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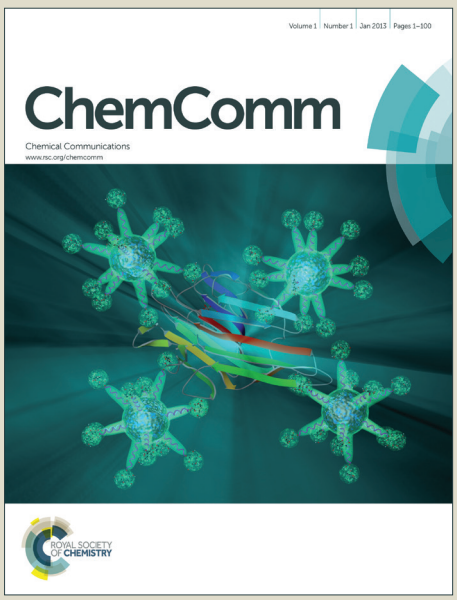

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Continuous Poly(2-oxazoline) Triblock Copolymer Synthesis in a Microfluidic Reactor Cascade

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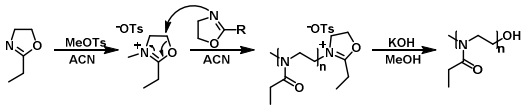
Cationic ring-opening polymerizations of 2-oxazolines were investigated in continuous microflow reactors. Fast homopolymerization of 2-ethyl-2-oxazoline (EtOx) and 2-n-propyl-2-oxazoline (*n*PropOx) were carried out up to 180°C, yielding well-controlled polymers. Also well-defined diblock and triblock copolymers were achieved in a microfluidic reactor cascade, demonstrating the high value of microflow synthesis for the built-up of advanced poly(2-oxazoline)-based polymers.

Continuous flow microreactor technology (MRT)[1,2] has become increasingly popular as alternative to conventional batch chemistry synthesis due to significant advantages stemming mostly from the ideal heat transfer in such reactors and the high process stability that can be reached. Providing a precise control over different reaction parameters, MRT allows for simple screening and optimization of reaction conditions. The small internal volume of microreactors assures a high surface-to-volume ratio, leading to an excellent thermal heat transfer. In this way, not only uniform temperature distributions can be reached throughout the whole reactor, but also unconventional temperature regimes above the boiling point of the solvent can be realized with ease, under slightly elevated pressure. Reactions can therefore be largely accelerated, allowing for fast kinetics and shorter reaction times compared to batch. Moreover, MRT is particularly interesting for industrial applications due to the ease of upscaling optimized flow processes, which can be realized via longer reaction run times, parallelization of reaction setups or via the transfer to well-designed larger reactor set-ups.[1-3]

While the concept of MRT has been introduced to many common organic reactions, it has only recently started to show its eminent potential for precision polymer synthesis.[3,4] Polymerizations – as all exothermic reactions – can largely benefit from flow processing, with the only inherent obstacle with respect to polymer reactions being problems associated with viscosity increases. Regardless, controlled and free radical polymerizations as well as ionic polymerizations were already performed in miniaturized flow reactors.[3-5] Also endgroup modifications[2] and polymer conjugations[6] are accessible. Still, most polymerizations performed in microflow so far were carried out as a proof of concept rather than for the synthesis of complex functional materials. Integration of several reactions in one reactor cascade is in the polymer field very scarce and largely unexplored, despite its high potential.

To show the value of microreactors for the synthesis of precision polymers, we focus on the living cationic ring-opening polymerization (CROP) of 2-oxazolines. Poly(2-oxazoline)s are generally biocompatible and non-toxic making them an extremely interesting alternative for poly(ethylene glycol).[7,8] Importantly, the properties of poly(2-oxazoline)s can be finely tuned by simply variation of the side chains.[9] Short side chains, such as methyl, ethyl, or n-propyl groups result in water-soluble and thermoresponsive polymers.[9,10] Longer side-chains result in hydrophobic polymers, which in combination with the living nature of the polymerization provides direct access to amphiphilic (multi-)block copolymers.[8,9,11] Such non-ionic amphiphilic polymers are interesting for a wide variety of applications as, e.g. carriers for drugs[12,13] and pigment dispersants in inks,[14] or as replacement of pluronics.[15]



Scheme 1. Reaction mechanism of the cationic ring-opening polymerization of 2-ethyl-2-oxazoline (EtOx).

