Parallel Optimization and High-Throughput Preparation of Well-Defined Copolymer Libraries Using Controlled/“Living” Polymerization Methods

C. Remzi Becer and Ulrich S. Schubert

Abstract This chapter highlights the application of controlled/“living” polymerization (CLP) techniques in automated parallel synthesizers for both optimizing reaction parameters as well as preparing copolymer libraries. Special attention is given to the use of CLP techniques for constructing well-defined copolymer libraries. Furthermore, alternative strategies for the preparation of block copolymer libraries are discussed.

Keywords Automated parallel synthesis · Block copolymers · High-throughput experimentation · Polymer libraries · Random copolymers

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Abbreviations

AA Acrylic acid
AcBr Acetyl bromide
AcCl Acetyl chloride
AcI Acetyl iodide
AFM Atomic force microscopy
AIBN \( \alpha, \alpha \)-Azobisisobutyronitrile
Amor \( N \)-Acryoyl morpholine
ATRP Atom transfer radical polymerization
BEB (1-Bromo ethyl) benzene
bpy 4,4′-Dialkyl substituted bipyridine
BrEBi/B 2-Bromo-2-methylpropanoyl bromide
CBDB 2-Cyano-2-butyl dithio benzoate
CLP Controlled/“living” polymerization
CROP Cationic ring opening polymerization
CRP Controlled radical polymerization
CTA Chain transfer agent
DMA \( N,N \)-Dimethyl acrylamide
DMAc \( N,N \)-Dimethyl acetamide
DMAEMA \( N,N \)-Dimethyl aminoethyl acrylamide
DMF \( N,N \)-Dimethyl formamide
DP Degree of polymerization
DSC Differential scanning calorimetry
EEA 1-Ethoxy ethyl acrylate
EBIB Ethyl-2-bromo-iso-butyrate
EtOx 2-Ethyl-2-oxazoline
GC Gas chromatography
HPA 2-Hydroxypropyl acrylate
iPrOx 2-iso-Propyl-2-oxazoline
LCST Lower critical solution temperature
MA Methyl acrylate
MAA Methacrylic acid
MADIX Macromolecular design via the interchange of xanthates
MBP Methyl bromo propionate
MMA Methyl methacrylate
MeOMA 2-Methoxyethyl 2-methylacrylate
MeO₂MA 2-(2-Methoxyethoxy)ethyl 2-methylacrylate
1 Introduction

Tailor-made macromolecules have come into the focus of polymer science to overcome the challenges of a number of complex applications from the nano to the macro scale. Materials scientists have been designing and synthesizing tailor-made macromolecules specific for each application. These materials are composed of different monomeric units, chemical functionalities, and topologies. The challenge has been to control precisely the position of the functionality on the polymer, to determine the necessary ratio of monomeric units, as well as to understand the effect of the molecular architecture on the material performance.
The development of controlled/“living” polymerization (CLP) techniques has opened a new window to researchers to gain control successfully over the synthesis of well-defined polymeric structures [1–5]. However, each polymerization technique requires specific catalysts, initiators, and optimum reaction conditions for different monomers. Optimization and understanding the effect of each input variable on the polymerization kinetics or the obtained macromolecule can be performed by the use of high-throughput experimentation techniques. There is no doubt that screening a wide range of reaction parameters will allow researchers to define the most efficient synthesis conditions for successfully designing and preparing tailor-made polymers. Following the identification of the optimum reaction parameters, systematic sets of copolymers can be synthesized to elucidate structure-property relationships. Alternatively, gradient thin film libraries allow screening the effect of two or more parameters on a relatively small scale [6–8]. There are several methods to create gradient thin film libraries, e.g., flow-coating and ink jet printing [9, 10]. Countless data sets are being obtained by analysis of large polymer libraries and these data sets allow pinpointing of the best performance materials [11–15].

In this chapter, we will focus on the use of CLP techniques for the synthesis of systematic copolymer libraries using high-throughput approaches. Prior to that, automated parallel optimization reactions that have been performed for different CLP techniques will be discussed. At the end of this chapter there will be a highlight on the latest synthetic approaches to synthesize well-defined polymer libraries.

2 Parallel Optimization of Controlled/“Living” Polymerizations

Absolute structural control over the polymer chain represents the primary target in modern synthetic polymer chemistry. In practice, the term “well-defined” is commonly used for polymers that exhibit low polydispersity indices; however their structural composition should also be known in some detail. Important key features can be listed such as the chemical structures of the initiating and the end groups, monomer composition, number of repeating units as well as topology. Different synthetic approaches have been developed to gain control over the architecture. Ionic and radical polymerization techniques have been the most promising ones to provide the desired macromolecules. There is still the need to develop and optimize these techniques further, not only to improve the synthesis procedures but also to provide a deeper insight into the fundamentals of polymerization mechanisms.

Researchers have already invested several decades to elucidate the effect of input variables on the polymerization kinetics and the polymer structures. Many research groups have devoted their resources to obtaining reproducible data on polymerization kinetics. One of the methods to achieve that is to conduct several experiments in parallel to keep most reaction inputs constant and to minimize unpredictable environmental effects. In these series of experiments it appeared to be necessary to apply
automated parallel synthesis platforms and standardized experimental protocols in order to provide extended and comparable data sets within a short period of time.

2.1 Radical Polymerization Techniques

Starting from 1956, living ionic polymerizations became the major interest for the synthesis of well-defined polymers. Szwarc reported that in the anionic polymerization of styrene (St) the polymer chains grew until all the monomer was consumed; the chains continued to grow upon addition of more monomer [16].

According to the IUPAC definition, ionic polymerization is a type of chain polymerization where the kinetic-chain carriers are ions or ion pairs [17]. However, these techniques have some limitations such as the necessity of extreme purity of the chemicals and the reaction medium, incompatibility between the reactive centers and monomers, and the sensitivity to certain chemical functionalities that limits the monomer selection. These challenges directed researchers to discover or develop alternative polymerization techniques. One of the alternative polymerization routes is radical polymerization since it is less discriminating regarding the types of polymerizable vinyl monomers and more tolerant to several functionalities. The most common method is free radical polymerization, which results in polymers with broad molar mass distributions. However, polymers with relatively high polydispersity indices may be of some advantage in industrial processing. For instance, low molar mass polymer chains in polymers with broad molar mass distributions provide a plasticizer effect during processing. However, these ill-defined polymers are not suited for advanced applications and are also not suitable for understanding structure-property relationships.

As a consequence of the free radical polymerization kinetics, the termination rates are extremely fast in comparison to the slow initiation rates. This results in the formation of high molar mass chains at the initial stage of the polymerization and decreasing molar masses in the latter stages due to the decrease in the monomer concentration. Under these circumstances, broad molar mass distributions are inevitable.

There were several attempts to gain better control on the free radical polymerization process [18, 19]. One of these methods was named the “iniferter” method. The compounds used in this technique can serve as initiator, transfer agent and terminating agent [20–22]. Another technique is based on the use of bulky organic compounds such as diaryl or triarylmethyl derivatives [23–25]. The main disadvantages of these systems comprise slow initiation, slow exchange, direct reaction of counter radicals with monomers, and their thermal decomposition. Therefore, these techniques did not offer the desired level of control over the polymerization.

Relatively new controlled radical polymerization (CRP) methods, which were discovered in the mid-1990s, focused on establishing a precise equilibrium between the active and dormant species. Three approaches, namely atom transfer radical
polymerization (ATRP) [1, 2], nitroxide mediated polymerization (NMP) [3, 26], and reversible addition fragmentation chain transfer (RAFT) [4, 27], out of several others, have attracted the most attention due to their success in providing relatively stable chain end functionalities that can be reactivated for subsequent block copolymerizations or post polymerization modifications.

2.1.1 Atom Transfer Radical Polymerization

ATRP has become the most widely applied CRP technique due to its simple mechanism and commercially available reagents. This technique was first reported in 1995, independently by Sawamoto and Matyjaszewski [28, 29]. The polymerization mechanism is based on the reversible redox reaction between alkyl halides and transition metal complexes. Scheme 1 illustrates the mechanism of normal ATRP.

The simplicity of the polymerization reaction is the result of intense research carried out by several groups on the importance and the fundamentals of each parameter. In particular, Matyjaszewski et al. have spent great effort on the construction of numerous comparison charts on the activity of initiators and ligands that are used in ATRP [30–32]. These published comparison tables represent the summary of hundreds of single experiments and are now a very important and reliable source of data for the ATRP technique.

It is obvious that automated parallel synthesis robots provide a great advantage to the researcher that has necessarily to keep all secondary parameters constant throughout the screening reactions. These commercially available robotic systems have been constantly tested not only by its producers but also by academic groups to verify the reproducibility of the high-throughput experimentation setups. Recently, we have reported a standard protocol on the automated kinetic investigation of controlled/living radical polymerization of various monomers as a first step to obtain comparable results independent of the research group [33].

Automated parallel experiments were carried out to rapidly screen and optimize the reaction conditions for ATRP of methyl methacrylate (MMA) [34]. A set of 108 different reactions was designed for this purpose. Different initiators and different metal salts have been used, namely ethyl-2-bromo-iso-butyrate (EBIB), methyl bromo propionate (MBP), (1-bromo ethyl) benzene (BEB), and p-toluene sulfonyl chloride (TsCl), and CuBr, CuCl, CuSCN, FeBr2, and FeCl2, respectively. 2,2’-Bipyridine and its derivatives were used as ligands. The overall reaction scheme and the structure of the used reagents are shown in Scheme 2.
RX = EBIB, MBP, BEB, TsCl
Metal salt = CuBr, CuCl, CuSCN, FeBr$_2$, FeCl$_2$
Ligand = bpy, dMbpy, dHbpy, dTbpy, 4,5'-dMbpy, 5,5'-dMbpy, 4Mbpy, 6Mbpy

\[ \text{RX} \rightarrow \text{MMA} \]

High-throughput experimentation of the ATRP of MMA was carried out in a Chemspeed ASW2000 automated synthesizer to screen rapidly and to optimize the reaction conditions. Two reactor blocks were used in parallel and each block consisted of 16 reaction vessels equipped with a double jacket heater. The typical layout of the automated synthesis platform is illustrated in Fig. 1. There are several locations for the reactor blocks in the platform and most commonly one or two blocks are used in parallel in order to keep the high-throughput workflow running without any bottlenecks. The stock solution rack is equipped with an argon inlet to keep the stock solutions under inert conditions. A solid phase extraction (SPE) unit, which is equipped with alumina columns, is used to remove the metal salt from the aliquots. The samples intended for characterization are transferred into small vials.
Fig. 1 Schematic representation of the automated synthesizer and combinations of metal salts, initiators and ligands used in this study. The symbols used in this figure are as follows: dMbpy, M; dHbpy, N; dTbpy, T; CuBr, CB; CuCl, CC; CuSCN, CS; FeBr₂, FB; FeCl₂, FC; CuBr + ligand + TsCl (ligand = 4,5'-dMbpy, 1; 5,5'-dMbpy, 2; 4Mbpy, 3; and 6Mbpy, 4), and CuCl + ligand + TsCl (ligand = 4,5'-dMbpy, 5; 5,5'-dMbpy, 6; 4Mbpy, 7; and 6Mbpy, 8). (Reprinted with permission from [34]. Copyright (2004) John Wiley & Sons, Inc.)

arranged in racks and the racks are transferred to the autosampler of the analytical instruments, such as gas chromatography (GC) or gas chromatography coupled with mass spectrometry (GC–MS), or size exclusion chromatography (SEC). In addition, there is an injection port for online SEC measurements. The technical details and further explanation on this system can be found in several reviews [35–40]. It should be noted that the computer-based planning and robotic performing of the reactions as well as the utilization of fast characterization techniques significantly decreased the research time for the designed library from several months to two weeks. The experimental results obtained could be compared and used for elucidation of structure-property relationships of monomer, initiator, and catalytic systems since all the reactions were carried under the same conditions.

