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Full Paper

Investigations on the Combination of Cationic Ring Opening Polymerization and Single Electron Transfer Living Radical Polymerization to Synthesize 2-Ethyl-2-Oxazoline Block Copolymers

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Cationic ring opening polymerization of 2-ethyl-2-oxazoline (EtOx) has been performed using α–bromoisobutyryl bromide (tertiary) and 2-bromopropionyl bromide (secondary) as initiators in acetonitrile. The reaction kinetics have been followed and selected P(EtOx) polymers have been used as macroinitiators for the single electron transfer living radical polymerization (SET-LRP) of methyl acrylate (MA), ethylene glycol methyl ether acrylate and 2-(dimethylamino)ethyl methacrylate. Moreover, the effect of solvent and catalyst concentration have been investigated on the SET-LRP of P(EtOx) initiated MA.

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Introduction

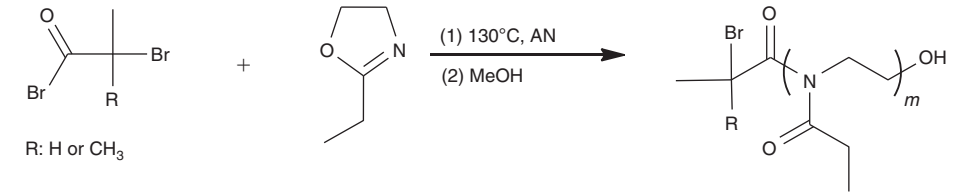
Biocompatible polymers have been used in the design of therapeutic agents for several decades.[1–4] In the early examples, polymers were used as wound dressings, blood plasma expanders and implantable depots.[5] Ringsdorf reported polymer-drug conjugates that are covalently bound in the late 1970s and this approach has found a wide application due to several significant advantages over traditional small molecule therapeutics.[6] The most widely used polymers for this purpose are poly(ethylene)glycol (PEG) and poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA).[7,8] Several PEGylated proteins have been already developed as therapeutics i.e. PEG-asparginase (Oncaspar),[9] PEG-adenosine deaminase (Adagen),[10] PEG-interferon α-2a (Pegasys),[11] PEG-interferon α-2b (PEG-Intron),[12] PEG-granulocyte colony-stimulating factor (Neulasta),[12] and PEG-growth hormone receptor antagonist (Somavert).[13] The polymeric drugs market has become a multi-billion dollar market and alternative designer polymers have been of great interest.

Poly(2-oxazoline)s have a potential to become an alternative player in polymer-drug conjugates due to their biocompatibility and their stealth behaviour.[14] Goddard has demonstrated the biocompatibility of poly(2-methyl-2-oxazoline) (PMeOx) by intraveneous administration to mice.[15] Poly(2-oxazoline)s present similar properties in biocompatibility, stealth behaviour, and biodistribution, in comparison to PEG, which promises the potential of widespread use in biomedical applications. Saegusa et al. reported PMeOx-peptide conjugates in 1990, demonstrating that the remaining enzyme activity depended on both the chain length of the polymer and the extent of modification.[16]

2-R-2-oxazolines have an R group at the 2 position, which can be varied to form hydrophilic (methyl and ethyl), hydrophobic (propyl and longer alkyl chain or aromatic groups), and fluorophilic polymers. These monomers can be polymerized by cationic ring opening polymerization (CROP) to yield well defined polymers.[17,18] It is relatively straightforward to copolymerize 2 to 3 different types of 2-oxazolines to tune the properties of functional polymers. However, chain end modification or the use of a heterofunctional initiator is required to prepare copolymers of 2-oxazolines and vinyl monomers.[19,20] Recently, we have reported the combination of atom transfer radical polymerization (ATRP) of styrene initiated from a poly (2-ethyl-2-oxazoline) P(EtOx) macroinitiator prepared using a heterofunctional initiator. The micelle formation of P(EtOx)-*b*-(styrene) block copolymers at different block lengths were demonstrated.[21] Furthermore, we have extended our research into other acetyl halide initiators, namely acetyl chloride, acetyl bromide and acetyl iodide.[18]