Yet, defined poly(2-oxazoline)s have so far not found widespread commercial application, originally due to extended

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polymerization times in batch (> 10 h) and immanent problems regarding the upscale of their synthesis.[16-18] Reaction times could already be significantly reduced via microwave-assisted polymerizations (< 1 min at 200°C; although side reactions were observed above 140°C)[18-21] and via pressurized batch reactors.[22] However scale-up in batch is limited due to the strong reaction exotherm and microwave-flow chemistry leads to severe temperature gradients through the reaction.[23,24] Additionally, integration of consecutive reaction steps is difficult to achieve for batch reactions due to the very high sensitivity of the reactions towards water. Therefore, microflow techniques seem to be an ideal alternative where a similar reduction of reaction time is expected, while providing an easy and safe scale-up of the polymerization in a hermetically sealed and hence chemically inert environment.

The possibility for scale-up and the inert reaction conditions are not the only advantage of employing flow chemistry towards high-added value polymer synthesis. By combination of several inlets into a specific reactor, entire reaction sequences can be carried out, allowing to target specialized polymer architectures in a one-step procedure. It is at this point that continuous flow unfolds its largest potential when compared to classical synthesis. At present, poly(2-oxazoline)s with many different polymer architectures have been synthesized in batch mode.[8] Several block copolymers[20,25] as well as brush[26,27] and star-shaped copolymers[26,28] are known. The preparation of multi-block poly(2-oxazoline) sequences is, however, challenging as during each monomer addition step extreme care has to be taken to not introduce any moisture in the reactors, which unavoidably leads to termination. Furthermore, such a multistep batch synthesis of multiblock copolymer is labour intensive and tedious. By using MRT, these hurdles can be overcome via direct preparation of such complex polymer structures in an integrated continuous flow process. In here, the cationic ring opening polymerization of 2-oxazolines is first evaluated with regards to reaction temperature for 2-ethyl-2-oxazoline (EtOx) and 2-n-propyl-2-oxazoline (*n*PropOx), followed by the continuous synthesis of multiblock copolymer consisting of various combinations of EtOx and *n*PropOx blocks in a one-step fashion by utilizing a reactor cascade in which consecutive blocks are polymerized directly after each other.

In a first step, the homopolymerization of 2-ethyl-2-oxazoline (EtOx) was carried out in a 19.5 μL microreactor to screen the kinetics of the process and to identify optimal process windows for further block copolymer synthesis. A typical stock solution – composed of EtOx (4 M, target degree of polymerization (DP) 60) and methyl tosylate in acetonitrile – was prepared under nitrogen atmosphere. By injecting this solution at a chosen flow rate, residence times were varied between 15 s and 20 min at reactor temperatures between 120°C and 180°C (note that reactions were carried out at 20 bar using a backpressure regulator). Due to the small volumes required for the flow reactions, a full set of kinetic data is accessed in a simple fashion within 24 hours using only 10 mL of stock solution, leading to the first order kinetic plot as depicted in Fig. 1a. In these kinetic plots, reactions are investigated for ideal living polymerization behaviour. When the concentration of actively propagating chains remains constant throughout the polymerization, linearity should be observed in the logarithmic plot with respect to monomer concentration (first order). From the slope of the plots, the overall propagation rate coefficient of the polymerization at the respective temperature can be obtained. The low scatter of the data in Fig. 1a underpins that the flow reactor is indeed performing very well with respect to reaction stability, batch-to-batch variation and synthesis precision. Practically full monomer conversions were obtained after 12 min 30 at 140°C, 5 min at 160°C and 2 min at 180°C. Closer inspection of the resulting molecular weight distributions reveal that some transfer reactions were occurring at high conversions and high temperatures since a small shoulder appears at the high molecular weight side in the SEC elugrams (Fig. 1b). Even though this observation is in line with literature, the effect appears to be less in the flow reaction.[18,19] The dispersities of the obtained polymers are well below 1.2, indicating a high control over the polymerization at all instances. Less transfer reactions are apparent when targeting lower molecular weights (DP 15 and DP 30, Fig. 1b, Table S1).

