and the obtained PDI values using both eluents. With the exception of the p(NonOx\(_{50}-b\)-EtOx\(_{50}\)) and p(NonOx\(_{50}-b\)-MeOx\(_{50}\)) block copolymers, all PDI values were found to be lower than 1.30 (10 of the 16 polymers exhibited polydispersity indices well below 1.20) indicating that the well-defined diblock copolymers were successfully synthesized. Moreover, most of the AB and BA block copolymers revealed similar PDI values. Pronounced deviations from the narrow PDI’s were observed for the p(NonOx\(_{50}-b\)-EtOx\(_{50}\)) (PDI = 1.64) and p(NonOx\(_{50}-b\)-MeOx\(_{50}\)) (PDI ~ 1.7), whereas the p(EtOx\(_{50}-b\)-NonOx\(_{50}\)) and p(MeOx\(_{50}-b\)-NonOx\(_{50}\)) revealed narrow molecular weight distributions. The GPC trace of p(NonOx\(_{50}-b\)-EtOx\(_{50}\)) (Figure 5.3 bottom left) revealed obvious shoulders at both higher molecular weight (shorter retention time) and lower molecular weight (longer retention time). These shoulders most likely result from chain-transfer reactions followed by chain coupling\(^24\) as was already discussed in section 3.2.2 (Scheme 3.2). The low molecular weight shoulder might result from \( \alpha\)-hydrogen subtraction of the oxazolinium propagating species by unreacted monomer resulting in both a cationic monomer and an enamine ether chain end. The cationic monomer can grow a new lower molecular weight polymer chain and coupling of the enamine chain end to the cationic propagating species can result in the high molecular weight polymers.
Table 5.3. Theoretical number average molecular weights ($M\text{\textsubscript{\text{n},th}}$) and PDI’s (bottom; measured with CHCl\textsubscript{3} / DMF as eluent) for the 4 chain-extended and 12 diblock copoly(2-oxazoline)s.

<table>
<thead>
<tr>
<th>2\textsuperscript{nd} block</th>
<th>MeOx</th>
<th>EtOx</th>
<th>NonOx</th>
<th>PhOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} block↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOx</td>
<td>8.5 kDa / 1.16</td>
<td>9.2 kDa / 1.17</td>
<td>14.2 kDa / ~1.3\textsuperscript{a}</td>
<td>11.6 kDa / −</td>
</tr>
<tr>
<td>EtOx</td>
<td>9.2 kDa / 1.18</td>
<td>9.9 kDa / 1.16 / 1.17</td>
<td>14.8 kDa / 1.15 / −</td>
<td>12.3 kDa / 1.27 / 1.19</td>
</tr>
<tr>
<td>NonOx</td>
<td>14.2 kDa / ~1.7 / −</td>
<td>14.8 kDa / 1.64 / −</td>
<td>19.7 kDa / 1.14 / −</td>
<td>17.2 kDa / 1.24 / −</td>
</tr>
<tr>
<td>PhOx</td>
<td>11.6 kDa / 1.18</td>
<td>12.3 kDa / 1.35 / 1.19</td>
<td>17.2 kDa / 1.28 / −</td>
<td>14.7 kDa / 1.27 / 1.16</td>
</tr>
</tbody>
</table>

\textsuperscript{a} GPC measurements performed with CHCl\textsubscript{3}:NEt\textsubscript{3}:2-PrOH (80:10:10) as eluent to suppress the column interactions of the pMeOx segment.

The proposed chain-transfer and subsequent chain coupling side-reactions were further investigated by GPC fractionation experiments. Using a fraction collector on the GPC apparatus, the molecular weight distribution of the p(NonOx\textsubscript{50}-b-EtOx\textsubscript{50}) was separated into two separate fractions of the major signal and the low molecular weight shoulder (Figure 5.4 left). \textsuperscript{1}H-NMR spectroscopy of the two fractions revealed that the low molecular weight fraction (fraction 2) almost solely consists of pEtOx, whereas fraction 1 consists of pNonOx and pEtOx in an approximately 1:1 ratio (Figure 5.4 right). The monomer contents were calculated on the basis of the integrals of the terminal CH\textsubscript{3} resonances of the pNonOx and pEtOx at 0.85 and 1.10 ppm, respectively. Moreover, IR-spectroscopy of the two fractions confirmed these observations (not shown) proving the occurrence of the proposed chain-transfer and chain coupling mechanism. Why the chain-transfer to monomer mainly occurs with pNonOx as first block and much less with the other first blocks (see Figure 5.3) is not clear at the moment. However, it can be concluded that the order of the monomers in the present block copolymer synthesis has to be chosen carefully to obtain well-defined copolymers.

\textbf{Figure 5.4.} Left: GPC traces obtained before and after fractionation of p(NonOx\textsubscript{50}-b-EtOx\textsubscript{50}). Right: \textsuperscript{1}H-NMR spectra obtained for the two GPC fractions (in CHCl\textsubscript{3}:NEt\textsubscript{3}:2-PrOH).
Due to the different chain folding of the various diblock copoly(2-oxazoline)s in the library, the molar mass and the number of incorporated monomer units could not be determined by GPC analysis. Therefore, $^1$H-NMR spectroscopy was used to investigate whether the number of incorporated monomer units resembles the theoretical number. The integral ratios of the different monomers were used to calculate the ratio of the two monomers in a diblock copolymer. Unfortunately, the methyl group resulting from the initiator could not be reliably integrated in the $^1$H-NMR spectra due to partial (or complete) overlap with the signals of the polymer backbone. Nevertheless, GPC characterization confirmed that all first blocks consisted of approximately 50 monomer units (Table 5.2). Combined GPC and $^1$H-NMR analyses demonstrated that all diblock copolymers consisted of 95 to 102 monomer units as depicted in Table 5.4, which is close to the desired 100 monomer units.

Table 5.4. Number of incorporated monomers in the 12 diblock copoly(2-oxazoline)s resulting from combined $^1$H-NMR and GPC analyses, whereby the value for the first monomer was set to 50.

<table>
<thead>
<tr>
<th>2nd block →</th>
<th>MeOx</th>
<th>EtOx</th>
<th>NonOx</th>
<th>PhOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st block ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOx</td>
<td>–</td>
<td>50:49</td>
<td>50:52</td>
<td>50:52</td>
</tr>
<tr>
<td>EtOx</td>
<td>50:50</td>
<td>–</td>
<td>50:50</td>
<td>50:52</td>
</tr>
<tr>
<td>NonOx</td>
<td>50:50</td>
<td>50:46</td>
<td>–</td>
<td>50:45</td>
</tr>
<tr>
<td>PhOx</td>
<td>50:48</td>
<td>50:46</td>
<td>50:50</td>
<td>–</td>
</tr>
</tbody>
</table>

5.2.3 Thermal analysis of the 4×4 library of diblock copoly(2-oxazoline)s

The thermal stability of the 4×4 library of chain-extended homo and diblock copoly(2-oxazoline)s was determined by thermogravimetical analysis (TGA) in the range from 30 to 500 °C (Figure 5.5 left). The polymers that contained a hygroscopic pMeOx or pEtOx segment revealed a ~10% weight loss around 100 °C due to the loss of water. All polymers were stable up to temperatures of at least 300 °C, whereby the 5% weight loss temperatures span a relatively broad range from 308 to 371 °C since this point was difficult to determine when water was present. All polymers degraded in one step with the inflection point in the range from 393 to 437 °C. This high thermal stability is comparable to other N-C=O containing polymers like poly($\varepsilon$-caprolactam) that degrades at 327 ºC.25

The thermal properties (glass transition temperature $T_g$ and melting point $T_m$) of the library of chain-extended and diblock copolymers were determined by differential scanning calorimetry (DSC). After the initial heating run, the polymers were heated four times from −100 to 200 °C using 40 K·min$^{-1}$ (3 times) to determine $T_g$ and 10 K·min$^{-1}$ to determine $T_m$. All pNonOx-containing polymers revealed a melting exotherm in the narrow range from 146 to 151 °C, which is close to the previously reported $T_m$ for pNonOx of 151 °C.26 Moreover, all copolymers, except for p(PhOx$_{50}$-b-NonOx$_{50}$), p(NonOx$_{50}$-b-PhOx$_{50}$) and p(NonOx$_{50}$-b-NonOx$_{50}$), exhibited a $T_g$ in DSC as shown in Figure 5.5 right. The $T_g$'s of the chain-extended homopolymers correspond well with the literature values as depicted by the stars in Figure 5.5 right.11,27,28 Moreover, the absence of a $T_g$ in DSC for pNonOx was also previously reported.26
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The observed $T_g$’s of all AB and BA diblock copolymers were found to be equal within the standard deviation. Surprisingly, this is also true for the $p$(NonOx$_{50}$-b-EtOx$_{50}$) and $p$(EtOx$_{50}$-b-NonOx$_{50}$) as well as the $p$(NonOx$_{50}$-b-MeOx$_{50}$) and $p$(MeOx$_{50}$-b-NonOx$_{50}$) combinations even though the side-reactions occurred during the synthesis of these diblock copoly(2-oxazoline)s (see section 5.2.2). All polymers that contained a pPhOx segment and the chain-extended pMeOx homopolymer revealed $T_g$’s in the range from 80 to 110 °C, whereas all other block copolymers revealed $T_g$’s below 80 °C. Moreover, the three diblock copolymers with the relatively flexible ethyl and/or nonyl side-chains [p(EtOx$_{50}$-b-EtOx$_{50}$), p(NonOx$_{50}$-b-EtOx$_{50}$) and p(EtOx$_{50}$-b-NonOx$_{50}$)] revealed the lowest $T_g$’s (T$_g$ $\leq$ 60 °C). Apparently, the $T_g$ of the poly(2-oxazoline) strongly depends on the flexibility of the side-chains: The rigid substituents like phenyl and methyl result in high $T_g$’s and the more flexible ethyl and nonyl substituents result in lower $T_g$’s. Moreover, a lower $T_g$ can be interpreted as a higher chain mobility of a polymer$^{29}$ meaning that the more flexible side chains increase the chain mobility of the poly(2-oxazoline). All diblock copolymers revealed only one $T_g$, which is probably due to the short block lengths (50 monomer units) that prevent the formation of large phase-separated domains with individual $T_g$’s.

5.2.4 Surface properties of the 4×4 library of diblock copoly(2-oxazoline)s

The surface properties of the library of diblock copoly(2-oxazoline)s were investigated by measuring the contact angles of both a polar (ethylene glycol) and an apolar (diiodomethane) test liquid on thin spin-coated polymer films. The resulting contact angles of ethylene glycol and diiodomethane are depicted in Figure 5.6. The contact angle plots of both test liquids are mirror symmetric indicating that the influence of the end groups is negligible. The typical error of the contact angles lies within 1-2°. However, the contact angles of ethylene glycol on polymer films containing pMeOx or pEtOx were slightly time-dependent. Therefore, the contact angle values were determined approximately 2 seconds after droplet deposition. Nevertheless, the influence of this time dependency on the calculated surface energies is negligible. Surprisingly, the contact angle of ethylene glycol on chain-extended pMeOx did not change with time.
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Figure 5.6. Contact angles of ethylene glycol (left) and diiodomethane (right) on thin films of the diblock copoly(2-oxazoline)s.

The surface energies (SE’s) of the diblock copolymers as depicted in Figure 5.7 were calculated from the contact angles of ethylene glycol and diiodomethane utilizing the equation of state method (see also section 3.4.2). All polymers that contain a pNonOx segment have a low SE in the range from 19 to 23 mN·m⁻¹ indicative of hydrophobic surfaces while all other poly(2-oxazoline)s exhibit SE’s in between 40 and 45 mN·m⁻¹. Similar results were obtained by Litt and Herz for poly(2-n-alkyl-2-oxazoline)s and by Kamagata and Toyama for poly(n-alkyl methacrylate). The lower SE found for polymers with long alkyl chains was attributed to a close packing of alkyl chains at the surface. The lower SE’s for the pNonOx-containing diblock copolymers correspond to the results reported for block copolymers consisting of a poly(2-undecyl-2-oxazoline) block and a pMeOx, pEtOx or pPhOx segment. It was shown that the low SE’s resulted from closely packed methyl groups on the surface due to preferential orientation of the undecyl chains towards the surface. Similarly, it can be concluded that the nonyl chains in the present diblock copolymers also preferentially orient towards the surface.

Figure 5.7. Surface energies of 4×4 library of poly(2-oxazoline)s calculated from the contact angles utilizing the equation of state method.
5.2.5 Thin film morphology of the 4×4 library of diblock copoly(2-oxazoline)s

The SE’s of the pNonOx-containing copolymers indicated full coverage of the surface with nonyl chains. However, the SE does not provide any information on the surface morphology. Therefore, non-annealed spin-cast films of the diblock copolymers and chain-extended homopolymers were investigated with atomic force microscopy (AFM). The resulting height images (not shown) revealed flat polymer films with a roughness below 2 nm except for the p(NonOx$_{50}$-b-PhOx$_{50}$), which had a roughness of ~10 nm. The corresponding phase images are depicted in Figure 5.8. These phase images revealed noteworthy phase contrast for the pNonOx-containing polymers and almost no phase contrast for the other 9 polymers. One exception is the p(NonOx$_{50}$-b-EtOx$_{50}$) that showed no significant phase contrast either, which is probably due to the chain-transfer that occurred during the polymerization resulting in a complex mixture of homo and block copolymers. Even though the SE’s of the pNonOx-containing polymers indicated complete surface coverage by the nonyl chains, phase contrast is observed for these polymers. A possible explanation for these conflicting observations might be that parts of the nonyl chains on the surface are crystallized resulting in harder areas leading to different phase contrast than amorphous pNonOX areas. Moreover, the p(NonOx$_{50}$-b-PhOx$_{50}$) block copolymer showed large features that were not present in the p(PhOx$_{50}$-b-NonOx$_{50}$). These ‘drops’ appear to be similar to the phase separation of poly(methyl methacrylate)-polystyrene blends in which the PMMA rich domains appear as circular features in a PS rich matrix. At this moment, no definite reason can be provided for the observed features in both phase and height images of the p(NonOx$_{50}$-b-PhOx$_{50}$) thin film.

Figure 5.8. AFM phase images (1×1 µm) obtained for the diblock copolymer library.
Moreover, the phase images of the p(MeOx\textsubscript{50}-b-NonOx\textsubscript{50}) and p(NonOx\textsubscript{50}-b-MeOx\textsubscript{50}) revealed regular patterns in the morphology as can be seen in the enlarged phase images (Figure 5.9). The formation of these structures might be driven by the strong phase separation of pMeOx and pNonOx (see also section 3.6.4), whereby the phase contrast could result from crystalline pNonOx domains.

**Figure 5.9.** Enlarged AFM phase images (1×1 µm) of the p(MeOx\textsubscript{50}-b-NonOx\textsubscript{50}) and p(NonOx\textsubscript{50}-b-MeOx\textsubscript{50}) diblock copolymers.

### 5.3 Microwave synthesis of a library of triblock copoly(2-oxazoline)s

The successful microwave-assisted synthesis of the 4×4 library of chain-extended and diblock copoly(2-oxazoline)s encouraged us to continue with the preparation of a triblock copoly(2-oxazoline) library under microwave heating. The combination of the MeOx, EtOx, NonOx and PhOx would allow the preparation of 64 different triblock copolymers. However, all polymers that would have two times the same block after each other were excluded resulting in a 36-membered library. Moreover, the triblock copolymers with pNonOx as first block and pMeOx or pEtOx as second block were also expelled since the corresponding diblock copolymerizations underwent extensive side-reactions. Nevertheless, the synthesis of triblock copolymers with pNonOx as second block and pMeOx and pEtOx as third block were attempted. The synthesis and characterization of the remaining 30-membered triblock copoly(2-oxazoline) library are described in this section.

#### 5.3.1 Synthesis and structural characterization of the triblock copoly(2-oxazoline)s

The triblock copolymers were synthesized in a similar manner as the diblock copolymers. The methyl tosylate initiated microwave polymerizations were performed in CH\textsubscript{3}CN at 140 °C aiming for a total number of 100 monomer units corresponding to 33 units per block. For the synthesis of the triblock copolymers, a stock solution containing the first monomer, initiator and solvent was divided over seven vials followed by microwave irradiation (the initial monomer concentration was the same as for the diblock copolymers). The first and last polymerizations were used to check the reproducibility of the polymerization of the first block. To the remaining five polymerization mixtures, the neat second monomer was added under an argon atmosphere. After microwave-assisted polymerization, the second and fifth vials were applied to check the reproducibility of the diblock copolymerizations. If these
Microwave-assisted synthesis of 2-oxazoline copolymers

diblock copolymers were the same, it was assumed that the first two blocks of the three triblock copolymers were the same as well. To the three middle vials, the three different monomers (excluding the monomer of the second block) were neatly added followed by microwave-assisted polymerization resulting in the formation of the three triblock copolymers. This complete polymerization procedure is depicted in Figure 5.10.

![Figure 5.10. Synthesis of three triblock copolymers with the same first and second blocks.](image)

GPC characterization of the triblock copoly(2-oxazoline)s was performed using DMF containing 5 mM NH₄PF₆ as eluent. Only some of the pNonOx-containing polymers were insoluble in DMF and these have been measured using CHCl₃:NEt₃:2-PrOH (94:4:2 or 80:10:10) as eluent. Both the triethylamine and 2-propanol were present to reduce the interactions between the column material and the polymers, whereby the pMeOx-containing polymer required much more additives to suppress the column interactions. The resulting molecular weights and PDI values are summarized together with the theoretical molecular weights in Table 5.5. Most of the triblock copolymers (22 out of 30) were obtained with reasonably narrow molecular weight distributions with PDI ≤ 1.33. Moreover, five triblock copoly(2-oxazoline)s were obtained with PDI ≥ 1.55. These five polymers all contained a pMeOx or pEtOx segment directly after a pNonOx block, which leads to chain-transfer and subsequent chain coupling reactions as was elucidated during the diblock copolymer synthesis. Surprisingly, the p(EtOx-b-NonOx-b-EtOx) was obtained with a narrow molecular weight distribution (PDI = 1.22). It is noteworthy to mention that all of these p(NonOx-b-MeOx) and p(NonOx-b-EtOx) containing triblock copolymers revealed low PDI values (PDI < 1.30) when measured with DMF as eluent due to different folding of the present homo, diblock and triblock copolymer fractions. As a result, the polymer mixtures elute as one distribution with some shoulders. The GPC traces of the remaining three triblock copolymers [p(MeOx-b-EtOx-b-NonOx), p(NonOx-b-PxOx-b-MeOx) and p(NonOx-b-PxOx-b-NonOx); 1.33 < PDI < 1.55] revealed tailing and shoulders indicating that some of the polymer chains were most likely terminated during the addition of the second and/or third monomer to the living propagating species. The obtained number average molecular weight values (Mₙ,GPC) for all triblock copoly(2-oxazoline)s are in the range of the theoretical molecular weights with exception of the p(MeOx-b-EtOx-b-NonOx), p(MeOx-b-NonOx-b-MeOx) and p(EtOx-b-NonOx-b-MeOx), which revealed much too low Mₙ values corresponding to their high PDI values. Even though the observed Mₙ’s lie in the expected range, they do not correlate directly with the theoretical Mₙ’s. In general, the pPhOx-containing polymers exhibit a Mₙ larger than theoretical and the pNonOx-containing triblock copolymers revealed Mₙ values smaller than theoretical in DMF. This can be explained by the different folding behavior of the pPhOx that is good soluble and thus swollen in DMF and the pNonOx that is poorly soluble and thus collapsed in DMF. As a result, the hydrodynamic volume of pPhOx will be much larger than the hydrodynamic volume of pNonOx in DMF and thus the observed molar mass of pPhOx-containing polymers will be larger than that of pNonOx-containing polymers even though the actual molar masses are the other way around.
The synthesized triblock copolymers were also characterized by \(^1\)H-NMR spectroscopy. The ratios of the different monomers were calculated from the integrals of the different monomers and the polymer backbone. To be able to integrate the aromatic protons of the pPhOx accurately, the pPhOx-containing polymers were measured in CD\(_2\)Cl\(_2\) instead of CDCl\(_3\). The GPC molecular weights of the first blocks corresponded well with the theoretical molecular weights justifying the assumption that all first blocks consisted of 33 monomer units. The number of incorporated monomer units that resulted from the \(^1\)H-NMR and GPC analyses are summarized in Table 5.6. Most of the triblock copolymers consist of the desired number of monomer units with a deviation of up to 5 monomer units. Four of the triblock copolymers [p(NonOx-b-PhOx-b-MeOx), p(NonOx-b-PhOx-b-EtOx), p(PhOx-b-EtOx-b-PhOx) and p(PhOx-b-NonOx-b-EtOx)] revealed a deviation of ~10 units, whereby it should be mentioned that the integration of the \(^1\)H-NMR spectra of the pPhOx-containing copolymers is more difficult due to the broad backbone signal of the pPhOx (3.9 to 2.4 ppm). In conclusion, the microwave-assisted polymerization procedure proved to be well-suited for the synthesis of well-defined triblock copoly(2-oxazoline)s.
Table 5.6. Number of incorporated monomers in the 30 triblock copoly(2-oxazoline)s resulting from combined $^1$H-NMR and GPC analyses, whereby the value for the first monomer was set to 33.

<table>
<thead>
<tr>
<th>3rd block →</th>
<th>MeOx</th>
<th>EtOx</th>
<th>NonOx</th>
<th>PhOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-2nd block ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOx-EtOx</td>
<td>33:28:33</td>
<td>–</td>
<td>33:31:33</td>
<td>33:33:32</td>
</tr>
<tr>
<td>MeOx-NonOx</td>
<td>33:28:33</td>
<td>33:30:37</td>
<td>–</td>
<td>33:29:29</td>
</tr>
<tr>
<td>MeOx-PhOx</td>
<td>33:31:33</td>
<td>33:33:36</td>
<td>33:30:32</td>
<td>–</td>
</tr>
<tr>
<td>EtOx-MeOx</td>
<td>–</td>
<td>33:33:33</td>
<td>33:34:31</td>
<td>33:29:27</td>
</tr>
<tr>
<td>EtOx-NonOx</td>
<td>33:33:37</td>
<td>33:33:33</td>
<td>–</td>
<td>33:33:31</td>
</tr>
<tr>
<td>EtOx-PhOx</td>
<td>33:31:30</td>
<td>33:30:33</td>
<td>33:30:36</td>
<td>–</td>
</tr>
<tr>
<td>NonOx-PhOx</td>
<td>33:23:27</td>
<td>33:26:24</td>
<td>33:32:33</td>
<td>–</td>
</tr>
<tr>
<td>PhOx-MeOx</td>
<td>–</td>
<td>33:35:35</td>
<td>33:31:31</td>
<td>33:27:33</td>
</tr>
<tr>
<td>PhOx-EtOx</td>
<td>33:35:34</td>
<td>–</td>
<td>33:38:38</td>
<td>33:42:33</td>
</tr>
<tr>
<td>PhOx-NonOx</td>
<td>33:38:34</td>
<td>33:45:37</td>
<td>–</td>
<td>33:36:33</td>
</tr>
</tbody>
</table>

5.3.2 Thermal analysis of the library of triblock copoly(2-oxazoline)s

The degradation temperatures of the synthesized triblock copolymers were not determined since all diblock copoly(2-oxazoline)s exhibited similar thermal stabilities (section 5.2.3) and thus the influence of monomer order in the triblock copoly(2-oxazoline)s will be negligible as well. DSC revealed melting points in the range from 143 to 157 ºC for all pNonOx-containing triblock copolymers. As a result, it can be concluded that the length of 33 monomer units in the pNonOx segments is sufficient for side-chain crystallinity. The $T_g$’s of the triblock copolymer library showed similar trends as the diblock copolymer library. First of all, the triblock copolymers having both a pPhOx and a pNonOx segment did not reveal a $T_g$ in DSC corresponding to the absence of a $T_g$ in DSC for the p(PhOx$_{50}$-b-pNonOx$_{50}$) and p(NonOx$_{50}$-b-pPhOx$_{50}$) diblock copolymers. Moreover, all other pNonOx-containing triblock copolymers revealed $T_g$’s in between 48 and 55 ºC due to the flexibility of the nonyl side chains. The only exception is the p(MeOx-b-NonOx-b-MeOx) in which the pMeOx segments compensate for the flexibility of the pNonOx resulting in a $T_g$ of 61 ºC. A similar $T_g$ (62 ºC) was found for the comparable p(MeOx-b-EtOx-b-MeOx) triblock copolymer that also has two hard outer segments and a flexible middle block. The triblock copolymers with one pPhOx segment revealed $T_g$’s in between 74 and 81 ºC due to the rigidity of the phenyl substituents. Again the triblock copolymer with two outer pMeOx segments exhibited a higher $T_g$ (84 ºC) than the other polymers with one pPhOx segment. The highest $T_g$’s were observed for the triblock copolymers with two pPhOx outer blocks, whereby the more flexible pEtOx middle block resulted in a $T_g$ of 86 ºC and the rigid pMeOx middle block resulted in a $T_g$ of 98 ºC, which is close to the $T_g$ of the homo pPhOx (107 ºC). These results clearly demonstrated that the $T_g$ of the poly(2-oxazoline)s can be systematically varied from 50 to 100 ºC by the synthesis of triblock copolymers with equal block lengths. Moreover, the observed trends closely resemble the rigidity of the incorporated monomers, whereby especially the effects of incorporating a pNonOx or pPhOx segment are remarkable.
5.3.3 Surface properties of the library of triblock copoly(2-oxazoline)s

The SE’s of the triblock copolymers were determined by contact angle measurements of ethylene glycol and diiodomethane on spin-cast polymer films. From these contact angles, the SE’s were calculated using the equation of state method. The resulting SE’s for non-annealed films are depicted in Figure 5.12. All triblock copolymers without a pNonOx segment revealed a SE close to 45 mN·m⁻¹ as expected since a similar SE was observed for the pMeOx, pEtOx and pPhOx homopolymers. Moreover, all triblock copolymers consisting of pNonOx with pPhOx and/or pMeOx revealed SE’s close to 25 mN·m⁻¹, which is close to the SE of pNonOx. This observation can be explained by effective phase separation between the pNonOx and pMeOx / pPhOx that facilitates preferential orientation of the nonyl side chains towards the surface. Moreover, the triblock copolymers that contain both pNonOx and pEtOx segments reveal SE’s in between 25 and 35 mN·m⁻¹. These values lie in between the SE’s of pNonOx and pEtOx indicating that the pNonOx and pEtOx segments mix instead of phase separate. The mixing of pNonOx and pEtOx was also observed for amphiphilic diblock copolymers in section 3.6.4.
The SE’s energies were also determined after annealing the polymer films of the triblock copolymers that contain a pNonOx segment (Figure 5.13). In principle, the pNonOx segments should orient towards the surface resulting in more favorable lower SE’s. Besides the pNonOx-containing polymers also two other polymers were annealed to verify that the SE’s of these polymer films do not change with annealing. After annealing at 65 °C, which is higher than the T\(_g\)’s of the investigated polymers, SE’s of the pNonOx- and pPhOx-containing triblock copolymers decreased below 25 mN·m\(^{-1}\) indicating strong phase separation between the pPhOx and pNonOx segments. The SE’s of the remaining triblock copolymers with pNonOx as middle block decreased below 25 mN·m\(^{-1}\) after annealing at 100 °C. After this second annealing step the p(MeOx-\(b\)-EtOx-\(b\)-NonOx) and p(EtOx-\(b\)-MeOx-\(b\)-NonOx) still revealed SE’s around 30 mN·m\(^{-1}\) demonstrating that also pEtOx remained at the surface. Only melting of these last two polymer films at 150 °C resulting in a drop of the SE below 25 mN·m\(^{-1}\). The difference in annealing behavior of the triblock copolymers consisting of pMeOx and/or pEtOx with pNonOx as middle or outer block probably result from the observed chain-transfer reactions that occur when polymerizing MeOx or EtOx after on the pNonOx block. As a result, the triblock copolymers with pNonOx as middle block consist of mixtures of homo, diblock and triblock copolymers simplifying the phase separation by the presence of pMeOx or pEtOx homopolymer.

Figure 5.13. SE’s of annealed polymer films of the triblock copoly(2-oxazoline)s. Me = pMeOx, Et = pEtOx, Non = pNonOx and Ph = pPhOx.

5.3.5 Solubility of the triblock copoly(2-oxazoline)s

The influence of the order of the segments in the triblock copolymers on their solubility was investigated. All pPhOx- and pNonOx-containing triblock copoly(2-oxazoline)s were not readily soluble in water (10 w% solutions); whereas, the triblock copolymers consisting of only the water-soluble pMeOx and pEtOx obviously did dissolve. To further expand the scope of the solubility studies, the solubilities (10 w%) were investigated in water:ethanol mixtures (50:50 w%). Again all pNonOx-containing polymers were insoluble as well as the triblock copolymers with two pPhOx segments. As expected, the p(MeOx-\(b\)-EtOx-\(b\)-MeOx) and p(EtOx-\(b\)-MeOx-\(b\)-EtOx) copolymers were also soluble in this mixture. The triblock copolymers containing one pPhOx segment revealed a strong correlation between the solubility of the polymer and the order of the monomers: When the pPhOx was present as outer block, white milky solutions were obtained, whereas triblock copolymers with pPhOx as
middle block formed clear solutions in the water:ethanol mixture (Figure 5.14). This difference most likely results from the formation of large aggregates when pPhOx is present as outer block, whereas the middle pPhOx segment is effectively solubilized when it has two neighboring soluble pMeOx and/or pEtOx blocks. However, further studies are required to confirm the proposed difference in aggregation behavior of these triblock copolymers.