Three main parameters were used to evaluate the efficiency of the polymerization, namely monomer conversion ($C_{\text{MMA}}$), initiation efficiency of the reaction ($f = M_{n,\text{theo}}/M_{n,\text{SEC}}$), and polydispersity index (PDI). These results are depicted in Fig. 2. It is obvious that the Cu(I)-catalyzed systems are more effective than the Fe(II)-catalyzed systems under the studied conditions. It was concluded that a bipyridine based ligand with a critical length of the substituted alkyl group (e.g., dHbpy) shows the best performance in Cu(I)-mediated systems. Besides, Cu(I) halide-mediated ATRP with 4,5'-Mbpy as the ligand and TsCl as the initiator was better controlled than that with dMbpy as the ligand, and polymers with much lower PDI values were obtained in the former case.

Another challenge in ATRP is to remove the catalyst prior to the analysis of the polymers. In the case of automated sample withdrawing, this leads to the necessity of an automated purification system. For this purpose, an SPE unit was utilized
Fig. 2  Effects of metal salts, ligands, and initiators on $C_{\text{MMA}}$ (a), $f$ (b), PDIs (c) of the polymers in the atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA) in $p$-xylene at 90°C. $[\text{MMA}]_0:[\text{initiator}]_0:[\text{metal salt}]_0:[\text{ligand}]_0 = 150:1:1:2$, MMA/$p$-xylene = 1:2 v/v. EBIB, MBP, BEB, and TsCl were used as initiator from right to left in each ligand column, respectively (Reprinted with permission from [34]. Copyright (2004) John Wiley & Sons, Inc.)

to purify the aliquots [41, 42]. Different column materials were investigated and deactivated aluminum oxide gave the best results. As shown in Fig. 3, the absorption band of the sample decreased significantly after the purification.

Fig. 3  UV-vis spectra of unpurified (solid line) and purified (dashed line) polymers in acetonitrile at same concentrations. (Reprinted with permission from [42]. Copyright (2003) John Wiley & Sons, Inc.)
2.1.2 Nitroxide Mediated Polymerization

Nitroxide mediated polymerization is one of the most environmentally friendly CRP techniques and has a relatively simple polymerization mechanism since there is no need for a catalyst [3]. Solomon, Rizzardo and Moad have demonstrated the reaction between 2,2,6,6-tetramethyl-1-piperidinyloxy stable radical (TEMPO) and vinyl monomers in the range of the free radical polymerization temperature (40–60°C) [43]. Since then, two different NMP concepts have been developed, namely the bimolecular and the unimolecular process, respectively. Georges et al. described the bimolecular process for the preparation of low PDI value polystyrene initiated by benzoylperoxide and mediated by TEMPO [44]. Following that, unimolecular initiators have been developed that have the similar concept of well-defined initiators in living anionic and cationic processes [45, 46]. In unimolecular polymerizations, the initiator and the mediator are combined in a single molecule (e.g., alkoxyamines) that also simplifies the polymerization kinetics. The investigation on stable free nitroxide compounds were started with TEMPO and extended to several different types of nitroxide-containing compounds [3], such as phosphonate derivatives [47] or arenes [48]. The use of alkoxyamines allows the greatest degree of control over the final polymeric structure with well-defined functional end groups. A schematic representation of the NMP of St initiated by \(N-(2\text{-methylpropyl})-N-(1\text{-diethylphosphono-}2,2\text{-dimethylpropyl})-O-(2\text{-carboxylprop-2-yl})\text{hydroxylamine (Bloc Builder}\text{TM})\) is illustrated in Scheme 3. Bloc Builder\text{TM} is an efficient alkoxyamine for styrenics as well as acrylates and currently commercially available from Arkema.

A systematic investigation has been performed on the homopolymerization of St and tert-butyl acrylate (tBA) in an automated parallel synthesizer [49]. The Chemspeed Accelerator SLT106\text{TM} was used in order to screen the effect of the polymerization temperature by the use of an individually heated reactor block. These blocks allow conducting up to 16 parallel reactions each at different temperatures, heated by electrical heating and controlled by an individual heat sensor in every reactor. The determination of the optimum polymerization temperature for a specific nitroxide compound plays a crucial role in the control of the polymer chain growth. Relatively high temperatures will cause an increase in the apparent radical concentration which will lead to increased side reactions such as termination by coupling or disproportionation. An example of this behavior is visible in Fig. 4. The apparent polymerization rates were increased by higher temperatures. Higher monomer conversions were obtained at shorter reaction periods; however, the PDI values of the polymers were increased above 1.4. The optimum polymerization temperature range using this type of alkoxyamine (Bloc Builder\text{TM}) was reported to be in the range of 110–125°C.

The most critical point of all CRP techniques is to gain absolute control over the activation and deactivation of the reactive chain end. This can be simply controlled by altering the polymerization temperature or increasing the deactivator concentration. Thus, additional stable free-nitroxide compounds can be added to the
Scheme 3 Schematic representation of the nitroxide mediated polymerization (NMP) of styrene (St)

Fig. 4 Semilogarithmic kinetic plot for the NMP of styrene (St) initiated by Bloc Builder™ (left), $M_n$ and PDI values vs conversion plot at different polymerization temperatures (right). (Reprinted with permission from [49]. Copyright (2006) John Wiley & Sons, Inc.)

polymerization medium besides the alkoxyamine initiator. This effect has been investigated in detail for different types of monomers as shown in Scheme 4 [50].

Based on the optimization reactions described, the polymerization temperature was kept constant at 110°C for the NMP of $N,N$-dimethyl acrylamide (DMA), $N$-acryloyl morpholine (Amor), and 2-hydroxypropyl acrylate (HPA). However, it
was necessary to add an excess of free nitroxide to obtain better control over the polydispersity of the polymers. On the other hand, the excess of free nitroxide dramatically decreased the apparent polymerization rate. Parallel optimization reactions were conducted for the monomers depicted in Scheme 4 in order to identify the right balance between the polymerization rate and sufficient control over the polydispersity. Some representative results from that report are illustrated in Fig. 5. All the reactions were performed in N,N-dimethyl formamide (DMF) as solvent, at a polymerization temperature of 110°C, a monomer concentration of 2 M, and a monomer to initiator ratio of 100:1. The free nitroxide (SG-1) ratio was varied from 0 up to 20% with respect to the amount of initiator (Bloc Builder™). Apparently, the polymerization rate of Amor was decreased by increasing amounts of SG-1, as shown in Fig. 5a. However, the lowest PDI values were obtained with the highest amount of SG-1 (20%) (Fig. 5b). Similar trends of the molar masses and the PDI values were observed for the polymerization of DMA and HPA. According to the kinetic results, the apparent rates of Amor, DMA, and HPA were found to be $16.0 \times 10^{-4} \text{L mol}^{-1} \text{s}^{-1}$, $7.7 \times 10^{-4} \text{L mol}^{-1} \text{s}^{-1}$, and $4.3 \times 10^{-4} \text{L mol}^{-1} \text{s}^{-1}$, respectively. In the case of copolymerization of these monomers, there will be different distributions of monomers throughout the polymeric chain depending on their reactivity. The optimization of key parameters and the determination of the polymerization rate constants provide critical knowledge on the construction of polymer libraries.

2.1.3 Reversible Addition Fragmentation Chain Transfer

The first well established RAFT polymerization using thio carbonylthio compounds was reported by CSIRO in 1998 [51]. Subsequently, another group reported a similar mechanism using xanthate RAFT agent; they named this technique macromolecular
Fig. 5  Semilogarithmic kinetic plot of Amor (top left), molar mass and PDI value vs conversion plots for Amor (top right), N,N-dimethyl acrylamide (DMA) (bottom left), and 2-hydroxypropyl acrylate (HPA) (bottom right). (Reprinted with permission from [50]. Copyright (2008) American Chemical Society)

design via the interchange of xanthates (MADIX) [52, 53]. RAFT polymerization has several advantages over other CRP techniques. The most significant advantage is the compatibility of the technique with a wide range of monomers, such as St, acrylates, methacrylates, and derivatives. This large number of monomers provides the opportunity of creating well-defined polymer libraries by the combination of different monomeric units. The mechanism of the RAFT polymerization comprises a sequence of addition-fragmentation processes as shown in Scheme 5.

The initiation and radical–radical termination reactions occur as in conventional free radical polymerization. This is followed by the addition of the propagating species (A) to the chain transfer agent (CTA), which leads to the formation of an intermediate species (B). Therefore, a new radical (D) can be released to form new propagating chains (E). In step IV, rapid equilibrium between active propagating radicals and the corresponding dormant species provides equal probability for all chains to grow and allows for the production of polymers with low PDI values. Termination reactions occur via combination or disproportionation (step V) to some extent, but can be largely eliminated by maintaining appropriate conditions that control the apparent radical concentration.
Some of the most important critical points in RAFT polymerizations are the relative concentrations of the free radical initiator, the CTA, and the monomer, since these will establish the delicate balance between the dormant and active species. Acrylate and methacrylate derivatives can be successfully polymerized using 2-cyano-2-butyl dithio benzoate (CBDB) as a CTA. However, the amount of free radical initiator (α, α-azobisisobutyronitrile (AIBN) is used in general) compared to CTA determines the rate of control over the polymerization. Therefore, eight different acrylates or methacrylates were polymerized with different ratios of CTA to AIBN [54]. The structures of the monomers and the design of the experiment are shown in Fig. 6.