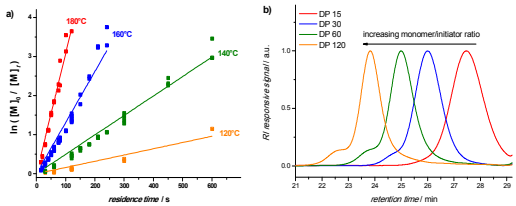


Fig. 1 a) First order kinetic plot for the cationic ring-opening polymerization of EtOx. b) SEC elugrams of EtOx homopolymers with an increasing degree of polymerization.

In a similar approach, the homopolymerization of *n*PropOx was investigated as well. The kinetics of both homopolymerizations are rather similar and full conversions were obtained in the same time intervals as for EtOx (Fig. S4). The use of microfluidic reactors can thus significantly reduce the reaction times in comparison to classical batch reactions (> 10 h),[16-18] in a comparable way to the previously investigated microwave-assisted and pressurized polymerizations of 2-oxazolines.[18-20,22] An almost identical Arrhenius relation of the propagation rate coefficient is obtained for the microflow (Fig. S3) and the microwave-assisted polymerization. Activation energies for EtOx are in excellent agreement (73.5 ± 3.8 kJ·mol^{-1} in microflow vs 73.4 ± 0.5 kJ·mol^{-1} in microwave), and also frequency factors between both techniques match very well ($(1.4 \pm 0.4)\cdot10^8$ L·mol^{-1}·s^{-1} in microflow vs $(2.0 \pm 0.9)\cdot10^8$ L·mol^{-1}·s^{-1} in microwave synthesis).[18] The activation energy and frequency factor of *n*PropOx was determined to be 70.9 ± 8.2 kJ·mol^{-1} and (0.68 ± 0.12) 10^8 L·mol^{-1}·s^{-1}, respectively.

Microfluidic reactors thus provide a high control over the homopolymerization of 2-oxazolines and provide conditions to target polymers with full monomer conversions within few minutes of reaction time. For further investigations, 160 °C was chosen as optimal reaction temperature as reasonable

reaction times could be achieved while keeping transfer reactions at a tolerable level. After optimization of the homopolymerizations, diblock copolymers were targeted in a direct continuous flow set-up. Therefore, a 15 µL microfluidic multi-compartment reactor chip was employed, containing an additional reactor inlet at 1/3 of the reactor, dividing the chip into two reactor compartments: the first with 5 µL internal volume – where the first monomer can be polymerized – and a second part with 10 µL internal volume where the second block is attached. The increase in reactor volume compensates the increase of total flow rate in the reactor and thus allows keeping residence time for both blocks constant. The polymerization stock solutions were injected at a total flow rate of 1 µL/min leading to 5 min residence time and thus full monomer conversions. It should be noted that trace amounts of monomer may be left, leading hence to random incorporation of minor amount of EtOx within the second block of the resulting block copolymers.[10] Those irregularities will, however, not be larger than in any comparable batch reaction and can be assumed to be irrelevant. The second monomer was directly injected without dilution. In this way, a flexible set-up is obtained where changing the flow rate of the second monomer leads to a change in the ratio of monomer 1 to monomer 2 and thus block copolymer composition. A change in individual block lengths can thus be realized simply by adjusting flow rates. By targeting different molecular weights for the first block as well, a variety of diblock copolymers was prepared (Table S2a). The SEC elugrams of the 15/15, 15/30 and 15/60 DP (EtOx/*n*PropOx) diblock copolymers are shown in Fig. 2a, together with the *n*PropOx (DP 15) homopolymer (note that distributions overlap on the low molecular weight shoulder with the used quench solutions that are used to stop the polymerizations directly at the reactor end and thus are cut off slightly). A clear shift of the distributions is observed with increasing *n*PropOx block length, indicating the pristine nature of the block copolymers and high re-initiation rate that is achieved in the second reactor compartment. Also ^{1}H NMR spectroscopic analysis demonstrates that the expected monomer ratios are obtained in the polymer. Further analysis, i.e. via mass spectrometry was not performed as such technique would not yield any information about the block structure. Diblock copolymers with an EtOx block of DP 60 were not targeted since some transfer reactions were already observed for DP 60 homopolymerizations. In a similar approach, *n*PropOx-*b*-EtOx diblock copolymers were targeted (Fig. 2b and Table S2b).