![Figure 5.14. Picture of the solubility test of the different pPhOx-containing triblock copolymers in a water:ethanol (50:50 w%) mixture.](image)

### 5.4 Synthesis and comparison of random copoly(2-oxazoline) series

The previous sections described the synthesis and characterization of libraries of diblock and triblock copoly(2-oxazoline). In this section, the investigations are expanded to random copolymers. Even though section 3.4 also dealt with random copolymers, here we describe the microwave-assisted synthesis of a library of random copolymers based on the MeOx, EtOx, PhOx and NonOx monomers focusing on the combinations of monomers that result in hydrophilic and hydrophobic polymers. Therefore, the copolymer series were synthesized with combinations of MeOx or EtOx and PhOx or NonOx resulting in four series. For each copolymer series, the monomer composition was varied in steps of 10 mol%. The copolymerizations of MeOx or EtOx with PhOx would require very long polymerization times under conventional heating, but can be performed within 30 minutes under microwave heating. The copolymerization parameters of the different combinations as well as the properties of the resulting copolymers were investigated in detail.

#### 5.4.1 Microwave-assisted synthesis of random copoly(2-oxazoline)s

To obtain a first impression of the copolymerization rates of the different combinations of monomers, kinetic investigations were performed with a \([M_A]:[M_B]:[I]\) ratio of 25:25:1 utilizing the same polymerization procedure as previously described (I = MeOTs; acetonitrile; 140 °C; ~40 w% of monomer). All investigated copolymerizations revealed linear first order kinetics for both monomers (Figures 5.15) and a linear increase of molecular weight with conversion (not shown). The copolymerization of MeOx:NonOx revealed slightly faster consumption of the MeOx; whereas, the EtOx:NonOx revealed similar polymerization rates for both monomers. Therefore, it can be expected that gradient copolymers are obtained in the copolymerization of MeOx:NonOx and random copolymers are obtained in the case of EtOx:NonOx. These observations are in line with the observed copolymerization parameters using benzyl bromide as initiator and conductive heating to 100 °C in DMAC (section 3.4). The copolymerizations of MeOx:PhOx and EtOx:PhOx showed a fast consumption of MeOx or EtOx and slow incorporation of PhOx resulting in the formation of quasi-block copolymers.
After this initial kinetic study, the systematic series of copolymers were synthesized utilizing microwave-assisted heating. All polymerizations were performed using 4 M total monomer concentration and a [M]/[I] ratio of 100. For each copolymerization series, 20 polymerization mixtures were prepared in the ASW2000 synthesis robot. Polymerization mixtures with 0 to 100 mol% (steps of 10 mol%; 11 polymerization mixtures) of the second monomer were applied for the synthesis of the library of copolymers. The remaining 9 polymerization mixtures (10-90 mol% of the second monomer) were polymerized up to half conversion to determine the reactivity ratios of the copolymerizations. The incorporated monomer fractions ($F_1$) at half and full conversion were determined by $^1$H-NMR spectroscopy. The incorporated monomer fractions ($F_1$) are plotted against the theoretical composition ($f_1$) for the NonOx-containing copolymers in Figure 5.16. The plot at half conversion (Figure 5.16 left) was used for the calculation of the reactivity ratios using the Mayo-Lewis terminal model (MLTM) and the Kelen-Tüdös method (KT; see also section 3.4.1 for a description of both methods). The reactivity ratios, $r_1$ and $r_2$, for the MeOx:NonOx copolymerizations (Figure 5.16 left top corner) show a large standard deviation; however, the obtained reactivity ratios from the MLTM and KT are similar within this deviation. Moreover, the found difference in $r_1$ and $r_2$ is larger than for the previously investigated conventional MeOx:NonOx copolymerizations ($r_1 = 1.26 \pm 0.05; r_2 = 0.66 \pm 0.03$; section 3.4.1) indicating that a larger gradient is formed during the microwave-assisted polymerization. This larger difference is most likely due to the different reaction conditions (solvent, temperature and initiator) and not from specific microwave absorption, because the monomers have the same 2-oxazoline ring that will have similar microwave absorptions. The reactivity ratios for the EtOx:NonOx copolymerizations are both equal to 1 within the standard deviation using both the MLTM and KT (Figure 5.16 right bottom corner) indicating the formation of truly random copolymers, as it was also
found for conventional heating (section 3.4.1). Moreover, the copolymerizations that aimed for full conversion resulted in the formation of copolymers with the desired compositions (Figure 5.16 right). All NonOx-containing copolymers revealed monomodal molecular weight distributions with PDI values below 1.30 [except p(EtOx<sub>90</sub>-r-NonOx<sub>10</sub>): PDI = 1.34 and the p(MeOx-r-NonOx) copolymers with less than 40 mol% MeOx due to interactions with the column material in GPC that resulted in broadening of the signal].

\[
\begin{align*}
&\text{MeOx:NonOx} \\
&\text{MLTM: } r_1 = 2.6 \pm 0.6 \\
&\quad r_2 = 0.6 \pm 0.2 \\
&\quad r_1 = 3.2 \pm 0.9 \\
&\quad r_2 = 0.3 \pm 0.3 \\
\end{align*}
\]

\[
\begin{align*}
&\text{EtOx:NonOx} \\
&\text{MLTM: } r_1 = 1.07 \pm 0.07 \\
&\quad r_2 = 1.05 \pm 0.14 \\
&\quad r_1 = 1.15 \pm 0.13 \\
&\quad r_2 = 1.11 \pm 0.12 \\
\end{align*}
\]

Figure 5.16. Relationship between the monomer feed (f<sub>i</sub>) and the actual incorporated monomer fraction (F<sub>i</sub>) for MeOx:NonOx and EtOx:NonOx at half conversion (left) and full conversion (right).

The copolymerization parameters for the MeOx:PhOx and EtOx:PhOx copolymerizations could not be determined due to too low PhOx conversion after five minutes polymerization time, at which approximately half conversion of MeOx or EtOx was reached. The \(^1\)H-NMR spectra of these polymerization mixtures revealed only very little incorporation of the PhOx when aiming at 90 mol% PhOx and no PhOx incorporation for all other ratios demonstrating that indeed blocky polymers are formed. Therefore, no reliable reactivity ratios could be determined, but it can be concluded that \(r_1 >> 1\) and \(r_2 << 1\). The final polymer composition of the MeOx:PhOx copolymers could not be accurately determined by \(^1\)H-NMR due to overlap of the MeOx methylene protons with the residual CH<sub>3</sub>CN signals. However, the initial monomer composition changed gradually from MeOx to PhOx as demonstrated by GC characterization (Figure 5.17 left). The initial composition together with the full monomer conversion (from \(^1\)H-NMR spectroscopy) demonstrate that indeed the desired copolymers were obtained. For the EtOx:PhOx copolymers, \(^1\)H-NMR spectroscopy was successfully applied to prove that the copolymers have the desired composition (Figure 5.17 right).

Figure 5.17. Left: Initial monomer to solvent ratios obtained by GC for the MeOx:PhOx copolymerizations. Right: \(^1\)H-NMR compositions of the EtOx:PhOx copolymers at full conversion.
In addition, GPC characterization revealed monomodal molecular weight distributions for all PhOx-containing copolymers. Moreover, the PDI values of the MeOx:PhOx and EtOx:PhOx copolymers revealed PDI values below 1.30, with only three exceptions [p(EtOx$_{40-r}$-pPhOx$_{60}$), p(EtOx$_{20-r}$-pPhOx$_{80}$) and p(EtOx$_{90-r}$-pPhOx$_{10}$) all PDI’s ~ 1.40].

5.4.2 Properties of the synthesized copoly(2-oxazoline) series

The four successfully synthesized copolymer series were investigated with regard to their thermal properties by DSC (Figure 5.18). The $T_g$’s and $T_m$’s for the NonOx-containing copolymers are depicted in Figure 5.18 left. The $T_g$’s decrease with the incorporation of NonOx as it is expected due to the absence of a $T_g$ for the pNonOx. The observed trend for the EtOx:NonOx copolymers is the same as for the conventionally synthesized copolymers (section 3.4). However, the $T_g$’s of the MeOx:NonOx are higher than of the conventionally synthesized copolymers, which is most likely due to the increased polymer chain length (100 instead of 60 monomer units per chain; see e.g. ref. 36 for molecular weight effects on $T_g$). Around 60 w% of NonOx incorporated, the $T_g$’s of both copolymer series leveled off around 30 °C and with even more NonOx the $T_g$’s disappeared in DSC. The $T_m$’s of the copolymer series decreased linearly with the incorporation of MeOx or EtOx into the pNonOx chains, whereby a larger decrease was observed for the incorporation of MeOx. Therefore, it can be concluded that the (gradient) incorporation of MeOx, which is incompatible with pNonOx, effectively disturbs the crystallization. On the contrary, incorporation of EtOx, which is compatible with pNonOx, disturbs the crystallization in a smaller extend. This difference might result from incorporation of some EtOx units into crystalline pNonOx domains; whereas, pMeOx cannot be incorporate and thus immediately disturbs the crystallization.

The $T_g$’s of the PhOx-containing copolymers are plotted against mol% of PhOx in Figure 5.18 right. These copolymers did not reveal a $T_m$ since none of the homopolymers of the incorporated monomers showed a $T_m$ before degradation. Even though these copolymers have quasi-block copolymer structures, only one $T_g$ was observed like for previously described block copolymers. As expected, the $T_g$’s of the copolymer series increased with increasing w% of PhOx. The increase of $T_g$ for the MeOx:PhOx copolymer series followed the theoretical prediction by the Fox-equation to a large extent [$T_g^{-1} = w_{PhOx}(T_{g,PhOx}^{-1} - T_{g,EtOx}^{-1}) + T_{g,EtOx}^{-1}$; dotted lines in Figure 5.20 right] indicating good mixing of the two monomers. On the contrary, the $T_g$ of the EtOx:PhOx copolymer series did not follow the Fox equation suggesting poor mixing (phase separation) of the monomers. In general, the MeOx:PhOx series revealed higher $T_g$’s than the EtOx:PhOx series due to the higher $T_g$ of pMeOx.

![Figure 5.18. Thermal and transitions ($T_g$ and $T_m$) MeOx:NonO, EtOx:NonO (Both left), MeOx:PhOx and EtOx:PhOx (right) copolymer series obtained by DSC.](image-url)
The SE’s were only investigated for the NonOx-containing polymer series since pMeOx, pEtOx and pPhOx all have SE’s around 45 mN·m⁻¹ and thus no difference is expected throughout these series. For the MeOx:NonOx and EtOx:NonOx series, a difference in SE throughout the series is expected due to the much lower SE of pNonOx (22 mN·m⁻¹). Figure 5.19 depicts the resulting SE’s before and after annealing for the MeOx:NonOx (left) and EtOx:NonOx (right) copolymer series plotted against w% of NonOx present. The EtOx:NonOx copolymers showed similar SE’s before annealing as the previously synthesized copolymers (section 3.4) with a similar decrease in SE around 70 w% NonOx. However, the MeOx:NonOx copolymers synthesized under microwave irradiation revealed a decrease in SE to a plateau of ~34 mN·m⁻¹ for the copolymers with 20-80 w% NonOx present (before annealing), whereas the conventionally synthesized MeOx:NonOx copolymers revealed similar SE’s as the EtOx:NonOx. When more NonOx is incorporated in the MeOx:NonOx copolymers, the SE decreased gradually to 22 mN·m⁻¹ for the pNonOx. The larger gradient in the microwave synthesized MeOx:NonOx copolymers, compared to the conventionally synthesized copolymers and the EtOx:NonOx copolymers, results in partial orientation of the nonyl side-chains during spin-coating, which could explain the lower SE’s. After annealing both the microwave synthesized MeOx:NonOx and EtOx:NonOx copolymer series revealed a slight decrease in SE’s due to partial orientation of the nonyl side-chains towards the surface. The largest effect of annealing was observed for the EtOx:NonOx copolymers with 60-80 w% NonOx. These copolymers do not phase separate during spin-coating, but upon annealing the nonyl side-chains will orient towards the surface resulting in a large decrease of the SE’s. Although the lower SE’s for the MeOx:NonOx series and the lower SE’s after annealing can be understood, the rationale behind the observed plateau formation is not clear at the moment.

Figure 5.19. SE’s for the MeOx:NonOx (left) and EtOx:NonOx (right) copolymer series before and after annealing.

5.4.3 Solubility of the random copoly(2-oxazoline) series

The effect of the polymer compositions on their solubility (10 w%) in a water:ethanol (50:50 w%) mixture was investigated. These investigations focused on the MeOx:PhOx and EtOx:PhOx copolymers, since the previous solubility investigations on the triblock copoly(2-oxazoline)s already revealed very poor solubility of NonOx-containing polymers. Figure 5.20 shows photographs of the solubility tests of the MeOx:PhOx (top row) and EtOx:PhOx (bottom row) copolymer series. The MeOx:PhOx copolymers resulted in clear solutions up to 70 mol% of PhOx present; whereas, the EtOx:PhOx copolymers were only soluble up to 50 mol% PhOx. This difference might result from the incompatibility of the pEtOx and
pPhOx in the quasi-block copolymers that was also observed for the dependence of \( T_g \) on the w\% of PhOx in the copolymers. The demixing could lead to a higher degree-of-aggregation of the pPhOx. Nevertheless, the aggregation behavior of these triblock copolymers should be studied in detail to determine the exact reason of the different solubilities.

### Figure 5.20.

**Figure 5.20.** Pictures of the solubility tests (10 w\% polymer in water:ethanol (50:50 w\%)) that were performed on the MeOx:PhOx and EtOx:PhOx copolymer series.

#### 5.5 Microwave synthesis of 2-`soy alkyl’-2-oxazoline containing copolymers

In the previous chapter, it was demonstrated that 2-`soy alkyl’-2-oxazoline (SoyOx) can be polymerized in a controlled way under microwave irradiation. Moreover, it was demonstrated that the unsaturated fatty acid side chains can be cross-linked under UV-curing. In this section, the cross-linkable SoyOx monomer was utilized for the synthesis of random and block copolymers. The resulting random copolymers were utilized to investigate the effect of cross-linking on the thermal and surface properties of the copolymers. Up to date, soy-bean fatty acids were almost completely unexplored as cross-linking agents. Direct UV-cross-linking of soy-bean fatty acid containing polyurethane was only reported recently. Moreover, soy-based epoxides, in which the double bonds were transformed into epoxides, have been cross-linked by UV-curing in the presence of a cationic photoinitiator. The here reported cross-linked p(EtOx-\( r \)-SoyOx) copolymers with a high pEtOx content will be temperature responsive due to the lower critical solution temperature of pEtOx. Therefore, the resulting thermosensitive polymer network might be an interesting material in tissue engineering or for the formation of microfluidic actuators.

The pSoyOx-containing block copolymers were tested for micellization and subsequent cross-linking resulting in cross-linked micelles. Cross-linked micelles have been the focus of many recent studies due to their potential application in drug delivery. Cross-linked micelles have been prepared using a variety of chemical cross-linking strategies like, e.g., the reaction of poly(acrylic acid) chains with a difunctional amine or coupling of poly(2-vinylpyridine) chains with 1,4-dibromobutane. Moreover, cross-linked micelles can be prepared by UV-irradiation as was demonstrated for acrylate end-functionalized polymers and for polymers that bear a double bond on each of the monomer units in the core of the micelles. However, cross-linked micelles that were prepared by UV-cross-linking of unsaturated fatty acid monomers have not been reported to the best of our knowledge.
5.5.1 Microwave synthesis, characterization and cross-linking of a 2-‘soy alkyl’-2-oxazoline containing random copolymer series

A random copolymer series based on EtOx and SoyOx (100 monomer units in total) was synthesized to investigate the effect of cross-linking (by UV-curing) on the thermal and surface properties of the resulting polymer network. The polymerization mixtures consisting of EtOx, SoyOx, MeOTs and CH₂CN were prepared utilizing the ASW2000 synthesis robot. The resulting reaction mixtures were heated to 140 ºC under microwave irradiation. The copolymerization parameters were investigated by the polymerization of different ratios of monomers up to half conversion. The actual monomer incorporation at half conversion is plotted against initial monomer feed in Figure 5.21 left. From this curve, it can be concluded that both EtOx and SoyOx have slightly higher reactivities to itself than to the other monomer. As a result, reactivity ratios larger than 1 were obtained using both the MLTM and KT calculation methods (Figure 5.21 left bottom corner). From the ¹H-NMR spectroscopic investigations, it could be concluded that the desired monomer ratios were obtained at full monomer conversion (Figure 5.21 right). In addition, narrow monomodal molecular weight distributions (DPI < 1.30) were obtained for all copolymers except p(EtOx₂₀₋r-SoyOx₈₀) and p(EtOx₁₀₋r-SoyOx₉₀) that revealed PDI value around 1.40.

The thermal properties (T_g and T_m) of the synthesized EtOx:SoyOx copolymer series are depicted in Figure 5.22 left before and after curing. The polymers with more than 80 w% SoyOx revealed a T_m in between 88 to 90 ºC. After UV-curing, small melting transition were observed for p(EtOx₂₀₋r-SoyOx₈₀) and p(EtOx₁₀₋r-SoyOx₉₀) at 85 ºC. Therefore, it can be concluded that cross-linking prevents the crystallization of the SoyOx due to the lower chain mobility. Why the two polymers with a larger PDI value still exhibit a melting transition is not clear, but it might result from the presence of shorter polymer chains that have a higher mobility to organize into crystalline domains. The T_g of the copolymers before UV-curing revealed a strong dependency on the incorporation of SoyOx into pEtOx: Up to 60 w% SoyOx, the T_g decreased rapidly after which it remained constant at ~15 ºC until the T_g disappeared (in DSC) with 90 w% SoyOx. After UV-curing, a similar trend was observed for the T_g of the copolymer series. However, polymers with 90 w% or more still revealed a T_g around 15 ºC after UV-curing due to the decreased chain mobility upon cross-linking.
Microwave-assisted synthesis of 2-oxazoline copolymers

Furthermore, the effect of cross-linking was also observed in the appearance of the copolymers (Figure 5.22 right). The cross-linked copolymers with up to 56 w% SoyOx were hygroscopic and were transparent due to the presence of water. The copolymers with higher SoyOx content appeared as yellowish solid before and after cross-linking. More interestingly, the cross-linked hygroscopic copolymers (up to 57 w% SoyOx) retained their shape when they absorbed water from the air, whereas the noncross-linked copolymers turned into transparent flat films on the bottom of the DSC-cup by the absorption of water. This observation demonstrates the potential of cross-linking the copolymers. Moreover, it can be concluded that as little as 13 w% (5 mol%) SoyOx is sufficient to form a cross-linked network.

The SE of the EtOx:SoyOx copolymers revealed a similar behavior as the EtOx:NonOx copolymers (Figure 5.23): A slow decrease in SE was observed up to 50 w% SoyOx after which it decreased rapidly to the SE of pSoyOx (24 mN·m⁻¹) due to preferential orientation of the ‘soy alkyl’ chains towards the surface. After annealing of the EtOx:SoyOx copolymers, the SE decreased to 30 mN·m⁻¹ where it reached a plateau value with increasing SoyOx as it was also observed for annealed EtOx:NonOx copolymers. Unexpectedly, the SE remained constant around 30 mN·m⁻¹ up to pure pSoyOx, which is different to the EtOx:NonOx for which the SE decreased to the pNonOx value. Furthermore, UV-curing of the EtOx:SoyOx copolymers under ambient or nitrogen atmosphere revealed similar trends in SE as the annealed polymer films indicating that annealing at 80 ºC also results in cross-linking of the pSOyOx side chains. The absence of a second decrease in SE to the SE of pSoyOx with higher SoyOx content can be explained by the lower chain mobility after cross-linking that prevents complete orientation of the SoyOx side-chains towards the surface. In conclusion, it was demonstrated that random EtOx:SoyOx copolymer can be synthesized under microwave irradiation. Moreover, the unsaturated fatty acid side chains of the SoyOx can be utilized for cross-linking of the polymers as was demonstrated by the $T_g$, $T_m$, appearance and SE of the cross-linked copolymers.

Figure 5.22. Left: Thermal properties ($T_g$ and $T_m$) of the EtOx:SoyOx copolymers before and after UV-curing. Right: Appearance of the copolymers after UV-curing.
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Figure 5.23. SE’s of the EtOx:SoyOx copolymers before and after annealing at 80 °C and after UV-curing under ambient and nitrogen atmosphere.

5.5.2 Microwave synthesis and characterization of poly(2-ethyl-2-oxazoline-b-2-‘soy alkyl’-2-oxazoline) block copolymers

The p(EtOx-b-SoyOx) block copolymers were synthesized to investigate whether it would be possible to prepare cross-linked micelles. For the formation of polymeric micelles in water amphiphilic block copolymer with a large water-soluble block are required. However, to prove the possibility of block copolymer synthesis, block copolymers with a short first pEtOx block and a large second pSoyOx block were synthesized. The polymerizations were performed in CH$_2$Cl$_2$ at 140 ºC under microwave irradiation. The CH$_2$Cl$_2$ was used since it dissolves pSoyOx better than CH$_3$CN. After polymerization of the first pEtOx block, the SoyOx monomer was neatly added under an argon atmosphere followed by a second heating step to 140 ºC. The resulting GPC traces clearly show that all polymer chains were chain-extended with SoyOx and that no ‘dead’ pEtOx remained (Figure 5.24).

Figure 5.24. GPC traces for the pEtOx first block and the final pEtOx-b-SoyOx block copolymers 1 (bottom) and 2 (top) (eluent: CHCl$_3$:NEt$_3$:2-PrOH (94:4:2)).
Microwave-assisted synthesis of 2-oxazoline copolymers

Table 5.7. GPC, $^1$H-NMR and SE data for the synthesized p(EtOx-b-SoyOx) block copolymers.

<table>
<thead>
<tr>
<th>polymer</th>
<th>$D_P^{EtOx,th}$</th>
<th>$D_P^{SoyOx,th}$</th>
<th>$D_P^{EtOx,NMR}$</th>
<th>$D_P^{SoyOx,NMR}$</th>
<th>w% SoyOx</th>
<th>$M_n$GPC</th>
<th>PDI_{GPC}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>23</td>
<td>70</td>
<td>9,900</td>
<td>1.19</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>25</td>
<td>45</td>
<td>21</td>
<td>58</td>
<td>10,750</td>
<td>1.16</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>20</td>
<td>70</td>
<td>19</td>
<td>45</td>
<td>9,100</td>
<td>1.19</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>10</td>
<td>70</td>
<td>11</td>
<td>32</td>
<td>8,000</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Next to these block copolymers with a large SoyOx second block, two longer amphiphilic block copolymers were prepared with 70 EtOx units as first block and 10 or 20 SoyOx units as second block. The structural data for the four synthesized p(EtOx-b-SoyOx) block copolymers are summarized in Table 5.7. The incorporated number of monomers was close to the desired amount as demonstrated by $^1$H-NMR spectroscopy and the polymers were synthesized in a controlled way as demonstrated by the low PDI values. However, the observed $M_n$GPC did not correspond with the theoretical $M_n$ values due to different folding behavior of the different copolymers as it was also observed for the library of diblock copolymers.

5.5.3 Preparation of cross-linked micelles from p(EtOx-b-SoyOx) block copolymers

Subsequently, the micelle formation of the p(EtOx$_{70}$-b-SoyOx$_{20}$) 3 and p(EtOx$_{70}$-b-SoyOx$_{10}$) 4 was investigated. The polymers were dissolved in acetone (1 g/L), which is a good solvent for both blocks, and it was verified by dynamic light scattering (DLS) that no aggregates were present. In a next step, water was added dropwise to induce micelle formation and the solution was dialyzed against water (24 hours) to remove the acetone. The resulting micellar solution was diluted to 20 mg/L and analyzed by AFM and DLS. The p(EtOx$_{70}$-b-SoyOx$_{10}$) 4 did not show the presence of uniform micelles, but many aggregates were observed instead indicating that the pSoyOx segment is too short. Nevertheless, the p(EtOx$_{70}$-b-SoyOx$_{20}$) 3 revealed uniform micelles in both AFM and DLS (Figure 5.25). The radius observed by AFM ($R = 18.7$ nm) is in good agreement with the radius observed by DLS ($R = 18.1$ nm). The height observed by AFM ($H = 4.9$ nm) might correspond to the core size of the micelles.

![AFM height image](image)  ![DLS data](image)

Figure 5.25. AFM height image (left) and DLS data (right) of the micelles that were prepared in water from p(EtOx$_{70}$-b-SoyOx$_{20}$) 3.
The micellar solution in water was UV-irradiated (20 J/cm) to cross-link the pSoyOx cores. After cross-linking, the micellar solution was vigorously stirred for one day to reduce the aggregation of the cross-linked micelles. The resulting micellar solution (10 mg/L) was analyzed by both AFM and DLS as depicted in Figure 5.26.

![AFM height image and DLS data](image)

**Figure 5.26.** AFM height image (left) and DLS data (right) of the cross-linked micelles in water.

The AFM shows the presence of spherical particles with two sizes (R = 17.6 nm, H = 4.5 nm; R = 28.8 nm, H = 5.7 nm). The smaller particles have a size similar to the size of the micelles before cross-linking and can be assigned as individual cross-linked micelles. The larger distribution seems to result from aggregation of the cross-linked micelles. However, from this AFM image it cannot be elucidated whether they are cross-linked together or that they are only aggregated. The DLS revealed the presence of larger aggregates (R = 99.6 nm) that are not present in the AFM image. Therefore, it appears that the cross-linked micelles have a large tendency to aggregate in solution. This aggregation might occur by organization of the cross-linked cores as depicted in Figure 5.27.

![Schematic diagram](image)

**Figure 5.27.** Schematic representation of the proposed aggregation mechanism of the cross-linked micelles of p(EtOx\textsubscript{70}-b-SoyOx\textsubscript{20})\textsubscript{3}.
To further proof the successful formation of cross-linked micelles, the cross-linked micelles were retransferred to the non-selective solvent acetone. The water of the micellar solution was removed by lyophilization after which the solid was redispersed in acetone. This acetone solution was filtered (0.2 µm filter) to remove any large aggregates that might be present. The resulting solution (3 mg/L) was analyzed using AFM and DLS (Figure 5.28).

The AFM again revealed the presence of two species proving successful cross-linking since noncross-linked polymer would be molecularly dissolved. The size of the small spherical particles (D = 20.6 nm, H = 8.2 nm) corresponds to swollen cross-linked micelles due to solvation of the core in acetone. The larger particles appeared as rice-like particles (L = 189.6 nm, W = 66.8 nm, H = 10.9 nm) instead of the larger spherical particles that were observed after cross-linking in water. DLS analysis of the cross-linked micellar solution in acetone revealed the presence of particles with a radius of 66.7 nm, which corresponds to the width of the larger rice-like particles. The DLS-data have not been number averaged meaning that the presence of large particles will be significantly overestimated. As a result, the individual cross-linked micelles are not detected by DLS. The presence of larger particles in acetone demonstrates that cross-linked aggregates have been formed during UV-irradiation. Apparently, the cross-linked aggregates undergo a sphere-to-rod transition when they are dissolved in a non-selective solvent: The cross-linked pSoyOx core swells in acetone forcing the aggregate into a rice-like particle as schematically depicted in Figure 5.29.

**Figure 5.28.** AFM height image (left) and DLS data (right) of the cross-linked micelles in acetone.

**Figure 5.29.** Schematic representation of the proposed sphere-to-rod transition of the cross-linked micelles of p(EtOx<sub>70</sub>–b-SoyOx<sub>20</sub>) 3.
5.6 Conclusions

The application of microwave-assisted synthesis for the preparation of poly(2-oxazoline) copolymers has been demonstrated in this chapter. A 4×4 library of 12 block copolymers and 4 chain-extended homopolymers was synthesized utilizing MeOx, EtOx, NonOx and PhOx. All block copolymers were successfully synthesized resulting in well-defined copolymers with the exception of the p(NonOx-b-MeOx) and p(NonOx-b-EtOx). These two diblock copolymers revealed trimodal molecular weight distributions resulting from chain-transfer and subsequent chain coupling side reactions as it was elucidated by a combination of GPC fractionation and $^1$H-NMR spectroscopy. Moreover, the presence of pNonOx in the block copolymer proved to be very important for the polymer properties. When pNonOx was present, the polymers exhibited a $T_m \approx 150^\circ C$ and a low SE due to preferential orientation of the nonyl side chains towards the surface. Moreover, lower $T_g$ values were found for pEtOx- and pNonOx-containing copolymers due to the higher flexibility of the side chains resulting in higher chain mobility’s. Next to the diblock copolymer library, a 30-membered triblock copoly(2-oxazoline) library was prepared using microwave irradiation. The fast and uniform non-contact heating allowed the controlled synthesis of these triblock copolymers. In general, only the triblock copolymers containing a p(NonOx-b-MeOx) or a p(NonOx-b-EtOx) combination could not be successfully synthesized due to chain-transfer and chain coupling reactions. Throughout the triblock copolymer library, the $T_g$’s changed gradually from 50 to 100 $^\circ C$ following the flexibility of the substituents of the incorporated monomers. The SE’s of the triblock copolymers were largely dependent on the presence of pNonOx as it was also observed for the diblock copolymers. Moreover, the solubility of the triblock copolymers was found to be affected by the monomer order: All triblock copolymers with pPhOx as middle block were soluble in water:ethanol (50:50 w%), whereas polymers with pPhOx as outer block resulted in milky solutions.

