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Brush copolymers from 2-oxazoline and acrylic monomers via an inimer approach

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Abstract: Brush shaped macromolecular architectures provide unique material properties owing to their dense branched structures. However, there are major challenges in obtaining brush shaped macromolecules when the required functional monomers are not compatible for copolymerization using the same synthetic technique. Herein, we present an inimer molecule structure that has both an initiating group for Cu-mediated radical polymerization and a 2-oxazoline monomer ring for cationic ring opening polymerization. Thus, various combinations of *poly(2-oxazoline-brush-acrylate/acrylamide)* copolymers could be obtained by grafting from a *poly(2-oxazoline)* backbone bearing radical initiator units. A simple two-step synthesis method for a novel 2-oxazoline inimer was established and used in the homo and block copolymerization with 2-ethyl-2-oxazoline to yield the brush-initiator structure. Moreover, selected acrylates and acrylamides were utilized for Cu(0)-mediated reversible deactivation radical polymerization (RDRP) initiated through the

brush-initiator. Finally, owing to the understanding obtained via optimization reactions, high/low density-, block-, and amphiphilic brush copolymers with narrow molecular weight distributions were successfully obtained.

Introduction

Polymer brushes are densely grafted polymer chains attached to either a surface or a polymeric backbone. They are most frequently synthesized *via* three different methods: “grafting through”, “grafting from” or “grafting to” approach.^[1] Their architecture allows brush polymers to have unique properties such as a stretched polymer backbone due to steric repulsion of the side chains, a high concentration of side chains and decreased spatial density of chain entanglement.^[2] Therefore, brush polymers are suitable for a wide range of applications, for example antifouling surfaces^[3] and biolubrication^[4-6] *via* surface modification or drug delivery due to their interesting self-assembly behavior.^[7-9] The invention of “click” chemistry combined with recent advances in the field of “living” polymerization techniques allow the synthesis of a vast number of brush polymers comprising a multitude of monomers and architectures thereof.^[1,10] Brush polymer architectures containing 2-oxazolines were only introduced less than a decade ago although, polymers from the class of 2-oxazolines were discovered over 50 years ago. Their true potential unfolded only recently.^[11-14] The living character of the CROP for a wide range of possible monomers and their biocompatibility paved the way to a successful renaissance of poly(2-oxazolines).^[15-17]

Their physiochemical properties and stealth behavior were harnessed to produce lubricious and biocompatible brushes, cyclic brushes and blocky brush polymers which showed superior properties compared to the “gold standard” PEG.^[18-24] The combination of 2-oxazolines with other

controlled polymerization techniques such as RAFT^[25–30], ROP^[31–33] and Cu-mediated RDRP^[34–36] underpins the versatility of this monomer class. In particular, Cu(0)-mediated RDRP is gaining growing attention due to the increasing compatibility with hydrophilic, hydrophobic and even fluorophilic monomers in a variety of solvents, solvents mixtures and a low catalyst load.^[37–39] Despite the extensive research in the field of 2-oxazolines, only a few examples for blocky brush polymers containing poly(2-oxazolines) are available to date.^[40–42] To our knowledge, there is no example for brush polymers, composed of a poly(2-oxazoline) backbone combined with grafted poly(acrylate) chains.

Herein, we demonstrate a synthetic protocol for novel brush polymer architectures *via* the combination of CROP and Cu(0) RDRP from a 2-oxazoline inimer bearing a tertiary alkyl bromide functionality as shown in **Figure 1**. With this motivation, synthesis of graft polymers with an adjustable backbone and brush density including blocky brush structures were obtained. It should also be noted that this is the first literature example of a 2-oxazoline backbone with acrylate side chains and the brushes are three atoms apart from each other as the backbone is formed of 2-oxazolines, whereas it would be only two atoms apart if the backbone was formed of acrylates. Therefore, having 2-oxazolines on the backbone provides a clear advantage as a new design parameter in complex macromolecular architectures.