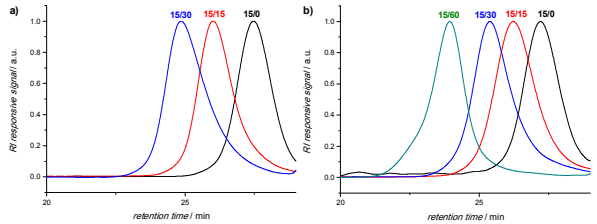
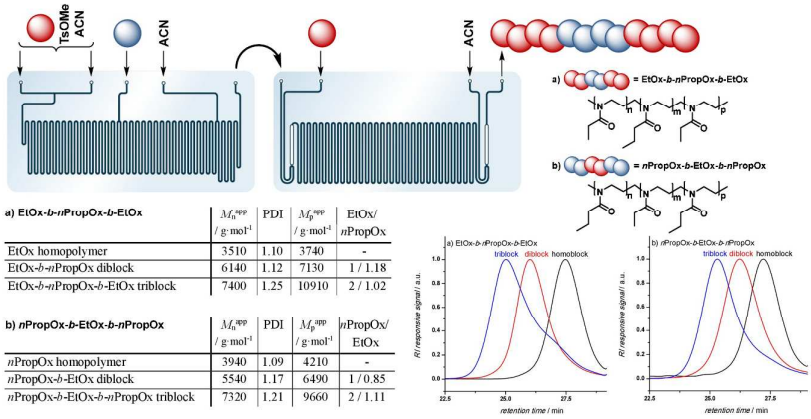


Fig. 2 a) SEC elugrams of the EtOx homopolymer and the EtOx-*b*-*n*PropOx diblock copolymers in different EtOx/*n*PropOx ratios; b) SEC elugrams of the *n*PropOx homopolymer and *n*PropOx-*b*-EtOx diblock copolymers in different *n*PropOx/EtOx ratios.

Diblock copolymers could thus directly be synthesized with high accuracy without any isolation step being required in between. Since variations of flow rates are easily realized, the reactor can be adjusted in very short time to produce a block copolymer with a composition of choice (typically about twice the reactor residence time is required to reach stable flow conditions). In principle, such setup can thus be used for high-throughput synthesis of libraries of block copolymers.

Encouraged by the success of the diblock copolymerizations, the reactor setup was extended by a second reactor chip to also target the direct continuous flow synthesis of triblock copolymers. Therefore, the multi-compartment 15 µL microfluidic system was coupled to a second, independently thermostatted microreactor of 19.5 µL featuring a single reaction channel. This way, a hermetically sealed microreactor cascade is obtained, consisting of three sequential reactor parts with increasing internal volumes (Fig. 3).



a) EtOx-*b*-*n*PropOx-*b*-EtOx

	M_n^{app} / g·mol^{-1}	PDI	M_p^{app} / g·mol^{-1}	EtOx/ *n*PropOx
EtOx homopolymer	3510	1.10	3740	-
EtOx-*b*-*n*PropOx diblock	6140	1.12	7130	1 / 1.18
EtOx-*b*-*n*PropOx-*b*-EtOx triblock	7400	1.25	10910	2 / 1.02

b) *n*PropOx-*b*-EtOx-*b*-*n*PropOx

	M_n^{app} / g·mol^{-1}	PDI	M_p^{app} / g·mol^{-1}	*n*PropOx/ EtOx
*n*PropOx homopolymer	3940	1.09	4210	-
*n*PropOx-*b*-EtOx diblock	5540	1.17	6490	1 / 0.85
*n*PropOx-*b*-EtOx-*b*-*n*PropOx triblock	7320	1.21	9660	2 / 1.11