Systematical copolymer series were synthesized under microwave irradiation using MeOx:NonOx, EtOx:NonOx, MeOx:PhOx and EtOx:PhOx monomer combinations. The monomer composition was changed gradually from one monomer to the other throughout these series. Moreover, the copolymerization parameters revealed that MeOx:NonOx copolymers have a gradient monomer composition, EtOx:NonOx copolymers have a random composition and MeOx:PhOx and EtOx:PhOx copolymers have quasi-block copolymer structures. The $T_g$ significantly decreased upon incorporation of pNonOx and with 80 mol% NonOx incorporated, the $T_g$ disappeared in the DSC traces. The MeOx:PhOx copolymers revealed an increase of $T_g$ with increasing mol% PhOx that followed the Fox-equation; whereas, the $T_g$ of the EtOx:PhOx did not follow this equation indicating good mixing of MeOx and PhOx and phase separation of the EtOx and PhOx. The SE’s of the MeOx:NonOx and EtOx:NonOx copolymers revealed phase separation in the case of the MeOx:NonOx copolymers and better mixing in the case of the EtOx:NonOx combinations. Moreover, it was observed that the MeOx:PhOx copolymers have a higher solubility in water:ethanol mixtures than EtOx:PhOx copolymers due to the better compatibility of the MeOx and PhOx. In conclusion, it can be stated that the polymers with flexible substituents (pEtOx and pNonOx) and the polymers with more rigid substituents (pMeOx and pPhOx) do mix; whereas, combinations of flexible and rigid substituent results in phase separation.

Besides the synthesis of copolymers with the MeOx, EtOx, NonOx and PhOx monomers, the incorporation of the SoyOx monomer was also investigated. A series of random EtOx:SoyOx copolymers was successfully synthesized under microwave irradiation. The copolymerization
parameters revealed that both monomers have a slightly higher reactivity towards itself. The resulting copolymers were cross-linked under UV-irradiation. Both DSC and contact angles measurements demonstrated the decreased chain mobility after cross-linking, which proves that the unsaturated fatty acid side-groups can be successfully applied for the formation of polymer networks. In addition, several p(EtOx-b-SoyOx) block copolymers were synthesized resulting in well-defined copolymers. The micelle formation of such a block copolymer was demonstrated by AFM and DLS. The resulting micellar solution was UV-irradiated to cross-link the micelles. The success of cross-linking was demonstrated by transferring the cross-linked micelles into the non-selective acetone. In acetone, cross-linked individual micelles were present together with larger, rice-like, structures. These structures most likely result from cross-linked aggregates that undergo a sphere-to-rod transition when going from a selective solvent (water) to a non-selective solvent due to the solubilization of the cross-linked cores.

In general, it was demonstrated that microwave irradiation is a powerful tool in the synthesis of poly(2-oxazoline) copolymers providing easy access to well-defined structures. Moreover, the synthesis of systematical libraries of block and random copolymer can result in novel insights into the copolymerization parameters and to determine structure property relationships.

5.7 Experimental part

Materials and Instrumentation

Solvents were purchased from Biosolve Ltd. Acetonitrile (size 3 Å) was dried with molecular sieves and CH$_2$Cl$_2$ was distilled over potassium. All other solvents were used without further purification. MeOx, EtOx (Aldrich), PhOx and NonOx (donated by Henkel) were distilled over barium oxide (BaO) and stored under argon. SoyOx (donated by Henkel) was purified over aluminum oxide with hexane as eluent. After drying over BaO it was stored under argon. Methyl tosylate (Aldrich) was distilled over P$_2$O$_5$ and stored under argon.

Polymerizations were carried out in an Emrys Liberator (Biotage, formerly PersonalChemistry) utilizing capped reaction vials. These vials were heated to 105 °C, allowed to cool to room temperature and filled with argon prior to use. All microwave polymerizations were performed with temperature control (IR sensor). A Chemspeed ASW2000 automated synthesizer was utilized for dispensing the stock solutions into the microwave vials and for automated sample preparation after the polymerizations. An inert atmosphere was maintained by applying 1.5 bar argon flow through the hood of the synthesizer.

$^1$H-NMR spectra were recorded on a Varian AM-400 spectrometer or a Varian Gemini 300 spectrometer. Chemical shifts are given in ppm relative to TMS or residual solvent signals.

Gel Permeation Chromatography (GPC) was measured on a Shimadzu system with a SCL-10A system controller, a LC-10AD pump, a RID-6A refractive index detector and a PLgel 5 µm Mixed-D column with chloroform:triethylamine:2-propanol (94:4:2 or 80:10:10) as eluent and the column oven set to 50 °C (polystyrene calibration) or on a Waters system with a 1515 pump, a 2414 refractive index detector and a Waters Styragel HT4 column utilizing DMF containing 5 mM NH$_4$PF$_6$ at a flow rate of 0.5 mL/min as eluent and the column oven set to 50 °C (PEG or PMMA calibration).

GC measurements were performed on an Interscience Trace GC with a Trace Column RTX-5 connected to a PAL autosampler. For the injection of polymerization mixtures, a special Interscience liner with additional glass wool was used.

Thermal transitions were determined on a DSC 204 F1 Phoenix by Netzsch under a nitrogen atmosphere with heating and cooling rates of 40 K·min$^{-1}$ (three measurements per sample after an initial first heating run that was not considered for the subsequent calculations); melting points were measured with a heating rate of 10 K·min$^{-1}$ and a cooling rate of 40 K·min$^{-1}$. Thermogravimetrical analyses were performed in a TG 209 F1 Iris by Netzsch under a nitrogen atmosphere in the range from 30 to 500 °C with a heating rate of 20 K·min$^{-1}$. 

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Contact angle measurements were performed on polymer films that were prepared by spincoating of chloroform solutions (20 mg/mL) of the polymers on pre-cleaned microscopy slides at 1000 rpm during 90 seconds using a WS-400/500 series spin coater from Laurell Technologies Corporation. An OCA30 optical contact angle measuring instrument from Dataphysics was used to determine the contact angles of both diiodomethane and ethylene glycol as apolar and polar test liquids, respectively.

**Microwave-assisted synthesis of diblock copoly(2-oxazoline)s**

All polymerizations were carried out in acetonitrile at 140 °C. For the synthesis of the first block, 2.0 mL polymerization mixtures were prepared with the following initial monomer concentrations: \([\text{MeOx}] = [\text{EtOx}] = 4 \text{ M}, [\text{PhOx}] = 3 \text{ M} \text{ and } [\text{NonOx}] = 2 \text{ M}\). The polymerizations were performed using MeOTs as initiator ([M\text{A}]:[MeOTs] = 50:1). After polymerization of the first monomer, the reaction vial was cooled to ambient temperature and the second monomer was neatly added ([M\text{B}]:[I]_0 = 50) under an inert argon atmosphere. Subsequently, the polymerization was continued in the microwave synthesizer and quenched with water after the predefined polymerization time.

**Microwave-assisted synthesis of triblock copoly(2-oxazoline)s**

The triblock copolymerizations were performed in a similar manner and with the same polymerization conditions as the diblock copoly(2-oxazoline)s. However, the first block was prepared with a [M\text{A}]:[I] ratio of 33 and the other monomer were added neatly with [M\text{B}]:[I]_0 = [M\text{C}]:[I]_0 = 33.

**Microwave-assisted synthesis of the 2-oxazoline random copolymer series**

The polymerization mixtures for the microwave-assisted synthesis of series of random copolymers were prepared in the ASW2000 synthesis robot. Different amounts of a stock solution of MeOTs in CH\text{3}CN, monomer A, monomer B and CH\text{3}CN were dispensed into the microwave vials resulting in 2.0 mL reaction mixtures containing 4 M total monomer concentration for all different monomers and a [M]/[I] ratio of 100. 20 vials were prepared: One series with 0-1.0 mol% monomer B (steps of 0.10 mol%; 11 vials) and a second series with 0.1-0.9 mol% monomer B (steps of 0.10 mol%; vials). After dispensing the solutions, the microwave vials were capped manually and shaken (using the glove-box that covers the synthesizer). After this manual shaking, 100 μL aliquots were sampled from the polymerization mixtures to sample vials for GC analysis by the synthesis robot. Subsequently, the first series of reaction mixtures was microwave heated to full conversion and the second series of polymerization mixtures was heated to half conversion to determine the copolymerization parameters. All polymerization mixtures were quenched after microwave heating to 140 °C by the automated addition of water (50 μL) using the liquid handling system of the microwave synthesizer.

The microwave-assisted synthesis of the random copolymers consisting of EtOx and SoyOx was performed in a similar manner. However, the concentration of the polymerization mixtures was gradually changed from 4 M for pure EtOx to 1.5 M for pure SoyOx. Moreover, the series of 11 random copolymers that were synthesized (full conversion) was expanded with copolymers containing 5, 15 and 25 mol% SoyOx.

**Cross-linking of p(EtOx-b-SoyOx) random copolymers**

The random copolymers were weighed into DSC pans or spin-coated onto glass slides. Subsequently, the DSC pans or glass slides were placed into a UV-irradiation chamber with 5.8 J/cm\text{2} for 2 hours. The DSC pans were used to determine the thermal properties of the cross-linked copolymers and the cross-linked polymer on the glass slides was applied for contact angle measurements to determine the surface energy of the polymer films after cross-linking.

**Microwave-assisted synthesis of p(EtOx-b-SoyOx) diblock copolymers**

The p(EtOx-b-SoyOx) copolymers were synthesized in a similar manner as the diblock copoly(2-oxazoline)s. Nevertheless, the [M]/[I] ratio of the first and second blocks were changed and, secondly, the polymerizations were performed in distilled CH\text{2}Cl\text{2} to prevent precipitation of the polymers.
Microwave-assisted synthesis of 2-oxazoline copolymers

Preparation of cross-linked micelles
To a solution of p(EtOx₅₇₋₃₀-SoyOx₃₀) in acetone (1 g/L), water was added dropwise resulting in the formation of micelles. This micellar solution was dialyzed for 24 hours against water to remove the acetone. The resulting micelles in water (20 mg/L) were analyzed by AFM (drop-cast sample) and DLS. Cross-linking of this micellar solution was performed by UV-irradiation (dose of 20 J/cm²). After 24 hours vigorous stirring, the resulting solution (10 mg/L) was analyzed again by AFM and DLS. The sample was dried by lyophilization and the resulting white powder was redispersed in acetone. The cross-linked micelles in acetone (3 mg/L) were also analyzed by AFM and DLS.

5.8 References and notes
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Chapter 6

Synthesis, characterization and complexation of functionalized 3,6-di(2-pyridyl)pyridazines

Abstract

3,6-Di(2-pyridyl)pyridazines are an interesting class of metal coordinating ligands, since they self-assemble into [2×2] grid-like metal complexes upon the addition of copper(I) or silver(I) ions. Nevertheless, 3,6-di(2-pyridyl)pyridazines have never been incorporated in polymers or other macromolecular structures. Therefore, our objective was to develop a synthetic route towards functionalized 3,6-di(2-pyridyl)pyridazines that could be used as building blocks for the construction of macromolecular [2×2] metal grids. A series of inverse-electron-demand Diels-Alder reactions of alkynes with different functional groups and 3,6-di(2-pyridyl)-1,2,4,5-tetrazine was investigated with conventional heating. Three of the resulting 3,6-di(2-pyridyl)pyridazines could be analyzed with single crystal X-ray crystallography. Moreover, the NMR spectroscopic investigations, including a variety of 2D NMR techniques, will be discussed in detail. To accelerate the slow inverse-electron-demand Diels-Alder reactions between the alkynes and 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, the effect of microwave heating was explored. The microwave heating allowed superheated conditions like heating to 150 °C in dichloromethane. Interestingly, the cycloaddition of acetone to the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine was observed when going to superheated microwave conditions. This cycloaddition will be discussed and explained. Moreover, cycloaddition reactions of various ketones and aldehydes were examined. Besides the synthesis of novel substituted 3,6-di(2-pyridyl)pyridazines, the complexation with copper(I) ions was also investigated to study the effect of the functional groups on the self-assembly process into [2×2] metal grids.

6.1 Introduction

In recent years, the incorporation of supramolecular moieties into well-defined macromolecular structures was explored as an attractive method for the construction of novel materials.\textsuperscript{1,2} For directed self-assembly, the most promising types of supramolecular interactions are hydrogen bonding and metal–ligand interactions because of their high directionality. Metal-coordinating units are especially interesting since their self-assembly can be easily tuned from very labile to inert by varying the employed metal ion. In addition, the complexation can be triggered by addition of metal ions and the formed complexes can be addressed and manipulated by changes in pH, electrochemistry, temperature or concentration.

Up to now, mainly bipyridine\textsuperscript{3-7} and terpyridine\textsuperscript{3,8,9} ligands have been incorporated into macromolecular structures. Those macroligands assemble upon the addition of metal ions with two or three ligands, respectively. However, in literature many ligands have been described that form larger grid-like metal complexes with various metal ions.\textsuperscript{10} Figure 6.1 depicts some examples of ligands that form [1×1], [2×2] or [3×3] metal complexes with copper(I) or silver(I) ions. To expand the scope of the formation of macromolecular metal complexes, the class of 3,6-di(2-pyridyl)pyridazine (DPP) ligands was chosen (Figure 6.1 middle structure), since it can be synthesized in a straightforward manner. The DPP’s can act as metal coordinating ligands for copper(I),\textsuperscript{11} silver(I)\textsuperscript{12,13} and nickel(II)\textsuperscript{14} ions resulting in [2×2] grid-like metal complexes. Moreover, many binuclear complexes of these ligands with e.g. nickel(II),\textsuperscript{15} copper(II)\textsuperscript{16} and platinum(II)\textsuperscript{17} ions have been reported.

![Figure 6.1. Examples of metal coordinating ligands that self-assemble into grid-like architectures with copper(I) and silver(I) ions.](image_url)

Highly functional pyridazines are easily accessible via an inverse-electron-demand Diels-Alder reaction between 1,2,4,5-tetrazines and a wide range of alkenes and alkynes; whereby, the 1,2,4,5-tetrazine acts as electron-deficient diene.\textsuperscript{18} Reactions of this type were reported with many different substituents on the 3- and 6-positions of the 1,2,4,5-tetrazines.\textsuperscript{19-26} The resulting substituted pyridazines have attracted much attention in the fields of organic chemistry for mechanistic investigations\textsuperscript{18,19,21,24-26} as well as in the field of natural-product syntheses.\textsuperscript{18,22,23,25} The Diels-Alder reactions between alkynes and tetrazines result directly in the formation of aromatic pyridazines after elimination of a nitrogen molecule as depicted in Scheme 6.1 top. Electron-rich alkynes readily undergo the inverse-electron-demand Diels-Alder reaction, but electron-poor acetylenes require more stringent reaction conditions.
When alkenes are used as dienophiles (Scheme 6.1 bottom), the Diels-Alder reactions yield dihydropyridazines after the elimination of nitrogen. Therefore, the preparation of substituted pyridazines via the alkene Diels-Alder reaction requires an additional oxidation step. To accelerate these Diels-Alder reactions and to simplify the additional oxidation step, electron rich groups that easily undergo oxidative elimination, like methoxy, ethoxy, morpholino or dimethylamino are often attached to the double bond; however, this strategy involves another synthetic step to activate the alkene.

The synthesis of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine and its utilization in inverse-type Diels-Alder reactions was first described by Butte and Case (Scheme 6.2). By coupling two 2-cyanopyridines with hydrazine hydrate, 3,6-di(2-pyridyl)dihydrotetrazine was obtained. Oxidation of this dihydrotetrazine resulted in the fully conjugated 3,6-di(2-pyridyl)tetrazine. Furthermore, the authors described the synthesis of unsubstituted, phenyl-substituted and cyano-substituted DPP’s by inverse-type Diels-Alder reactions with the corresponding acetylenes. Other groups later reported similar cycloadditions to the 3,6-di(2-pyridyl)tetrazine resulting in monosubstituted octyl, carboxyethyl, (tetrahydropropyranyl) ethers of methanol, hexanol and fullerene DPP’s. Furthermore, cyclic aliphatic 3,6-di(2-pyridyl)pyridazines have been synthesized as well, whereby cyclooctyne could be most easily coupled to the tetrazine because the large ring strain is relieved. Other cyclic substituted DPP’s were synthesized by Diels-Alder reactions with 1-morpholinocycloalkenes, followed by oxidative elimination with hydrogen peroxide; whereby, the electron-donating morpholino group accelerated the inverse-electron-demand Diels-Alder reaction.

Scheme 6.2. Synthesis of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine from 2-cyanopyridine and hydrazine.
Chapter 6

Up to this point, all described examples resulted in the formation of DPP’s without functional groups. As a result, these reported DPP’s cannot be applied to the synthesis of larger macromolecular architectures. Therefore, we have investigated the inverse-electron-demand Diels-Alder reaction between the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine and a variety of (functional) acetylenes (section 6.2). The resulting DPP’s were characterized by X-ray analysis (section 6.3) and 2D-NMR spectroscopy (section 6.4). To accelerate the cycloaddition and to avoid the use of high boiling solvents, the effect of microwave irradiation on these reactions was studied as well (section 6.5). Furthermore, the [2×2] grid formation of the functionalized DPP’s was examined to study the effect of the functional groups on the complexation behavior (section 6.6).

6.2 Synthesis of functionalized 3,6-di(2-pyridyl)pyridazines

For the synthesis of functionalized DPP’s, we choose to investigate in particular the Diels-Alder reactions of alkynes with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1; Scheme 6.3), since these cycloadditions directly results in the desired DPP’s. Moreover, for the preparation of a wide range of different substituted DPP’s it is not required to utilize the synthetic route via the alkenes, since many alkynes are commercially available nowadays. Additionally, the starting material, 3,6-di(2-pyridyl)-1,2,4,5-tetrazine, recently became available (€ 135,- per 5 g, Aldrich). However, for these studies the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine was synthesized in 20 gram scale according to the procedure of Butte and Case (Scheme 6.2).

Scheme 6.3. Schematic representation of the investigated inverse-electron-demand Diels-Alder reactions between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine 1 and various alkynes.

The applied alkynes, reaction conditions, purification methods and yields for the syntheses of the novel DPP’s are summarized in Table 1. The cycloaddition reactions of the alkynes to 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) are generally slow reactions, whereby the disappearance of the intense violet color of the tetrazine indicates the progress of the reaction. The synthesized DPP’s were obtained pure after column chromatography and/or recrystallization steps. The reactions with hydroxy-functionalized acetylenes all succeeded in refluxing toluene. Column chromatography of the crude products resulted in both an orange fraction (identified as 3,6-di(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine) and a fraction containing the expected compounds 3-8. Subsequent recrystallization afforded the pure compounds 3-8. Up to now, the direct hetero Diels-Alder reaction between a hydroxy-functional alkynne and a tetrazine was not reported. However, 3,6-di(2-pyridyl)-4-(1-hydroxyhexyl)pyridazine has been previously synthesized via the cycloaddition of 8-[(tetrahydropyran-2-yl)oxy]-1-octyne to tetrazine 1 followed by deprotection of the hydroxyl group with hydrochloric acid.
Aliphatic acetylenes are less reactive in inverse-electron-demand Diels-Alder reactions than the hydroxyl-alkynes due to the absence of electron donating groups. As a result, more stringent reaction conditions were required for the cycloaddition of these aliphatic acetylenes to 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1). Even 10-undecyn-1-ol, where the hydroxyl group is far away from the triple bond, was found to be more reactive in the inverse-electron-demand Diels-Alder reaction than e.g. 1-undecyne. This might be due to the comparable polarity of the hydroxyl group and the pyridine rings leading to closer proximity of the reactants in toluene and thus faster reaction. The Diels-Alder reactions with the aliphatic acetylenes did not proceed in toluene and had to be performed in refluxing DMF, whereby the violet color of the tetrazine disappeared within 16 hours. Subsequent evaporation of the solvent gave orange/brown oils indicating the formation of 3,6-di(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (orange compound) and decomposition of the tetrazine 1 (brown) next to the targeted DPP’s. After column chromatography and recrystallization, the DPP’s 9-11 were obtained as pure compounds as well.
Furthermore, cycloaddition of the even less reactive 3-hexyne to the tetrazine was attempted in refluxing DMF. After several days, a dark brown reaction mixture was obtained. From this reaction mixture, a very small impure fraction of product could be isolated. In addition, more electron-rich alkynes (propargyl chloride, 1,4-dichloro-2-butyn e, acetylenedicarboxylic acid and tributylstannylacetylene) were also tested for the inverse-electron-demand Diels-Alder reaction. The reactions with the chloro and acid substituted acetylenes turned black, whereas the bulky tributylstannyl-acetylene reacted successfully with tetrazine 1 resulting in 3,6-di(2-pyridyl)-4-tributylstannylpyridazine (12). Other bulky acetylenes like 2-butyn-1,4-diol diacetate and tert-butylacetylene could not be coupled to the tetrazine indicating the large influence of the electron-rich tributylstannyl group on the cycloaddition reaction.

### 6.3 X-ray crystal structures of the substituted 3,6-di(2-pyridyl)pyridazines

Single crystals suitable for X-ray analysis were obtained for 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine (8; recrystallization from ethanol), 3,6-di(2-pyridyl)-4-n-butylpyridazine [9; recrystallization from ethanol:water (2:1)] and 3,6-di(2-pyridyl)-4-tributylstannylpyridazine (12; crystallization from the melt). The observed molecular structures (ORTEP-plot) and the packing diagrams of these compounds are shown in Figure 6.2, whereby the hydrogen atoms are omitted for clarity.

The most intriguing difference between crystal structures of the bis(hydroxymethyl)-substituted DPP 8 and the other two compounds is the torsion angle between the inner and the outer rings, which is 43.5° for the mean-plane through the central aromatic ring N(1)-C(6) and the outer pyridine ring C(7)-C(12), and 40.5° between the central ring and C(13)-C(18). The resulting torsion between the mean planes of the outer rings (C(7)-C(12)/C(13)-C(18)) is 13.7°. In compound 9, the torsion angles are much smaller: N(1)-C(12)/C(7)-C(12): 9.3°, N(1)-C(12)/C(13)-C(18): 12.9°, and C(7)-C(12)/C(13)-C(18): 22.1°. This difference is due to the formation of hydrogen bonds between the nitrogen atoms of the pyridyl rings and the hydroxyl groups of the substituents, whereby seven-membered rings are formed. This is supported by the rather short nitrogen-oxygen distances, which are in the range of hydrogen bonds [N(8)-O(20): 276.9 pm; N(14)-O(22): 274.1 pm]. The hydrogen bonds are probably also the reason that the outer rings are not collinear but bend away from the substituents resulting in different angles of the connecting bonds [N(2)-C(3)-C(7): 112.98(15); C(4)-C(3)-C(7): 123.52(16); N(1)-C(6)-C(13): 113.10(15); C(5)-C(6)-C(13): 123.71(16)]. This distortion is nearly symmetrical in compound 8. A similar distortion can also be observed in compound 9; however, there it is unsymmetrical and is particularly pronounced for the pyridine bonding next to the substituent. Therefore, it can lead back to a sterical effect of the substituent [N(1)-C(6)-C(13): 112.28(14); C(5)-C(6)-C(13): 126.03(14); N(2)-C(3)-C(7): 116.71(13); C(4)-C(3)-C(7): 123.52(16)].

Solid state ATR-FTIR spectroscopy of the hydroxymethyl substituted compounds 3 and 8 also demonstrated intramolecular hydrogen bonding between the OH and the nitrogen atoms of the outer pyridyl rings (hydroxyl stretch vibration at 3200 cm^-1), which corresponds to the X-ray structure of 8. The hydroxyethyl substituted DPP 4 showed two hydroxyl vibrations at 3200 and 3350 cm^-1 in the solid state, which suggests that both intramolecular and intermolecular hydrogen bonding occurs. For the other hydroxy-functionalized compounds 5-7, the hydroxyl stretch vibrations were present between 3300 and 3500 cm^-1, indicating intermolecular hydrogen bonding in solid state.
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Figure 6.2. ORTEP plots (50% probability) and packing diagrams of the structures of 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine 8 (top), 3,6-di(2-pyridyl)-4-n-butylpyridazine 9 (middle) and 3,6-di(2-pyridyl)-4-tributylstannylpyridazine 12 (bottom). Hydrogen atoms are omitted for clarity.

The molecular structure of compound 12 is somewhat different to the other two molecules. The torsion of the aromatic rings against each other is smaller C(7)-C(12)/N(1)-C(6): 7.2°, C(7)-C(12)/C(13)-C(18): 10.3°, N(1)-C(6)/C(13)-C(18): 17.3°. This can be partially the result of an intramolecular nitrogen-tin interaction leading to a weak pentacoordination of Sn which is displayed by the short Sn-N distance [Sn(1)-N(1): 277.1 pm] and which is supported by the deviation of the tetrahedral coordination geometry around the Sn atom [mean angle C(12)-Sn(1)-C(23), C(19)-Sn(1)-C(23), C(23)-Sn(1)-C(27): 103.4° vs. C(12)-Sn(1)-C(19), C(12)-...
Sn(1)-C(27), C(19)-Sn(1)-C(27): 114.75]. Therefore the tin atom can be described to be in a pseudo-trigonal bipyramidal coordination sphere, which is known for several molecules with intramolecular Sn-N interactions.\textsuperscript{38,39} Typically such a distortion around the tin atom is accompanied by a lengthening of the Sn-C bond in \textit{trans}-position to the Sn-N interaction if similar substituents are present at the Sn atom. This effect can also be observed in compound 12 if the three Sn-C\textsubscript{alkyl} bonds are compared: a bond length increase of 3 pm is detected [Sn(1)-C(12): 217.6(3) vs. Sn(1)-C(19): 214.6(3), Sn(1)-C(27): 214.7(3)].

For all three single crystal X-ray structures of 8, 9 and 12, extensive π-π stacking between the aromatic systems was observed in the packing diagrams (Figure 6.2 right).

6.4 NMR spectroscopy of the substituted 3,6-di(2-pyridyl)pyridazines

In order to fully assign the NMR-spectra of the obtained DPP’s 2-12, which would simplify the comparison with the corresponding metal complexes, the compounds were characterized in detail with 1D and 2D-NMR techniques (all in deuterated chloroform).\textsuperscript{40}

For the mono-substituted DPP’s, the assignment of the \textsuperscript{1}H-NMR spectra was difficult since the protons of the two pyridine rings showed different resonances. Therefore, \textsuperscript{1}H-\textsuperscript{1}H correlated spectroscopy (\textsuperscript{1}H-\textsuperscript{1}H COSY) was performed in which neighboring protons give rise to cross-peaks. Figure 6.3 depicts the aromatic regions of typical \textsuperscript{1}H-\textsuperscript{1}H COSY spectra as they were recorded for compounds 9 and 12. In the left spectrum of 3,6-di(2-pyridyl)-4-n-butylpyridazine (9) also some cross-peaks can be observed that arise from long-range interactions between the H-3 and H-6 and between H-6'' and H-5' that appear as small signals. Furthermore, it can be clearly seen that the H-3 and H-5' resonances of the 3,6-di(2-pyridyl)-4-tributylstannylpyridazine 12 are shifted downfield compared to the \textit{n}-butyl DPP 9 due to the strong electron-donating effect of the tributylstannyl group.

\textbf{Figure 6.3.} \textsuperscript{1}H-\textsuperscript{1}H COSY spectra of DPP’s 9 (left) and 12 (right) in CDCl\textsubscript{3}. 

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To be able to assign the $^{13}$C-NMR spectra of the asymmetrical DPP’s, $^1$H-$^{13}$C heteronuclear multiple quantum coherence ($^1$H-$^{13}$C HMQC) spectra were recorded. Figure 6.4 left shows a typical HMQC spectra for 3,6-di(2-pyridyl)-4-n-butylpyridazine (9), whereby cross-peaks appear at the chemical shifts of proton (horizontal scale) and carbon (vertical scale) atoms that are attached to each other. By combining $^1$H-$^1$H COSY and $^1$H-$^{13}$C HMQC NMR techniques, almost all chemical shifts of the proton and carbon atoms could be assigned, whereby significantly different resonances were observed for the protons and carbon atoms of the two pyridine rings from the monofunctionalized compounds.