Percec et al. reported single electron transfer living radical polymerization (SET-LRP) that utilizes Cu(0) instead of Cu(I) and this technique has several advantages over ATRP.[22] For instance, SET-LRP uses Cu wire as a catalyst and the polymerization can be typically performed at room temperature.[23–26] In most cases, SET-LRP provides a very high chain end fidelity which is very important when the polymer is used for conjugation to a drug or a peptide.[27]

In this report, we demonstrate for the first time the combination of CROP of 2-ethyl-2-oxazoline and SET-LRP of methyl acrylate (MA), ethylene glycol methyl ether acrylate (EGA), and dimethyl(aminoethyl) methacrylate (DMAEMA). Moreover, 2-bromopropionyl bromide was used for the first time as



Scheme 1. Cationic ring opening polymerization of 2-ethyl-2-oxazoline initiated by 2-bromopropionyl bromide (BrPBr) or α-bromoisobutyryl bromide (BriBBr).

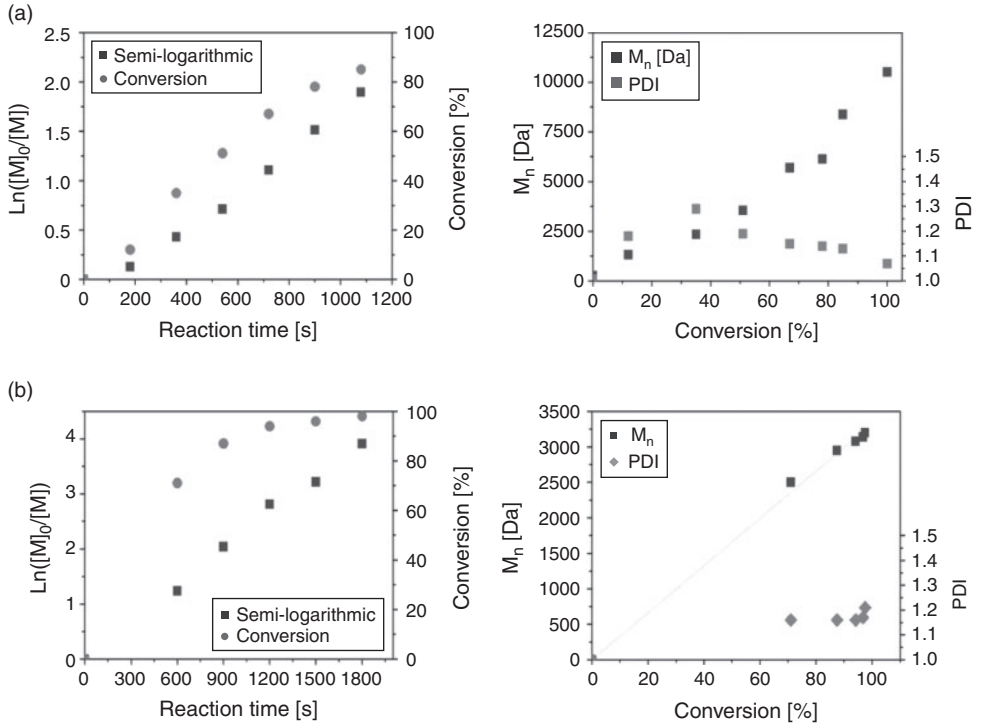


Fig. 1. Semi-logarithmic kinetic plots (left) and molar mass and polydispersity vs conversion plots (right) of (a) α-bromoisobutyryl bromide (BriBBr)-initiated and (b) 2-bromopropionyl bromide (BrPBr)-initiated cationic ring opening polymerization of EtOx.

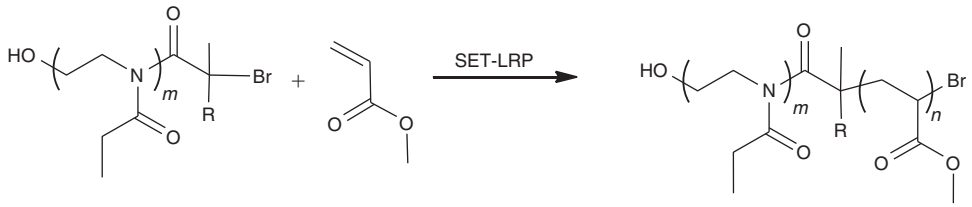
a heterofunctional initiator. A detailed kinetic investigation has been performed to provide insights on the SET-LRP block copolymerization. The reaction solvent and the ratio of Cu(0) and Cu(II) have been varied to optimize the reaction conditions.