A reactor block consisting of 16 reactors was divided into 4 zones with 4 different CTA to initiator ratios, and 4 different acrylates or methacrylates were used in each set of experiments. The polymerization of tert-butyl methacrylate was repeated four times to demonstrate the reproducibility of the polymerization in an automated parallel synthesizer. Structural analysis of the polymers revealed that there was less than 10% deviation in the number average molar mass ($M_n$) and the PDI values.

The polymerization of four different acrylates at four different CTA to initiator ratios are shown in Fig. 7, as a representative example. The increased ratio of CTA to AIBN resulted in improved PDI values; however, there is a decrease
observed in the $M_n$ of the polymers. All polymerizations were conducted at 70°C for 10 h. Due to the different initiator concentrations, the rate of polymerization differs and a significant decrease occurs in the molar mass for a certain reaction time. Nevertheless, this systematic study not only proved the reproducibility of the RAFT polymerization of several (meth)acrylates but also provided the optimum ratio of CTA to initiator to be used in further reactions.
2.2 Ionic Polymerization Techniques

2.2.1 Anionic Polymerization

Anionic polymerization represents a powerful technique for synthesizing polymers with low PDI values, thus providing good control over the chain length. This method leads to less side reactions than radical polymerizations. For instance, unlike in radical polymerization, there is no termination by the combination of two active chains. However, the mechanism is more sensitive to impurities and functional groups, and therefore applicable for only a limited class of monomers.

It still represents a great challenge to conduct anionic polymerizations in an automated parallel synthesizer. Above all, the technique requires an intensive purification of the reagents and the polymerization medium in order to obtain well-defined polymers. Therefore, a special procedure has been described for the inertization of the reactors [55]. It is called “chemical cleaning,” which is essentially rinsing all the reactors with sec-butyllithium (s-BuLi) prior to the reaction in order to eliminate all chemical impurities. This process can be performed in an automated manner. Due to the extreme sensitivity of the polymerization technique to oxygen, moisture, and impurities, detailed investigations on the inertization procedure and the reproducibility of the experiments need to be conducted.

The inertization procedure applied for the Chemspeed ASW2000 robot was started with flushing the hood with argon overnight while the reactors were heated up to 140°C and were exposed to six cycles of vacuum (25 min)-argon (5 min) to eliminate oxygen and moisture completely. Afterwards, s-BuLi in cyclohexane was added to all reactors and vortexed for 1.5 h at room temperature and 30 min at 50°C with fresh cyclohexane solutions. As a final step, the washing solution was aspirated from all the reactors and one more vacuum–argon cycle was applied to finalize the inertization of the automated parallel synthesizer for the anionic polymerization.

The reproducibility of the reaction was examined by performing the parallel anionic polymerization of St. The polymerizations were performed in cyclohexane and initiated by s-BuLi. The obtained polymers were analyzed by SEC and the difference between the results was less than 3%. This corresponds to less than 5% deviation after calculating the real concentration of the initiator in the reactors by a double titration method [56].

Once the robotic system and procedure passed the optimization and reproducibility tests for a certain type of reaction, the researcher has the chance to move on to the most delightful part of a high-throughput experimentation workflow that is to follow the reaction kinetics of the reaction by withdrawing several samples under comparable conditions. The characterization of these samples allows the determination of the apparent rate constants and activation energies in a very reproducible way. As an example, the anionic polymerization of St in cyclohexane initiated by s-BuLi under different reaction conditions was investigated. Several samples were withdrawn during the reaction into small vials which were prefilled with 25 μL of...
Fig. 8  Semilogarithmic kinetic plot of the anionic polymerization of St (left) and molar mass and PDI values vs conversion plot (right). (Reprinted with permission from [55]. Copyright (2005) John Wiley & Sons, Inc.)

Table 1  Values of the activation energy reported in the literature for the propagation reaction of the anionic polymerization of styrene (St) in different solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Activation energy (kJ mol(^{-1}))</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylbenzene</td>
<td>75</td>
<td>[57]</td>
</tr>
<tr>
<td>Benzene</td>
<td>59.9</td>
<td>[58]</td>
</tr>
<tr>
<td>Toluene</td>
<td>64.8</td>
<td>[59]</td>
</tr>
<tr>
<td>Toluene</td>
<td>59.9</td>
<td>[60]</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>63 ± 2</td>
<td>[55]</td>
</tr>
</tbody>
</table>

methanol to quench the polymerization. The monomer conversion and molar masses of each sample were determined by GC and SEC measurements. Figure 8 illustrates a representative example of the results obtained from these reactions.

Based on these results, the activation energy of the anionic polymerization of St in cyclohexane was determined as 63 ± 2 kJ mol\(^{-1}\) [55]. The results obtained were comparable to the literature results obtained with other solvents and are summarized in Table 1.

2.2.2  Cationic Ring Opening Polymerization

The living cationic ring opening polymerization (CROP) of 2-oxazolines was first reported in the 1960s [61, 62]. The polymerization can be initiated by an electrophile such as benzyl halides, acetyl halides, and tosylate or triflate derivatives. The typical polymerization mechanism for 2-alkyl-2-oxazoline initiated by methyl tosylate is shown in Scheme 6.

The alkyl group attached at the 2 position of the 2-oxazoline provides extraordinary possibilities for variations in the monomer structure and the proper-
Scheme 6 Schematic representation of the CROP of 2-ethyl-2-oxazoline (EtOx) initiated by the methyl tosylate

ties. This monomer family is a good candidate for high-throughput experimentation and allows creating different copolymer libraries by a combination of 2-oxazolines with different side groups. However, the typical required polymerization times for this type of monomers were previously in the range of 10–20 h. Nevertheless, the reaction time for 2-ethyl-2-oxazoline (EtOx) in acetonitrile could be reduced from 6 h under standard conditions (oil bath heating, reflux at 82 °C) to less than 1 min (at 200 °C) under microwave irradiation. Thus, a high-throughput experimentation workflow could be applied for CROP of 2-oxazolines. Several reaction parameters, such as temperature, pressure, and solvent were investigated under microwave irradiation and using automated parallel synthesizers [63–67].

The living CROP of 2-methyl, 2-ethyl, 2-nonyl, and 2-phenyl-2-oxazolines (PheOx) were investigated at different temperatures in the range 80–200 °C using a single mode microwave synthesizer [68]. The reaction rates were enhanced by a factor of up to 400. The livingness of the polymerization over the whole range of polymerization temperatures was examined by following the first-order kinetics of the monomer consumption. The semilogarithmic kinetic plots for 2-methyl-2-oxazoline (MeOx), EtOx, 2-nonyl-2-oxazoline (NonOx), and PhOx are shown in Fig. 9. All reactions show a linear increase which is an indication of a living polymerization. Besides, each sample was characterized by SEC, and a linear increase in their $M_n$ was observed.

The apparent rate constants for CROP of each monomer at each investigated temperature were calculated and the corresponding activation energy plots were obtained. These plots are shown in Fig. 10 and they exhibit good agreement between theoretical and experimental data. It was concluded that a temperature of 140 °C represents the optimum polymerization temperature since it leads to almost perfect agreement with the theoretical values [69].

There are numerous reports available on the optimization of reaction conditions of 2-oxazolines. For instance, the effect of solvent, temperature, pressure, monomer to initiator ratio, and many other critical parameters have been investigated to obtain the optimum conditions [64–68]. Besides these parameters, the initiator structure has also a great effect on the polymerization. The investigation on different initiator structures provided the necessary kinetic parameters for the use of functional initiators [69]. Heterofunctional initiators have been used in polymer science for the combination of different types of monomers that can be polymerized with different polymerization techniques, such as ATRP and CROP [70–72].
For instance, the CROP of EtOx using four different acetyl halide type of initiators showed that the rate of polymerization increases with the decreased basicity of the counter ion: acetyl iodide < acetyl bromide < acetyl chloride. The apparent rates of polymerization of EtOx with different initiators are listed in Table 2.

### 3 Synthesis of Well-Defined Copolymer Libraries

#### 3.1 Preparation via Controlled Radical Polymerization Techniques

Free radical polymerization remains the most versatile technique due to its compatibility with a wide range of monomers, its compatibility with protic and aqueous media, and experimentally less demanding conditions. Development of
Table 2  Polymerization rates (in $10^{-3}$ L mol$^{-1}$ s$^{-1}$) of CROP of EtOx with different initiators at various temperatures – acetyl chloride (AcCl), acetyl bromide (AcBr), acetyl iodide (AcI), and 2-bromo-2-methylpropanoyl bromide (BrEBiB)

<table>
<thead>
<tr>
<th>Initiator</th>
<th>80°C</th>
<th>90°C</th>
<th>100°C</th>
<th>120°C</th>
<th>140°C</th>
<th>160°C</th>
<th>180°C</th>
<th>200°C</th>
<th>220°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcCl</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11.4</td>
<td>47.4</td>
<td>111.3</td>
<td>342</td>
<td>–</td>
</tr>
<tr>
<td>AcBr</td>
<td>–</td>
<td>–</td>
<td>7.8 ± 0.1</td>
<td>15 ± 1</td>
<td>54 ± 4</td>
<td>149 ± 1</td>
<td>342 ± 18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AcI</td>
<td>3.5 ± 0.3</td>
<td>7.7 ± 0.3</td>
<td>14.3 ± 0.1</td>
<td>42 ± 1</td>
<td>150 ± 9</td>
<td>351 ± 1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BrEBiB</td>
<td>–</td>
<td>–</td>
<td>7.9</td>
<td>24.9</td>
<td>44.6</td>
<td>202</td>
<td>351</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

controlled/“living” radical polymerization techniques combined the advantages of “living” polymerizations and free radical polymerizations. Thus, tailor-made macromolecules could be synthesized from a variety of monomeric units bearing different functional side groups. These special side groups bring an additional property to the polymeric material and influence the whole material properties such as solubility, mechanical properties, thermal properties as well as optical properties.

The combination of different monomeric units at various ratios generates totally new materials, in most cases with the expected properties and rarely with unexpected, superior properties. Therefore, the investigation of series of polymers in parallel has a great importance not only to elucidate structure-property relationships but also to be able to realize “magic” compositions.
3.1.1 Random Copolymer Libraries

Copolymers containing oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and methacrylic acid (MAA) were synthesized via RAFT polymerization in an automated synthesizer [73]. OEGMA containing polymers exhibit a phase transition behavior upon changes in temperature. This thermo-responsive behavior is based on the formation or breakage of hydrogen bonds between OEGMA units and water molecules at a critical temperature which is also known as lower critical solution temperature (LCST). Polymers with LCST behavior show a sudden and reversible change from hydrophilic to hydrophobic behavior that makes them attractive for usage as “smart” switchable materials in applications ranging from, e.g., drug delivery systems, soft actuators or valves, coatings to textile materials.