![Figure 6.4. $^1$H-$^{13}$C HMQC spectrum of 3,6-di(2-pyridyl)-4-n-butylpyridazine 9 (left) and $^{13}$C-$^{13}$C INADEQUATE spectrum of 2,6-di(2-pyridyl)-4-n-octylpyridazine 10 (right) in CDCl₃.](image)

However, the chemical shifts of the H-4 and H-4” protons and also those of the H-5 and H-5” protons appear at the same resonances for compounds 6, 7, 9, 10 and 11, whereas the corresponding carbon signals show different resonances. Therefore, an assignment of the carbon atoms was not possible using HMQR. In order to unambiguously assign these carbon atoms, an incredible natural abundance double-quantum transfer experiment ($^{13}$C-$^{13}$C INADEQUATE) was performed on 3,6-di(2-pyridyl)-4-n-octylpyridazine (10). The detection of coupled $^{13}$C resonances is very difficult and requires a signal-to-noise ratio larger than 20 for a one-transient $^{13}$C-NMR spectrum, which was achieved by dissolving ~500 mg of compound 10 in 0.7 mL CDCl₃. Figure 6.4 right depicts the obtained $^{13}$C-$^{13}$C INADEQUATE spectrum of 10, whereby all dipolar coupled two-spin systems (i.e. neighboring carbon atoms) result in horizontally connected $^{13}$C-$^{13}$C doublets that cross the skew diagonal of slope 2. These horizontal slices are located at the sum of the resonances of the two coupled carbon atoms on the vertical scale. From this experiment all the carbon resonances could unambiguously be assigned for DPP 10 and thus also for compounds 6, 7, 9 and 11.
The chemical shifts of the hydroxyl groups revealed sharp triplets for all hydroxyl functionalized compounds 2-8, whereby the signal appeared at 2.01 ppm for the butyl (6) and nonyl (7) spacers, at 5.36 ppm for the hydroxypropyl substituted compound 5 and higher than 6 ppm for the other three compounds with shorter spacers (3, 4, 8). This suggests that intramolecular hydrogen bonding is present in chloroform solution for the compounds with hydroxymethyl 3, 8, hydroxyethyl 4 and hydroxypropyl 5 substituents. This was proven for 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine 8 by nuclear Overhauser effect spectroscopy (1H-1H NOESY) that demonstrated the through-space coupling of the hydroxyl protons with the H-6 protons of the pyridyl rings (indicated by arrows; Figure 6.5).

Figure 6.5. 1H-1H NOESY spectrum of 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine 8 in CDCl3.

6.5 Microwave-assisted synthesis of 3,6-di(2-pyridyl)pyridazines

In recent years, microwave irradiation was demonstrated to be a valuable tool in organic synthesis resulting in faster and cleaner reactions that sometimes exhibit different reactivities due to specific microwave absorption. Cycloaddition reactions were also successfully applied under microwave irradiation and, more specifically, also intramolecular inverse-electron demand Diels-Alder reactions between 1,2,4-triazines and indoles or imidazoles could be performed under (superheated) microwave conditions. However, these microwave reactions were carried out in high-boiling solvents like N,N-dimethylformamide (DMF) or o-dichlorobenzene.

In this section, microwave-assisted inverse-electron-demand Diels-Alder reactions between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) and alkynes 13-15 are described resulting in the substituted DPP’s 6, 9 and 16. The initial focus of our experiments was the acceleration of the inverse-electron-demand Diels-Alder reactions. Therefore, first the slow cycloaddition of 1-hexyne 13 to tetrazine 1 was attempted under microwave irradiation (Table 1, entries 1-5). This reaction required 16 hours reflux in DMF with conventional heating (71% isolated yield; section 6.2). Under microwave irradiation, no reaction occurred after 5 minutes heating to 160 or 200 ºC in DMF. However, after 15 minutes heating to 225 ºC the intense violet reaction mixture (resulting from tetrazine 1) turned brown and the n-butyl DPP 9 could be isolated in 49% yield. This low yield is due to the high reaction temperature, which induces side-reactions like decomposition of the tetrazine resulting in, e.g., 2-cyanopyridine and reduction of the tetrazine resulting in 3,6-di(2-pyridyl)-dihydro-1,2,4,5-tetrazine.
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Table 6.2: Overview of the investigated microwave-assisted inverse-electron-demand Diels-Alder reactions between 3,6-di(2-pyridyl)tetrazine (1) and different alkynes 13-15.

To avoid the use of high-boiling solvents, this cycloaddition reaction of 1-hexyne was also attempted in dichloromethane (CH$_2$Cl$_2$) and acetone under superheated microwave conditions. The Diels-Alder reaction in CH$_2$Cl$_2$ yielded the desired DPP 9 after only 90 minutes heating to 150 ºC. Although the reaction mixture turned brown, the product could be isolated by column chromatography resulting in 69% yield which is slightly lower than the yield obtained with conventional heating (71%). The cycloaddition reaction in acetone at 150 ºC was completed after only 30 minutes. However, gas chromatography with mass spectrometric detection (GC-MS) and $^1$H-NMR spectroscopy revealed the presence of two DPP’s. Besides the expected n-butyl BPP 9 also 3,6-di(2-pyridyl)-4-methylpyridazine (17) was present. The appearance of this methyl BPP 17 will be discussed later. However, from this initial solvent screening it can be concluded that the inverse-electron-demand Diels-Alder reaction between tetrazine 1 and 1-hexyne (13) can be accelerated from 16 hours DMF reflux to 90 minutes under microwave heating (150 ºC in CH$_2$Cl$_2$). Additionally, the use of CH$_2$Cl$_2$ instead of DMF simplifies the work-up procedure that includes evaporation of the solvent. The reason for the acceleration in CH$_2$Cl$_2$ is not clear at this moment, but it might result from the different nature of this solvent when compared to DMF.

Inspired by these first results, the cycloadditions of 5-hexyn-1-ol (14) and 1-phthalimido-4-pentyne (15) were also attempted under microwave irradiation in CH$_2$Cl$_2$ at 150 ºC (entries 6 and 7; Table 6.2). Both DPP’s 6 and 16 were obtained in good yields, whereby the yield of the hydroxybutyl-pyridazine 6 is slightly higher than the yield obtained after 40 hours reflux in toluene (70%). The 3,6-di(2-pyridyl)-4-phthalimidopropylpyridazine 16 was prepared for the first time. This phthalimido compound can be converted into an amino-functionalized BPP by cleavage with hydrazine.
The unexpected formation of 3,6-di(2-pyridyl)-4-methylpyridazine (17) during the Diels-Alder reaction between tetrazine 1 and 1-hexyne (13) in acetone was further investigated by heating a solution of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) in acetone for 30 minutes to 150 °C under microwave irradiation. The obtained 1H-NMR spectra for the attempted microwave Diels-Alder reactions of tetrazine 1 and 1-hexyne (13) in DMF and acetone are depicted in Figure 6.6 together with the resulting 1H-NMR spectrum after heating a solution of 1 in acetone. The inset shows an enlargement of the H-3 and H-5’ resonances illustrating the appearance of different DPP’s.

Heating the solution of tetrazine 1 in acetone resulted in the formation of 3,6-di(2-pyridyl)-4-methylpyridazine (17; 75% isolated yield) demonstrating that the acetone participates in the inverse-electron-demand Diels-Alder reaction. In addition, heating tetrazine 1 and acetone to 150 °C with conventional heating using a pressure reactor also resulted in the formation of DPP 17, which demonstrates that the observed cycloaddition results from superheating and not from so-called microwave effects. However, previously only alkenes and alkynes were reported to undergo this inverse-electron-demand Diels-Alder reaction with 1. Therefore, it is most likely that the enol-tautomer of acetone participates in the cycloaddition instead of the keto-tautomer. The proposed reaction mechanism for the cycloaddition of acetone to tetrazine 1 is depicted in Scheme 6.4.

**Figure 6.6.** 1H-NMR spectra obtained after the reaction between tetrazine 1 and 1-hexyne (13) in DMF (bottom) and acetone (middle) together with the spectrum obtained after heating 1 in acetone (top). All spectra were recorded in CDCl3.

**Scheme 6.4.** Proposed reaction mechanism for the inverse-electron-demand Diels-Alder reaction of tetrazine 1 with the enol-tautomer of acetone (propen-2-ol).
Reaction of propen-2-ol with tetrazine 1 results in the formation of the unstable intermediate 17’ that eliminates a nitrogen molecule generating the second intermediate 3,6-di(2-pyridyl)-4-hydroxy-4-methyl-dihydropyridazine 17’’. Under the applied reaction conditions (150 °C microwave heating), spontaneous oxidative elimination of water occurs yielding the formation of 3,6-di(2-pyridyl)-4-methylpyridazine (17). Even though the amount of present enol-tautomer in acetone is significantly less than the amount of keto-tautomer, the electron-rich hydroxyl-group of the propen-2-ol facilitates the inverse-electron-demand Diels-Alder reaction. Moreover, it has been reported that the keto-enol equilibrium is shifted towards the enol-tautomer under high-temperature (conventional heating) and pressure conditions. However, these examples demonstrated a shift in the equilibrium for acetone in solution, whereas the present experiments were performed in neat acetone. Nevertheless, it may be assumed that also for neat superheated acetone, the equilibrium is shifted towards the enol-tautomer. Furthermore, it was demonstrated that this shift in equilibrium accelerates the oxidation of acetone in superheated water or the deuterium exchange of acetone in superheated D₂O. Nevertheless, the enol-tautomer of acetone has never been applied as reagent in organic synthesis to the best of our knowledge.

Encouraged by the successful cycloaddition reaction of acetone, tetrazine 1 was heated in several other ketones as depicted in Table 6.3 (entries 1-4). The reaction with 2-butanone at 150 °C under microwave irradiation yielded cycloadducts of both enol-tautomers 1-buten-2-ol and 2-buten-2-ol, namely 3,6-di(2-pyridyl)-4-n-ethylpyridazine (18) and 3,6-di(2-pyridyl)-4,5-dimethylpyridazine (19). Even though the more stable 2-buten-2-ol tautomer will be present in a larger extend in 2-butanone than the 1-buten-2-ol tautomer, both DPP’s 18 and 19 were obtained in a 1 to 1 ratio according to the crude ¹H-NMR spectrum. This inconsistency can be explained by the higher electron density of the double bond of the 1-buten-2-ol that results in higher reactivity of this tautomer which, apparently, compensates the lower abundance. The two different DPP’s 18 and 19 were separated by repetitive column chromatography (2 × aluminum oxide; 1 × silica) resulting in substantial loss of compound.

Table 6.3: Overview of the investigated microwave-assisted inverse-electron-demand Diels-Alder reactions between 3,6-di(2-pyridyl)tetrazine 1 and various ketones and aldehydes. R₁ and R₂ represent the substituents on the 4 and 5 position of the resulting 3,6-di(2-pyridyl)pyridazines.

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<th>Entry</th>
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<th>Boiling point</th>
<th>Reaction temperature</th>
<th>Reaction time</th>
<th>Product</th>
<th>R₁</th>
<th>R₂</th>
<th>Isolated yield</th>
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<td>CH₃</td>
<td>H</td>
<td>75%</td>
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<tr>
<td>2</td>
<td>2-butanone</td>
<td>80 °C</td>
<td>150 °C</td>
<td>30 min</td>
<td>18</td>
<td>CH₂CH₃</td>
<td>H</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>3-pentanone</td>
<td>101 °C</td>
<td>180 °C</td>
<td>60 min</td>
<td>20</td>
<td>CH₃</td>
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<tr>
<td>4</td>
<td>3-methyl-2-butanone</td>
<td>94-95 °C</td>
<td>180 °C</td>
<td>30 min</td>
<td>21</td>
<td>i-propyl</td>
<td>H</td>
<td>na³</td>
</tr>
<tr>
<td>5</td>
<td>water</td>
<td>100 °C</td>
<td>150 °C</td>
<td>20 min</td>
<td>23</td>
<td></td>
<td>ring-opened</td>
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<tr>
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<td>acetaldehyde</td>
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<td>75 °C</td>
<td>150 °C</td>
<td>30 min</td>
<td>18</td>
<td>CH₂CH₃</td>
<td>H</td>
<td>48%</td>
</tr>
<tr>
<td>8</td>
<td>hexanal</td>
<td>131 °C</td>
<td>170 °C</td>
<td>30 min</td>
<td>9</td>
<td>n-butyl</td>
<td>H</td>
<td>16%</td>
</tr>
<tr>
<td>9</td>
<td>octanal</td>
<td>171 °C</td>
<td>200 °C</td>
<td>30 min</td>
<td>24</td>
<td>n-hexyl</td>
<td>H</td>
<td>9%ᵇ</td>
</tr>
</tbody>
</table>

³ This product mixture was only used for GC-MS analysis.
ᵇ This compound was not completely pure, but too little quantity for further purification.
Chapter 6

The inverse-electron-demand Diels-Alder reactions with 3-pentanone and 3-methyl-2-butanone did not proceed at 150 °C under microwave irradiation. However, at 180 °C these cycloadditions occurred as well indicating that the ketones need to be heated to at least 70 °C above the boiling point to have sufficient quantities of the enol-tautomers present. However, 180 °C results in decomposition of the tetrazine 1 and thus very low yields were obtained, namely 13% isolated yield of 3,6-di(2-pyridyl)-4-ethyl-5-methylpyridazine (20). The reaction between 1 and 3-methyl-2-butanone was performed to prove the proposed reaction mechanism. Reaction of the enol-tautomers, 3-methyl-1-buten-2-ol and 3-methyl-2-buten-2-ol, with tetrazine 1 would result in 3,6-di(2-pyridyl)-4-iso-propylpyridazine (21) and 3,6-di(2-pyridyl)-4-hydroxy-4,5,5-trimethyl-dihydropyridazine (22; Figure 6.7 left).

![Image](image-url)

**Figure 6.7.** Left: Schematic representation of the inverse-electron-demand Diels-Alder reaction between tetrazine 1 and 3-methyl-2-butanone. Right: GC-MS spectrum obtained of the crude reaction mixture showing the presence of both DPP 21 and dihydroDPP 22.

The dihydropyridazine 22 cannot aromatize by oxidative elimination of water and thus the presence of this hydroxy-pyridazine 22 would prove the proposed reaction mechanism. GC–MS of the crude reaction mixture indeed revealed the presence of DPP 21 and dihydropyridazine 22 together with many side products like 3,6-di(2-pyridyl)-4-iso-propyl-5-hydroxy-dihydropyridazine, 3,6-di(2-pyridyl)-1,2,4,5-dihydropyridazine, 2,5-di(2-pyridyl)-1,3,4-oxadiazole and 2-pyridinecarboxylic acid (2-pyridylmethylene)hydrazide (Figure 6.7 right). The deliberate insertion of water to 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) was also attempted by heating 1 in water for 20 minutes to 150 °C under microwave irradiation. Although the violet tetrazine did not dissolve in water at ambient temperature, microwave heating resulted in the quantitative formation of 2-pyridinecarboxylic acid (2-pyridylmethylene)hydrazide (23; 96% isolated yield; Scheme 6.5). Previously, the synthesis of 23 was only reported via Schiff base condensation of 2-pyridinecarboxaldehyde and 2-pyridinecarboxylic acid hydrazide.52

![Image](image-url)

**Scheme 6.6.** Reaction that was observed upon heating tetrazine 1 in water to 150 °C under microwave irradiation resulting in 2-pyridinecarboxylic acid (2-pyridylmethylene)hydrazide (23).
From literature it is known that the enol-tautomers of aldehydes are present when compared to ketones. Therefore, a series of aldehydes was tested in the inverse-electron-demand Diels-Alder reaction with tetrazine 1 as well (Table 6.3; entries 6-9). When heating a mixture of 1 in acetaldehyde to 120 °C under microwave irradiation, the unsubstituted DPP 2 was formed in good yield demonstrating that superheated aldehydes are also suitable reagents in the inverse-electron-demand Diels-Alder reaction. The cycloadditions of butanal, hexanal and octanal required 150, 170 and 200 °C, respectively. After 30 minutes heating, GC-MS of the crude reaction mixtures revealed full conversion of tetrazine 1 and the presence of the expected pyridazine, the corresponding dihydropyridazine and dihydrotetrazine in a 6:2:2 ratio. Both the dihydropyridazine and the dihydrotetrazine were not observed in such large quantities in the case of the ketone cycloadditions. From these results, it can be concluded that the dihydropyridazines resulting from aldehyde addition are stable and do not undergo spontaneous oxidative elimination of water. Moreover, the increased amount of dihydrotetrazine might be due to hydrogen transfer from the dihydropyridazine to tetrazine 1 resulting in oxidation of the dihydropyridazine (similar hydrogen transfer from dihydropyridines to tetrazine 1 has been reported). Nevertheless, the $n$-ethyl DPP 18, $n$-butyl DPP 9 and $n$-hexyl DPP 24 could be obtained in reasonable yield and purity, whereby the yield (and ease of purification) decreased with longer chain lengths due to the required higher reaction temperatures.

In conclusion, the cycloaddition reactions of alkynes to 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) could be accelerated under superheated microwave conditions. Moreover, a novel mechanism for the synthesis of substituted DPP’s was described in which ketones and aldehydes are applied as dienophiles in the inverse-electron-demand Diels Alder reaction with tetrazine 1. This strategy avoids the usage of gaseous reagent like acetylene, propyne and butyne for the synthesis of DPP’s with short side-chains. Furthermore, the application of 2-butanone of 3-pentanone as reagents yielded the formation of a noncyclic dialkyl-substituted DPP’s for the first time.

### 6.6 Complexation studies of functionalized 3,6-di(2-pyridyl)pyridazines

DPP ligands are known to self-assembly into [2×2] grid-like complexes with copper(I) and silver(I) ions as depicted in Scheme 6.6. To investigate whether the hydroxyl groups would interfere with the grid-formation, the complexation of 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (6) and 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine (8) with copper(I) ions was studied. These two ligands were chosen, because they are the most obvious building blocks for the synthesis of macromolecular ligands. Therefore, before continuing with further synthetic procedures, their self-assembly had to be investigated.

![Scheme 6.6](image)

Moreover, the DPP 8 was chosen because it has a specific conformation driven by intramolecular hydrogen bonding that has to be changed upon complexation. Thus, if this ligand would self-assemble into grid-like complexes with the loss of the hydrogen bonding interactions, a similar behavior can be expected for the other functional DPP’s as well. In addition, the symmetry of BPP 8 will make the $^1$H-NMR spectroscopic characterization of the resulting symmetrical [2×2] copper grids more straightforward.

Self-assembly of the ligands with copper(I) ions was performed by addition of a solution of the ligand (1 eq.) in dichloromethane to a solution of tetrakisacetonitrile copper(I) hexafluorophosphate (1 eq.) in dichloromethane resulting in instantaneous formation of a brown precipitate, which is the desired [2×2] grid-like copper(I) complex. The resulting copper-grids 25 and 26 appeared to be only soluble in acetone and methanol, whereas the free ligands as well as the used copper(I) salt are well-soluble in dichloromethane. The $^1$H-NMR spectrum of copper(I) grid 26 revealed only four aromatic signals (Figure 6.8 left) demonstrating the high symmetry of the created metal complex. This high symmetry and the clear coupling of the proton resonances demonstrate the formation of defined species and not polymeric species. Moreover, the H-3 and H-6 protons switched positions upon complexation with copper(I) ions, which is also a proof for the successful complexation. Unlike the clear $^1$H-NMR spectrum for copper(I) grid 26, a remarkably undefined $^1$H-NMR spectrum was obtained for the copper(I) complex 25 of the unsymmetrical DPP 6. However, the indicative downfield movement of the H-5’ resonance was observed together with an upfield shift of the H-3’’, H-6 and H-6’’ resonances. These observations indicate the successful complexation of DPP 6. However, as many as 4 broad resonances that all appeared to consist of several overlapping signals (see inset Figure 6.8 left) were observed for the H-5’ proton from 8.95–9.15 ppm.

![Figure 6.8. $^1$H-NMR spectra obtained before and after complexation of DPP 8 resulting in [2×2] copper(I) grid 26 (left) and before and after complexation of DPP 6 resulting in complex 25 (right). All spectra were recorded in acetone-d$_6$. The inset of the right figure shows a close-up of the 5’ region.](image)

The appearance of so many different resonances results from the different isomers that can be formed when self-assembling four asymmetrical ligands in one [2×2] grid. Figure 6.9 depicts the eight different isomers that can be formed in both a space-filling and a schematic representation. The structures A and B, C and D, E and F, and G and H are mirror images of each other as represented by a line in-between the schematic representations. From these four
couples of structures, only G and H are identical making the total number of possible isomers seven. Although the schematic representation of E and F would suggest that these structures are the same, the space-filling representations cannot be converted into each other by rotation. This difference is due to the fact that the upper and lower substituents are not exactly on top of each other as it is drawn in the schematic representation. Even though seven different isomers can be formed, the total number of theoretical resonances for the H-5’ proton cannot be distinguished since different H-5’ chemical shifts may arise from one single isomer when it is not symmetrical.

Figure 6.9. Space-filling and schematical representation of the different isomers (A−H) that can be formed by self-assembly of the asymmetrical DPP 6 into [2×2] copper(I) grid 25. The space-filling representations were drawn using Chemsketch 3D from ACD-labs.
The UV-spectra of the DPP’s 6 and 8 and the corresponding copper(I) grids 25 and 26 are depicted in Figure 6.10 left. Upon complexation with copper(I) ions, the metal to ligand charge transfer (MLCT) band appeared at 436 nm (25) or 439 nm (26). These MLCT bands are very similar to the one described in literature for the [2×2] copper grids with the unsubstituted DPP 2 (436 nm) demonstrating that both BPP 6 and BPP 8 also self-assemble into [2×2] copper(I) metal grids.¹¹

The [2×2] copper(I) grid 26 was further investigated with ESI-QTOF-MS (Figure 10 right). With this mass spectrometry method, a small amount of complete grids and many fragmentation products were observed proving the existence of [2×2] grid-like complexes. The insets of Figure 6.10 right depict both a single charged grid with three counterions (right) and a double charged grid (line spacing 0.50 m/z) with two counterions (left). The isotopic pattern matches exactly with a simulated spectrum. A triple charged grid with four ligands, four copper(I) ions, one PF₆ counterion and a sodium ion could also be observed (not shown), whereby the different signals from the isotopic pattern appeared at a distance of 0.333 m/z form each other. Furthermore, complexes with two or three ligands containing one, two or three copper(I) ions resulting from fragmentation of the grids could be assigned in the spectrum as well.

![Figure 6.10. Left: UV-vis spectra of DPP’s 6 and 8 and copper(I) complexes 25 and 26. Left: ESI-QTOF-MS spectrum of copper(I) grid 26.](image)

The ¹H-NMR spectroscopy together with the additional characterization utilizing UV-vis spectroscopy and ESI-QTOF-MS clearly demonstrated the possibility of self-assembling the hydroxyfunctionalized BPP’s 6 and 8 with copper(I) ions into [2×2] metal complexes. Even though the structure of 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine (8) is stabilized by intramolecular hydrogen bonding, the compound is still capable of flipping the outer rings to act as ligand for copper(I) ions to form grid-like architectures. Therefore, it may be concluded that most of the other functional DPP’s that were described in this chapter will also self-assemble with copper(I) ions into grid-like architectures.
6.7 Conclusions

In this chapter, the synthesis, characterization and metal complexation of novel substituted DPP’s are described. Especially, functionalized DPP’s are of interest since they can be applied as building blocks for the construction of macromolecular [2×2] grid-like metal complexes.

The inverse-electron-demand Diels-Alder reactions between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) and various (functional) alkynes were investigated. Alkynes of different lengths bearing unprotected alcohol groups were successfully reacted resulting in hydroxy-functional DPP’s. Although the hetero Diels-Alder reaction of aliphatic acetylenes required more stringent reaction conditions, three different alkyl substituted DPP’s were obtained as well. More bulky acetylenes could not be reacted with the tetrazine except for tributylstannylacetylene in which the electron-donating tributylstannyl group accelerates the reaction.

Single crystal X-ray crystal structures were obtained for 3,6-di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine (8), 3,6-di(2-pyridyl)-4-n-butylpyridazine (9) and 3,6-di(2-pyridyl)-4-tributylstannylpyridazine (12). The structure of 8 clearly revealed the presence of intramolecular hydrogen bonding between the hydroxyl groups and the nitrogen atoms of the outer pyridyl rings. The structure of 12 revealed intramolecular nitrogen-tin interaction leading to a weak pentacoordination of the stannyl atom. In all compounds, extensive π-π stacking was observed between the aromatic systems in the packing diagrams.

NMR spectroscopic investigations revealed different chemical shifts for the two outer pyridyl rings for all unsymmetrical DPP’s. For a complete assignment of all proton and carbon resonances, $^1$H-$^1$H COSY, $^1$H-$^{13}$C HMQC and $^{13}$C-$^{13}$C INADEQUATE spectra were combined. Moreover, $^1$H-$^1$H NOESY demonstrated the through space coupling of the hydroxyl protons of DPP 8 with the H-6 protons of the pyridine rings, which proves the presence of intramolecular hydrogen bonding in chloroform.

To accelerate the slow inverse-electron-demand Diels-Alder reactions, the effect of microwave irradiation was investigated. By going to superheated CH$_2$Cl$_2$ (150 ºC) as solvent, the reactions were completed within several hours instead of several days. In contrast, applying superheated acetone (150 ºC) as solvent to acetone led to an unexpected mixture of DPP’s. It could be elucidated that the enol-tautomer of acetone, which presence is enhanced under superheated conditions, reacts with tetrazine 1. Upon elimination of a nitrogen molecule and subsequent oxidative elimination of water 3,6-di(2-pyridyl)-4-methylpyridazine (17) was formed. This novel synthetic pathway was also successfully applied with different ketones and aldehydes under superheated microwave conditions. However, the oxidative elimination after cycloaddition of the aldehydes did not proceed spontaneously, but hydrogen transfer to unreacted tetrazine 1 was observed leading to the desired DPP’s and dihydrotetrazine. Only the cycloaddition of acetaldehyde resulted in quantitative formation of the unsubstituted DPP 2.

Finally, the effect of hydroxyl groups on the self-assembly of the DPP’s was investigated. Therefore, self-assembly of the hydroxybutyl DPP 6 and bis(hydroxymethyl) DPP 8 ligands was performed by addition of copper(I) ions. $^1$H-NMR spectroscopy revealed highly symmetrical metal complexes for the symmetrical DPP 8, whereby shifts indicative of metal complexation were observed for the aromatic protons. This together with the observation of complete grids in ESI-QTOF-MS and the appearance of the characteristic MLCT band in the
UV-vis spectrum clearly indicated the successful formation of [2×2] metal grids. Thus, DPP 8 is still capable of flipping the outer pyridyl rings (and breaking the intramolecular hydrogen bonds) to act as coordinating ligand for copper(I) ions. Therefore, it may be assumed that the other functional DPP’s will also be able to form supramolecular [2×2] grids with copper(I) ions. Moreover, the 1H-NMR spectrum of the [2×2] copper(I) grids of the asymmetrical DPP 6 revealed many different resonances in the aromatic region. More specifically, several resonances were observed for the H-5’ singlet due to the possible formation of seven unsymmetrical isomers. In contrast, the UV-vis spectrum clearly revealed the MLCT band of the copper-grid. Therefore, the many different observed resonances in the 1H-NMR spectrum result from the seven different isomers that can be formed upon [2×2] grid formation of an unsymmetrical ligand.

6.8 Experimental part

Materials and instrumentation

Solvents were purchased from Biosolve and all other compounds were obtained from Aldrich or Fluka. All compounds were used without further purification.

1H-NMR, 1H-1H COSY and 13C-NMR were recorded on a Varian Gemini 300 spectrometer or a Varian Mercury 400 spectrometer. The 1H-1H NOESY, 1H-13C HMQC and 13C-13C INADEQUATE (delay time = 1.5 s, τ = 4.2 ms) spectra were recorded on a Varian Inova 500 spectrometer, whereby the HMQC experiments were performed with an indirect probe. Chemical shifts are given in ppm relative to TMS or solvent signals for proton and carbon spectra. UV-vis spectroscopy was done on a Perkin Elmer Lambda 45 apparatus utilizing 1 cm cuvets. MALDI-TOF-MS was performed on a Voyager-DE™ PRO Biospectrometry™ Workstation (Applied Biosystems) time-of-flight mass spectrometer using linear mode for operation. The spectra were obtained in the positive ion mode and ionization was performed with a 337 nm pulsed nitrogen laser, whereby dithranol was used as matrix. ESI-QTOF-MS was performed on a Micromass Q-TOF Ultima global apparatus. GC-MS analysis was performed on a Shimadzu GC-MS-QP5000, the mass values are reported as mass/charge ratio (m/z). All spectra were measured with a column temperature program from 80-300 °C (25 °C/min) and 3 minutes hold time at 300 °C. The injection temperature was 300 °C and the detector temperature 250 °C. IR-spectra were recorded on a Perkin Elmer 1600 FT-IR. Elemental analyses were done on a Carlo Erba Instruments EA1108 CHNS/O Elemental Analyzer or on an EuroEA3000 Series EuroVector Elemental Analyzer for CHNS-O. Melting points were determined utilizing a Büchi B-540 apparatus or a differential scanning calorimeter (DSC 204 F1 Phoenix by Netzsch) under a nitrogen atmosphere with a heating rate of 5 K·min⁻¹. Microwave-assisted synthesis was performed utilizing an Emrys Liberator microwave synthesizer (Biotage) utilizing capped reaction vials. All microwave reactions were performed with temperature control (IR sensor).