Results and Discussion

CROP of EtOx has been performed using α-bromoisobutyryl bromide (BriBBr) and 2-bromopropionyl bromide (BrPBr) as initiators in acetonitrile at 130°C as shown in Scheme 1. The polymerization of EtOx was performed both in an oil bath and in a microwave reactor using BriBBr as an initiator with a degree of polymerization (DP) of 20. Both reactions were conducted for 20 min and reached to full conversion. The molecular weight of 1890 g mol^{-1} (polydispersity index, PDI = 1.18) and 1780 g mol^{-1} (PDI = 1.21) were obtained in the microwave and the oil bath, respectively. As expected, there is no significant effect observed between microwave assisted CROP and conventionally heated CROP.[28]

The reaction kinetics for BrPBr and BriBBr initiated CROP of EtOx are shown in Fig. 1. Degree of polymerization of 100 and 30 were used for BriBBr and BrPBr initiated polymerizations, respectively. Semi-logarithmic kinetic plots exhibited first-order kinetics as expected from a living cationic polymerization and the monomer conversion reached more than 98 % for both initiators in less than 30 min. The polymerizations were performed at 130°C in closed vials. BriBBr initiated polymerization (Fig. 1a) showed a linear increase of molar mass with monomer conversion and the calculated values are found to be close to the theoretical values. The molar mass of the polymers were measured using size exclusion chromatography (SEC) and the number average molar mass was calculated according to polystyrene standards. The polydispersity values decreased from 1.3 to below 1.1 with increasing monomer conversion. Similar results were obtained using BrPBr initiator with the exception of slightly higher polydispersity values (Fig. 1b).

SET-LRP of (MA) has been performed using Cu(0) wire as a catalyst as illustrated in Scheme 2. A typical SET-LRP reaction was performed at 30°C using a monomer to macroinitiator ratio of 222 to 1 and 10 % of $CuBr_2$ in DMSO. In general, addition of $CuBr_2$ improves the initiation and prevents the inhibition.[24,29] Therefore, the effect of $CuBr_2$ concentration on the reaction kinetics was investigated.



Scheme 2. Single electron transfer living radical polymerization of methyl acrylate initiated by P(EtOx) macroinitiator.

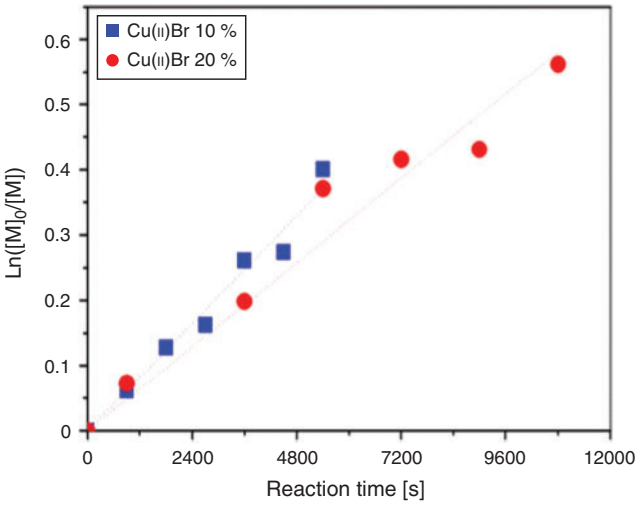


Fig. 2. Semi-logarithmic kinetic plot of single electron transfer living radical polymerization of methyl acrylate initiated by P(EtOx) in the presence of 10 and 20 % $CuBr_2$.

As shown in Fig. 2, the apparent propagation rate constants with 10 and 20 % $CuBr_2$ did not differ significantly, calculated as 6.87×10^{-5} and $5.37 \times 10^{-5}\ s^{-1}$, respectively. Several samples were withdrawn during the reaction and analyzed by SEC and ^1H NMR for the determination of the molecular weight, polydispersity, and monomer conversion. The results obtained with different $CuBr_2$ concentrations are listed in Table 1 and Table 2. The molecular weight of the P(EtOx) macroinitiator was $1800\ g\,mol^{-1}$ and the molecular weight of the block copolymer increased very rapidly even at the initial stages of the polymerization. While the conversion values increased steadily the M_n values of the block copolymers were found to be 10 to 20 times higher than the theoretical molecular weights. This is most likely due to the low initiation efficiency of the P(EtOx) macroinitiators.