Thermoresponsive polymers have in common hydrogen donor or acceptor groups mostly present on their side chains. The most well-known and investigated structures can be listed as N-isopropyl acrylamide (NIPAM), N,N-dimethyl aminoethyl acrylamide (DMAEMA), 2-isopropyl-2-oxazoline (iPrOx), and oligo(ethylene glycol) methacrylates [74]. Monomers composed of relatively short poly(ethylene glycol) (PEG) chains and radically polymerizable methacrylate moieties represent versatile building blocks for thermoresponsive materials. Some of the OEGMA based on monomers, i.e., 2-methoxyethyl 2-methylacrylate (MeOMA), Me2OMA, OEGEMA246, OEGMA475, and OEGMA1100, are commercially available and their chemical structures are schematically depicted in Scheme 7.

The monomers in Scheme 7 show increased hydrophilicity with increased side chain length, and thereby the cloud points are expected to be higher. A wide range of LCST values could be achieved by combining OEGMA monomers having short and

Scheme 7  Schematic representation of the chemical structures of monomers which may exhibit thermo-responsive behavior
Fig. 11 Plots of the measured lower critical solution temperature (LCST) as a function of the theoretical average number of OEGMA\textsubscript{475} units per chain for a series of P(MeO\textsubscript{2}MA-co-OEGMA\textsubscript{475}) copolymers of various composition. Hydrophobic and hydrophilic molecular regions on the copolymer are indicated in red and blue, respectively. (Reprinted with permission from [76]. Copyright (2008) John Wiley & Sons, Inc.)

long PEG side chains. Lutz et al. have investigated a series of these combinations to determine the right balance between hydrophilicity and hydrophobicity [75]. As shown in Fig. 11, the combination of OEGMA\textsubscript{475} and 2-(2-methoxyethoxy)ethyl 2-methylacrylate (MeO\textsubscript{2}MA) building blocks at various ratios results in thermoresponsive polymers with cloud points in the range 27–60°C [76].

Further detailed studies on the LCST properties of OEGMA based polymers have been conducted by Schubert et al. Several homopolymer and copolymer libraries of the monomers listed in Scheme 7 have been synthesized in an automated parallel synthesizer using the RAFT polymerization process [74]. Homopolymers with different chain lengths were prepared to understand the effect of the chain length on the LCST behavior of this class of monomers. As expected, polymers containing longer PEG chains as side groups revealed relatively higher cloud point temperatures than the others. For instance, cloud points for P(MeO\textsubscript{2}MA), P(OEGMA\textsubscript{246}), and P(OEGMA\textsubscript{475}) were found to be 21.8, 21.6, and 89.8°C, respectively. All the polymers were prepared with a 100 to 1 monomer to initiator ratio and their corresponding cloud points were measured in a buffer solution of pH 7. As the number of hydrogen bond forming functionalities increases in the macromolecule, the energy required to break these bonds also increases. Therefore, homopolymers with longer PEG side chains required higher temperatures in order to break the hydrogen bonds and, as a result, precipitate in the solution. However, homopolymers of P(MAA) and P(OEGMA\textsubscript{1100}) with up to 100 repeating units did not show LCST behavior due to their highly hydrophilic structures.

Copolymers of MAA and OEGMA were prepared via RAFT polymerization in ethanol. A systematic parallel synthesis was performed to obtain copolymers containing different ratios of two monomers. Therefore, a complete screening in composition of P(MAA)-\textsubscript{r}-(OEGMA)\textsubscript{n} copolymers was elaborated from 0% OEGMA\textsubscript{n} to 100% OEGMA\textsubscript{n}. As representative examples, the $M_n$ and PDI values of two libraries, namely P(MAA)-\textsubscript{r}-(OEGMA\textsubscript{475}) and P(MAA)-\textsubscript{r}-(OEGMA\textsubscript{1100}),
are depicted in Fig. 12. The $M_n$,GPC values of the copolymers increased linearly with increasing OEGMA$_n$ content whereas the PDI values remained below 1.3.

Depending on the length of the side chain of the OEGMA$_n$ monomers, their corresponding reactivity ratios are expected to be different. This may result in slight differences in the copolymer composition. Therefore, it is necessary to quantify the amount of each repeating unit in the copolymer. Based on $^1$H NMR spectroscopy measurements the content of MAA and OEGMA$_n$ could be determined. Thus, the amount of OEGMA$_n$ repeating units in P(MAA)-$r$-(OEGMA)$_n$ copolymers were found to be slightly higher than the theoretical values, as depicted in Fig. 13.

The LCST properties of P(MAA)-$r$-(OEGMA$_{475}$) and P(MAA)-$r$-(OEGMA$_{1100}$) libraries were determined in buffer solutions with different pH values. As illustrated in Fig. 14, the copolymer library of P(MAA)-$r$-(OEGMA$_{475}$) revealed cloud points from 25 to 90°C at pH values of 2 and 4, respectively. It was mentioned

Fig. 12  $M_n$ and PDI values data of copolymers synthesized with different comonomer feed ratios. (Reprinted with permission from [73]. Copyright (2008) John Wiley & Sons, Inc.)

Fig. 13  Theoretical composition vs calculated composition. (Reprinted with permission from [73]. Copyright (2008) John Wiley & Sons, Inc.)
previously that homopolymers of P(MAA) and P(OEGMA)_{1100} did not show any LCST due to their highly hydrophilic structures. However, the copolymers of these two monomers do exhibit cloud points at certain comonomer compositions. Besides, these polymers were found to be double-responsive to both temperature and pH values. For instance, the copolymer P(MAA)_{0.9}-r-(OEGMA)_{1100} \text{_{0.1}} is soluble at pH 4 whereas it is not soluble at pH 2 in water at 37°C. The determination of these “magic” compositions is easily feasible by screening large libraries of polymers for the best performance.

The phase transition is directly related to the hydrophilic/hydrophobic balance in a copolymer and controlling the polymer composition provides a highly effective way of tuning the LCST. Another example of responsive polymer libraries was based on the combination of 2-hydroxypropylacrylate and DMA or N-acryloyl morpholine [50]. The nitroxide mediated copolymerization conditions were chosen on the basis of the kinetic investigation of the homopolymerizations, as discussed in this chapter (see, e.g., Sect. 2.1.2).

The copolymers obtained for the P(Amor)-stat-(HPA) library (Scheme 8) revealed relatively low PDI values in the range from 1.16 to 1.32 and increasing M_{n,GPC} values with increasing HPA content, as listed in Table 3. The observed copolymerization rates for both monomers decreased with increasing HPA content due to the slower HPA-SG1 dissociation and association kinetics. The copolymer compositions were calculated from the monomer conversions obtained by GC as well as from $^1$H NMR spectroscopy of the precipitated polymers.

The thermal transition behavior within the P(Amor)-stat-(HPA) copolymer library was investigated using differential scanning calorimetry (DSC). For all members of this library, single glass transition temperatures ($T_g$) were obtained, which is an indication of a good mixing of the two different monomers. The homopolymer
Table 3  Copolymerization results of the p(Amor-stat-HPA) library

<table>
<thead>
<tr>
<th>Name</th>
<th>Conversionb (%)</th>
<th>Mn c (g mol⁻¹)</th>
<th>PDI d</th>
<th>Composition GCb (mol%)</th>
<th>Composition NMRd (mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A100</td>
<td>70/0 e</td>
<td>6,900</td>
<td>1.32</td>
<td>100/0</td>
<td>100/0</td>
</tr>
<tr>
<td>A90H10</td>
<td>63/69</td>
<td>7,700</td>
<td>1.27</td>
<td>89/11</td>
<td>90/10</td>
</tr>
<tr>
<td>A80H20</td>
<td>48/51</td>
<td>7,200</td>
<td>1.22</td>
<td>79/21</td>
<td>78/22</td>
</tr>
<tr>
<td>A70H30</td>
<td>56/53</td>
<td>8,300</td>
<td>1.26</td>
<td>71/29</td>
<td>68/32</td>
</tr>
<tr>
<td>A60H40</td>
<td>45/38</td>
<td>8,100</td>
<td>1.21</td>
<td>64/36</td>
<td>58/42</td>
</tr>
<tr>
<td>A50H50</td>
<td>45/42</td>
<td>8,500</td>
<td>1.23</td>
<td>52/48</td>
<td>47/53</td>
</tr>
<tr>
<td>A40H60</td>
<td>37/28</td>
<td>8,300</td>
<td>1.20</td>
<td>47/53</td>
<td>38/62</td>
</tr>
<tr>
<td>A30H70</td>
<td>37/31</td>
<td>8,800</td>
<td>1.20</td>
<td>34/66</td>
<td>29/72</td>
</tr>
<tr>
<td>A20H80</td>
<td>34/28</td>
<td>8,400</td>
<td>1.20</td>
<td>23/77</td>
<td>18/82</td>
</tr>
<tr>
<td>A10H90</td>
<td>28/20</td>
<td>8,100</td>
<td>1.16</td>
<td>13/87</td>
<td>7/93</td>
</tr>
<tr>
<td>H100</td>
<td>0/22</td>
<td>8,200</td>
<td>1.16</td>
<td>0/100</td>
<td>0/100</td>
</tr>
</tbody>
</table>

a Names indicate the monomer feed: A50H50 = p(Amor50-stat-HPA50)
b Calculated by GC using monomer/DMF ratios
c Of precipitated polymer, determined by GPC in DMAc using p(MMA) calibration
d H NMR spectra were recorded in CDCl₃
e Conversion calculated by ¹H NMR spectroscopy

of P(Amor) exhibits a Tg of 146.5°C whereas it was found as 21.7°C for P(HPA). Their copolymers exhibited Tg values in between these temperatures, as listed in Table 4. The cloud points were determined by turbidimetry measurements in a parallel turbidimetry instrument (Crystal16, Avantium Technologies). This instrument measures the turbidity from the transmission of red light through the sample vial as a function of temperature. One of the alternative techniques to measure turbidity is UV-Vis spectroscopy which requires at least 1 h per sample and per cycle. However, the Crystal16 turbidimeter is capable of measuring 16 samples in parallel and repeating as many cycles as programmed. Thus, the turbidimetry property of the samples could be determined in an accelerated manner. As can be seen in Table 4, the cloud points of the P(Amor)-stat-(HPA) copolymers could be tuned from 20 to 90°C by varying the comonomer composition.
Table 4 Thermal and lower critical solution temperature (LCST) properties for the copolymers of the p(Amor-stat-HPA) library