3,6-Di(2-pyridyl)-1,2,4,5-tetrazine (1)

This compound was synthesized as reported in literature (52% overall yield for two reaction steps; lit. 49%). M.p. 219-220 °C (lit. 222 °C). 1H-NMR (CDCl3): δ 8.99 (dd, J = 3.9, 1.1 Hz, 2H, H-6,6’’), 8.75 (d, J = 7.7 Hz, 2H, H-3,3’’), 8.01 (dt, J = 7.7, 1.6 Hz, 2H, H-4,4’’), 7.58 (dt, J = 3.9, 1.1 Hz, 1H, H-5,5’’). 13C-NMR (CDCl3): δ 163.7 (C-3’,6’’), 150.9 (C-2,2’’), 150.0 (C-6,6’’), 137.4 (C-4,4’’), 126.5 (C-5,5’’), 124.5 (C-3,3’’). IR (ATR): ν 3097 cm⁻¹, 3061, 3047, 1582, 1387, 1259, 1240, 128, 993, 919, 796, 743, 732, 594. MALDI-TOF-MS: m/z 237 [M⁺]. UV-vis (chloroform): λmax 546 nm, 293 nm.

3,6-Di(2-pyridyl)pyridazine (2)

3,6-Di(2-pyridyl)pyridazine 2 was synthesized as described in literature (81% yield; lit. 78%). M.p. 178-179 °C (lit. 179-180 °C). Microwave: A solution of 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1; 100 mg, 0.42 mmol) in acetaldehyde (2 mL) was heated to 120 °C for 30 minutes under microwave irradiation. After evaporation of the acetaldehyde, the brown residue was filtered over aluminum oxide (chloroform as eluent) and recrystallized from ethanol yielding the product, as yellowish crystals (83 mg, 84%).
3,6-Di(2-pyridyl)-4-(hydroxymethyl)pyridazine (3)

A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.12 mmol) and propargyl alcohol (238 mg, 4.24 mmol) in toluene (50 mL) was refluxed for 75 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, ethyl acetate as eluent). After recrystallization from diethyl ether:dichloromethane (2:1) at −25 °C the product was obtained as white needles (480 mg, 88%). M.p. 128-129 ºC (decomposition).

IR (ATR): ν 3296 cm⁻¹, 3092, 3063, 1585, 1568, 1399, 1050, 992, 876, 737, 619. C₆H₁₂N₂O₂: calcd. C 69.05, H 5.07, N 20.13; found C 68.74, H 4.93, N 19.69.

MALDI-TOF-MS: m/z [M⁺] 265 (100%). UV-vis (chloroform): λ_max 295 nm.

3,6-Di(2-pyridyl)-4-(1-hydroxyethyl)pyridazine (4)

A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 4-pentyn-1-ol (335 mg, 4.2 mmol) in toluene (50 mL) was refluxed for 75 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, ethyl acetate as eluent). After recrystallization from diethyl ether:dichloromethane (2:1) at −25 °C the product was obtained as yellow crystals (456 mg, 77%). M.p. 65-66 °C. ¹H-NMR (CDCl₃, ¹H-¹H correlated spectroscopy (COSY)): δ 8.72 (m, 4H, H-3'',6'',5'',6''), 8.68 (dd, J = 4.4, 1.7 Hz, 1H, H-6), 8.62 (s, 1H, H-5''), 8.32 (dd, J = 8.2, 1.1 Hz, 1H, H-3), 8.00 (dt, J = 7.7, 1.7 Hz, 1H, H-4), 7.91 (dt, J = 7.7, 1.7 Hz, 1H, H-5''), 7.49 (dt, J = 7.7 Hz, 1.7, 1H, H-5), 7.42 (dt, J = 7.7 Hz, 1.7, 1H, H-5''), 6.71 (t, J = 4.4 Hz, 1H, OH), 4.17 (q, J = 5.5, 4.4 Hz, 2H, CH₂OH), 3.17 (t, J = 5.5 Hz, 2H, CH₂CH₂OH). ¹³C-NMR (CDCl₃, ¹H-¹³C HMBC): δ 158.9 (C-3''), 157.5 (C-6''), 154.8 (C-2''), 153.2 (C-2''), 149.4 (C-6), 147.5 (C-5), 142.8 (C-5''), 124.1 (C-5), 121.8 (C-3''), 63.3 (CH₂OH), 34.6 (CH₂CH₂OH). IR (ATR): ν 3353 cm⁻¹, 3158, 3054, 2852, 1579, 1579, 1379, 1074, 1052, 993, 790, 745, 728, 656. C₁₀H₁₂N₂O₂: calcd. C 69.05, H 5.07, N 20.13; found C 68.74, H 4.93, N 19.69.

MALDI-TOF-MS: m/z [M⁺] 279 (100%). UV-vis (chloroform): λ_max 290 nm.

3,6-Di(2-pyridyl)-4-(1-hydroxypropyl)pyridazine (5)

A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 4-pentyn-1-ol (335 mg, 4.2 mmol) in toluene (50 mL) was refluxed for 40 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, chloroform as eluent). After recrystallization from chloroform:diethyl ether:hexane (1:2:1) the product was obtained as yellowish crystals (257 mg, 80%). M.p. 74-76 °C. ¹H-NMR (CDCl₃, ¹H-¹H COSY): δ 8.75 (m, 2H, H-3'',6''), 8.68 (d, J = 4.4 Hz, 1H, H-6), 8.57 (s, 1H, H-5''), 8.19 (d, J = 7.3 Hz, 1H, H-3), 7.97 (t, J = 7.3 Hz, 1H, H-4), 7.91 (t, J = 7.3 Hz, 1H, H-5''), 7.46 (t, J = 7.3 Hz, 1H, H-5), 7.42 (t, J = 7.3 Hz, 1H, H-5''), 5.36 (t, J = 5.1 Hz, 1H, OH), 3.60 (q, J = 5.1 Hz, 2H, CH₂OH), 3.13 (t, J = 7.3 Hz, 2H, CCH₂), 2.15 (m, 2H, CH₂CH₂OH). ¹³C-NMR (CDCl₃): δ 158.7 (C-3''), 156.9 (C-6''), 155.4 (C-2''), 152.9 (C-2''), 149.1 (C-6''), 147.7 (C-6), 141.7 (C-4'), 137.2 (C-4''), 136.9 (C-4), 125.6 (C-5''), 125.1 (C-3), 124.5 (C-5'), 123.5 (C-5), 121.4 (C-3''), 60.2 (CH₂OH), 32.5 (CCH₂), 27.5 (CH₂CH₂OH). IR (ATR): ν 3330 cm⁻¹, 2933, 2902, 2865, 1583, 1570, 1400, 1056, 993, 790, 743, 726, 658. C₁₀H₁₄N₂O₂: calcd. C 69.85, H 5.22, N 19.16; found C 69.73, H 5.45, N 18.78. MALDI-TOF-MS: m/z [M⁺] 293 (100%). UV-vis (chloroform): λ_max 288 nm.
3,6-Di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (6)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 5-hexyne-1-ol (410 mg, 4.2 mmol) in toluene (25 mL) was refluxed for 40 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, chloroform as eluent). Recrystallization from chloroform:diethyl ether (1:2:1) yielded the product as a white solid (448 mg, 70%).

Microwave: A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 5-hexyne-1-ol (312 mg, 3.2 mmol) in dichloromethane (4.0 mL) was heated for 90 minutes to 150 ºC under microwave irradiation. After evaporation of the solvent, the product (504 mg, 78%) was obtained by column chromatography (SiO₂ with ethyl acetate).

M.p. 79.5-80 ºC. ¹H-NMR (CDCl₃): δ 8.79-8.70 (m, 3H, H-6,3'',6''), 8.48 (s, 1H, H-5'), 8.15 (d, J = 8.2 Hz, 1H, H-3), 7.88 (dt, J = 7.7, 2.2 Hz, 2H, H-4,4''), 7.40 (m, 3H, H-5,5''), 3.62 (q, J = 4.9 Hz, 2H, CH₂OH). 13C-NMR (CDCl₃): δ 158.7 (C-3'), 157.0 (C-6'), 155.9 (C-2), 153.1 (C-2''), 149.1 (C-6''), 148.3 (C-6), 142.4 (C-4'), 137.0 (C-4''), 136.8 (C-4), 125.5 (C-5'), 124.7 (C-3), 124.5 (C-5''), 123.5 (C-5), 121.6 (C-3''), 61.5 (CH₂OH). IR (ATR): ν = 3328 cm⁻¹, 1588, 1559, 1420, 1398, 1054, 1030, 991, 784, 746, 730. C₁₉H₁₈N₈O: calcd. C 70.6, H 5.9, N 18.5; found C 71.0, H 5.7, N 18.5. MALDI-TOF-MS: m/z [M⁺] 307 (100%). UV-vis (chloroform): λ_max 288 nm.

3,6-Di(2-pyridyl)-4-(1-hydroxynonyl)pyridazine (7)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 10-undecyn-1-ol (427 mg, 2.5 mmol) in toluene (50 mL) was refluxed for 75 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, chloroform as eluent). Recrystallization from diethyl ether yielded the product as a white solid (750 mg, 89%). M.p. 71-72 ºC.

UV-vis (chloroform): 2864, 1580, 1410, 1398, 1054, 1030, 991, 798, 746, 730. C₁₉H₁₈N₈O: calcd. C 70.6, H 5.9, N 18.5; found C 71.0, H 5.7, N 18.5. MALDI-TOF-MS: m/z [M⁺] 377 (100%). UV-vis (chloroform): λ_max 288 nm.

3,6-Di(2-pyridyl)-4,5-bis(hydroxymethyl)pyridazine (8)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 2.0 g, 8.5 mmol) and 2-butyln-1,4-diol (1.5 mg, 17.4 mmol) in toluene (50 mL) was refluxed for 40 hours. The crude reaction mixture was filtered over Al₂O₃ and subsequently the solvent was removed under reduced pressure. Recrystallization from ethanol yielded the product as white needles (1.76 g, 71%). M.p. 198-200 ºC (decomposition). ¹H-NMR (CDCl₃, ¹H-¹H COSY): δ 8.71 (d, J = 5.1 Hz, 2H, H-6,6''), 8.43 (d, J = 8.1 Hz, 2H, H-3,3''), 8.00 (dt, J = 8.1, 1.5 Hz, 2H, H-4,4''), 7.51 (dt, J = 5.1, 1.5 Hz, 2H, H-5,5''), 6.14 (t, J = 8.1 Hz, 2H, OH), 4.82 (d, J = 8.1 Hz, 4H, CH₂OH). ¹³C-NMR (CDCl₃, ¹H-¹C HMOC): δ 159.2 (C-3',6''), 155.5 (C-5,5''), 149.4 (C-6''), 148.6 (C-6), 142.9 (C-4'), 137.2 (C-4''), 136.9 (C-4), 125.6 (C-5'), 124.8 (C-3), 124.7 (C-7''), 123.5 (C-5), 121.8 (C-3''), 63.0 (CH₂OH), 32.8 (CCH₂), 32.3 (C(CH₂)₂), 29.7-29.1 (other CH₂). IR (ATR): ν = 3328 cm⁻¹, 2926, 2885, 1579, 1398, 1054, 997, 792, 744, 656, 622, 599. C₁₉H₁₈N₈O • ½ H₂O: calcd. C 72.51, H 7.54, N 14.70; found C 72.69, H 7.34, N 14.72. MALDI-TOF-MS: m/z [M⁺] 377 (100%). UV-vis (chloroform): λ_max 286 nm.

3,6-Di(2-pyridyl)-4-n-butylpyridazine (9)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 1-hexyne (344 mg, 4.2 mmol) in toluene (25 mL) was refluxed for 40 hours. Subsequently, DMF (25 mL) was added and after evaporation of the toluene, the reaction mixture was stirred at 160 ºC for 16 hours. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography...
(Al₂O₃, chloroform as eluent). Recrystallization from ethanol:water (2:1) yielded the product as yellowish crystals (434 mg, 71%).

**Microwave A:** A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) and 1-hexyne (67 mg, 0.84 mmol) in DMF (2.5 mL) was heated for 15 minutes to 225 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, chloroform as eluent) yielding the product as yellowish solid (60 mg, 49%).

**Microwave B:** A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) and 1-hexyne (67 mg, 0.84 mmol) in CH₂Cl₂ (2.5 mL) was heated for 90 minutes to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al₂O₃, chloroform as eluent) yielding the product as yellowish solid (84 mg, 69%).

**Microwave C:** A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in hexanal (2.0 mL) was heated for 30 minutes to 150 °C under microwave irradiation. After evaporation of the solvent, the brown residue was purified by column chromatography (SiO₂, ethyl acetate:hexane (1:1)) yielding the product as yellowish solid (20 mg, 16%).

M.p. 70-71 °C. ¹H-NMR (CDCl₃, ¹H-¹H COSY): δ 8.75-8.70 (m, 3H, H-6,3'',6''), 8.49 (s, 1H, H-5'), 8.09 (d, J = 8.1 Hz, 1H, H-3'), 7.89 (dt, J = 8.1, 2.2 Hz, 2H, H-4,4''), 7.40 (dt, J = 8.1, 1.5 Hz, 2H, H-5,5''), 3.08 (t, J = 8.1 Hz, 2H, CCH₃), 1.59 (quintet, J = 7.3 Hz, 2H, CCH₂CH₂), 1.32 (sixtet, J = 7.3 Hz, 2H, CH₃CH₃), 0.86 (t, J = 8.1 Hz, 2H, CH₂). ¹³C-NMR (CDCl₃, ¹H-¹³C HMBC): δ 159.2 (C-3'), 157.3 (C-6'), 156.5 (C-2), 149.4 (C-6''), 148.5 (C-6), 142.9 (C-4'), 137.2 (C-4''), 136.9 (C-4), 125.6 (C-5'), 124.8 (C-3), 124.6 (C-5''), 123.5 (C-5), 121.8 (C-3''), 32.0 (CCH₂), 31.9 (C(CH₂)₃CH₃), 22.6 (C(CH₂)₃), 13.8 (CH₃CH₂). IR (ATR): ν 3056 cm⁻¹, 2927, 2861, 1579, 1570, 1406, 1378, 1251, 1150, 1099, 991, 801, 780, 744, 728. C₁₉H₁₄N₄: calcd. C 74.46, H 6.25, N 19.29; found C 74.44, H 6.09, N 19.04. MALDI-TOF-MS: m/z [M⁺] 291 (100%). UV-vis (chloroform): λ_max 288 nm.

**3,6-Di(2-pyridyl)-4-n-octylpyridazinone (10)**

A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 1-decyne (351 mg, 2.5 mmol) in DMF (50 mL) was refluxed for 16 hours. After evaporation of the solvent under reduced pressure, the crude product was recrystallized from methanol:water (3:1) resulting in a white solid (481 mg, 58%; lit. 62%). M.p. 38 °C (lit. 35 °C). ¹H-NMR (CDCl₃): δ 8.75-8.71 (m, 3H, H-6,3'',6''), 8.49 (s, 1H, H-5'), 8.09 (d, J = 8.1 Hz, 1H, H-3'), 7.89 (dt, J = 8.1, 2.2 Hz, 2H, H-4,4''), 7.38 (dt, J = 8.1, 1.5 Hz, 2H, H-5,5''), 3.08 (t, J = 8.1 Hz, 2H, CCH₂), 1.60 (quintet, J = 7.3 Hz, 2H, CCH₂CH₂), 1.31-1.21 (m, 10H, CH₂), 0.85 (t, J = 6.6 Hz, 2H, CH₃). ¹³C-NMR (CDCl₃) INCREDIBLE NATURAL ABUNDANCE DOUBLE-QUANTUM TRANSFER EXPERIMENT (INADEQUATE), CDCl₃: δ 159.2 (C-3'), 157.3 (C-6'), 156.5 (C-2), 153.7 (C-2''), 149.4 (C-6''), 142.9 (C-4'), 137.2 (C-4''), 136.9 (C-4), 125.6 (C-5'), 124.8 (C-3), 124.6 (C-5''), 123.5 (C-5), 121.8 (C-3''), 32.0 (CCH₂), 31.9 (C(CH₂)₃CH₃), 22.6 (C(CH₂)₃), 13.8 (CH₃CH₂). IR (ATR): ν 3056 cm⁻¹, 2916, 2851, 1583, 1575, 1469, 1394, 1094, 992, 787, 742, 716, 657, 620, 599. C₁₉H₂₆N₄·¼H₂O: calcd. C 75.29, H 7.61, N 15.96; found C 75.63, H 7.22, N 16.17. MALDI-TOF-MS: m/z [M⁺] 347 (100%). UV-vis (chloroform): λ_max 287 nm.

**3,6-Di(2-pyridyl)-4-n-tridecylpyridazinone (11)**

A solution of 3,6-di(2-pyridyl)tetrazine (1, 500 mg, 2.1 mmol) and 1-pentadecyne (530 mg, 2.5 mmol) in DMF (50 mL) was refluxed for 16 hours. After evaporation of the solvent under reduced pressure, the crude product was recrystallized from methanol:water (3:1) resulting in a white solid (536 mg, 57%). M.p. 52-53 °C. ¹H-NMR (CDCl₃): δ 8.76-8.71 (m, 3H, H-6,3'',6''), 8.49 (s, 1H, H-5'), 8.09 (d, J = 7.8 Hz, 1H, H-3'), 7.89 (dt, J = 7.7, 1.6 Hz, 2H, H-4,4''), 7.39 (dt, J = 7.7, 1.1 Hz, 2H, H-5,5''), 3.08 (t, J = 7.8 Hz, 2H, CCH₂), 1.60 (quintet, J = 7.7 Hz, 2H, CCH₂CH₂), 1.29-1.21 (m, 20H, CH₃), 0.87 (t, J = 6.6 Hz, 2H, CH₂). ¹³C-NMR (CDCl₃): δ 159.0 (C-3'), 157.1 (C-6'), 156.4 (C-2), 153.6 (C-2''), 149.2 (C-6''), 148.4 (C-6), 142.7 (C-3'), 147.0 (C-4'), 136.7 (C-4'), 125.5 (C-5'), 124.9 (C-3'), 124.5 (C-5''), 123.4 (C-5), 121.7 (C-3''), 32.2 (CCH₂), 31.8 (C(CH₂)₃CH₃), 28.8-29.0 (C(CH₂)₃CH₃), 11), 22.6 (C(CH₂)₃), 14.0 (CH₃CH₂). IR (ATR): ν 3054 cm⁻¹, 2964, 2918, 2850, 1583, 1570, 1469, 1421, 1403, 993, 787, 738, 719, 616. C₂₃H₄₀N₄·½H₂O: calcd. C 77.84, H 8.71, N 13.45; found C 77.45, H 8.56, N 13.19. MALDI-TOF-MS: m/z [M⁺] 417 (100%). UV-vis (chloroform): λ_max 287 nm.
3,6-Di(2-pyridyl)-4-tributylstannylpyridazine (12)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in acetone (2.5 mL) was heated for 1 hour to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al2O3, dichloromethane as eluent). Upon standing the resulting yellow oil crystallized (368 mg, 70%). M.p. 168 °C.

3,6-Di(2-pyridyl)-4-phthalimidopropylpyridazine (16)
A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in acetone (2.5 mL) was heated for 30 minutes to 150 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al2O3, dichloromethane as eluent). Upon slow evaporation of a solution in dichloromethane:hexane (1:1) the product was obtained as white crystals (147 mg, 83%). M.p. 168 °C.

3,6-Di(2-pyridyl)-4-n-ethylpyridazine (18) and 3,6-di(2-pyridyl)-4,5-dimethylpyridazine (19)
Chapter 6
3,6-Di(2-pyridyl)-4-n-ethylpyridazine (18): M.p. 100 °C. 1H-NMR (CDCl3): δ 8.76-8.72 (m, 3H, H-6,3′,6′′), 8.53 (s, 1H, H-5′), 8.10 (d, J = 7.9 Hz, 1H, H-3′), 7.89 (tt, J = 7.7, 1.9 Hz, 2H, H-4″,4′′), 7.40 (dt, J = 6.1, 1.5 Hz, 2H, H-5,5′′), 3.12 (q, J = 7.5 Hz, 2H, CH2), 13C-NMR (CDCl3): δ 158.9 (C-3′), 157.2 (C-6′), 156.2 (C-2), 153.4 (C-2″), 149.2 (C-6″), 148.2 (C-6), 143.7 (C-4′), 136.9 (C-4″), 136.6 (C-4), 124.6 (C-5′), 124.5 (C-5), 123.4 (C-3), 123.3 (C-5′), 121.8 (C-3″), 25.5 (CH3CH2), 13.7 (CH3). C15H12N2: calcd. C 73.89, H 5.84, N 20.27; found C 73.47, H 5.91, N 20.57. GC-MS retention time (minutes): 8.21 [M]+ (100%).

3,6-Di(2-pyridyl)-4,5-dimethylpyridazine (19): M.p. 97 °C. 1H-NMR (CDCl3): δ 8.73 (d, J = 6.1 Hz, 4H, H-6,6′), 7.98 (d, J = 7.6 Hz, 4H, H-3,3′,3″), 7.89 (dt, J = 7.6, 1.8 Hz, 4H, H-4,4″), 7.39 (dt, J = 6.1, 1.3 Hz, 4H, H-5,5′′), 2.50 (s, 6H, CH3). 13C-NMR (CDCl3): δ 158.5 (C-3′,6′), 156.7 (C-2″), 148.4 (C-6″), 136.9 (C-4″), 136.7 (C-4′), 124.9 (C-3′), 124.3 (C-5″), 123.2 (C-5,5′′), 15.5 (CH3). C15H16N2: calcd. C 72.98, H 5.38, N 21.63; found C 72.98, H 5.42, N 21.52. GC-MS retention time (minutes): 8.55 [M]+ (100%).

3,6-Di(2-pyridyl)-4-ethyl-5-methylpyridazine (20) A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in 3-pentanone (2.5 mL) was heated for 60 minutes to 180 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (Al2O3, ethyl acetate) resulting in 3,6-di(2-pyridyl)-4-ethyl-5-methylpyridazine (20) as yellowish solid (15 mg, 13%). M.p. 52-54 °C. 1H-NMR (CDCl3): δ 8.74 (t, J = 5.1 Hz, 2H, H-6,6′), 7.95 (d, J = 7.8 Hz, 1H, H-3′), 7.92-7.85 (m, 3H, H-3,3′,3″), 7.40 (dt, J = 5.1, 1.5 Hz, 2H, H-5,5′′), 2.99 (q, J = 7.5 Hz, 2H, CH2), 2.55 (s, 3H, CH3). 13C-NMR (CDCl3): 121.0 (C-3). C15H15N2: calcd. C 72.98, H 5.42, N 21.63; found C 72.98, H 5.42, N 21.52. GC-MS retention time (minutes): 8.64 [M]+ (100%).

3,6-Di(2-pyridyl)-4-isopropylpyridazine (21) and 3,6-di(2-pyridyl)-4-hydroxy-4,5,5-trimethyl-dihydropyridazine (22) A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in 3-methyl-2-butane (2.5 mL) was heated for 30 minutes to 180 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the residue was analyzed by GC-MS. GC-MS retention time (minutes): 2.71 [pyridine-2-carboxaldehyde, 4.8%], 4.27 [3-(2-pyridyl)-1,2,4,5-tetrazine, 9.4%], 7.48 [2,5-di(2-pyridyl)-1,3,4-oxadiazole, 30%], 7.59 [2,5-di(2-pyridyl)-2,3-dihydro-1,3,4-oxadiazole, 4%], 7.93 [3,6-di(2-pyridyl)-dihydro-1,2,4,5-tetrazine, 7.4%], 8.28 [3,6-di(2-pyridyl)-4-i-propylypyridazine 21, 10%], 8.53 [3,6-di(2-pyridyl)-4-i-propyl-dihydropyridazine, 12.3%], 8.73 [3,6-di(2-pyridyl)-4-hydroxy-4,5,5-trimethyl-dihydropyridazine 22, 24.9%].

2-Pyridinecarboxylic acid (2-pyridylmethylene)hydrazide (23) The synthesis of this compound has been previously reported by Schiff base condensation of 2-pyridinecarboxaldehyde and 2-pyridinecarboxylic acid hydrazide (no yield or characterization data reported). A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in water (2.0 mL) was heated for 20 minutes to 150 °C under microwave irradiation. Cooling down to 38 °C resulted in the formation of a white precipitate. After addition of methanol (5.0 mL), a clear solution was obtained and the solvent was evaporated under reduced pressure. The 2-pyridinecarboxylic acid (2-pyridylmethylene)hydrazide 23 was obtained pure (91 mg, 96%) by slow evaporation from an ethyl acetate:hexane (2:1) solution. M.p. 156 °C. 1H-NMR (CDCl3): δ 11.21 (s, 1H, NH), 8.58 (d, J = 4.9 Hz, 1H, H-6′), 8.54 (d, J = 4.7 Hz, 1H, H-6″), 8.38 (s, 1H, CH), 8.26 (d, J = 7.8 Hz, 1H, H-3′), 8.20 (d, J = 8.0 Hz, 1H, H-3), 7.85 (dt, J = 7.8, 1.6 Hz, 1H, H-4″), 7.70 (dt, J = 8.0, 1.3 Hz, 1H, H-4), 7.44 (dt, J = 4.9, 0.9 Hz, 1H, H-5″), 7.25 (dt, J = 4.7, 0.8 Hz, 1H, H-5), 13C-NMR (CDCl3): δ 160.1 (C-5′), 152.6 (C-2″), 149.1 (C-6″), 148.6 (C-6), 148.5 (C-2), 147.8 (C-2″), 137.3 (C-4′), 136.1 (C-4), 126.6 (C-5″), 124.1 (C-5), 122.7 (C-3″), 121.0 (C-3). C15H13N2O: calcd. C 73.61, H 4.46, N 24.76; found C 73.62, H 4.47, N 24.74. GC-MS retention time (minutes): 7.59 [M]+ (100%).
3,6-Di(2-pyridyl)-4-n-hexylpyridazine (24)

A solution of 3,6-di(2-pyridyl)tetrazine (1, 100 mg, 0.42 mmol) in octanlan (2.5 mL) was heated for 30 minutes to 200 °C under microwave irradiation. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (SiO2, chloroform:methanol (95:5)) resulting in 3,6-di(2-pyridyl)-4-n-hexylpyridazine (24) as impure yellowish solid (15 mg, 9%). However, the obtained amount was too small for further purification.

Copper(I) grid of 3,6-di(2-pyridyl)-4-hydroxybutylpyridazine (25)

Both 6 (10 mg, 32.7 mmol) and tetrakis(acetonitrile)-copper(I)-hexafluorophosphate (12.2 mg, 32.7 mmol) were dissolved in acetone-d6 (1 mL). The resulting brown mixture was used for NMR-spectroscopic investigations and subsequently the solvent was removed under reduced pressure yielding complex 25, as brown solid (quantitative).

Copper(I) grid of 3,6-di(2-pyridyl)-4,5-bishydroxymethylpyridazine (26)

To a solution of tetrakis(acetonitrile)-copper(I)-hexafluorophosphate (112 mg, 0.30 mmol) in dichloromethane (10 mL) was added dropwise a solution of 8 (88.2 mg, 0.30 mmol) in dichloromethane (5 mL), which resulted in instantaneous precipitation of a brown solid. The solid was collected and recrystallized from acetone:diethyl ether (1:1) resulting in complex 26, as a brown solid (quantitative).

X-ray Crystallographic Data

Selected crystals were mounted on a Bruker-AXS APEX diffractometer with a CCD area detector. Graphite-monochromated Mo-Kα radiation (71.073 pm) was used for the measurements. The nominal crystal-to-detector distance was 5.00 cm. A hemisphere of data was collected by a combination of three sets of exposures at 173 K. Each set had a different φ angle for the crystal, and each exposure took 20 s and covered 0.3° in ω. The data were corrected for polarization and Lorentz effects, and an empirical absorption correction (SADABS)54 was applied. The cell dimensions were refined with all unique reflections. The structures were solved by direct methods (SHELXS97). Refinement was carried out with the full-matrix least-squares method based on F2 (SHELXL97)55 with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were inserted in calculated positions and refined riding with the corresponding atoms. \footnote{36}

6.9 References and notes


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Synthesis, characterization and complexation of functionalized 3,6-di(2-pyridyl)pyridazines

(36) CCDC 219857-219859 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (international) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
In addition, the reported $^{13}$C-resonances for 4′,5′-substituted 3,6-di(2-pyridyl)pyridazines (ref. 17 and A. K. Qisari, *Spectroscopy* 2002, 16, 37-41) did not match, which elevated our interest to come to a conclusive assignment.