Fig. 3 illustrates the SEC traces of the SET-LRP of MA in different solvents and with different amounts of $CuBr_2$. In all cases, it is clearly evident that there is still uninitiated P(EtOx) macroinitiator left even at the later stages of the polymerizations. In the presence of 10 % $CuBr_2$ there is a slight formation of a shoulder at high molecular weight. This should be due to the undesired termination reactions forming A-B-B-A triblock copolymers. Adding more $CuBr_2$ did not have a significant effect, which also indicates that $CuBr_2$ does not work as a deactivator in this system. However, the solvent has a major effect on both the propagation rate of polymerization and termination reactions. When propanol was used as the reaction solvent, the chain coupling reactions were significantly reduced. This can be due to the low monomer conversion in the reaction but it is also possible that Cu(0) generates less active species in propanol compared to DMSO or DMF. It should also be taken into account that P(EtOx) contains nitrogen groups that can coordinate Cu and can significantly affect the course of polymerization. Relatively better results were obtained when DMF was used as the reaction solvent, Fig. 3d. The conversion, molecular weight, and polydispersity values of block copolymerization in propanol and DMF are listed in Tables 3 and 4, respectively. The polymerization proceeded slightly faster in DMF in comparison to propanol and twice as fast in DMSO. The major concern was the uninitiated P(EtOx) macroinitiators that caused the formation of very high molecular weight block copolymers. The typical challenge in CROP of 2-oxazolines is the hydrogen initiated polymer chains, which we believe is the origin of the contamination in the block copolymerization. Nevertheless, it is possible to separate out the dead P(EtOx) homopolymers from the block copolymer by selective precipitation or dialysis as demonstrated in our previous report.[21]

Table 1. Single electron transfer of methyl acrylate using P(EtOx) as macroinitiator with 10 % $CuBr_2$
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P01	15	6	2640	26130	1.10
P02	30	12	3790	56690	1.15
P03	45	15	4360	80670	1.18
P04	60	23	5890	114400	1.26
P05	75	24	6080	130000	1.26
P06	90	33	7990	144900	1.30

[A]Calculated from ^1H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to PS standards.

Table 2. Single electron transfer of methyl acrylate using P(EtOx) as macroinitiator with 20 % $CuBr_2$
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P11	15	7	3070	16200	1.58
P12	60	18	5200	58900	1.27
P13	90	31	7740	79300	1.33
P14	120	34	8390	77900	1.46
P15	150	35	8500	77900	1.50
P16	180	43	10140	93200	1.50

[A]Calculated from ^1H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to polystyrene standards.