<table>
<thead>
<tr>
<th>Name</th>
<th>Amor/HPA (wt%)</th>
<th>T_g(C)</th>
<th>Cloud point (^{c}) 0.5 wt% (°C)</th>
<th>Cloud point (^{c}) 1.0 wt% (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A100</td>
<td>100/0</td>
<td>146.5</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>A90H10</td>
<td>90/10</td>
<td>130.6</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>A80H20</td>
<td>80/20</td>
<td>106.4</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>A70H30</td>
<td>69/31</td>
<td>95.8</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>A60H40</td>
<td>60/40</td>
<td>84.0</td>
<td>Soluble</td>
<td>88.0</td>
</tr>
<tr>
<td>A50H50</td>
<td>49/51</td>
<td>75.2</td>
<td>79.5</td>
<td>65.9</td>
</tr>
<tr>
<td>A40H60</td>
<td>40/60</td>
<td>61.4</td>
<td>62.7</td>
<td>53.0</td>
</tr>
<tr>
<td>A30H70</td>
<td>30/70</td>
<td>51.8</td>
<td>49.2</td>
<td>38.3</td>
</tr>
<tr>
<td>A20H80</td>
<td>19/82</td>
<td>41.7</td>
<td>41.5</td>
<td>30.9</td>
</tr>
<tr>
<td>A10H90</td>
<td>8/82</td>
<td>31.3</td>
<td>33.9</td>
<td>25.3</td>
</tr>
<tr>
<td>H100d</td>
<td>0/100</td>
<td>21.7</td>
<td>26.7</td>
<td>21.4(^{d})</td>
</tr>
</tbody>
</table>

\(^{a}\) Calculated from \(^{1}\)H NMR spectroscopy  
\(^{b}\) Mid-temperature  
\(^{c}\) 50% transmittance point in first heating curve  
\(^{d}\) p(HPA) synthesized with 15 h reaction time

Scheme 9 Schematic representation of the synthesis of statistical copolymers of 2-hydroxypropyl acrylate (mixture of isomers) and DMA

The copolymers obtained for the P(DMA)-stat-(HPA) (Scheme 9) library revealed relatively low PDI values below 1.3 and increasing M_n,GPC values with increasing HPA content, as listed in Table 5. It should be noted that a poly(methyl methacrylate) (PMMA) calibration was used for the calculation of the M_n,GPC values and this causes an overestimation for HPA containing polymers. The copolymer compositions were calculated from the \(^{1}\)H NMR spectra; however, this method was not suitable for reliable conversion determination since the DMA-CH\(_3\) groups overlap in the \(^{1}\)H NMR spectra not only with the HPA-OH group but also with broad backbone signals, which obstruct any reliable integration. Therefore, elemental analysis was used as an alternative method for the calculation of the molecular composition of the copolymers.

Similarly, the thermal transition behavior of the members of the P(DMA)-stat-(HPA) copolymer library was investigated using DSC. For all members of this library, single T_g were obtained, which is an indication of a good mixing of the two
Table 5  Copolymerization results of the p(DMA-stat-HPA) library

<table>
<thead>
<tr>
<th>Name</th>
<th>Conversionb (%)</th>
<th>Mn(^c) (g mol(^{-1}))</th>
<th>PDI(^c)</th>
<th>Composition NMRd (mol%)</th>
<th>Composition EA (mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D100</td>
<td>53/0</td>
<td>4,500</td>
<td>1.23</td>
<td>100/0</td>
<td>100/0</td>
</tr>
<tr>
<td>D90H10</td>
<td>60/93</td>
<td>6,800</td>
<td>1.20</td>
<td>85/15</td>
<td>88/12</td>
</tr>
<tr>
<td>D80H20</td>
<td>46/36</td>
<td>6,500</td>
<td>1.23</td>
<td>75/25</td>
<td>78/22</td>
</tr>
<tr>
<td>D70H30</td>
<td>67/73</td>
<td>8,400</td>
<td>1.27</td>
<td>69/31</td>
<td>68/32</td>
</tr>
<tr>
<td>D60H40</td>
<td>57/56</td>
<td>8,500</td>
<td>1.24</td>
<td>53/48</td>
<td>59/41</td>
</tr>
<tr>
<td>D50H50</td>
<td>66/53</td>
<td>9,800</td>
<td>1.27</td>
<td>46/54</td>
<td>50/50</td>
</tr>
<tr>
<td>D40H60</td>
<td>58/53</td>
<td>9,600</td>
<td>1.26</td>
<td>33/67</td>
<td>41/59</td>
</tr>
<tr>
<td>D30H70</td>
<td>82/29</td>
<td>10,900</td>
<td>1.24</td>
<td>28/72</td>
<td>32/68</td>
</tr>
<tr>
<td>D20H80</td>
<td>57/44</td>
<td>10,700</td>
<td>1.22</td>
<td>18/82</td>
<td>22/78</td>
</tr>
<tr>
<td>D10H90</td>
<td>71/48</td>
<td>10,500</td>
<td>1.20</td>
<td>9/91</td>
<td>12/88</td>
</tr>
<tr>
<td>H100</td>
<td>0/33</td>
<td>11,100</td>
<td>1.21</td>
<td>0/100</td>
<td>0/100</td>
</tr>
</tbody>
</table>

\(^a\) Names indicate monomer feed: D50H50 = p(DMA\(_{50}\)-stat-HPA\(_{50}\))

\(^b\) Calculated by GC using monomer/DMF ratios

\(^c\) Determined by GPC in DMAc using p(MMA) calibration

\(^d\) \(^1\)H NMR spectra recorded in CDCl\(_3\)

different monomer structures. The homopolymer of P(DMA) has a T\(_g\) of 111.4\(^\circ\)C whereas a T\(_g\) of 21.7\(^\circ\)C was measured for P(HPA). Besides, their copolymers exhibited T\(_g\) values in between these temperatures, as listed in Table 6. The T\(_g\) of P(DMA)-stat-(HPA) copolymers show a positive deviation from the Fox equation, which is an indication of the presence of some weak hydrogen bonding of the hydroxyl group of HPA with the amide group of DMA. The cloud points were

Table 6  Thermal and LCST properties for the copolymers of the p(DMA-stat-HPA) library

<table>
<thead>
<tr>
<th>Name</th>
<th>Compositiona (DMA/HPA (wt%))</th>
<th>T(_g)^b (°C)</th>
<th>Cloud pointc 0.5 wt% (°C)</th>
<th>Cloud pointc 1.0 wt% (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D100</td>
<td>100/0</td>
<td>111.4</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>D90H10</td>
<td>85/15</td>
<td>97.6</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>D80H20</td>
<td>73/27</td>
<td>87.7</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>D70H30</td>
<td>62/38</td>
<td>79.7</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>D60H40</td>
<td>52/48</td>
<td>63.4</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>D50H50</td>
<td>43/57</td>
<td>58.8</td>
<td>Soluble</td>
<td>82.9</td>
</tr>
<tr>
<td>D40H60</td>
<td>34/66</td>
<td>51.6</td>
<td>71.6</td>
<td>62.3</td>
</tr>
<tr>
<td>D30H70</td>
<td>26/74</td>
<td>44.6</td>
<td>55.8</td>
<td>48.7</td>
</tr>
<tr>
<td>D20H80</td>
<td>18/82</td>
<td>36.0</td>
<td>46.7</td>
<td>38.6</td>
</tr>
<tr>
<td>D10H90</td>
<td>10/90</td>
<td>30.5</td>
<td>35.3</td>
<td>28.5</td>
</tr>
<tr>
<td>H100</td>
<td>0/100</td>
<td>21.7</td>
<td>26.7</td>
<td>21.4</td>
</tr>
</tbody>
</table>

\(^a\) Calculated from elemental analysis

\(^b\) Mid-temperature

\(^c\) 50% transmittance point in first heating curve
determined by turbidimetry in the Crystal16. The phase transition temperature of P(DMA)-stat-(HPA) copolymers could be tuned from 20 to 90°C by varying the comonomer composition.

### 3.1.2 Block Copolymer Libraries

The synthesis of well-defined block copolymers has been a challenge for decades. Block copolymers consist of segments with different solubility typically resulting in phase separation [77, 78] and solution aggregation behavior [79-81]. The efforts to synthesize them have strongly accelerated the development of CLP techniques. Several catalysts, functional initiators, and CTAs have been investigated for different classes of monomers to synthesize well-defined block copolymers. RAFT polymerization represents one of the most versatile techniques that can be applied for a wide range of monomers not only in organic solvents but also in aqueous media.

Poly(acrylic acid) (PAA) is a water soluble polymer that has been used in various applications. Direct synthesis of well-defined PAA-containing polymers has been a challenge for CRP techniques because of the acid-containing monomer. So far, RAFT polymerization and NMP techniques could be successfully employed for unprotected acrylic acid (AA) [82, 83]. Even though it is possible to polymerize AA directly, the applied polymerization solvents had to be polar, implying that block copolymers with a variety of apolar monomers cannot be synthesized in a straightforward manner. Therefore, the protected analogues of AA, e.g., tBA [84] and benzyl acrylate [85], are often used for the polymerization and deprotected following the polymerization [86]. Du Prez et al. investigated a new route toward near-monodisperse PAA and derived block copolymer structures by the RAFT polymerization of 1-ethoxy ethyl acrylate (EEA) [87].