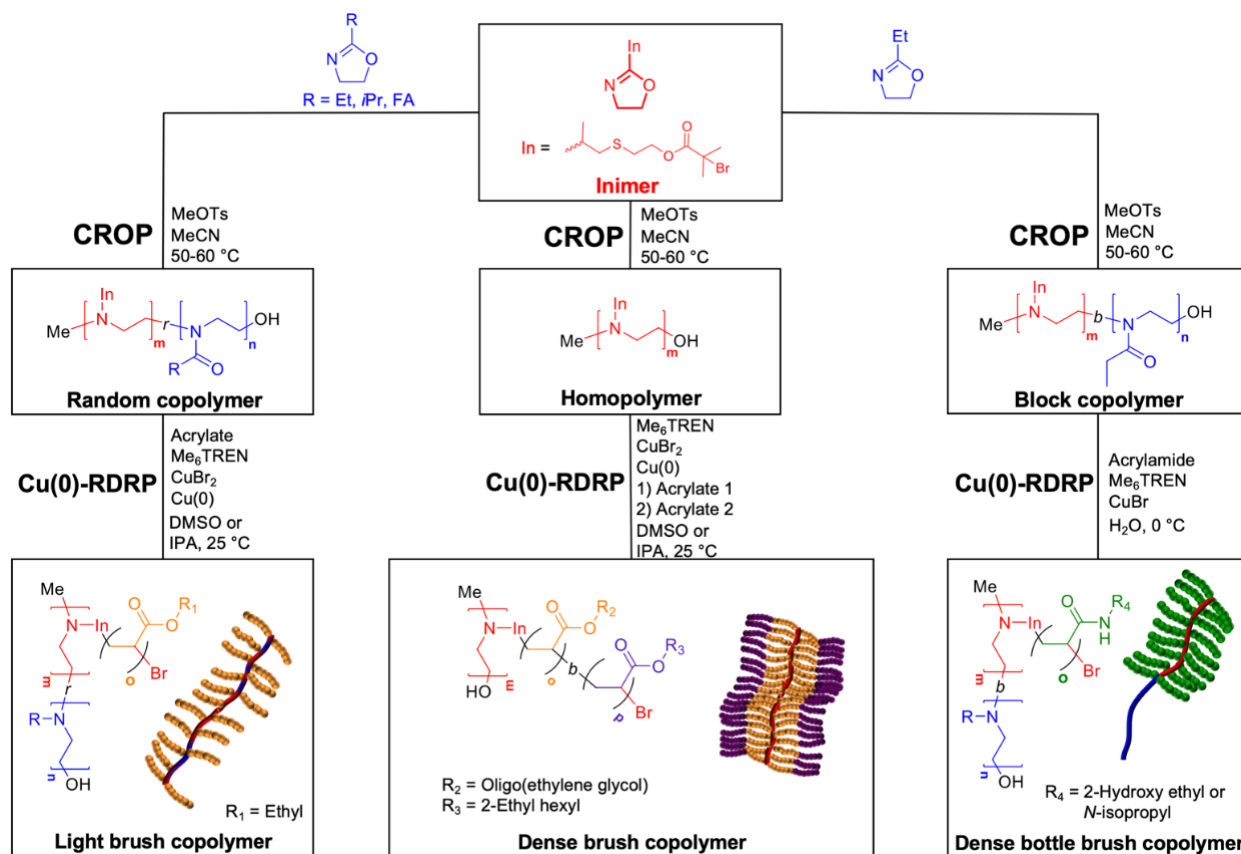


Figure 1. Synthetic strategies to prepare homo, random, and block brush macroinitiator and their utilization to prepare light brush, dense brush and dense bottle brush copolymers by combination of 2-oxazolines and acrylates/acrylamides.

Results and discussion

Synthesis of 2-oxazoline inimer InOx

In order to tailor complex brush polymers via CROP and Cu(0)-mediated RDRP, a novel oxazoline inimer was synthesized in a facile and straight-forward 2-step reaction sequence. Due to the high reactivity of the cyclic iminoether, a direct bromination of 2-oxazoline derivatives was challenging and resulted in a mixture of products. Therefore, the versatile and commercially available 2-isopropenyl-2-oxazoline (iPOx) was employed in a high-yielding thiol-ene reaction with 2-mercaptoethanol. The esterification of the introduced hydroxyl group was readily achieved by

DIC coupling with bromo isobutyric acid. This reaction was easily scaled up to 20 g-scale (**Figure 2**).