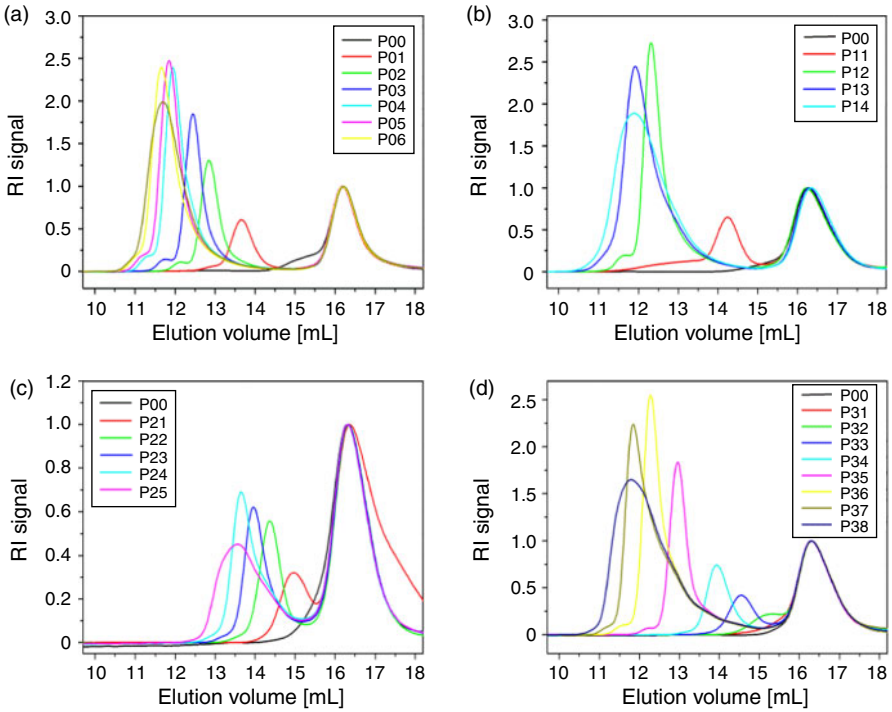


Fig. 3. (a) 10 % Cu(II) in DMSO, (b) 20 % Cu(II) in DMSO, (c) 10 % Cu(II) in propanol, (d) 10 % Cu(II) in DMF.

Table 3. Single electron transfer of methyl acrylate using P(EtOx) as macroinitiator with propanol as solvent
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P21	15	3	2370	5540	1.07
P22	30	4	2560	8970	1.08
P23	45	5	2760	11700	1.11
P24	60	9	3520	13700	1.17
P25	90	12	4090	14500	1.29

[A]Calculated from ^{1}H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to polystyrene standards.

Table 4. Single electron transfer of methyl acrylate using P(EtOx) as macroinitiator with DMF as solvent
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P31	15	1	2060	1690	1.23
P32	30	2	2310	1840	1.33
P33	45	4	2830	8510	1.09
P34	60	8	3860	13800	1.11
P35	90	19	6700	27300	1.26
P36	120	26	8520	39700	1.46
P37	150	31	9800	50300	1.55
P38	180	33	10300	56000	1.64

[A]Calculated from ^{1}H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to polystyrene standards.

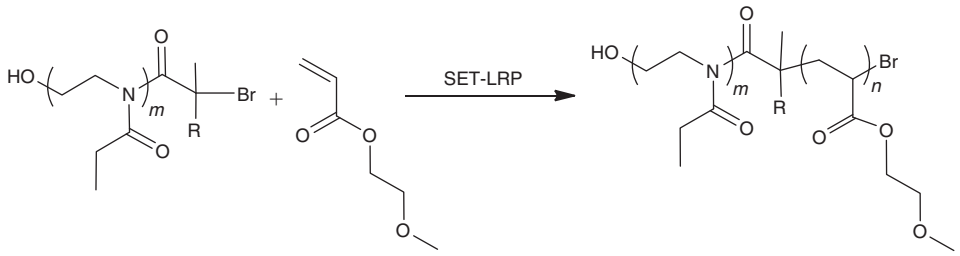
SET-LRP of (EGA) was performed in DMSO at 30°C, Scheme 3. The monomer to initiator ratio of 222 : 1 was used and 10 % $CuBr_2$ was added. The reaction initiated very slowly and the amount of uninitiated macroinitiator was significant. The molecular weight increased with conversion, however, at the later stages of the polymerization chain-chain coupling reactions were observed (Table 5). Besides, the long tailing at lower molecular weight side of the SEC traces indicates the formation of chain transfer initiated homopolymers of EGA. Even though the block copolymers of P(EtOx) and EGA could be prepared with relatively low PDI values, it is necessary to further optimize the reaction conditions.

SET of DMAEMA was performed using P(EtOx) macroinitiator, Scheme 4. The reaction was performed in DMSO at 30°C using a monomer to initiator ratio of 222 : 1. Even though the reaction was stopped at relatively low conversion SET-LRP of DMAEMA proceeded slightly faster than EGA. The molecular weight of the obtained block polymer was 100 times more than the theoretical value which indicates ultra-fast chain growth (Table 6). As shown in Fig. 4, the SEC traces were quite broad and close to the exclusion limit of the SEC column.