The temperature optimization for the RAFT polymerization of EEA revealed an optimum reaction temperature of 70°C. Block copolymers with a poly(methyl acrylate) (PMA), a poly(n-butyl acrylate) (PnBA), a PMMA, or a poly(N,N-dimethyl aminoethyl methacrylate) (PDMAEMA) first block and a poly(1-ethoxyethyl acrylate) (PEEA) second block were successfully synthesized in an automated synthesizer. The synthesis robot was employed for the preparation of 16 block copolymers consisting of 25 units of the first block composed of PMA (exp. 1–4), PnBA (exp. 5–8), PMMA (exp. 9–13), and PDMAEMA (exp. 13–16) and a second block of PEEA consisting of 25, 50, 75, or 100 units, respectively. The first blocks were polymerized for 3 h and a sample from each reaction was withdrawn for SEC analysis. Subsequently, EAA was added and the reactions were continued for 12 h. The molar masses and PDI values of the obtained block copolymers are shown in Fig. 15. The composition of the resulting block copolymers was further characterized by 1H NMR spectroscopy and the results are summarized in Table 7. The integral values of the aromatic resonances of the RAFT agent were applied to calculate the number average degree of polymerization (DP) for the monomers present in the block copolymers. Deprotection of the PEEA containing block copolymers was performed in CHCl3 by heating to 80°C for 3 h. The solutions exhibited a cloudy
Fig. 15 Number average molar masses ($M_n\text{GPC}$) and PDI values obtained for the first blocks and for the final copolymers of PMA, PnBA, PMMA, or PDMAEMA (25 units) with PEEA (25, 50, 75, and 100 units for 100% conversion). All $M_n\text{GPC}$ values are calculated against PMMA standards. SEC eluent CHCl$_3$:NEt$_3$:i-PrOH. (Reprinted with permission from [87]. Copyright (2005) American Chemical Society)

Table 7 Compositions of the synthesized copolymers as determined by $^1$H NMR spectroscopy

<table>
<thead>
<tr>
<th>Exp</th>
<th>Mon A</th>
<th>$D_P_{A,th}$</th>
<th>$D_P_{EEA,th}$</th>
<th>$f_{EEA,th}$</th>
<th>$D_P_{A,NMR}$</th>
<th>$D_P_{EEA,NMR}$</th>
<th>$f_{EEA,NMR}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MA</td>
<td>25</td>
<td>25</td>
<td>0.5</td>
<td>19</td>
<td>9</td>
<td>0.32</td>
</tr>
<tr>
<td>2</td>
<td>MA</td>
<td>25</td>
<td>50</td>
<td>0.67</td>
<td>17</td>
<td>22</td>
<td>0.56</td>
</tr>
<tr>
<td>3</td>
<td>MA</td>
<td>25</td>
<td>75</td>
<td>0.75</td>
<td>18</td>
<td>35</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>MA</td>
<td>25</td>
<td>100</td>
<td>0.8</td>
<td>20</td>
<td>52</td>
<td>0.72</td>
</tr>
<tr>
<td>5</td>
<td>n-Ba</td>
<td>25</td>
<td>25</td>
<td>0.5</td>
<td>18</td>
<td>20</td>
<td>0.53</td>
</tr>
<tr>
<td>6</td>
<td>n-Ba</td>
<td>25</td>
<td>50</td>
<td>0.67</td>
<td>18</td>
<td>44</td>
<td>0.71</td>
</tr>
<tr>
<td>7</td>
<td>n-Ba</td>
<td>25</td>
<td>75</td>
<td>0.75</td>
<td>19</td>
<td>73</td>
<td>0.79</td>
</tr>
<tr>
<td>8</td>
<td>n-Ba</td>
<td>25</td>
<td>100</td>
<td>0.8</td>
<td>22</td>
<td>87</td>
<td>0.80</td>
</tr>
<tr>
<td>9</td>
<td>MMA</td>
<td>25</td>
<td>25</td>
<td>0.5</td>
<td>23</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>10</td>
<td>MMA</td>
<td>25</td>
<td>50</td>
<td>0.67</td>
<td>23</td>
<td>12</td>
<td>0.34</td>
</tr>
<tr>
<td>11</td>
<td>MMA</td>
<td>25</td>
<td>75</td>
<td>0.75</td>
<td>23</td>
<td>20</td>
<td>0.47</td>
</tr>
<tr>
<td>12</td>
<td>MMA</td>
<td>25</td>
<td>100</td>
<td>0.8</td>
<td>23</td>
<td>32</td>
<td>0.58</td>
</tr>
<tr>
<td>13</td>
<td>DMAEMA</td>
<td>25</td>
<td>25</td>
<td>0.5</td>
<td>22</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>14</td>
<td>DMAEMA</td>
<td>25</td>
<td>50</td>
<td>0.67</td>
<td>22</td>
<td>20</td>
<td>0.48</td>
</tr>
<tr>
<td>15</td>
<td>DMAEMA</td>
<td>25</td>
<td>75</td>
<td>0.75</td>
<td>22</td>
<td>35</td>
<td>0.61</td>
</tr>
<tr>
<td>16</td>
<td>DMAEMA</td>
<td>25</td>
<td>100</td>
<td>0.8</td>
<td>22</td>
<td>51</td>
<td>0.70</td>
</tr>
</tbody>
</table>

appearance which is an indication of the PAA formation. $^1$H NMR spectroscopy revealed 85–100% deprotection for selected copolymers.

NMP is as successful as RAFT polymerization for the construction of block copolymers. A small library of block copolymers comprised of poly(styrene) (PSt) and poly(tert-butyl acrylate) (PrBA) was designed and the schematic representation of the reaction is depicted in Scheme 10 [49]. Prior to the block copolymerization, the optimization reactions for the homopolymerization of St and t-BA were performed as discussed in this chapter (e.g., see Sect. 2.1.2). Based on these results,
[Scheme 10] Schematic representation of the nitroxide mediated block copolymerization of P(St)-b-(t-BA)

Table 8 Block copolymerization of poly(styrene)-b-(tert-butyl acrylate) at different macroinitiator to monomer ratios. PSₙ(n) = degree of polymerization of the PS macroinitiator

<table>
<thead>
<tr>
<th>Run</th>
<th>PSₙ (n)</th>
<th>Initiator/t-BA</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Mₙ,tho (g mol⁻¹)</th>
<th>Mₙ,GPC (g mol⁻¹)</th>
<th>PDI (Mₘ/Mₙ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>1:50</td>
<td>20</td>
<td>65</td>
<td>13,600</td>
<td>6,700</td>
<td>1.17</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>1:100</td>
<td>20</td>
<td>18</td>
<td>7,500</td>
<td>6,600</td>
<td>1.12</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>1:150</td>
<td>20</td>
<td>40</td>
<td>10,300</td>
<td>14,800</td>
<td>1.33</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>1:50</td>
<td>20</td>
<td>10</td>
<td>9,400</td>
<td>8,900</td>
<td>1.10</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>1:100</td>
<td>14</td>
<td>15</td>
<td>10,200</td>
<td>9,900</td>
<td>1.09</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>1:150</td>
<td>20</td>
<td>23</td>
<td>11,100</td>
<td>11,100</td>
<td>1.15</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>1:50</td>
<td>14</td>
<td>11</td>
<td>14,800</td>
<td>14,800</td>
<td>1.13</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
<td>1:100</td>
<td>14</td>
<td>10</td>
<td>14,100</td>
<td>15,600</td>
<td>1.10</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>1:150</td>
<td>14</td>
<td>13</td>
<td>14,500</td>
<td>17,300</td>
<td>1.11</td>
</tr>
</tbody>
</table>

PS macroinitiators were prepared with chain lengths of 50, 78, and 120, respectively. These three different PS macroinitiators were reacted with different amount of t-BA to obtain a 3 × 3 library of P(St)-b-(t-BA). The resulting block copolymers were characterized by SEC to determine the Mₙ,GPC and PDI values, which are listed in Table 8.

### 3.2 Preparation via Ionic Polymerization Techniques

Ionic polymerization techniques are very powerful for the construction of well-defined block copolymers having controlled architectures, microstructures and molar masses, narrow molar mass distributions, and chemical and compositional homogeneity. Under the appropriate experimental conditions, anionic polymerizations are associated with the absence of any spontaneous termination or chain transfer reactions. One important limitation of ionic polymerizations is the demanding experimental conditions required to achieve a living polymerization system and its applicability to a rather narrow range of monomers. However, recent developments not only in polymerization kinetics and reagents but also in synthesis methods and instrumentation have allowed extending the utility of the method to a broader range of monomers.
3.2.1 Random Copolymer Libraries

A library of random copolymers comprised of MeOx, EtOx, and NonOx has been established, and the properties of the members have been studied [88]. Systematic copolymerization studies and corresponding structure-property investigations have been performed in detail by Schubert et al. For this purpose, nine copolymers were synthesized with 0–100 mol% (steps of 12.5 mol%) of the second monomer, resulting in 27 polymerizations for three different combinations of MeOx, EtOx, and NonOx. The monomer conversion was followed by GC measurements. As shown in Fig. 16, the content of the second monomer increases linearly with increasing mole fraction of the second monomer, whereas the content of the first monomer decreases linearly.

The resulting semilogarithmic kinetic plots for the 50 mol% copolymerizations are depicted in Fig. 17. The linearity in these first-order plots indicates a constant concentration of the living polymer chains as expected for a living polymerization. The plots also revealed a slightly higher reactivity of MeOx in comparison to EtOx and NonOx. To elucidate further the copolymer compositions, the reactivity ratios were determined from the relation between fraction of monomer A in the monomer feed ($f_i$) and the incorporated fraction of monomer A at both ~20 and ~60% monomer conversion. The corresponding reactivity ratios calculated for MeOx, EtOx, and NonOx using two different methods, namely the Mayo-Lewis terminal model and the extended Kelen–Tüdös, are listed in Table 9.

The synthesis of statistical copolymers consisting of EtOx and 2-“soyalkyl”-2-oxazoline (SoyOx) via a microwave assisted CROP procedure was reported by Schubert et al. [89]. The SoyOx monomer is based on soybean fatty acids and has an average of 1.5 double bonds per monomer unit. The designed polymer
Fig. 17 Top row: conversion \(\ln([M_0]/[M_t])\) against time plots for 50 mol% copolymerizations (a, c, 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, f). Both conversion and monomer incorporation are shown for EtOx:NonOx (a, b), MeOx:NonOx (c, d), and MeOx:EtOx (e, f) copolymerizations. (Reprinted with permission from [88]. Copyright (2006) American Chemical Society)

Table 9 Reactivity ratios determined for 2-oxazoline copolymerizations utilizing both the Mayo-Lewis terminal model (MLTM) and the extended Kelen–Tüdös (KT) method. Initial defines ~20% conversion and final defines >50% conversion

<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>

library consisted of a series of copolymers in which the monomer composition was systematically varied allowing the determination of structure-property relationships. The monomer structures and the polymerization mechanism are depicted in Scheme 11.