Both these side products were identified by GC-MS.


G. M. Sheldrick, SHEX97 Programs for Crystal Structure Analysis (Release 97-2), Universität Göttingen, Göttingen (Germany), 1998.
Chapter 7

Synthesis of macromolecular [2×2] grid-like metal complexes based on the 3,6-di(2-pyridyl)pyridazine ligand

Abstract

The utilization of the 3,6-di(2-pyridyl)pyridazine (DPP) ligand for the preparation of macromolecular [2×2] grid-like metal complexes is described in this chapter. Three different synthetic routes were successfully applied to synthesize macromolecular DPP’s. The direct synthesis of a poly(ε-caprolactone) functionalized DPP ligand was performed via the inverse-electron-demand Diels-Alder reaction of an acetylene functionalized poly(ε-caprolactone) with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine. Secondly, a hydroxyl-functionalized DPP was used as initiator for the controlled ring-opening polymerization of L-lactide. The third synthetic pathway includes the coupling of the hydroxyl-functionalized DPP with an amino-functionalized poly(ethylene glycol). All resulting polymeric DPP’s were fully characterized by $^1$H-NMR spectroscopy, GPC and MALDI-TOF-MS to demonstrate the successful incorporation of the DPP into the polymers. Furthermore, the complexation of these macromolecular DPP’s into macromolecular [2×2] grid-like metal complexes was investigated by UV-titration experiments. For the poly(L-lactide) DPP’s, the observed complexation behavior was modeled to gain insights into the different complexation steps. In addition, the effect of the copper(I) [2×2] grid formation on the polymeric morphology was investigated by AFM for these poly(L-lactide) DPP’s as well. The final part of this chapter discusses the synthesis and complexation of a multimetallic [2×2] grid. An iridium(III) functionalized DPP was synthesized via the coupling of an amino-functionalized iridium(III) complex to the DPP. The self-assembly of this ligand into multimetallic [2×2] grids was investigated by both UV-vis and fluorescence titration experiments.

7.1 Introduction

In recent years, well-defined (block co)polymers have attracted significant attention for the preparation of novel nanostructures like micelles\textsuperscript{1-6} and controlled architectures.\textsuperscript{7-10} Moreover, the introduction of supramolecular interactions into defined polymeric systems can lead to materials combining interesting (responsive) architectures with new mechanical, physical and optical properties.\textsuperscript{11,12} The most commonly used types of supramolecular interactions are hydrogen bonding, metal–ligand interactions and ionic interactions, whereby the first two are highly directional and thus preferable for the directed self-assembly of (macro)molecules. We choose to use metal-coordinating units because the self-assembly can be easily tuned from very labile to inert by varying the metal ion.\textsuperscript{13} Metal coordinating units can be introduced into macromolecules \textit{via} the polymerization of functional monomers,\textsuperscript{14-16} end group\textsuperscript{17,18} or side group\textsuperscript{19,20} functionalization and \textit{via} functional initiators.\textsuperscript{21-25} For the synthesis of polymers with exactly one metal coordinating ligand, the end-group functionalization and functional initiator approach are best suitable. However, mainly bipyridine and terpyridine ligands have been incorporated into macromolecular structures so far. To construct larger well-defined supramolecular structures, grid-forming ligands can be utilized instead of bipyridine and terpyridine moieties: Grid-like complexes containing up to 20 ligands (e.g. [2×2],\textsuperscript{26,27} [2×3],\textsuperscript{28,29} [3×3],\textsuperscript{30,31} [4×4]\textsuperscript{32} and [4×5]\textsuperscript{33}) have been reported, whereas simple terpyridine and bipyridine units can form complexes with only two or three ligands, respectively. The incorporation of these grid-forming ligands into polymers seems to be very promising since materials with properties of both the grid-like metal complexes [e.g. (reversible) self-assembly of up to 20 polymer chains, special magnetic, electrochemical and optical properties] and the polymers (e.g. film forming and good solubility) can be obtained. Furthermore, the complexation strength as well as the size and amount of polymer chains can be adjusted in these supramolecular polymers by utilizing different grid-forming ligands and metal salts. Up to now, the incorporation of such grid-forming ligands into macromolecules has been unexplored.

A synthetically easily accessible grid-forming ligand is 3,6-di(2-pyridyl)pyridazine (DPP), which self-assembles into [2×2] grids upon addition of copper(I) ions.\textsuperscript{26} The synthesis of functionalized DPP’s was already described in the previous chapter. Three different strategies can be used to introduce these DPP ligands into macromolecular structures as depicted in Figure 7.1: Direct functionalization (A), polymerization (B) and polymer coupling (C).

![Figure 7.1. Different routes towards polymer functionalized 3,6-di(2-pyridyl)pyridazines.](image-url)
Direct functionalization (A) of a metal coordinating ligand by applying a polymeric reagent has never been reported to the best of our knowledge. Nevertheless, performing the inverse-electron-demand Diels-Alder reaction between the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine with an acetylene functionalized polymer would directly lead to a polymer functionalized DPP. In the polymerization route (B), a functionalized DPP is applied as initiator for a living/controlled polymerization technique resulting in the desired polymer functionalized DPP ligands. The third method to functionalize the DPP ligand comprises a coupling reaction between a functional DPP and a functional polymer, which is referred to as polymer coupling (C).

This chapter describes our investigation to synthesize macromolecular DPP’s via all three functionalization routes: Direct functionalization (A, section 7.2), polymerization (B, section 7.3) and polymer coupling (C, section 7.4). Moreover, the complexation of these DPP’s with copper(I) ions into well-defined macromolecular [2×2] grid-like structures as depicted in Figure 7.2 will be described in these sections as well. Furthermore, the synthesis and characterization of an iridium(III) containing macroligand will be discussed in section 7.5. Moreover, the complexation of this iridium(III) DPP with copper(I) ions and thus the formation of a [2×2] metal grid with both iridium(III) and copper(I) ions will be reported.

7.2 Direct synthesis of a macromolecular 3,6-di(2-pyridyl)pyridazine ligand

The direct functionalization method to synthesize macromolecular DPP’s comprises the inverse-electron-demand Diels-Alder reaction between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (I) and a macromolecular acetylene. The main advantage of this functionalization route is the exclusion of a preceding synthetic step to create a functionalized DPP that subsequently can be functionalized with a macromolecular structure. However, a limitation of this direct functionalization route is the difficult purification of the resulting macromolecular DPP’s from the starting acetylene when the Diels-Alder reaction is not quantitative. In this section, the synthesis of a poly(e-caprolactone) functionalized DPP via the direct functionalization route will be described. The success of this DPP functionalization reaction will be discussed on the basis of 1H-NMR spectroscopy, GPC and MALDI-TOF-MS. Furthermore, the complexation of this poly(e-caprolactone) macroligand into polymeric [2×2] grid-like metal complexes by the addition of copper(I) ions was investigated in different solvents.
7.2.1 Synthesis of a poly(ε-caprolactone) functionalized 3,6-di(2-pyridyl)pyridazine

The direct synthesis of a poly(ε-caprolactone) (pεCL) functionalized DPP was performed via the inverse-electron-demand Diels-Alder reaction between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (I) and an acetylene terminate pεCL as depicted in Scheme 7.1. Therefore, an acetylene terminated pεCL had to be synthesized. Recently, the synthesis of various acetylene functionalized polymers has been described in literature since they can be applied as reagents in the Huisgens reaction, which is nowadays better known as ‘click’ chemistry. However, most of these acetylene functionalized polymers have been prepared by end-group functionalization methods or via the use of protected acetylenes. On the contrary, we have investigated the controlled ring-opening polymerization of ε-caprolactone utilizing the unprotected 5-hexyn-1-ol as initiator and tin(II) octoate as catalyst. At first, the polymerization was attempted at 130 °C resulting in uncontrolled polymerizations. The resulting polymers had broad molecular weight distributions (PDI > 1.4) and the GPC traces revealed shoulders at higher molecular weights. Lowering the polymerization temperature to 110 °C resulted in the controlled ring-opening polymerization of ε-caprolactone. The 1H-NMR spectrum of the synthesized acetylene terminated pεCL 2 showed the presence of both the polymer backbone and the acetylene signals (Figure 7.3 left, bottom). The integrals of the acetylene signal (e) and the terminal CH₂OH resonances of the polymer (E’) were obtained in a 1 to 2 ratio demonstrating that each polymer has an acetylene group attached. Moreover, a monomer to initiator ([M]/[I]) ratio of 20, corresponding to a number average molecular weight (Mn) of 2,380 Da, was calculated from the 1H-NMR spectrum which fits to the theoretical [M]/[I] ratio of 20. GPC characterization revealed a much too high Mn of 4,460 Da due to the used polystyrene calibration as it has been previously observed for poly(L-lactide)s as well. The narrow monomodal molecular weight distribution (PDI = 1.19) that was obtained by GPC (RI-detector) demonstrated that the polymer was synthesized in a controlled manner (Figure 7.3 right, dotted lines). This was further confirmed by MALDI-TOF-MS that revealed a narrow molecular weight distribution (Figure 7.4 bottom). The observed spacing between the signals corresponds exactly to the mass of one monomer unit (114 Da). The Mn that was determined by MALDI-TOF-MS analysis (2,200 Da) is in very good agreement with the Mn obtained by 1H-NMR spectroscopy. Furthermore, end-group analysis of the MALDI-TOF-MS spectrum revealed that indeed all polymer chains bear an acetylene end-group.

Scheme 7.1. Schematic representation of the direct synthesis of 3,6-di(2-pyridyl)-4-poly-(ε-caprolactone)pyridazine (3) from tetrazine 1 and acetylene terminated poly(ε-caprolactone) 2.
The acetylene functionalized pεCL was reacted with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (1) for 2.5 hours at 150 °C under microwave irradiation. The tetrazine 1 was added in two-fold excess to drive the cycloaddition reaction to completion, which simplifies the purification of the pεCL DPP 3. The crude reaction mixture was purified by column chromatography to remove unreacted acetylene pεCL 2 and preparative size exclusion chromatography to remove the excess of tetrazine 1. $^1$H-NMR spectroscopy of the purified pεCL DPP 3 revealed complete functionalization as indicated by the disappearance of the acetylene signal (e) at 1.95 ppm and appearance of the DPP resonances (Figure 7.3 left). Moreover the integrals revealed a ratio of 1 to 1 for the CH$_2$OH (E') resonance of the polymer and the CCH$_2$ (a) signal of the DPP and a $[M]/[I]$ ratio of 20 ($M_n = 2590$) proving the success of the inverse-electron demand Diels-Alder reaction. Furthermore, GPC analysis showed a signal with both UV-vis (290 nm) and RI detectors proving that the ligand is coupled to the polymer that does not absorb at 290 nm. The obtained molecular weights (UV-detector: $M_n = 4800$, PDI = 1.23; RI-detector: $M_n = 4660$, PDI= 1.21) are slightly higher than for the acetylene pεCL 2 due to the incorporation of the ligand. End-group analysis of the MALDI-TOF-MS spectrum also demonstrated the success of the coupling reaction (Figure 7.4). A shift of 208 Da was observed after reaction of pεCL 2 with tetrazine 1, which fits to the formation of the DPP 3.

**Figure 7.3.** $^1$H-NMR spectra (left) and GPC traces (right) of the acetylene terminated pεCL 2 and the pεCL DPP 3. $^1$H-NMR spectra were recorded in CDCl$_3$ and GPC was measured with CHCl$_3$:NEt$_3$:2-PrOH (94:4:2) as eluent.

**Figure 7.4.** MALDI-TOF-MS spectra of the acetylene terminated pεCL 2 and the pεCL DPP 3.
The effect of the ε-caprolactone substituent on the self-assembly of the DPP into [2×2] grid-like copper(I) complexes was investigated by UV-vis spectroscopy. To a solution of εCL DPP 3 in dichloromethane (CH$_2$Cl$_2$), a solution of tetrakis(acetonitrile hexafluorophosphate Cu(CH$_3$CN)$_4$(PF$_6$)) in CH$_2$Cl$_2$ was added step-wise. Upon addition of copper(I) salt, the color changed instantaneously due to the spontaneous self-assembly of the macroligands with copper(I) ions. After each titration step, a UV-Vis spectrum was recorded in order to investigate the complexation behavior of the macroligands in detail. The UV-vis spectra resulting from this titration are depicted in Figure 7.5 left. The possibility of performing this UV-titration study in CH$_2$Cl$_2$ solution already demonstrates that the properties of both the ligand and the polymer are combined in the macroligands: Adding the same copper(I) salt solution to a solution of 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine in CH$_2$Cl$_2$ instantaneously led to precipitation of the self-assembled copper(I) metal grids (see also section 6.6). Upon addition of copper(I) ions to the macroligands, a metal to ligand charge transfer (MLCT) band appeared with an absorption maximum ($\lambda_{\text{max}}$) at 457 nm. This $\lambda_{\text{max}}$ shifted toward 437 nm after the addition of 0.5 equivalents of copper(I) ions. The basis of this shift could not be unambiguously proven. However, it most likely results from a transition from complexes with two ligands and one copper(I) ion into complete polymeric [2×2] grid-like complexes. This shift in $\lambda_{\text{max}}$ will be discussed in detail in section 7.3.2. The increase in absorption at 437, 467 and 567 nm is plotted against the added equivalents of copper(I) ions in the inset of Figure 7.5 left. This Figure clearly shows that a maximal absorption is obtained at the addition of 1 equivalent of copper(I) ions, which corresponds to the formation of complete [2×2] grid-like metal complexes. Moreover, the resulting UV-vis spectrum after addition of 1 equivalent of copper(I) ions closely resembles the spectra obtained for small ligand [2×2] grid-like copper(I) complexes (section 6.6), which proves that indeed macromolecular [2×2] grid-like complexes are formed from the εCL DPP 3. The change in the slopes of the increase in absorption at 467 and 567 nm against equivalents of copper(I) ions will be discussed in section 7.3.2. Upon overtitration of copper(I) ions to εCL DPP 3, the absorption remained constant indicating that the formed [2×2] grids are stable and do not regularly exchange copper(I) ions since this would lead to the formation of mono-complexes. However, the Cu(I)PF$_6$ is not soluble in CH$_2$Cl$_2$ without the coordinating acetonitrile. Therefore, no exchange is expected when the titration is performed in CH$_2$Cl$_2$.

![Figure 7.5. UV-vis spectra obtained during the titration of [Cu(CH$_3$CN)$_4$(PF$_6$)] to solutions of εCL DPP 3 in dichloromethane (left) and acetone (right). The insets show the increase of absorption at 437, 467 and 567 nm with the addition of copper(I) ions.](image-url)
To further investigate the stability of the macromolecular [2×2] grid-like copper(I) complexes, the UV-titration was repeated in acetone in which the Cu(I)PF$_6$ is soluble (Figure 7.5 right). The UV-vis spectra were only recorded from 320 nm since below this wavelength acetone absorbs the UV-light. Again, the appearance of the MLCT band at 467 nm was observed upon the addition of copper(I) ions. This MLCT band also shifted towards 437 nm after the addition of more than 0.5 equivalents of copper(I) ions indicating the formation of complete [2×2] grid-like complexes. Moreover, the absorption against equivalents of copper(I) ions plot revealed the same behavior as in CH$_2$Cl$_2$ demonstrating that in acetone the grids are also stable and do not exchange rapidly at ambient temperature. In contrast, it was previously reported that main-chain copper(I) bipyridine supramolecular polymers are only stable in non-coordinating solvents.\textsuperscript{45} In coordinating solvent (like acetone) exchange of the metal complexes was observed. Moreover, exchange of copper(I) metal complexes with benzimidazole-pyridine ligands even occurred in CD$_2$Cl$_2$ at ambient temperatures.\textsuperscript{46} The increased stability of the [2×2] grid-like copper(I) complexes of the DPP’s can be ascribed to the cooperativity of the metal coordination in the [2×2] grids.

7.3 The utilization of 3,6-di(2-pyridyl)pyridazines as initiator for controlled polymerization techniques

The functional initiator approach for living polymerizations seems to be the most promising, since all polymer chains contain a metal coordinating unit after simple purification of the polymer by precipitation. By introducing more initiating groups onto the central metal complex, a wide variety of linear and star-shaped polymers is accessible.\textsuperscript{21,47} Furthermore, the nature of the polymers can be controlled by utilizing different monomers and polymerization techniques. So far, the feasibility of this approach has been successfully demonstrated for bipyridine and terpyridine systems utilizing controlled radical polymerizations,\textsuperscript{48,49} living cationic ring-opening polymerizations of 2-oxazolines\textsuperscript{21,23,50-52} and the controlled polymerization of lactides and lactones.\textsuperscript{21,23,24}

In this section, our efforts to expand the supramolecular initiator approach towards [2×2] grid-like metal complexes are described. The application of a hydroxyl-functionalized DPP for the controlled ring-opening polymerization of L-lactide is demonstrated. Characterization of the resulting polymers was performed by $^1$H-NMR spectroscopy, GPC and MALDI-TOF-MS. Moreover, the self-assembly of the polymer DPP’s into [2×2] grid-like copper(I) complexes will be discussed. In addition, it was attempted to model the observed complexation behavior. The final part of this section deals with atomic force microscopic (AFM) investigations on the polymeric grid-like metal complexes.

7.3.1 Polymerization of L-lactide utilizing a 3,6-di(2-pyridyl)pyridazine as (co)initiator

The synthesis of DPP macroligands \textit{via} the functional initiator approach requires a functional handle on the ligand. Therefore, the hydroxyl functionalized 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine ligand 4 was chosen as cointiator for the controlled polymerization of L-lactide as described by Kricheldorf et al.\textsuperscript{53,54} An aluminum alkoxide was generated \textit{in situ} from the hydroxyl functionalized DPP 4 by reacting it with triethyl aluminum. This aluminum alkoxide was utilized as initiator for the controlled ring-opening polymerization of L-lactide resulting in macroligands 5-7 as depicted in Scheme 7.2.
Scheme 7.2. Synthesis of the poly(L-lactide) macroligands 5-7 from 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (4).

After purification of the synthesized polymers by precipitation in methanol, the resulting poly(L-lactide)s (pLL’s) were characterized with $^1$H-NMR spectroscopy, gel permeation chromatography (GPC) and MALDI-TOF-MS. The $^1$H NMR spectra of ligand 4 and macroligands 5-7 (Figure 7.6 left) clearly demonstrated the successful incorporation of the DPP ligand into the polymer chains: The aromatic signals of the DPP are present in both the free ligand 4 and in the polymers 5-7 that also exhibited the polymer backbone resonances at 5.2 (f) and 1.6 ppm (g). In addition, the signal of the CH$_2$ protons next to the hydroxyl group of the ligand shifted from 3.72 to 4.12 ppm upon polymerization since the environment changes to an ester group. The integral ratios of the ligand (aromatic resonances) and the poly(L-lactide)s revealed [M]/[I] ratios of 25 (3,840 Da), 45 (6,800 Da) and 75 (11,100 Da) for pLL DPP’s 5, 6 and 7, respectively. The [M]/[I] ratio of DPP 7 is lower than the theoretical [M]/[I] ratio of 100 due to insufficient reaction time and thus incomplete polymerization. GPC analysis of the polymeric ligands 5-7 (Figure 7.6 right) demonstrated narrow polydispersity indices around 1.20, which is indicative for controlled polymerizations. Moreover, the polymers were detected with both RI- and UV-detector, which proves the incorporation of the ligand into the polymers since the poly(L-lactide) backbone has no UV absorption at 254 nm. The molecular weights obtained from GPC are about 1.5 times higher than the molecular weights calculated from the NMR integrals. This discrepancy is most likely due to the polystyrene calibration of the GPC [the polystyrene will have a different hydrodynamic volume compared to poly(L-lactide)s with similar molecular weight].
Synthesis of macromolecular [2×2] grid-like metal complexes

Figure 7.6. $^1$H-NMR spectra (left; in CDCl$_3$) and GPC traces (right; measured with CHCl$_3$ as eluent) obtained for the synthesized pLL macroligands 5-7.

The pLL DPP’s 5-7 were also characterized with MALDI-TOF-MS (Figure 7.7). The obtained mass spectra revealed well-resolved signals that can be assigned to poly(L-lactide) chains containing the 3,6-di(2-pyridyl)pyridazine moiety. The mass peaks correspond exactly to the masses calculated for single polymer chains with an additional proton (see insets of Figure 7.7). However, the presence of both even-membered and odd-membered oligomers implies that transesterification reactions occurred during the polymerization.$^{55}$ The molecular weights ($M_n$) obtained for macroligands 5-7 from $^1$H-NMR spectroscopy, GPC (both with UV and RI-detector) and MALDI-TOF-MS are plotted against the initial [M]/[I] ratios in Figure 7.7 right. The molecular weights correspond well to the theoretical molecular weights, whereby only the molecular weight of the largest macroligand is slightly lower due to insufficient reaction time. Moreover, the $M_n$GPC is too high due to its polystyrene calibration and the $M_n$MALDI is too low due to the higher ionization probability of the lower molecular weight poly(L-lactide) chains. MALDI-TOF-MS and GPC characterization of the macroligands 5-7 revealed narrow molecular weight distributions with polydispersity indices equal or lower than 1.20. The good correspondence between the theoretical and obtained molecular weights and these low PDI values clearly demonstrate that the polymers were synthesized in a controlled manner.

Figure 7.7. Left: MALDI-TOF-MS spectra obtained for the pLL DPP’s 5-7. Right: Dependence of the number average molecular weight ($M_n$) on the initial monomer initiator ([M]/[I]) ratio.
7.3.2 Complexation studies on the poly(L-lactide) 3,6-di(2-pyridyl)pyridazine macroligands

The complexation of the macroligands 5-7 was investigated by UV-vis titration studies. To a solution of the macroligand in dichloromethane (CH₂Cl₂), a tetraakisacetonitrile copper(I) hexafluorophosphate [Cu(CH₃CN)₄(PF₆)] solution in CH₂Cl₂ was added step-wise. After each titration step an UV-vis spectrum was recorded resulting in the titration graphs as depicted in Figure 7.8 left for the three pLL macroligands 5-7. The success of these UV-titration studies in CH₂Cl₂ solution demonstrates that the macroligands exhibit properties of both the ligand and the polymer. Upon addition of copper(I) ions to the macroligands, a metal to ligand charge transfer (MLCT) band appeared. The λ_max of this MLCT shifted from 467 to 437 nm during the titration experiments (see insets of the titration graphs of Figure 7.8 left). This shift seems to result from a transition from complexes with two ligands and one copper(I) ion into complete polymeric [2×2] grid-like complexes. Remarkably, this shift in λ_max already occurs with the first titration step (~ 0.1 equivalents of copper(I) ions) for the smallest macroligand 5 suggesting strong cooperativity leading to grid-formation, whereas λ_max only shifts with the addition of ~0.5 equivalents of copper(I) ions for the other macroligands 6 and 7. The shift at 0.5 equivalents of copper(I) ions to have a statistical basis: Complete complexation into complexes with two ligands and one copper(I) ion requires 0.5 equivalents of copper(I). As a result, adding more copper(I) ions will lead to the formation of complexes with more copper(I) ions and to the formation of grid-like metal complexes. To further elucidate the ongoing complexation processes, the increase in absorption at 437, 467 and 567 nm was plotted against the added equivalents of copper(I) ions (Figure 7.8 right). The difference in complexation behavior of the smaller macroligand 5 compared to the other macroligands 6 and 7 is also clearly noticeable from these plots.

To gain further insight into the complexation mechanism, the titration data were modeled (Figure 7.8 right, dotted lines). To simplify the modeling of this complexation that consists of various equilibria (over ten different processes), it was assumed that the grid-formation only consists of two discernible complexation steps (L = ligand):

**Step 1:**  
\[2 \cdot L + Cu(I) \rightleftharpoons k_1 \cdot L_2Cu(I)\]

**Step 2:**  
\[2 \cdot L_2Cu(I) + 2 \cdot Cu(I) \rightleftharpoons k_2 \cdot L_4Cu(I)_4\]

The experimental data obtained for macroligands 6 and 7 can be nicely fitted with only these two equilibria. Unfortunately, no reliable values for the complexation constants could be extracted from these fits: The two sharp transitions in the data at 0.5 and 1.0 equivalents of copper(I) ions render this impossible in this concentration regime. However, the positions of the inflection points confirm the overall stoichiometries of the complexes. Moreover, the experimental data obtained during the titration of macroligand 5 could be fitted with the two-step process as well. However, also modeling utilizing only a one-step complexation event to the copper(I) grids resulted in an adequate fit to the data. This is likely to reflect an increased stability of the grid relative to the ML₂ complex for this particular ligand, which is attributed to less steric hindrance in this case compared to the larger ligands 6 and 7 leading to efficient cooperativity and thus favoring the direct formation of the grid instead of the intermediate ML₂ complex. In conclusion, no quantitative complexation constants could be determined from the modeling but the stoichiometries are supported by the inflection points. Moreover, the possibility of fitting the titration data of macroligand 5 with a one-step process, which is not possible for macroligands 6 and 7, suggests that the formation of complete copper(I) grids is stronger for this smaller macroligand 5.
From these new insights in the complexation behavior of the pLL DPP macroligands 5-7, the observed complexation behavior of the pεCL DPP 3 (section 7.2.2) can be interpreted to proceed via a two-step process as well. This implies, that the flexibility of the pεCL induces more steric hindrance for the grid-formation than the more rigid pLL side chains since the pεCL DPP 3 with 2,590 Da does not show cooperativity, whereas the pLL DPP 5 with 3,840 Da does show efficient cooperativity.

Figure 7.8. Left: UV-vis spectra obtained during the titration of [Cu(CH₃CN)₄PF₆] to a solution of the macroligands 5 (top), 6 (middle) and 7 (bottom); the insets show the observed shifts in MLCT from 467 nm to 437 nm; Right: Observed (symbols) and modeled (dotted lines) change in absorption at 437, 467 and 567 nm for the macroligands 5 (top), 6 (middle) and 7 (bottom).
Figure 7.9. AFM height (left) and phase (right) images of the polymeric [2×2] grid-like copper(I) complexes of pLL DPP’s 5 (a and b; 1.33 µm images), 6 (c and d; 1.0 µm) and 7 (e and f; 1.0 µm). The inset of image a shows a line scan of an isolated particle. The insets of images b, c and e display magnified phase (b) and height images (c and e), respectively.
7.3.3. Atomic Force Microscopy of the Poly(L-lactide) 3,6-di(2-pyridyl)pyridazines

The morphology of the polymeric [2×2] copper(I) grids from macroligand 5-7 were investigated by AFM: A solution of the polymeric grid was dropcast on mica and measured in tapping mode. Figure 7.9 depicts the obtained height (left) and phase (right) images. The effect of coupling the polymer chains by metal complexation is immediately visible since the uncomplexed macroligands 5-7 did not reveal any features in the morphology. In addition, a large difference in morphology was observed for the [2×2] grid-like complexes of the different macroligands. Clusters of single spherical particles piled up on each other surrounded by a corona of single particles were observed for the copper(I) complex of pLL DPP 5 (Figure 7.9; images a and b). These single particles have a height of 1.4 nm (Figure 7.9a, inset height image over a single particle). The inset of the phase image (Figure 7.9b) shows a quarter of one of the large clusters, whereby both the single particles in the cluster and the corona of single particles around the cluster can be observed. The diameter (not corrected for the tip shape) of these single particles is 13-15 nm. The size and height of these single particles imply that they are individual grid-centered polymers (as schematically depicted in Figure 7.2), whereby the poly(lactide) chains are flattened on the surface, which is likely because they are attracted to the mica. AFM imaging of dropcast polymeric grids of pLL DPP 6 revealed large clusters of polymer (not shown) and areas with low surface coverage of the compound as depicted in Figure 7.9 c and d. Small spherical particles were observed together with larger aggregates. The inset of the height image (Figure 7.9c) shows a magnified image of a different area with individual particles. The height of these particles was found to be 1.2 nm, which corresponds to the height observed for the grids of the smaller macroligand 5. The uncorrected lateral size of the spherical particles is 20-30 nm. These dimensions suggest that also single polymeric grids are observed for this macroligand 6. Moreover, the larger polymer chains might induce aggregation of the polymer grids. In contrast, the AFM images of the polymeric grids from macroligand 7 (Figure 7.9 e and f) showed a network of larger aggregates with a height of approximately 3.7 nm. The network formation might be a result of interactions between the long polymer chains connected to different polymer grids. As a result, the metal complexes act as crosslinking points resulting in network formation. When zooming into the region in between the large aggregates, small spherical particles appear as depicted in the inset of Figure 7.9e. These particles have a height of 1.5 nm and a size of 25 nm, which suggest that the particles might be single polymer [2×2] grids of pLL DPP 7. In conclusion, AFM imaging demonstrated the presence of single polymeric grids for complexes of all macroligands. However, the presence of larger aggregates and networks of polymers was observed with increasing polymer chain length.