Fig. 3 Schematic representation of the microfluidic cascade consisting of a two stage 15 µL and a 19.5 µL microreactor. Injection of pure monomer (in a 1/1 ratio to the first monomer) via the additional inlet in the 15 µL reactor enables the formation of diblock copolymers, while the injection of monomer in the 19.5 µL reactor leads to triblock copolymers. a) EtOx-*b*-*n*PropOx-*b*-EtOx: 5 min + 6 min 48 s + 6 min 58 s; b) *n*PropOx-*b*-EtOx-*b*-*n*PropOx: 5 min + 7 min 09 s + 6 min 58 s.

The first reactor chip was used as described above, with the third reactor being used to attach a third polymer block. In this way, an EtOx-*b*-*n*PropOx-*b*-EtOx triblock copolymer (15/15/15) in a 2/1.02 EtOx/*n*PropOx ratio could be obtained, with an apparent molecular weight of 7400 g·mol^{-1} and a dispersity of 1.25. Also its mirror image, the *n*PropOx-*b*-EtOx-*b*-*n*PropOx triblock copolymer was developed in a 2/1.11 *n*PropOx/EtOx ratio with a molecular weight of 7320 g·mol^{-1} and a dispersity of 1.21. The corresponding molecular weight distribution are shown in Fig. 3, in comparison to the homo- and diblock copolymers discussed above. Triblock copolymers with longer block lengths (DP 30 for each block) were likewise targeted and are included in the supporting information (Table S3). Overall, some broadening of the molecular weight distributions is observed during the attachment of the third block. Nevertheless, overall dispersities are relatively low and the reaction outcome is considered to be very successful. The broadening that is observed may stem from slight impurities being entered into the reactor by the multiple injection points, but can also be due to diffusion (back mixing) occurring during transfer of the reaction solutions from reactor 1 to 2, where a short piece of non-heated PEEK tubing was used (see SI).

In conclusion, it was shown that poly(2-oxazoline) triblock copolymers – otherwise difficult to access – are successfully synthesized by the use of a microreactor cascade consisting of two commercially available microreactor systems. First, the homopolymerizations of EtOx and *n*PropOx were investigated in detail with respect to changing reaction temperature. The use of microfluidic reactors provides a high control over the homopolymerization of these 2-oxazolines and full monomer conversions are obtained after 12 min 30 at 140°C, 5 min at 160°C and 2 min at 180°C for both monomers. Via operation at 160°C, diblock copolymers were directly synthesized in a two-compartment reactor chip without any additional isolation step in between the individual polymerizations. A large variety of diblock copolymers could be obtained by simply varying the flow rate of the second monomer. Afterwards, the microfluidic system was coupled to a second microreactor, resulting in a hermetically sealed microreactor cascade where triblock copolymers of the structure EtOx-*b*-*n*PropOx-*b*-EtOx and *n*PropOx-*b*-EtOx-*b*-*n*PropOx could successfully be obtained in one step. The use of such microreactor cascades demonstrates the high potential that continuous flow chemistry has for the precision synthesis of complex macromolecules. Cationic ring opening polymerizations are – due to their high sensitivity to water – not easy to be carried out conventionally and the above work shows how microfluidics can help to overcome a significant synthetic hurdle – while still providing conditions that allow intrinsically for facile scale-up of the reactions. Further investigations towards to further variation of block copolymer structures and architectures are currently underway in our laboratories.