The polymerization mixtures consisting of EtOx, SoyOx, methyl tosylate, and acetonitrile were automatically prepared utilizing the liquid handling system of
Parallel Optimization and High-Throughput Preparation

Scheme 11 Schematic representation of the polymerization mechanism as well as the EtOx and 2-"soyalkyl"-2-oxazoline (SoyOx) monomer structures

Table 10 Structural characterization of the synthesized P(EtOx)-\textit{stat}-(SoyOx) copolymers

<table>
<thead>
<tr>
<th>Entry</th>
<th>(f_{\text{SoyOx,th}})</th>
<th>(f_{\text{SoyOx}})</th>
<th>(M_n,\text{GPC})</th>
<th>PDI</th>
<th>(f_{\text{SoyOx}})</th>
<th>(M_n,\text{GPC})</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>5,500</td>
<td>1.11</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.04</td>
<td>6,250</td>
<td>1.16</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>0.06</td>
<td>4,700</td>
<td>1.12</td>
<td>0.08</td>
<td>6,900</td>
<td>1.15</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.13</td>
<td>8,000</td>
<td>1.15</td>
</tr>
<tr>
<td>5</td>
<td>0.20</td>
<td>0.20</td>
<td>5,300</td>
<td>1.19</td>
<td>0.18</td>
<td>8,500</td>
<td>1.19</td>
</tr>
<tr>
<td>6</td>
<td>0.25</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.22</td>
<td>9,450</td>
<td>1.16</td>
</tr>
<tr>
<td>7</td>
<td>0.30</td>
<td>0.29</td>
<td>6,550</td>
<td>1.16</td>
<td>0.28</td>
<td>11,100</td>
<td>1.12</td>
</tr>
<tr>
<td>8</td>
<td>0.40</td>
<td>0.41</td>
<td>7,050</td>
<td>1.17</td>
<td>0.38</td>
<td>11,300</td>
<td>1.19</td>
</tr>
<tr>
<td>9</td>
<td>0.50</td>
<td>0.51</td>
<td>7,250</td>
<td>1.17</td>
<td>0.48</td>
<td>12,100</td>
<td>1.26</td>
</tr>
<tr>
<td>10</td>
<td>0.60</td>
<td>0.63</td>
<td>7,950</td>
<td>1.18</td>
<td>0.58</td>
<td>12,700</td>
<td>1.31</td>
</tr>
<tr>
<td>11</td>
<td>0.70</td>
<td>0.76</td>
<td>7,550</td>
<td>1.31</td>
<td>0.70</td>
<td>14,400</td>
<td>1.28</td>
</tr>
<tr>
<td>12</td>
<td>0.80</td>
<td>0.88</td>
<td>9,100</td>
<td>1.24</td>
<td>0.81</td>
<td>13,100</td>
<td>1.43</td>
</tr>
<tr>
<td>13</td>
<td>0.90</td>
<td>0.85</td>
<td>7,500</td>
<td>1.38</td>
<td>0.91</td>
<td>13,000</td>
<td>1.54</td>
</tr>
<tr>
<td>14</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.00</td>
<td>15,000</td>
<td>1.75</td>
</tr>
</tbody>
</table>

\(a\) Determined by \(^1\)H NMR spectroscopy  
\(b\) \(M_n\) values are given in Dalton

The ASW2000 synthesis robot. The total degree of polymerization was aimed for 100 and compositions of EtOx and SoyOx were altered in steps of 10 mol\%. The prepared vials were placed in the autosampler of the microwave synthesizer and were irradiated one by one for a predefined reaction time and temperature. The structural characterizations of the resulting polymers were performed by SEC as well as \(^1\)H NMR spectroscopy measurements and are summarized in Table 10. The reactivity ratios of EtOx and SoyOx were examined and it could be concluded that both monomers have slightly higher reactivity to itself than to the other monomer. The Mayo-Lewis terminal model with nonlinear least square fitting of the data revealed reactivity ratios of \(r_{\text{EtOx}} = 1.4 \pm 0.3\) and \(r_{\text{SoyOx}} = 1.7 \pm 0.3\). These values
indicate that two different monomers will be present almost in a random fashion, whereby small clusters of the same monomer may be present in the polymer chains.

The unsaturated side chain of the SoyOx repeating units could be used for cross-linking well-defined P(EtOx)-stat-(SoyOx) copolymers. Thus, the effect of cross-linking on the thermal properties of the polymers was investigated. The thermal properties of the synthesized P(EtOx)-stat-(SoyOx) copolymers before and after UV-curing are illustrated in Fig. 18.

### 3.2.2 Block Copolymer Libraries

A library of 4 chain extended homopolymers and 12 diblock copoly(2-oxazoline)s was prepared from 2-methyl, 2-ethyl, 2-nonyl, PheOx in a very short period of time [90]. The CROP was initiated by methyl tosylate and performed in acetonitrile at 140°C in a single-mode microwave synthesizer. A total number of 100(50 + 50) repeating units was incorporated into the respective polymer chains. The concentration of the solutions and predefined polymerization times for each monomer and comonomer are summarized in Table 11.

The structural characterization of the resulting diblock copolymers was performed by means of SEC, $^1$H NMR spectroscopy, thermal gravimetric analysis (TGA), and DSC. In most of the cases the PDI values were found to be lower than 1.3. However, the calculation of the molar masses of the diblock copolymers was not straightforward since the calibration standards (PEG, PS, and PMMA) used in SEC systems do not provide accurate data. Moreover, the folding behavior of the different block copolymers significantly influence the hydrodynamic volume and,
### Table 11
Reaction time for the preparation of the diblock copoly(2-oxazolines). In each cell, the corresponding entries indicate the initial concentration of the first monomer (first line), and the reaction times for the polymerization of the first and the second monomer, respectively (second line).

<table>
<thead>
<tr>
<th>First monomer</th>
<th>Second monomer</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>400 s + 400 s</td>
<td>400 s + 500 s</td>
<td>400 s + 400 s</td>
<td>400 s + 1,800 s</td>
<td></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></td>
</tr>
<tr>
<td>500 s + 400 s</td>
<td>500 s + 500 s</td>
<td>500 s + 400 s</td>
<td>500 s + 1,800 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonOx</td>
<td>2 M</td>
<td>2 M</td>
<td>2 M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 s + 800 s</td>
<td>800 s + 1,000 s</td>
<td>800 s + 800 s</td>
<td>800 s + 3,600 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhOx</td>
<td>3 M</td>
<td>3 M</td>
<td>3 M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,400 s + 600 s</td>
<td>2,400 s + 800 s</td>
<td>2,400 s + 600 s</td>
<td>2,400 s + 2,400 s</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 12
Theoretical number average molar masses ($M_n^{th}$) and polydispersity indices for the for chain extended and 12 diblock copoly(2-oxazolines). In each cell, the first and second entry for the PDI values results from the GPC measurements in different eluents, chloroform and N,N-dimethyl formamide (DMF), respectively.

<table>
<thead>
<tr>
<th>First monomer</th>
<th>Second monomer</th>
<th>MeOx</th>
<th>EtOx</th>
<th>NonOx</th>
<th>PhOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOx</td>
<td>$M_n^{th} = 8.5 \text{kDa}$</td>
<td>$M_n^{th} = 9.2 \text{kDa}$</td>
<td>$M_n^{th} = 14.2 \text{kDa}$</td>
<td>$M_n^{th} = 11.6 \text{kDa}$</td>
<td></td>
</tr>
<tr>
<td>PDI: --/1.16</td>
<td>PDI: --/1.17</td>
<td>PDI: --/1.16</td>
<td>PDI: --/1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtOx</td>
<td>$M_n^{th} = 9.2 \text{kDa}$</td>
<td>$M_n^{th} = 9.9 \text{kDa}$</td>
<td>$M_n^{th} = 14.8 \text{kDa}$</td>
<td>$M_n^{th} = 12.3 \text{kDa}$</td>
<td></td>
</tr>
<tr>
<td>PDI: --/1.18</td>
<td>PDI: 1.12/1.16</td>
<td>PDI: 1.15/1.25</td>
<td>PDI: 1.27/1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonOx</td>
<td>$M_n^{th} = 14.2 \text{kDa}$</td>
<td>$M_n^{th} = 14.8 \text{kDa}$</td>
<td>$M_n^{th} = 19.7 \text{kDa}$</td>
<td>$M_n^{th} = 17.2 \text{kDa}$</td>
<td></td>
</tr>
<tr>
<td>PDI: --/1.18</td>
<td>PDI: 1.64/1.16</td>
<td>PDI: 1.14/1.16</td>
<td>PDI: 1.24/1.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhOx</td>
<td>$M_n^{th} = 11.6 \text{kDa}$</td>
<td>$M_n^{th} = 12.3 \text{kDa}$</td>
<td>$M_n^{th} = 17.2 \text{kDa}$</td>
<td>$M_n^{th} = 14.7 \text{kDa}$</td>
<td></td>
</tr>
<tr>
<td>PDI: --/1.18</td>
<td>PDI: 1.35/1.19</td>
<td>PDI: 1.28/1.25</td>
<td>PDI: 1.27/1.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consequently, the $M_n$. Theoretical $M_n$ and PDI values of the synthesized diblock copolymer library are summarized in Table 12.

The glass-transition temperatures and the corresponding specific heats were measured three times for each sample in order to enable the calculation of the standard deviations, which were in the range of ±3% or lower. Apparently, the kind of substituent greatly influences the $T_g$ values, and rigid substituents (phenyl or methyl) or flexible substituents (ethyl or nonyl) cause an increase or decrease in corresponding $T_g$ values, respectively. The measured $T_g$ values are plotted in Fig. 19.

A library of 30 triblock copolymers was synthesized from 2-methyl, 2-ethyl, 2-nonyl, and PhOx in a single mode microwave synthesizer [92]. The polymers exhibited narrow PDI values and showed slight deviations from the targeted monomer ratio of 33:33:33. The design of the experiments is shown in Scheme 12.
Fig. 19  Glass-transition temperatures for the chain extended and the diblock copoly(2-oxazoline)s (the error bars represent the range of standard deviation). Non50Non50, Non50Phe50, and Phe50Non50 did not exhibit a glass transition temperature ($T_g$). The stars represent the literature values for Me50Me50, Et50Et50, and Non50Non50, respectively. (Reprinted with permission from [90]. Copyright (2005) American Chemical Society)

Scheme 12  Schematic representation of the synthetic procedure that was applied for the preparation of three triblock copolymers with the same first and second blocks

The designed set of 2-oxazoline monomers that was used for the synthesis of the triblock copolymers (MeOx, EtOx, PheOx, and NonOx) yielded polymers of different polarity [91]. P(MeOx) and P(EtOx) are hydrophilic, whereas P(PheOx) and P(NonOx) are hydrophobic. All possible combinations of these four different monomers would result in 64 different structures. However, all polymers that would have two times the same block after each other were excluded since they do represent diblock copolymers. Additionally, some structures, which have NonOx as the first block and EtOx or MeOx as the second block, were excluded due to extensive side reactions. Consequently, 30 different triblock copolymers were synthesized, and they are listed in Table 13 with their corresponding structural characterization.