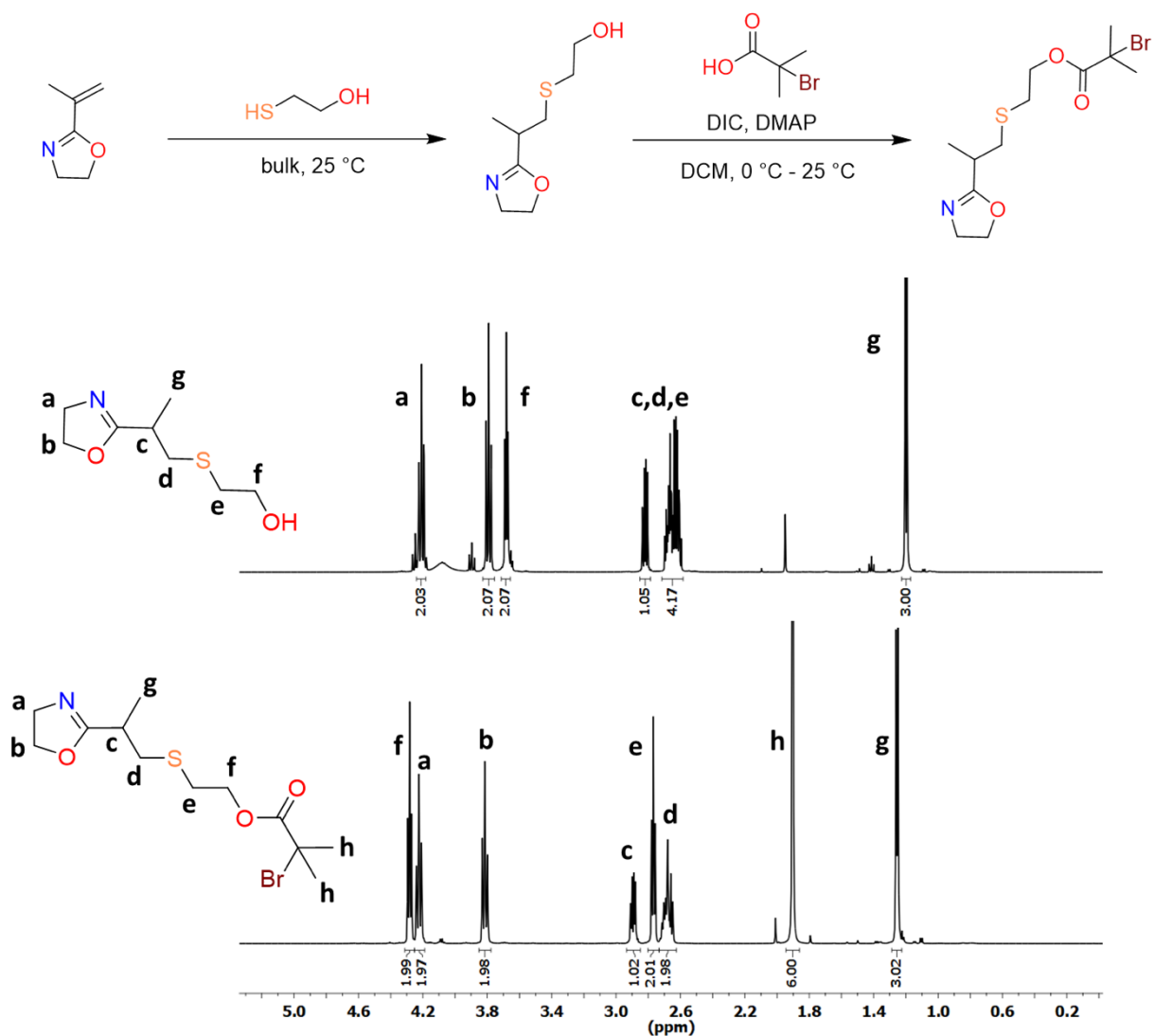


Figure 2: Reaction scheme for the synthesis of 2-oxazoline inimer (*top*) and ¹H NMR of the intermediate (mercaptoethanol-functionalized 2-isopropenyl oxazoline, *middle*) and the product (InOx, *bottom*).