7.4 Synthesis of Macromolecular 3,6-di(2-pyridyl)pyridazines via Coupling with End-Functional Polymers

The third possible synthetic route towards macromolecular DPP’s is the coupling of a functional DPP to an end-group functionalized polymer. The disadvantage of this approach is the necessity of having both a functional DPP and a functional polymer. Nevertheless, not all polymerization techniques are compatible with the DPP ligand and other living/controlled polymerization procedures are difficult to perform with a DPP initiator due to the extensive monomer, initiator and solvent purification that are required. To couple functionalized polymers to a DPP ligand, the end-group modification method seems to be very promising since many functionalized polymers are commercially available nowadays. As a result, the
end-group functionalization route expands the scope of polymers that could be attached to the DPP ligands.

In this section, the coupling of a poly(ethylene glycol) (PEG) to the DPP is described resulting in a water soluble macroligand. Moreover, the complexation of the resulting PEG-DPP will be discussed.

### 7.4.1 Synthesis of a poly(ethylene glycol) functionalized 3,6-di(2-pyridyl)pyridazine

The synthesis of a water-soluble macromolecular DPP ligand was performed via the polymer coupling route. The 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (3) was activated by reaction with carbonyldiimidazole\(^{56,57}\) resulting in the imidazol-1-carboxylic acid [3,6-di(2-pyridyl)-pyridazin-4-yl] butyl ester (8). This imidazolide is reactive towards amine groups, but unreactive towards alcohols and water, which is a clear advantage when working with hygroscopic PEG. The coupling of the imidazolide DPP 8 with \(\alpha\)-hydroxy-\(\omega\)-amino-PEG was performed in refluxing THF. The progress of the coupling was followed by TLC [aluminum oxide with \(\text{CH}_2\text{Cl}_2:\text{MeOH} (95:5)\)] and GPC with UV-detector. However, it appeared that the coupling proceeded very slowly and after 12 days reflux the reaction was stopped even though it was not complete. The unreacted imidazolide 8 and amino-PEG were removed by column chromatography and the desired 3,6-di(2-pyridyl)-4-(\(\alpha\)-hydroxy-PEG)pyridazine (9) was obtained in 20% yield after precipitation in diethyl ether.

![Diagram](image)

**Scheme 7.3.** Synthesis of PEG-functionalized DPP 9 via the end-group functionalization route.

\(^1\text{H}-\text{NMR} \) spectroscopy on macroligand 9 (not shown) revealed both the signals of the PEG backbone and the DPP unit. Moreover, the N-H proton appeared at 5.27 ppm and the \(\text{CH}_2\) protons next to the hydroxyl group of the DPP 3 shifted from 3.65 ppm to 4.05 (via 4.42 ppm for the imidazolide 8) upon coupling. GPC analysis of the PEG DPP 9 revealed the incorporation of the DPP by detecting the trace with both the RI-detector and the UV-detector at 290 nm where the PEG itself does not absorb (Figure 7.10 left). Moreover, MALDI-TOF-MS demonstrated the successful functionalization of the amino-PEG to PEG DPP 9 as well (Figure 7.10 right).
The obtained molecular weights from $^1$H-NMR spectroscopy, GPC and MALDI-TOF-MS are summarized in Table 7.1. The $M_n$’s obtained with GPC and MALDI-TOF-MS correspond very well for the amino-PEG. Moreover, $^1$H-NMR spectroscopy and MALDI-TOF-MS revealed the expected shift in molecular weight for DPP 9 upon incorporation of the DPP unit. Only the GPC resulted in slightly lower $M_n$ values for the PEG DPP 9, which might be due to some interactions of the DPP with the column material or due to different folding of the PEG DPP 9.

Table 7.1. Determined molecular weights (Da) and PDI values for the amino-PEG and PEG-DPP 9.

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<th>M$_n$,$^{GPC,UV}$</th>
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<td>1.08</td>
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</tr>
</tbody>
</table>

7.4.2. Complexation of the 3,6-di(2-pyridyl)-4-(α-hydroxyPEG)pyridazine ligand

The complexation behavior of this novel water-soluble PEG DPP 9 was first studied in CH$_2$Cl$_2$ by an UV-titration experiment as depicted in Figure 7.11 left. The characteristic appearance of the MLCT band was observed upon addition of copper(I) ions and the maximal absorption was reached at one equivalents of copper(I) ions indicating the formation of [2×2] copper(I) grids. Moreover, the change in $\lambda_{max}$ of the MLCT from 467 to 437 nm was observed around the addition of 0.5 equivalents of copper(I) ions indicating the absence of strong cooperativity due to sterical hindrance of the PEG-chains (see also section 7.3.2). The grid-formation of PEG DPP was also investigated in water. However, during several attempts the maximal absorption was obtained in between 1 and 2 equivalents of copper(I) ions. Moreover, an unexpected change of the ligand absorption bands was observed. To elucidate this unexpected complexation behavior, an UV-titration experiment was performed with copper(II) triflate [Cu(OTf)$_2$] in CD$_2$Cl$_2$ as depicted in Figure 7.11 right.
During the titration of copper(II) ions to PEG DPP 9, the ligand absorption increased at 215, 310 and 322 nm, whereas it decreased at 277 nm. Moreover, no distinct MLCT band was observed. The maximum (cq. minimum) absorption was obtained after the addition of two equivalents of copper(II) ions (see inset Figure 7.11 right) indicating the formation of dicopper(II) mono-complexes of the DPP ligand. Crystal structures of such dicopper(II) DPP complexes have been reported in literature. 58, 59 The unexpected change in absorption that was observed during the Cu(I) titration in water resembles that observed spectra during the Cu(II) titration in CH₂Cl₂. From these UV-titrations, it can be concluded that the titrations in water lead to partial oxidation of the copper(I) to copper(II) ions. Even after stringent degassing and freeze-thaw cycles, this oxidation could not be fully suppressed. Moreover, preparing PEG DPP [2×2] copper(I) grids in CH₂Cl₂ followed by transfer to water (after evaporation of the solvent) also led to partial oxidation of the copper(I) ions. Therefore, it can be concluded that the [2×2] copper(I) grids are not stable in water.

7.5 Synthesis of macromolecular bimetallic [2×2] grid-like metal complexes

Besides the polymeric macroligands that were described in the previous sections, the synthesis and complexation of an iridium(III) containing macroligand were investigated. The combination of different metal ions in one metal complex might be applied for two-stage catalysis as well as energy and electron transfer processes. Furthermore, star-shaped mixed metal complexes based on an iron(II) bipyridine or iron(II) terpyridine core with dangling gadolinium complexes were reported as high relaxivity MRI contrast agents. However, when going to grid-like complexes only few examples have been reported in which different metal ions were combined in one structure. In all these examples, the different metals were incorporated in the grid itself. In this section, the synthesis of a DPP with a dangling iridium(III) complex will be reported. Furthermore the complexation of this ligand with copper(I) ions and the effect of complexation on the phosphorescence of the iridium(III) complex will be discussed.
7.5.1 Synthesis of a 3,6-di(2-pyridyl)pyridazine ligand functionalized with a dangling iridium(III) complex

In a first attempt to synthesize bimetallic grid-like metal complexes, the DPP metal coordinating moiety was coupled to a terpyridine ligand. Hydroxybutyl DPP 4 was coupled to an isocyanato-terpyridine 10 with dibutyltindilaurate as catalyst (Figure 7.12 left). The isocyanato-terpyridine was prepared from an aminoterpyridine and di-tert-butyltricarbonate. After column chromatography, the ditopic ligand 11 was obtained pure according to $^1$H-NMR spectroscopy and MALDI-TOF-MS. However, elemental analysis demonstrated the presence of one water molecule per ligand, which could be explained by hydrogen bonding between water and the urethane moiety making it very difficult to remove the water molecules. Figure 7.12 right depicts the $^1$H-NMR spectra of the hydroxybutyl DPP 4 (bottom), the isocyanato terpyridine 10 (top) and the resulting bifunctional ligand 11 (middle). All resonances of the starting ligands can be recognized in the spectrum of the product 11. In addition, the appearance of the N-H proton and the shift of the CH$_2$ protons next to the hydroxyl group from 3.65 to 4.05 ppm clearly revealed the successful coupling of the two ligands via the formation of an urethane bond. Even though the ditopic ligand 11 was successfully prepared, selective metal complexation proved to be very difficult due to the similar binding capabilities of the two combined ligands. As a result, we did not succeed in the preparation of well-defined bimetallic complexes using this ligand.

Since selective complexation of the ditopic ligand 11 was unsuccessful, the functionalization of the DPP ligand with a preformed metal complex was attempted as depicted in Figure 7.13. The DPP imidazolide 8 (see section 7.4.1) was reacted with an amino-functionalized iridium(III) complex 12. This iridium(III) complex has two 2-phenylpyridine (ppy) ligands and one 4'-{(1-aminoheptyloxy)-2,2':6',2''-terpyridine (tpy) ligand. Similarly to the coupling of DPP imidazolide 8 to the amino-PEG, the coupling with the amino-iridium(III) complex only proceeded very slowly resulting in low conversion even after 8 days heating to 50 ºC in tetrahydrofuran (THF). The resulting mixture was purified by column chromatography to remove the remaining amino-iridium(III) complex 12 (aluminum oxide with acetone) and preparative size exclusion chromatography to remove the unreacted DPP imidazolide 8 resulting in the iridium(III) functionalized DPP 13 in only 14% yield.
Figure 7.13. Synthesis of the iridium(III) functionalized DPP 13 from the DPP imidazolide 8 and the amino-functionalized iridium(III) complex 12.

$^1$H-NMR spectroscopy of the iridium functionalized DPP ligand 13 revealed many signals in the aromatic region due to the asymmetry of the Ir(III)(ppy)$_2$(tpy) in which one of the pyridine rings of the terpyridine is uncomplexed (Figure 7.14 left). Nevertheless, all aromatic resonances could be assigned using $^1$H-$^1$H COSY demonstrating that the DPP and iridium(III) complex were successfully coupled. Moreover, the N-H resonance appeared at 4.75 ppm and the characteristic shifts for urethane formation were observed as well (Figure 7.14 bottom). Besides $^1$H-NMR spectroscopy, MALDI-TOF-MS also proved the successful synthesis of Ir(III) DPP 13 as can be concluded from Figure 7.14 right. The only significant signal could be assigned to the product and the isotopic pattern could be simulated assuming that half of the product was protonated, which can occur during the MALDI-process.

Figure 7.14. $^1$H-NMR (left; in CD$_2$Cl$_2$) and MALDI-TOF-MS (right) spectra of the iridium(III) DPP 13. The top $^1$H-NMR spectrum (left) shows a magnification of the aromatic region with the corresponding assignment (ppy = 2-phenylpyridine; tpy = 2,2’:6’2”-terpyridine; dpp = 3,6-(2-dipyridyl)pyridazine). The insets of the MALDI-TOF-MS (right) depicts the obtained and simulated isotopic pattern of the Ir(III) DPP 13.
7.5.2 Self-assembly of bimetallic [2×2] copper(I) grids with dangling iridium(III) complexes

The self-assembly of the iridium(III) functionalized DPP 13 with copper(I) ions will be discussed in this section. Figure 7.15 shows a space-filling representation of the resulting metal complex with the [2×2] copper(I) grid in the middle and the four dangling iridium(III) complexes around, whereby hydrogen atoms and counterions were omitted for clarity. This resulting mixed metal complex would consist of four copper(I) ions and four iridium(III) ions and thus would have a high charge density and a total mass of 6,139 Da (including eight PF$_6^-$ counterions). Nevertheless, this space-filling representation demonstrates that, in principle, sufficient space is available for the grid formation. Therefore, it might be expected that the addition of copper(I) ions to the Ir(III) DPP 13 will result in self-assembly into a [2×2] grid-like structure.

![Space-filling representation of the [2×2] copper(I) grid with the four dangling iridium(III) complexes](image)

*Figure 7.15. Space-filling representation of the [2×2] copper(I) grid with the four dangling iridium(III) complexes (Chemsketch 3D from ACD labs) that results from self-assembling Ir(III) DPP 13 with four copper(I) ions. The hydrogen atoms and counterions are omitted for clarity.*

The self-assembly of the Ir(III) DPP 13 was investigated by an UV-titration experiment with [Cu(CH$_3$CN)$_4$(PF$_6$)] as depicted in Figure 7.16 left. The resulting UV-spectra show an increase in absorption around 450 nm, but due to the underlying Ir(III)(ppy)$_2$(ppy) absorption, the [2×2] copper(I) grid MLCT band could not be distinguished. Therefore, the Ir(III) DPP 13 absorption was subtracted from all UV spectra that were obtained during the titration. The resulting subtracted spectra are depicted in the inset of Figure 7.16 left demonstrating the appearance of the characteristic MLCT band. The increase in absorption at 437, 467 and 567 nm obtained from these subtracted UV-spectra is plotted against the added equivalents of copper(I) ion) to 440 nm (full grids) demonstrating effective cooperativity for the self-assembly into [2×2] grids.

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Figure 7.16. Left: UV-spectra obtained during the stepwise addition of copper(I) ions to Ir(III) DPP 13 in CH$_2$Cl$_2$. The inset shows the UV-spectra after subtraction of the Ir(III) DPP 13 spectrum. Right: Increase in absorption at 437, 467 and 567 nm upon the addition of copper(I) ions. The inset depicts the change in $\lambda_{\text{max}}$ of the MLCT band upon addition of copper(I) ions. All shown trends were determined from the subtracted UV-spectra.

During the course of the titration, it was noticed that the iridium(III) phosphorescence was quenched upon copper(I) complexation. This behavior was further investigated by the stepwise addition of copper(I) ions [Cu(CH$_3$CN)$_4$(PF$_6$)] to DPP 13, whereby after each addition step an emission spectrum was recorded with an excitation wavelength ($\lambda_{\text{ex}}$) of 385 nm. The resulting emission spectra are shown in Figure 7.17 left. Upon addition of copper(I) ions to the Ir(III) DPP 13, the emission decreased resulting in almost complete quenching of the phosphorescence. Moreover, the phosphorescence decreased linearly with equivalents of copper(I) ions that were added (Figure 7.17 right). A reference experiment in which a preformed copper(I) grid was added to a solution of the amino Ir(III) complex 12 did not show quenching of the phosphorescence. In addition, the close proximity of the four iridium(III) complexes cannot be the basis of the quenching since the iridium(III) complex also shows phosphorescence as bulk material. Therefore, it might be assumed that the observed quenching is a consequence of the close proximity of the [2×2] copper(I) grids to the iridium(III) complexes. This close proximity might facilitate fast energy transfer of the iridium complex to the copper(I) grid followed by non-radiative decay of the copper(I) complex.

Figure 7.17. Left: Emission spectra obtained during the stepwise addition of copper(I) ions to Ir(III) DPP 13 in CH$_2$Cl$_2$ ($\lambda_{\text{ex}} = 385$ nm). Right: Decrease in emission upon addition of copper(I) ions.

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7.6 Conclusions

The utilization of the 3,6-di(2-pyridyl)pyridazine (DPP) ligand to construct macromolecular [2×2] grid-like metal complexes was described in this chapter. Three different synthetic routes were successfully followed to synthesize macromolecular DPP’s.

At first, an acetylene functionalized poly(ɛ-caprolactone) was synthesized via controlled ring-opening polymerization of ɛ-caprolactone with 5-hexyn-1-ol as initiator. The resulting polymer was applied as reagent in the inverse-electron-demand Diels-Alder reaction with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine resulting in the poly(ɛ-caprolactone) functionalized DPP ligand as it was demonstrated by 1H-NMR spectroscopy, GPC and MALDI-TOF-MS. The complexation of this macromolecular DPP with copper(I) ions was investigated by UV-titration experiments. In both dichloromethane and acetone, the macroligand self-assembled into full macromolecular [2×2] copper(I) grids demonstrating the stability of the [2×2] grids regardless of the solubility of the copper(I) salt in the utilized solvent. Moreover, the possibility of performing the UV-titration in CH$_2$Cl$_2$ demonstrated that the macroligand combines both the properties of the ligand and the polymer: The complexation behavior of the ligand is retained together with the good solubility of the polymer in CH$_2$Cl$_2$.

Secondly, a hydroxyfunctional DPP was utilized as coinitiator for the aluminum oxide mediated controlled ring-opening polymerization of L-lactide. Using this synthetic method, DPP’s with three different lengths of poly(L-lactide) substituents were prepared. The successful incorporation of the ligand in the polymer was proven by 1H-NMR spectroscopy, GPC and MALDI-TOF-MS. Complexation studies of these macroligands were also performed by UV-vis titration experiments. Similarly to the poly(ɛ-caprolactone) DPP, macromolecular [2×2] copper(I) grids were formed with all macroligands. However, the UV-titration and additional modeling of these data demonstrated effective cooperativity in the grid-formation of the smallest macroligand, which is most likely due to less sterical hindrance with a smaller polymer chain present. The effect of the copper(I) [2×2] grid formation on the polymer morphology was clearly demonstrated by AFM: Without copper(I) ions a flat film was obtained, whereas single spherical particles were determined for all three poly(L-lactide) [2×2] copper(I) grids. These spherical particles were assigned to be single polymeric grids. Moreover, with increasing polymer chain length, more and more large aggregates were observed, which most likely results from interactions between the polymer chains of different grids.

The third employed synthetic route towards macromolecular DPP’s is the coupling of both a functionalized DPP and an end-functionalized polymer. The application of this synthetic route was demonstrated by coupling an amino-functional poly(ethylene glycol) with a carbonyldimidazole activated DPP. Even though the coupling was not very efficient (~ 20%), the PEG substituted DPP could be obtained pure as demonstrated by 1H-NMR spectroscopy, GPC and MALDI-TOF-MS. Like all previously described macroligands, this PEG DPP also self-assembled into polymeric [2×2] copper(I) grids as demonstrated by an UV-titration in CH$_2$Cl$_2$. Furthermore, the self-assembly of this water–soluble ligand was investigated in water. However, partial oxidation of the copper(I) ions to copper(II) ions was observed in several titration experiments demonstrating that the [2×2] grids are not stable in water. The formation of copper(II) mono-complexes was demonstrated by comparison to the spectra obtained during the UV-titration with copper(II) triflate in CH$_2$Cl$_2$. 
In the final part of this chapter, the synthesis and complexation of a multimetallic grid are described. In a first attempt, a ditopic ligand was synthesized by coupling an isocyanato 2,2’:6,2’’-terpyridine to a 3,6-di(-2-pyridyl)-4-(1-hydroxybutyl)pyridazine. However, the resulting ligand did not show specific complexation of one of the ligands with different metal ions and thus no well-defined multimetallic [2×2] grids could be obtained. Therefore, an iridium(III) functionalized DPP was synthesized by coupling of an amino-functional iridium(III) complex to the carbonyldimidazole activated DPP. The self-assembly of this ligand into multimetallic [4 copper(I) ions and 4 iridium(III) ions] [2×2] grids was successful and revealed effective cooperativity in the UV-titration. In addition, the phosphorence of the iridium(III) complex was quenched, whereby the phosphorence decreased linearly with the equivalents of added copper(I) ions resulting in almost complete quenching upon addition of 1 equivalent of copper(I) ions. This quenching most likely resulted from fast energy transfer from the iridium(III) complex to the copper(I) grids, facilitated by their close proximity, followed by non-radiative decay of the copper(I) complex.

In conclusion, it was demonstrated that the class of 3,6-di(2-pyridyl)pyridazines is well-suitable for the construction of well-defined star-shaped metallo-supramolecular polymers. A variety of polymeric ligands was successfully synthesized and self-assembled into polymeric [2×2] grid-like complexes. As a result, it can be concluded that the range of available ligands in the field of metallo-supramolecular polymers has been successfully expanded with the 3,6-di(2-pyridyl)pyridazine ligand.

7.7 Experimental part

Material and instrumentation
Solvents were purchased from Biosolve and all other compounds were obtained from Aldrich or Fluka. All compounds were used without further purification. α-Hydroxy-ω-aminoPEG was obtained from Shearwater. 3,6-Di(2-pyridyl)-1,2,4,5-tetrazine (1) and 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (4) were synthesized as described in chapter 6. The amino-functionalized iridium(III) complex (12) was synthesized as described in literature.\(^{58}\)\(^{1}\)H-NMR, \(^{1}H\)-\(^{1}\)H COSY and \(^{13}\)C-NMR spectra were recorded on a Varian Mercury 400 spectrometer or a Varian Gemini 300 spectrometer. Chemical shifts are given in ppm relative to TMS or solvent signals for proton and carbon spectra. UV-vis spectroscopy was done on a Perkin Elmer Lambda 45 apparatus utilizing 1 cm cuvets. Emission spectra were recorded on a Perkin Elmer LS50B Luminescence spectrometer. IR-spectra were recorded on a Perkin Elmer 1600 FT-IR. MALDI-TOF-MS was performed on a Voyager-DE™ PRO Biospectrometry™ Workstation (Applied Biosystems) time-of-flight mass spectrometer using linear mode for operation. The spectra were obtained in the positive ion mode and ionization was performed with a 337 nm pulsed nitrogen laser, whereby dithranol was used as matrix. Gel Permeation Chromatography (GPC) was measured on a Shimadzu system with a SCL-10A system controller, a LC-10AD pump, a RID-6A refractive index detector, a SPD-10A UV detector and a PL-gel 5 μm Mixed-D column, whereby chloroform:triethylamine:2-propanol (94:4:2) was used as eluent at 1 mL/min and the column oven was set to 50 °C. The molecular weights were calculated against PS or PEG standards.

AFM imaging was performed on a multimode scanning probe microscope by Digital Instruments (DI, Santa Barbara, CA). Images were obtained in tapping mode with silicon tips (NSG11, obtained from NT-MDT).

Microwave-assisted synthesis was performed utilizing an Emrys Liberator microwave synthesizer (Biotage) utilizing capped reaction vials. All microwave reactions were performed with temperature control utilizing an IR sensor for the temperature determination.
UV-vis titration experiments
A stock solution (3.0 mL) of the DPP ligand in dichloromethane (~ 0.5 · 10⁻² M) was transferred into a quartz UV-cuvet. Small portions (~ 25 µL) of a stock solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate in dichloromethane (~ 0.45 mg/mL) were added stepwise to this solution and the mixtures were shaken for several seconds. After each addition, an UV-Vis spectrum was recorded. The fluorescence titration was performed in a similar manner, whereby after each addition step an emission spectrum as recorded.

Acetylene terminated poly(ε-caprolactone) (2)
1-Hexyn-5-ol (65.4 mg, 0.67 mmol) was dissolved in ε-caprolactone (1.5 g, 13.1 mmol) and heated to 110 °C. After addition of one drop of tin octoate, the solution was stirred for 3 hours at 110 °C. The obtained solid was dissolved in CH₂Cl₂ and precipitated in methanol:water (2:1) resulting in the acetylene terminated poly(ε-caprolactone) 2, as white solid (1.28 g, 82%).

MALDI-TOF-MS: Mₙ = 4,460 Da, PDI = 1.19. MALDI-TOF-MS: Mₙ = 2,200 Da, PDI = 1.03. ³¹H-NMR: Mₙ = 2,380 Da.

3,6-Di(2-pyridyl)-4-poly(ε-caprolactone)pyridazine (3)
A solution of the acetylene terminated poly(ε-caprolactone) 2 (200 mg, 0.084 mmol) and 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (47.2 mg, 0.2 mmol) in CH₂Cl₂ (2.0 mL) was heated to 150 ºC for 150 minutes under microwave irradiation. After evaporation of the solvent, the crude product was purified by column chromatography (silica, chloroform with 1% methanol) and preparative size exclusion chromatography (Biobeads SX-1, CH₂Cl₂) resulting in the 3,6-di(2-pyridyl)-4-poly(ε-caprolactone)pyridazine (3), as white solid (158 mg, 73%).

MALDI-TOF-MS: Mₙ = 2,590 Da.

3,6-Di(2-pyridyl)-4-poly(L-lactide)pyridazine (5)
The polymerization was performed in a silanized Schlenk tube under an argon atmosphere. 3,6-Di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (47.2 mg, 0.2 mmol) in dry toluene (5.0 mL) and cooled to 0 °C. Triethylaluminum (1.9 M, 62 µL, 0.12 mmol) was added dropwise and the reaction mixture was allowed to warm to ambient temperature. Subsequently, L-lactide (392 mg, 2.7 mmol) was added, the reaction tubes were sealed and the mixture was stirred for 20 hours at 80 °C. The polymerization was quenched with 5 drops of water and the desired polymer 5 (285 mg, 67%) was obtained by precipitation in ice-cold methanol.

MALDI-TOF-MS: Mₙ = 3,000 Da, PDI = 1.12. ³¹H-NMR: Mₙ = 3,840 Da.
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1H NMR (CDCl3): δ 8.79-8.70 (m, 3H, H-5,3''',5'''), 8.48 (s, 1H, H-5'), 8.15 (d, J = 7.3 Hz, 1H, H-3), 7.88 (t, J = 7.1 Hz, 2H, H-4,4''), 7.4 (t, J = 6.3 Hz, 2H, H-4,4''), 5.22-5.1 (q, J = 7.4 Hz, 90H, CH3CH2), 4.38 (m, 1H, CH3OH) 4.12 (m, 2H, CH2), 3.08 (m, 2H, CCH3), 2.78 (m, 1H, OH), 1.76-1.4 (d, J = 6.5 Hz, 368H, CCH2CH2CH2 + CCH3 + H2O). IR (ATR): v = 2998 (CH3 stretch), 2947 (CH3 stretch), 1756 (C=C stretch), 1586 (C=N stretch), 1456 (CH3 deformation), 1360 (CH3 deformation), 1182 (C-O stretch), 1130 (C-C vibration), 1086 (C-C vibration), 1044 (C-C vibration).

GPC (MALDI-TOF-MS): Mn = 9,600 Da, PDI = 1.21; RI-detector: Mn = 10,700 Da, PDI = 1.22. MALDI-TOF-MS: Mn = 5,000 Da, PDI = 1.11. 1H-NMR: Mn = 6,800 Da.

3,6-Di(2-pyridyl)-4-poly(l-lactide)pyridazine (7)

Same procedure as for poly(l-lactide) DPP 5 but with the following amounts of reagents: 4 (16.5 mg, 0.050 mmol), toluene (5.0 mL), triethylaluminum (1.9 M, 26.3 µL, 0.050 mmol) and L-lactide (720 mg, 5.00 mmol). Yield: 523 mg, 71%.

1H NMR (CDCl3): δ 8.79-8.70 (m, 3H, H-5,3''',5'''), 8.48 (s, 1H, H-5'), 8.15 (d, J = 7.3 Hz, 1H, H-3), 7.88 (t, J = 7.1 Hz, 2H, H-4,4''), 7.4 (t, J = 6.3 Hz, 2H, H-4,4''), 5.22-5.1 (q, J = 7.4 Hz, 150H, CH3CH2), 4.38 (m, 1H, CH3OH) 4.12 (m, 2H, CH2), 3.08 (m, 2H, CCH3), 2.78 (m, 1H, OH), 1.76-1.4 (d, J = 6.5 Hz, 368H, CCH2CH2CH2 + CCH3 + H2O). IR (ATR): v = 2998 (CH3 stretch), 2947 (CH3 stretch), 1756 (C=C stretch), 1586 (C=N stretch), 1456 (CH3 deformation), 1360 (CH3 deformation), 1182 (C-O stretch), 1130 (C-C vibration), 1086 (C-C vibration), 1044 (C-C vibration).

GPC (chromatography): UV-detector: Mn = 15,600 Da, PDI = 1.20; RI-detector: Mn = 17,300 Da, PDI = 1.18. MALDI-TOF-MS: Mn = 8,700 Da, PDI = 1.06. 1H-NMR: Mn = 11,100 Da.

AFM measurements on poly(l-lactide)s 5-7

For the AFM measurements, a solution of the copper complex of 5-7 in chloroform (0.050 mg/mL) was drop-cast onto mica. The measurements were performed in tapping mode.

Imidazol-1-carboxylic acid [3,6-di(2-pyridyl)pyridazin-4-yl] butyl ester (8)

A solution of 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (4; 166 mg, 0.54 mmol) and carbonyldiimidazole (147 mg, 0.91 mmol) in dried CH2Cl2 (10 mL) was stirred for two hours at ambient temperature. The mixture was diluted with CH2Cl2 (15 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 25 mL) and water (1 × 25 mL.). After drying the organic layer with sodium sulphate, the solvent was evaporated resulting in the 3,6-di(2-pyridyl)-4-(1-imodazolide buyloxy)pyridazine (8), as white solid (153 mg, 71%). This product was used in the subsequent reactions without further purification.