The $T_g$ values of all investigated triblock copolymers are plotted in Fig. 20. The increasing trend in the measured values is due to the incorporation of monomers with rigid substituent such as methyl or phenyl. Moreover, the $T_g$ values did not
Table 13 Number of incorporated monomer units into the 30 triblock copoly(2-oxazoline)s resulting from combined \(^1\)H NMR spectroscopy analyses (top) of the model \([A\text{ and } AB\text{ (block co)}]\) polymers and final polymers as well as the measured number average molar masses (\(M_n,\text{SEC/PDI}\); bottom). \(^1\)H NMR spectra were recorded in CDCl\(_3\) or CD\(_2\)Cl\(_2\) (PhOx containing polymers) and GPC analyses were performed using DMF (with 5 mM NH\(_4\)PF\(_6\)) as eluent. \(M_n,\text{GPC}\) was calculated utilizing poly(methyl methacrylate) (PMMA) standards.

<table>
<thead>
<tr>
<th>1st–2nd block</th>
<th>3rd block</th>
<th>MeOx</th>
<th>EtOx</th>
<th>PhOx</th>
<th>NonOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOx-EtOx</td>
<td>33:31:33</td>
<td>33:33:36</td>
<td>–</td>
<td>33:30:32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.1 kDa/1.22</td>
<td>13.9 kDa/1.15</td>
<td>–</td>
<td>10.2 kDa/1.21</td>
<td></td>
</tr>
<tr>
<td>MeOx-PhOx</td>
<td>33:28:33</td>
<td>33:30:37</td>
<td>33:29:29</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.9 kDa/1.20</td>
<td>10.0 kDa/1.21</td>
<td>10.6 kDa/1.27</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>EtOx-MeOx</td>
<td>–</td>
<td>33:33:33</td>
<td>33:29:27</td>
<td>33:34:31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>10.9 kDa/1.32</td>
<td>12.4 kDa/1.23</td>
<td>9.5 kDa/1.28</td>
<td></td>
</tr>
<tr>
<td>EtOx-PhOx</td>
<td>33:31:30</td>
<td>33:30:33</td>
<td>–</td>
<td>33:30:36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16.2 kDa/1.20</td>
<td>15.3 kDa/1.24</td>
<td>–</td>
<td>11.4 kDa/1.22</td>
<td></td>
</tr>
<tr>
<td>EtOx-NonOx</td>
<td>33:33:37</td>
<td>33:33:33</td>
<td>33:33:31</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.1 kDa/1.27</td>
<td>9.9 kDa/1.22</td>
<td>11.3 kDa/1.25</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PhOx-MeOx</td>
<td>–</td>
<td>33:35:35</td>
<td>33:27:33</td>
<td>33:31:31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>15.3 kDa/1.21</td>
<td>15.2 kDa/1.19</td>
<td>9.1 kDa/1.23</td>
<td></td>
</tr>
<tr>
<td>PhOx-EtOx</td>
<td>33:35:34</td>
<td>–</td>
<td>33:42:33</td>
<td>33:38:38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.8 kDa/1.32</td>
<td>19.1 kDa/1.28</td>
<td>14.1 kDa/1.21</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PhOx-NonOx</td>
<td>33:38:34</td>
<td>33:45:37</td>
<td>33:36:33</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.7 kDa/1.21</td>
<td>8.8 kDa/1.21</td>
<td>11.6 kDa/1.22</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>NonOx-PhOx</td>
<td>33:23:27</td>
<td>33:26:24</td>
<td>–</td>
<td>33:32:33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.2 kDa/1.40</td>
<td>7.8 kDa/1.33</td>
<td>–</td>
<td>10.3 kDa/1.38(^a)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)GPC measurement with CHCl\(_3\):NEt\(_3\):2-PrOH (94:4:2) as eluent (PS calibration)

It should also be noted that none of the triblock copolymers showed more than one \(T_g\) value, indicating that there was no macroscopic phase separation occurring in the bulk state. This is most likely due to the relatively short segments (33 repeating units) that were incorporated.

### 3.3 Supramolecular Synthesis – LEGO\(^\text{®}\) Approach

An alternative route to prepare well-defined block copolymers is first to prepare the homopolymers with functional groups and then to connect them by noncovalent interactions [92–99]. A systematic \(4 \times 4\) library of block copolymers based on PST and PEG connected by an asymmetrical octahedral \(bis\) (terpyridine) ruthenium complex at the block junction was reported [78]. Moreover, the thin film morphology of this library was investigated.
C.R. Becer and U.S. Schubert

Fig. 20 Glass transition temperatures of the triblock copoly(2-oxazoline)s and the P(MeOx), P(EtOx), and P(PhOx) homopolymers, sorted in ascending order. The polymers that contained (at least) one block of P(NonOx) and P(PhOx) at the same time did not exhibit any $T_g$ in differential scanning calorimetry (DSC). ($Me = P(MeOx), Et = P(EtOx), Non = P(NonOx)$, and $Ph = P(PhOx)$). (Reprinted with permission from [91]. Copyright (2006) American Chemical Society)

Functional homopolymers can be synthesized by essentially two different methods. The first and more preferred way is to use a functional initiator which will ensure a high rate of chain end functionality. For instance, the polymerization of St initiated by a unimolecular terpyridine-functionalized nitroxide initiator yields well-defined PS homopolymers. The second technique is based on post-polymerization modifications. In this case, the reaction between mPEG and chloroterpyridine yields terpyridine-functionalized PEG building blocks, as illustrated in Scheme 13.

The theoretical molar masses and the corresponding volume fractions of PS, the metal complex, and PEG content of the block copolymers are summarized in Table 14. The metal complex has been treated as the third block. All block copolymers have been purified by preparative SEC and column chromatography, with isolated yields between 10% and 80%. The expected ratios (within 10% error) for all components in the library were obtained from the integration of $^1$H NMR spectrum.

The morphology of this supramolecular diblock copolymer library has been investigated by means of atomic force microscopy (AFM) measurements. As illustrated in Fig. 21, at first glance different morphologies were obtained for different compositions. However, interpreting the phase behavior of supramolecular block copolymers is not straightforward. There are several important parameters that play a role in the phase behavior. For instance, the amorphous phase of PEG, the crystalline phase of PEG, the metal complex, and the amorphous PST contribute to
the phase contrast. Besides, the final morphology is greatly affected by competitions between self-organization, crystallization of the PEG block and vitrification of the PSt block [100].

4 Conclusion

Automated parallel synthesizers provide high-quality experimental data in relatively short periods of time. High-throughput experimentation techniques have become an inevitable reality in the field of polymer science, since there is a large
parameter space not only including the reaction parameters but also the use of different monomers, catalysts, and polymerization techniques. The application of CLP techniques in automated synthesizers have been demonstrated by several research groups. These techniques enable the synthesis of well-defined homo, block, or random copolymers and even more complex architectures such as graft, star, or dendritic shaped polymers.

The combination of CLP techniques and high-throughput experimentation tools accelerates the research in this field significantly. Besides, on the data collected, the construction of 3D-plots and extensive databases will provide the basis for deeper understanding of the underlying principles. As a consequence, the elucidation of quantitative structure-property relationships will be feasible.

Fig. 21 Atomic force microscopy (AFM) phase images of all block copolymers in the library after spin coating from 2% w/v solution in toluene. No annealing has been performed. The scale bar represents 100 nm. (Reprinted with permission from [78]. Copyright (2005) Royal Society of Chemistry)
Table 14  The block copolymers in the library are displayed in the table by name, by theoretical molar masses and by the volume fractions of PSt, -[Ru]-, and poly(ethylene oxide) (PEO) (annotated between brackets)

<table>
<thead>
<tr>
<th>PEO&lt;sub&gt;70&lt;/sub&gt;-&lt;br&gt;[RuCl&lt;sub&gt;3&lt;/sub&gt;]</th>
<th>PS&lt;sub&gt;20&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;70&lt;/sub&gt;</th>
<th>PS&lt;sub&gt;70&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;70&lt;/sub&gt;</th>
<th>PS&lt;sub&gt;200&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;70&lt;/sub&gt;</th>
<th>PS&lt;sub&gt;240&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;70&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn = 6,100 Da  (35:16:49) 1</td>
<td>Mn = 11,400 Da  (65:8:27) 2</td>
<td>Mn = 25,100 Da  (84:4:12) 3</td>
<td>Mn = 29,300 Da  (87:3:10) 4</td>
<td></td>
</tr>
<tr>
<td>PEO&lt;sub&gt;125&lt;/sub&gt;-&lt;br&gt;[RuCl&lt;sub&gt;3&lt;/sub&gt;]</td>
<td>PS&lt;sub&gt;20&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;125&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;70&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;125&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;200&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;125&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;240&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;125&lt;/sub&gt;</td>
</tr>
<tr>
<td>Mn = 8,400 Da  (25:11:64) 5</td>
<td>Mn = 13,700 Da  (54:7:39) 6</td>
<td>Mn = 27,400 Da  (77:4:19) 7</td>
<td>Mn = 31,600 Da  (80:3:17) 8</td>
<td></td>
</tr>
<tr>
<td>PEO&lt;sub&gt;225&lt;/sub&gt;-&lt;br&gt;[RuCl&lt;sub&gt;3&lt;/sub&gt;]</td>
<td>PS&lt;sub&gt;20&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;225&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;70&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;225&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;200&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;225&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;240&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;225&lt;/sub&gt;</td>
</tr>
<tr>
<td>Mn = 12,800 Da  (16:8:76) 9</td>
<td>Mn = 18,100 Da  (41:5:54) 10</td>
<td>Mn = 31,800 Da  (67:3:30) 11</td>
<td>Mn = 36,000 Da  (71:3:26) 12</td>
<td></td>
</tr>
<tr>
<td>PEO&lt;sub&gt;375&lt;/sub&gt;-&lt;br&gt;[RuCl&lt;sub&gt;3&lt;/sub&gt;]</td>
<td>PS&lt;sub&gt;20&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;375&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;70&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;375&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;200&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;375&lt;/sub&gt;</td>
<td>PS&lt;sub&gt;240&lt;/sub&gt;-[Ru]-&lt;br&gt;PEO&lt;sub&gt;375&lt;/sub&gt;</td>
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<tr>
<td>Mn = 19,400 Da  (11:5:84) 13</td>
<td>Mn = 24,700 Da  (31:4:65) 14</td>
<td>Mn = 38,400 Da  (56:3:41) 15</td>
<td>Mn = 42,600 Da  (60:2:38) 16</td>
<td></td>
</tr>
</tbody>
</table>

Acknowledgement  Financial support from the Dutch Polymer Institute (DPI project #502) is gratefully acknowledged.

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