Experimental

Materials

Methyl acrylate (MA) (Aldrich, 99 %), styrene (Sigma-Aldrich, ≥99 %), pentafluorostyrene (Acros Organics, 96 %), ethlyene glycol methyl ether acrylate (EGA) (Aldrich, 98 %), 2-(dimethylamino)ethyl methacrylate (DMEAMA) (Aldrich, 98 %), copper wire (Cormax, 0.25 mm), copper(II) bromide (Aldrich, 99 %), DMSO (Romil, >99.9 %), DMF (Fischer-Scientific, >99 %), propanol (Fischer Scientific Far UV grade, 99.99 %), anisole (Sigma-Aldrich, 99.9 %), α-bromoisobutyryl bromide (Aldrich, 98 %) and α-bromopropionyl bromide

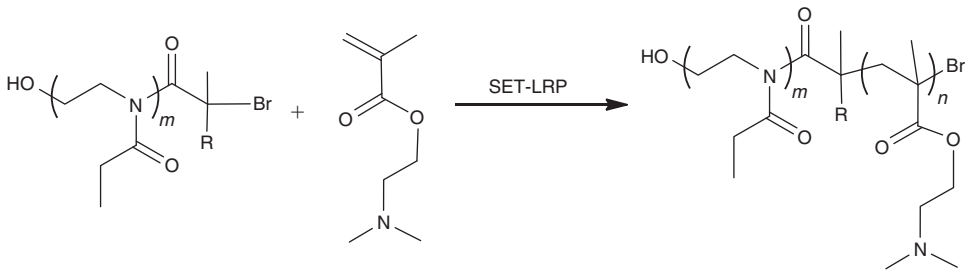


Scheme 3. Single electron transfer living radical polymerization of EGA in DMSO at 30°C.

Table 5. Single electron transfer living radical polymerization of ethylene glycol methyl ether acrylate using P(EtOx) as macroinitiator
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P41	30	4	2320	9370	1.04
P42	60	12	3340	23200	1.09
P43	90	13	3530	32400	1.22
P44	150	14	3640	35300	1.27

[A]Calculated from ^{1}H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to polystyrene standards.



Scheme 4. Single electron transfer living radical polymerization of dimethyl(aminoethyl) methacrylate initiated by P(EtOx) in DMSO at 30°C.

Table 6. Single electron transfer of methyl acrylate of dimethyl(aminoethyl) methacrylate using P(EtOx) as macroinitiator
PDI, polydispersity index

Run	Time [min]	Conversion [%][A]	$M_{n,theo}$ [Da]	$M_{n,SEC}$ [Da][B]	PDI
P00	0	0	1800	1800	1.13
P51	30	5	2320	196500	1.34
P52	60	9	3340	306500	1.35
P53	90	12	3530	371000	1.63
P54	120	18	3640	383500	1.59

[A]Calculated from ^{1}H NMR spectrum.
[B]Measured by size exclusion chromatography and calculated relative to polystyrene standards.

(Aldrich, 97 %) were used as received. Copper(I) bromide (Aldrich, 99 %) was purified by stirring in glacial acetic acid for 2 h and then washing the filtrate with absolute ethanol. The powder was filtered and vacuum dried overnight to yield a pale green powder. 2-Ethyl-2-oxazoline (Aldrich, 99 %) was distilled over CaH_2. All monomers were passed through a basic alumina column to remove inhibitors before reactions.

Equipment

^{1}H NMR spectra were recorded on Bruker DPX-300 spectrometers using $CDCl_3$ obtained from Aldrich. SEC measurements were conducted on a Varian 390-LC system operating in THF : triethylamine (98 : 2) and equipped with refractive index and light scattering detectors, 2 PLgel 5 μm mixed-D columns

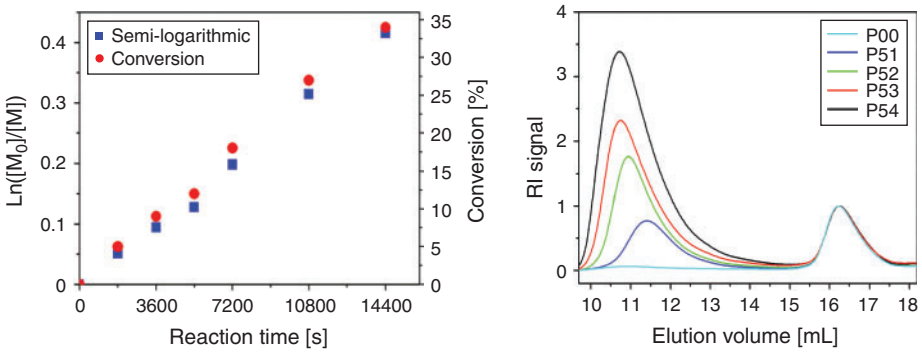


Fig. 4. Semi-logarithmic kinetic plot (left) and size exclusion chromatography traces (right) of the DMAEMA polymerization.