Notes and references

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1 Wiles, C.; Watts, P. *Eur. J. Org. Chem.*, 2008, 1655.
2 Vandenbergh, J.; Junkers, T. *Polym. Chem.,* 2012, **3**, 2739.
3 Tonhauser, C.; Natalello, A.; Löwe, H.; Frey, H. *Macromolecules*, *2012*, **45**, 9551.
4 Wilms, D.; Klos, J.; Frey, H. *Macromol. Chem. Phys.,* 2008, **209**, 343.
5 Vandenbergh, J.; de Moraes Ogawa, T.; Junkers, T. *J. Polym. Sci. Part A: Polym. Chem.,* 2013, **51**, 2366.
6 Vandenbergh, J.; Tura, T.; Baeten, E.; Junkers, T. *J. Polym. Sci. Part A: Polym. Chem.*, 2014, **52**, 1263.
7 Barz, M.; Luxenhofer, R.; Zentel, R.; Vicent, M. J. *Polym. Chem.,* 2011, **2**, 1900.
8 Adams, N.; Schubert, U. S. *Adv. Drug Deliv. Rev.,* 2007, **59**, 1504.
9 Hoogenboom, R.; Schlaad, H. *Polymers,* 2011, **3**, 467.
10 Hoogenboom, R.; Thijs, H. M. L.; Jochems, M. J. H. C.; van Lankvelt, B. M.; Fijten, M. W. M.; Schubert, U. S. *Chem. Commun.,* 2008, 5758.
11 Persigehl, P.; Jordan, R.; Nuyken, O. *Macromolecules,* 2000, **33**, 6977.
12 Luxenhofer, R.; Schulz, A.; Roques, C.; Li, S.; Bronich, T. K.; Batrakova, E. V.; Jordan, R.; Kabanov, A. V. *Biomaterials,* 2010, **31**, 4972.
13 Luxenhofer, R.; Han, Y.; Schulz, A.; Tong, J.; He, Z.; Kabanov, A. V.; Jordan, R. *Macromol. Rapid Commun.,* 2012, **33**, 1613.
14 Ma, S.-H.; Rodriguez-Parada, N. 1998; Vol. US5854331.
15 Kobayashi, S.; Igarashi, T.; Moriuchi, Y.; Saegusa, T. *Macromolecules,* 1986, **19**, 535.
16 Aoi, K.; Okada, M. *Prog. Polym. Sci.,* 1996, **21**, 151.
17 Kagiya, T.; Narisawa, S.; Maeda, T.; Fukui, K. *J. Polym. Sci. B: Polym. Lett.,* 1966, **4**, 441.
18 Wiesbrock, F.; Hoogenboom, R.; Leenen, M. A. M.; Meier, M. A. R.; Schubert, U. S. *Macromolecules,* 2005, **38**, 5025.
19 Wiesbrock, F.; Hoogenboom, R.; Abeln, C. H.; Schubert, U. S. *Macromol. Rapid Commun.,* 2004, **25**, 1895.
20 Wiesbrock, F.; Hoogenboom, R.; Leenen, M.; van Nispen, S. F. G. M.; van der Loop, M.; Abeln, C. H.; van den Berg, A. M. J.; Schubert, U. S. *Macromolecules,* 2005, **38**, 7957.
21 Litt, M.; Levy, A. H., J. *Macromol. Sci. Chem.,* 1975, **5**, 703.
22 Hoogenboom, R.; Fijten, M. W. M.; Paulus, R. M.; Thijs, H. M. L.; Hoeppener, S.; Kickelbick, G.; Schubert, U. S. *Polymer,* 2006, **47**, 75.
23 Hoogenboom, R.; Paulus, R. M.; Pilotti, Å.; Schubert, U. S. *Macromol. Rapid Commun.,* 2006, **27**, 1556.
24 Paulus, R. M.; Erdmenger, T.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.,* 2007, **28**, 484.
25 Trinh, L. T. T.; Lambermont-Thijs, H. M. L.; Schubert, U. S.; Hoogenboom, R.; Kjoniksen, A.-L. *Macromolecules,* 2012, **45**, 4337.
26 Lach, C.; Hanselmann, R.; Frey, H.; Mülhaupt, R. *Macromol. Rapid Commun.,* 1998, **19**, 461.
27 Zhang, N.; Luxenhofer, R.; Jordan, R. *Macromol. Chem. Phys.,* 2012, **213**, 1963.
28 McAlvin, J. E.; Fraser, C. L. *Macromolecules,* 1999, ***32***, 1341.