1H-NMR (CDCl3, 1H-H COSY): δ 8.77-8.72 (m, 3H, H-5,3'',6''), 8.66 (d, J = 4.8 Hz, 1H, H-6), 8.49 (s, 1H, H-5'), 8.17 (d, J = 7.9 Hz, 1H, H-3), 8.07 (s, 1H, NCH3), 7.91-7.83 (m, 2H, H-4,4''), 7.42-7.35 (dt, J = 6.5 Hz, 2H, CCH3), 7.04 (d, J = 6.1 Hz, 2H, CCH3), 3.19 (t, J = 7.5 Hz, 2H, CCH3), 1.88-1.74 (m, 4H, CCH2CH2CH3).

13C-NMR (CDCl3): δ 158.7 (C-3'), 157.3 (C-6'), 156.2 (C-2'), 153.4 (C-2''), 149.3 (C-6''), 148.6 (C=O), 148.3 (C-6), 141.7 (C-4'), 137.2 (C=O), 136.9 (C-4), 130.6 (C=ONC) 125.6 (C-5'), 124.8 (C-3',5'), 123.8 (C-5), 121.7 (C-3''), 117.0 (C=ONCH3) 67.8 (CH2O), 31.9 (CH2), 28.2 (CH2CH2O), 26.0 (CCH2CH3).

3,6-Di(2-pyridyl)-4-poly(ethylene glycol)pyridazine (9)

A solution of imidazol-1-carboxylic acid [3,6-di(2-pyridyl)pyridazin-4-yl] butyl ester (8; 40 mg, 0.10 mmol) and α-hydroxy-ω-aminopoly(ethylene glycol) (252 mg, 0.074 mmol) in tetrahydrofuran (10 mL) was refluxed for 12 days. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (aluminum oxide, chloroform with 1% methanol) followed by precipitation in cold diethyl ether. The 3,6-di(2-pyridyl)-4-poly(ethylene glycol)pyridazine (9) was obtained as white solid (54 mg, 23%).

1H-NMR (CDCl3, 1H-H COSY): δ 8.74-8.69 (m, 3H, H-5,3''',6'''), 8.48 (s 1H, H-5'), 8.12 (d, J = 7.9 Hz, 1H, H-3), 7.91-7.85 (dt, J = 7.8, 1.6, 2H, H-4,4''), 7.42-7.35 (dt, J = 4.6,1.2, 2H, H-5,3''), 5.6-5.20 (br s, 1H, NH), 4.01 (t, J = 6.1 Hz, 2H, CH2O), 3.85 (t, J = 4.9 Hz, 2H, CCHN), 3.80-3.55 (m, 320H, PEG) 3.12 (t, J = 7.5 Hz, 2H, CCH3), 1.76-1.59 (m, 4H, CCH2CH2CH3).

GPC (chromatography): UV-detector: Mn = 3,250 Da, PDI = 1.08; RI-detector: Mn = 3,260 Da, PDI = 1.06. MALDI-TOF-MS: Mn = 3,660 Da, PDI = 1.03. 1H-NMR: Mn = 3,900 Da.
4'-Isocyanatopentolxyloxy-2',2'':6',2'''-terpyridine (10)

To a stirred solution of di-tert-butyltricarbonic acid (40 mg, 0.15 mmol) in CH2Cl2 (8 mL) at room temperature, a solution of aminopentolxyloxy-2',2':6',2'''-terpyridine (40 mg, 0.12 mmol) was added over a period of 5 minutes. After 15 min stirring, the solvent was evaporated yielding 10, as colorless oil (quantitative).

1H NMR (CDCl3): δ 8.69 (ddd, J = 1.0, 1.5, 4.8 Hz, 2H, H-6'''), 8.52 (ddd, J = 1.0, 1.5, 8.0 Hz, 2H, H-3'''), 8.01 (s, 2H, H-3',5'), 7.85 (ddd, J = 1.5, 7.2, 8.0 Hz, 2H, H-4''), 7.33 (ddd, J = 1.5, 4.8, 7.2 Hz, 2H, H-5'''), 4.25 (t, J = 6.2 Hz, 2H, H-α), 3.36 (t, J = 6.5 Hz, 2H, H-ε), 1.89 (tt, J = 6.2, 6.5 Hz, 2H, H-β), 1.55-1.78 (m, 4H, H-γ,δ). 13C NMR (CDCl3): δ 167.2 (C-4'), 157.1 (C-2',6'), 156.1 (C-2''',6''',6''''), 149.0 (C-6'''), 136.8 (C-3',5'), 121.3 (C-3''',6'''), 107.3 (C-5'''), 67.8 (C-ε), 42.9 (C-ε), 30.9 (C-β), 28.4 (C-δ). MALDI-TOF-MS: m/z = 335 [MH⁺]. C25H20N4O2 (360.41): calcd. C 69.98, H 5.59, N 15.55; found: C 70.23, H 5.34, N 15.29.

5-(2',2':6',2'''-Terpyridin-4'yl-oxyloxy)-pentyl carboxylic acid 4-[3,6-di(2-pyridyl)pyridazin-4-yl]butyl ester (11)

Isocyanato-terpyridine 13 (100 mg, 0.28 mmol) and two drops of dibutyltinlindilaurate were added to a solution of 3,6-di(2-pyridyl)-4-(1-hydroxybutyl)pyridazine (4: 74 g, 0.22 mmol) in chloroform (25 mL). After 16 hours stirring at room temperature, the solvent was evaporated and the crude product was purified by column chromatography (aluminum oxide, acetone) and preparative size exclusion chromatography (Biobeads SX-3, CH2Cl2) resulting in as white solid (113 mg, 77%).

Mp 130-131 °C. 1H NMR (CDCl3): 8.59-8.75 (m, 7H, H-3',3'',6'',6'',7''',7''',8''',8''',9'''; 25 mg, 0.061 mmol) and iridium(III) (2',2':6',2'''-terpyridine) functionalized 3,6-di(2-pyridyl)pyridazine (12; 40 mg, 0.047 mmol) in tetrahydrofuran was stirred at 50 °C for 8 days. After evaporation of the solvent, the crude residue was purified by column chromatography (aluminum oxide, acetone) and preparative size exclusion chromatography (Biobeads SX-3, CH2Cl2) resulting in the pure iridium(III) functionalized 6-di(2-pyridyl)terpyridazine (13), as yellow solid.

Iridium(III)(phenylpyridine)4[2',2':6',2'''-terpyridine] functionalized 3,6-di(2-pyridyl)pyridazine (13)

A solution of imidazol-1-carboxylic acid 4-[3,6-di(2-pyridyl)pyridazin-4-yl]butyl ester (8; 25 mg, 0.061 mmol) and iridium(III)(2-phenylpyridine)c1(1-aminohexyloxopyridine) (12; 40 mg, 0.047 mmol) in tetrahydrofuran was stirred at 50 °C for 8 days. After evaporation of the solvent, the crude residue was purified by column chromatography (aluminum oxide, acetone) and preparative size exclusion chromatography (Biobeads SX-3, CH2Cl2) resulting in the pure iridium(III) functionalized 3,6-di(2-pyridyl)pyridazine (13), as yellow solid.

1H-NMR (CDCl3, 1H-1H COSY): δ 8.76 (d, J = 5.0 Hz, 1H, H-6'''), 8.65-8.60 (m, 3H, H-3'',6'',7''',7''',8''',8''',9''',9''''), 8.54-8.38 (m, 2H, H-5''',6'''), 8.09 (d, J = 4.7 Hz, 1H, H-3'''), 8.05-7.98 (m, 2H, H-5'''), 7.90-7.68 (m, 8H, H-4'',4'',3',4',3'',5'',5'',6'',6'',7'',7'',8'',8'',9'',9'',9''''), 7.52 (dd, J = 7.8, 1.1 Hz, 1H, H-3'''), 7.38-7.29 (m, 3H, H-5,''',6'''), 7.29-7.24 (m, 2H, H-4'',3'',3'',3'',4'',4'',5'',5'',6'',6'',7'',7'',8'',8'',9'',9'',9''',9''''), 7.06 (dt, J = 6.5, 1.5 Hz, 1H, H-5'''), 6.99 (dt, J = 7.7 Hz, 1.2, 1H, H-4'), 6.92-6.84 (m, 2H, H-3',4',5',5',6'',6'',7'',7'',8'',8'',9'',9'',9''',9''''), 6.67 (dt, J = 7.5, 1.3 Hz, 1H, H-5''''), 6.54 (dt, J = 7.5 Hz, 1.2, 1H, H-4'''), 6.38 (d, J = 7.7 Hz, 1H, H-3'''), 6.23 (dt, J = 7.5, 1.2 Hz, 1H, H-5'''), 5.80 (dd, J = 7.7, 0.8 Hz, 1H, H-6'''), 5.36 (dd, J = 7.7, 0.8 Hz, 1H, H-6'''), 4.75 (br s, 1H, NH), 4.11 (t, J = 6.0 Hz, 2H, H-α), 3.90 (t, J = 6.1 Hz, H-δ), 3.06-2.93 (m, 4H, H-α, H-γ), 1.80-1.22 (m, 12H, H-β, H-δ, H-ε), MALDI-TOF-MS: m/z 1182 [M+]. UV-vis: λmax 261, 276, 342, 381, 420 nm.
7.8 References and notes

Synthesis of macromolecular [2×2] grid-like metal complexes

(52) J. E. McAlvin, C. L. Fraser, Macromolecules 1999, 32, 6925-6932.
Summary

Polymer science is a broad field of research even though the most widespread applications in e.g. packaging and casings are dominated by only a few bulk polymers. Nevertheless, academic polymer research is largely focusing on the synthesis and properties of well-defined macromolecular architectures like random, block, graft and comb copolymers. These well-defined polymer structures are accessible by the utilization of living/controlled polymerization techniques. In contrast to the polymerization processes itself, the experimentation tools have not changed to a large extend in the last decades. Therefore, the research described in this thesis focused on expanding the polymer science toolbox by the introduction of high-throughput experimentation techniques and microwave irradiation. Moreover, the scope of polymer chemistry was further expanded by the introduction of grid-like metallo-supramolecular systems into macromolecular structures.

The success of living/controlled polymerization techniques largely depend on the applied reagents and polymerization conditions. Moreover, when the appropriate polymerization conditions are known, a wide variety of copolymer architectures can be prepared by systematically changing, e.g., the monomers, the monomer composition and the polymer molecular weight. Therefore, the introduction of high-throughput experimentation techniques seems to be very promising to accelerate these investigations. The automated parallel synthesis robots and accompanying online characterization techniques (GC and GPC) that were used in these studies are discussed in detail. Moreover, their applicability to polymer science was demonstrated on the basis of feasibility studies for the cationic ring-opening polymerization of 2-ethyl-2-oxazoline and the reversible addition-fragmentation chain-transfer polymerization of methyl methacrylate. After these feasibility studies, the synthesis robots were applied for the automated parallel optimization of the cationic ring-opening polymerization of different 2-oxazoline monomers with regard to polymerization temperature, initiator, monomer concentration and pressure conditions. The synthesis of statistical and block copoly(2-oxazoline)s was performed utilizing the optimized polymerization procedures. The kinetic information on the copolymerization of MeOx:EtOx, MeOx:NonOx and EtOx:NonOx from the automated parallel investigations revealed the formation of gradient MeOx:EtOx and MeOx:NonOx copolymers and statistical EtOx:NonOx copolymers. In addition, the surface energies of the 50:50 mol% MeOx:NonOx and EtOx:NonOx copolymers were found to be much higher than for comparable block copolymers due to the restricted orientation of the pNonOx in the copolymers. The synthesized block copoly(2-oxazoline)s revealed significant phase separation for the MeOx:NonOx combination and good mixing of the EtOx:NonOx blocks.

Microwave irradiation is an alternative heating source to conventional conductive heating. The microwave energy is in the range of the rotational energy of molecules and, as a result, molecules with a dipole moment will be rotated by the microwaves which is nothing else than heat. Microwave irradiation is a well-established tool in organic synthesis, but it is still rather unexplored in polymer chemistry. The cationic ring-opening of polymerization of 2-oxazolines could be successfully performed under microwave irradiation. More specifically, it was found that the microwave-assisted polymerizations (under pressure conditions) could be accelerated by a factor of 350 compared to conventional polymerizations (ambient pressure). However, it was demonstrated that the acceleration results from thermal effects and could be reproduced using high-boiling solvents or pressure conditions with conventional...
heating. The microwave-assisted heating also revealed living polymerizations with reduced solvent amounts. Moreover, the livingness of the polymerizations with increasing monomer to initiator ratios was also investigated demonstrating a maximum $[M]/[I]$ of 150 for MeOx and NonOx and a maximum $[M]/[I]$ of 300 for EtOx and PhOx. The generality of the microwave-assisted 2-oxazoline polymerizations was demonstrated by the livingness of the homo polymerizations of a series of 2-alkyl-2-oxazolines, a 2-soy alkyl’-2-oxazoline (SoyOx) monomer and by the application of a tetrafunctional porphyrine based initiator.

Additionally, the developed microwave-assisted polymerization procedure was applied for the synthesis of libraries of diblock, triblock and random copoly(2-oxazoline)s. The resulting block copolymers demonstrated that the glass transition temperature of the poly(2-oxazoline)s is influenced by the flexibility of the side-chain. The rigid methyl and phenyl side-chains result in high glass transition temperatures and the more flexible ethyl and nonyl side-chains result in a lower glass transition temperature or the absence thereof (nonyl). Moreover, the presence of NonOx in the block copolymers resulted in a low surface energy, whereas all block polymers without NonOx had a high surface energy. Furthermore, the copolymer series of MeOx:NonOx (gradient composition), EtOx:NonOx (statistical monomer distribution), MeOx:PhOx and EtOx:PhOx (both block structures) were found to have different monomer distribution throughout the polymer chains. In addition, the thermal and surface properties revealed that the polymers that consist of two monomers with rigid substituents (MeOx and PhOx) or two monomers with flexible substituents (EtOx and NonOx) are compatible, whereas combinations of rigid and flexible substituents into one polymer result in phase separation. The preparation of SoyOx containing polymers revealed the added value of such an unsaturated fatty acid base monomer: Besides being a monomer based on renewable resources, it was found that it can effectively act as cross-linker. The successful cross-linking upon UV-irradiation was demonstrated by the different thermal and surface properties of EtOx:SoyOx copolymers and by the preparation of core cross-linked micelles of a poly(EtOx-b-SoyOx) block copolymer.

The last part of the thesis dealt with the introduction of grid-like metal complexes in polymer science. The 3,6-di(2-pyridyl)pyridazine (DPP) ligand was identified as a suitable candidate that self-assembles into [2×2] grids with copper(I) ions. To be able to incorporate this ligand into polymer structures, the synthesis of substituted DPP’s via the inverse-electron-demand Diels-Alder reaction between 3,6-di(2-pyridyl)-1,2,4,5-tetrazine and acetylenes was investigated. A variety of alkyl substituted, hydroxy-functionalized and tributylstannyl functionalized ligands could be prepared. Moreover, it was found that the long reaction times (several days) could be reduced to several hours by the utilization of superheated conditions (dichloromethane 150 °C) under microwave irradiation. Unexpectedly, it was discovered that ketones and aldehydes also undergo cyclo-additions to the 3,6-di(2-pyridyl)-1,2,4,5-tetrazine under superheated conditions resulting in the corresponding DPP’s. It was found that these reactions occur via the enol tautomers followed by elimination of both a nitrogen and a water molecule resulting in the DPP’s. The microwave-assisted Diels-Alder reaction of an acetylene functionalized poly($\varepsilon$-caprolactone) with the tetrazine was also performed successfully resulting in the poly($\varepsilon$-caprolactone) substituted DPP. Moreover, a hydroxy-functionalized DPP was applied as initiator for the polymerization of $L$-lactide and for the coupling to an amine-functionalized poly(ethylene glycol) and to an amine-functionalized iridium(III) complex. All resulting macroligands self-assembled into [2×2] grid-like copper(I) complexes as was demonstrated by UV-vis titration experiments. However, effective cooperativity was observed for the grid-formation of the smaller polymeric poly($L$-lactide) macroligand and the
iridium(III) functionalized DPP, whereas this cooperativity was absent for the other polymeric ligands, which is probably due to steric effects. The polymeric [2×2] copper(I) grids combined the optical properties of the complexes with the good solubility of the polymers. Moreover, the poly(L-lactide) macroligands formed thin flat films, whereas the corresponding grid-like complexes could be observed (AFM) as single objects with the smallest polymer side-chain and as a larger network with larger polymeric side chains. During the self-assembly of the iridium(III) DPP ligand with copper(I) ions it was observed that the phosphorescence of the iridium(III) was effectively quenched. This quenching most likely results from energy transfer from the iridium(III) complex to the copper(I) grids which is facilitated by their close proximity.

In general, it can be concluded that high-throughput experimentation methods and microwave irradiation are versatile tools for polymer research. The feasibility of both experimentation techniques for polymer science was demonstrated throughout this thesis. Moreover, their added value was demonstrated for the cationic ring-opening (co)polymerizations of 2-oxazolines. In addition, the field of metallo-supramolecular polymers was successfully expanded with grid-like metal complexes that allow the formation of larger self-assembled structures.
Samenvatting

De polymerewetenschap is een breed onderzoeksgebied ondanks dat het merendeel van de bekende toepassingen, zoals verpakkingen en kunststoffen, wordt gedomineerd door slechts een klein aantal bulkpolymeren. Desalniettemin richt universitair onderzoek naar polymeren zich in grote mate op de synthese en eigenschappen van goed gedefinieerde macromoleculaire structuren, zoals random-, blok-, graft- en kamcopolymeren. De synthese van deze goed gedefinieerde polymerestructuren is toegankelijk door middel van het gebruik van levende en gecontroleerde polymerisatietechnieken. In tegenstelling tot de polymerisatietechnieken zelf, zijn de experimentele technieken niet veel veranderd in de laatste decennia. Het doel van het onderzoek beschreven in dit proefschrift, is daarom het uitbreiden van de beschikbare experimentele technieken middels het toepassen van hoge doorvoer experimenten ('high-throughput experimentation') en microgolfbestraling. De mogelijkheden in de polymeerchemie zijn verder uitgebreid door het inbouwen van rasterachtige supramoleculaire metalcomplexen in macromoleculaire structuren.

Het succes van levende en gecontroleerde polymerisatietechnieken hangt in grote mate af van de gebruikte reagentia en de polymerisatiecondities. Als de geschikte polymerisatiecondities eenmaal bekend zijn, kan een grote variëteit van copolymeren gemaakt worden door middel van het systematisch variëren van bijvoorbeeld de monomeren, de monomeersamenstelling en het molecuulgewicht van het polymeer. Het gebruik van 'high-throughput experimentation' technieken lijkt veelbelovend te zijn om polymeeronderzoek te versnellen. De automatische parallele syntheserobotten en de gekoppelde karakterisatietechnieken (gaschromatografie en gel-permeatiechromatografie) die gebruikt zijn in dit onderzoek, worden in detail beschreven. De geschiktheid van deze apparatuur voor polymeerwetenschap was aangetoond aan de hand van haalbaarheidsstudies voor de kationische polymerisatie van 2-ethyl-2-oxazoline en de reversibele koppeling-fragmentatie ketenoverdracht polymerisatie van methyl methacrylate. Na deze haalbaarheidsstudies zijn de syntheserobotten gebruikt voor de automatische parallele optimalisatie van de polymerisatietemperatuur, initiator, monomeerconcentratie en het gebruik van drukcondities voor de kationische polymerisatie van verschillende 2-oxazoline monomeren. De resulterende optimale condities zijn toegepast voor de synthese van statistische en blokcopolymeren. De polymerisatiekinetiek voor de MeOx:EtOx, MeOx:NonOx en EtOx:NonOx copolymersaties die is verkregen door middel van de automatische parallele experimenten, toonde aan dat gradiënt copolymeren worden gevormd tijdens de copolymersaties van MeOx:EtOx en MeOx:NonOx en dat random copolymeren worden gevormd tijdens de copolymersaties van EtOx:NonOx. De oppervlakte-energie van de 50:50 mol% MeOx:NonOx en EtOx:NonOx copolymeren is beduidend lager dan de oppervlakte-energie van vergelijkbare blokcopolymeren door de beperkte oriëntatie van de nonyl zijketens in de statistische copolymeren. De gesynthetiseerde blokcopolymeren met pMeOx en pNonOx blokken resulteerde in significante fasescheiding, terwijl een goede menging in blokcopolymeren met pEtOx en pNonOx blokken was waargenomen.

Microgolfbestraling is een alternatieve verwarmingsmethode. De energie van deze microgolven is in dezelfde ordegrootte als de rotatie-energie van een molecuul. Moleculen met een dipoolmoment zullen dus in beweging gebracht worden door de microgolven en beweging van een molecuul is hetzelfde als warmte. Verwarming door middel van microgolven is een veelgebruikte techniek in organische synthese, maar het wordt nog nagenoeg niet gebruikt in de polymeerchemie. De kationische polymerisatie van 2-oxazolines
was succesvol uitgevoerd onder microgolfbestraling. De polymerisaties onder microgolfbestraling (en druk condities) verliepen tot 350 keer sneller dan de polymerisaties met normale verwarming (onder atmosferische druk). Niettemin, het was ook aangetoond dat deze versnelling alleen afkomstig is van thermische effecten: Het gebruik van druk reactoren of hoogkokinge oplosmiddelen met normale verwarming resulteerde in dezelfde versnelling van de polymerisaties. De polymerisaties onder microgolfbestraling verliepen ook via een levend mechanisme met een gereduceerde hoeveelheid oplosmiddel. De kationische polymerisaties met microgolfbestraling zijn verder onderzocht met toenemende monomeer tot initiator ([M]/[I]) verhoudingen. De polymerisaties behielden het levende karakter tot een [M]/[I] verhouding van 150 (MeOx en PhOx) of 300 (EtOx en NonOx). De algemene toepasbaarheid van microgolfbestraling voor de kationische polymerisatie van 2-oxazolines was aangetoond aan de hand van de succesvolle polymerisaties van een serie van lineaire 2-alkyl-2-oxazolines, een 2-'soja-alkyl’2-oxazoline (SoyOx) en aan de hand van de toepassing van een tetrafunctionele initiator gebaseerd op een porphyrine molecuul.

De ontwikkelde microgolf polymerisatiemethode was toegepast voor de synthese van bibliotheken met diblok-, triblok- en random copolymeren. Aan de hand van de blokcopolymeren kon het geconcludeerd worden dat de glastransitietemperatuur ($T_g$) afhankelijk is van de flexibiliteit van de zijketens. De rigide methyl of fenyl zijkroepen resulteren in hoge $T_g$’s en de flexibele ethyl en nonyl zijketens resulteren in een lage $T_g$ of de afwezigheid van een $T_g$ (nonyl). De aanwezigheid van pNonOx in de blokcopolymeren leidde tot een lage oppervlakte-energie, terwijl de blokcopolymeren zonder pNonOx een hoge oppervlakte-energie hadden. De monomeerdistributie in de polymeerketens van de copolymeren was afhankelijk van de monomeercombinatie: MeOx:NonOx resulteerde in een gradiënt compositie, EtOx:NonOx in een random monomeerdistributie en MeOx:PhOx en EtOx:PhOx copolymerisaties resulteerden beiden in de vorming van quasi-blokcopolymeren. De thermische en oppervlakte eigenschappen van deze copolymeren wezen uit dat polymeren bestaande uit twee monomeren met rigide zijkroepen (MeOx en PhOx) of twee monomeren met flexibele monomeren (EtOx en NonOx) goed mengen. Als echter rigide en flexibele zijkroepen gecombineerd worden in een polymeer resulteert dit in fase scheiding. De synthese van SoyOx bevattende copolymeren bewees de toegevoegde waarde van de onverzadigde vetzuurzijtketens: Naast het voordeel van het gebruik van een natuurlijke grondstof, sojabonen, was het aangetoond dat de onverzadigde vetzuren gebruikt kunnen worden om de verschillende polymeerketens te koppelen resulterend in een netwerk. Het succes van deze netwerkvorming onder UV-bestraling was gedemonstreerd aan de hand van veranderingen in de thermische en oppervlakte eigenschappen van EtOx:SoyOx copolymeren en de bereiding van micellen, gebaseerd op een poly(EtOx-b-SoyOx) blokcopolymeer, die in de kern gekoppeld zijn.

Het laatste gedeelte van het proefschrift beschrijft de toepassing van rasterachtige metaalcomplexen in de polymeerwetenschap. Het 3,6-di(2-pyridyl)pyridazine (DPP) ligand was gekozen als geschikte kandidaat, omdat het zich in [2×2] rasters organiseert met koper(I) ionen. De introductie van functionele groepen in dit ligand, die nodig zijn om het aan een polymeer te kunnen koppelen, was onderzocht gebruikmakend van de omgedraaide Diels-Alder reactie tussen 3,6-di(2-pyridyl)-1,2,4,5-tetrazine en functionele acetylenen. Verschillende alkyl, hydroxy en tributylstannyl gesubstitueerde liganden zijn gesynthetiseerd. De lange reactie tijden (enkele dagen) konden verkort worden tot enkele uren door het gebruik van microgolf bestraling onder druk condities (150 °C in dichloormethaan). Tijdens deze experimenten was het ontdekt dat ketonen en aldehydes ook reageren met
2,6-di(2-pyridyl)-1,2,4,5-tetrazine, waarbij de overeenkomstige DPP gevormd worden. Deze reacties verlopen via de enol tautomeren gevolgd door de eliminatie van zowel een stikstof als een water molecuul. Een poly(ε-caprolactone) gefunctionaliseerde acetylene was ook gebruikt in de Diels-Alder reactie met de tetrazine resulterend in de poly(ε-caprolactone) gefunctionaliseerde DPP. Een van de hydroxyfunctionele DPP’s was toegepast als co-initiator voor de gecontroleerde polymerisatie van L-lactide en voor de koppeling met een aminofunctionele poly(ethylene glycol) en een aminofunctioneel irridium(III) metaalcomplex. Een poly(ε-caprolactone) gefunctioneerd acetyleen werd ook gebruikt in de Diels-Alder reactie met de tetrazine resulterend in de poly(ε-caprolactone) gefunctionaliseerde DPP. Een van de hydroxyfunctionele DPP’s was toegepast als co-initiator voor de gecontroleerde polymerisatie van L-lactide en voor de koppeling met een aminofunctionele poly(ethylene glycol) en een aminofunctioneel irridium(III) metaalcomplex. Alle resulterende macroliganden assembleren in [2×2] rasterachtige metaalcomplexen met koper(I) ionen, zoals was aangetoond met UV-titratie experimenten. Hierbij was effectieve versterking van de associatie in [2×2] rasters waargenomen voor het kleinste poly(L-lactide) macroligand en het irridium(III)-gefunctionaliseerde macroligand. De afwezigheid van deze positieve samenwerkende interacties voor de grotere macroliganden kan waarschijnlijk toegeschreven worden aan de sterische hindering door de aanwezigheid van lange polymeerketens. De gevormde polymere [2×2] koper(I) rasters combineerden de optische eigenschappen van het metaal complex met de goede oplosbaarheid van de polymeren. Verder vormden de poly(L-lactide) macroliganden vlakke films, terwijl de corresponderende koper(I) raterachtige complexen als individuele deeltjes konden worden waargenomen met de rastersondemicroscoop voor de kleinsten polymerici zijketens en als een continu netwerk voor de langste polymerici zijketens. Tijdens de assembleage van de irridium(III) liganden in raterachtige structuren was het waargenomen dat de fosforescentie van het irridium(III) complex afnam. Deze afname resulteert hoogstwaarschijnlijk van energie overdracht van het irridium(III) complex naar het koper(I) metaalcomplex dat bevorderd wordt door de kleine afstand tussen de beide complexen.

In het algemeen kan geconcludeerd worden dat zowel ‘high throughput experimentation’ als microgolf bestraling breed toepasbaar zijn in polymeeronderzoek. De geschiktheid van beide experimentele technieken voor polymeerwetenschap was aangetoond in dit proefschrift. De toegevoegde waarde van deze technieken was gedemonstreerd aan de hand van de kationische ring-opening (co)polymerisatie van 2-oxazolines. Verder was het onderzoeksgebied dat metaalcomplexen en polymeren combineert verder uitgebreid met reasterachtige metaalcomplexen die de mogelijk bieden voor de vorming van grotere geassembleerde structuren.
Richard Hoogenboom was born in 1978 in Rotterdam. After finishing his gymnasium degree (pre-university education) at the Kruisherens Kollege in Uden, he started in 1996 with the chemical engineering program at the Eindhoven University of Technology. His undergraduate research concerning quadruple hydrogen bonding of the 2-ureido-4[H]-pyrimidinone unit in water was performed in the group of professor Bert Meijer. After a three Months internship within the group of professor Andrew Holmes (Cambridge, United Kingdom), he obtained his M.Sc. degree in 2001. In November 2001 he started with his Ph.D. work under supervision of professor Ulrich Schubert at the Eindhoven University of Technology. The most important results of this work are described in this thesis.
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    bipyridine macroligands

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  Fabrication of organic-inorganic semiconductor composites utilizing the different aggregation states of a single amphiphilic dendrimer
  *Langmuir* 2002, 18, 2571-2576 (front cover).
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