(300 × 7.5 mm), a PLgel 5 mm guard column (50 × 7.5 mm) and an autosampler. The instrument was calibrated with linear narrow polystyrene standards. Microwave assisted polymerizations were performed in a CEM Discovery monomode microwave synthesizer.

Cationic Ring Opening Polymerization of PEtOx Initiated by BrPBr

A stock solution was prepared with EtOx (99.1 mmol, 10 mL), acetonitrile (AN) (20 mL), and α-bromopropionyl bromide (3.3 mmol, 346 µL). From this stock solution, 3.5 mL aliquots were transferred into several microwave vials. After which, five of these vials were heated to 130°C with altering predefined reaction times. All were terminated with the addition of 0.1 mL H_2O. Samples (100 µL) were taken from the microwave reactors and diluted with 2 mL THF : TEA (98 : 2) for SEC analysis. A few drops of crude mixture were diluted in 600 µL $CDCl_3$ and the monomer conversion was calculated via ^{1}H NMR. Samples were precipitated in cold Et_2O.

Cationic Ring Opening Polymerization of PEtOx Initiated by BriBBr

A stock solution was prepared with EtOx (198 mmol, 20 mL), AN (30 mL), and BriBBr (1.98 mmol, 245 µL). From this stock solution, 3.5 mL aliquots were transferred into several microwave vials. After which, seven of these vials were heated to 130°C with altering predefined reaction times. All were terminated with the addition of 100 µL H_2O. Samples (100 µL) were taken from the microwave vials and diluted with 2 mL THF : TEA (98 : 2) for SEC analysis. A few drops of crude mixture were diluted in 600 µL $CDCl_3$ and the monomer conversion was calculated via ^{1}H NMR. Samples were precipitated in cold Et_2O.

Typical Procedure for SET-LRP Using P(EtOx) Macroinitiator

Cu(0) wire (12.5 cm), pre-degassed DMSO (1 mL) and $CuBr_2$ (0.02 mmol, 4.47 mg) were added to a Schlenk tube and degassed via N_2 purging for 20 min. Tris[2-(dimethylamino) ethyl]amine (Me_6TREN) (0.0045 mmol, 12 µL) was added and further purged with N_2 for 10 min. Pre-degassed MA (44.4 mmol, 3.96 mL) or DMAEMA (44.4 mmol, 7.42 mL) or ethyleneglycol methylether acrylate (EGA) (44.4 mmol, 5.66 mL) was transferred and purged for another 10 min. After 30 min, 0.401 g (0.2 mmol) P(EtOx) macroinitiator dissolved in 1 mL DMSO, which was degassed in another flask, were added to the Schlenk tube via a degassed syringe. An initial sample was taken and the Schlenk tube was placed in an oil bath preheated to 30°C. At certain intervals, aliquots (100 µL) were removed with an airtight syringe and quenched with air. Samples were analyzed by both ^{1}H-NMR and SEC to obtain conversion and molecular weight. Moreover, $CuBr_2$ concentrations were changed (0.04 mmol, 8.94 mg) to investigate the effects of Cu(II) on SET-LRP. Propanol and DMF solvents were also used instead of DMSO to examine solvent effects.

Conclusion

CROP of EtOx was performed using two different heterofunctional initiators and the polymerization kinetics was followed. This allowed the combination of CROP EtOx and SET-LRP of various monomers. The monomers investigated in this study were MA, EGA, and DMAEMA. The effect of reaction solvent and the concentration of Cu(II) have been examined for SET-LRP of MA using P(EtOx) macroinitiator. Relatively better results were obtained in DMSO and in the presence of 10 % Cu(II). Similar reaction conditions were employed for EGA and DMAEMA as well. However, very low initiator efficiency was observed and this resulted in extremely high molecular weight block copolymers. These reactions need further optimization. Furthermore, the complexation of Cu and PEtOx might be disturbing the kinetics and 2-alkyl-2-oxazolines with longer alkyl chains will be investigated to overcome this problem.

Acknowledgements

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