The thiol-ene reaction was screened for different conditions with a butylamine-modified solid phase resin and under UV irradiation with the photocatalyst DMPA. Both reactions yielded

the desired product quantitatively. By simply mixing iPOx and 2-mercaptoethanol in an equimolar ratio, the desired product was obtained in 97% yield within 5 minutes. The double bond of the iPOx is highly activated by the neighboring iminoether function, creating a *Michael* system, which reacted eagerly with the thiol moiety of 2-mercaptoethanol. The redundancy of catalyst or solvents allowed the use of the hydroxyl functionalized 2-oxazoline as obtained in the next reaction step without any purification. The esterification of the hydroxyl function in order to introduce an initiator moiety for Cu-mediated RDRP could not be carried out with the respective acid bromide (BiBB), which obviously causes a ring-opening reaction of the 2-oxazoline. Therefore, the milder DIC coupling with α -bromo isobutyric acid was employed to obtain the 2-oxazoline inimer (InOx) in a two-step reaction sequence (**Figure 2**).

Optimization of CROP conditions for 2-oxazoline inimer InOx

The compatibility of tertiary alkyl bromides under CROP conditions was investigated by utilizing a model compound for the ring-opening polymerization of 2-ethyl-2-oxazoline (EtOx). Therefore, EtOx was reacted with ethyl bromoisobutyrate (EBiB) at different polymerization temperatures, monitoring the reaction by size exclusion chromatography (SEC) for polymer formation. Surprisingly, EBiB initiated the CROP of 2-ethyl-2-oxazoline (EtOx) at 80 °C and 140 °C, reaching full conversion after 72 h and 18 h, respectively. However, when the experiment was conducted at 40 °C, no polymerization was observed after 5 days of reaction time (**Figure 3**).

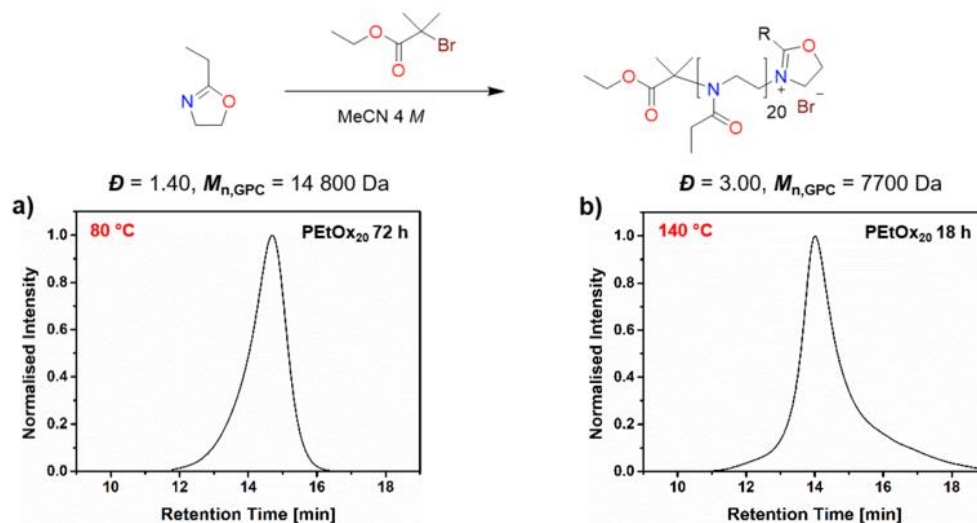


Figure 3: SEC traces of EBiB-initiated CROP of EtOx at 80 °C (a) and 140 °C (b).

Based on these findings, the oxazoline inimer (InOx) was further screened to find a suitable temperature range for its ring-opening polymerization in order to avoid self-initiation. InOx showed an excellent stability at 40 °C over a period of 9 days. However, at 50 °C, a polymer shoulder was visible in SEC spectrum after 3 days and at 60 °C, full monomer conversion was observed after 6 days. When the reaction was carried out at 80 °C, full monomer conversion was observed after only 2 days and no SEC trace was obtained at 140 °C due to potential crosslinking reaction in less than 3 h (**Figure 4**). The focus of this study was to obtain brush copolymers rather than hyperbranched or network polymers. Therefore, we have focused on the controlled polymerization of InOx in this study but another advantage of InOx would be a straightforward synthesis of hyperbranched polymers at relatively higher reaction temperatures.

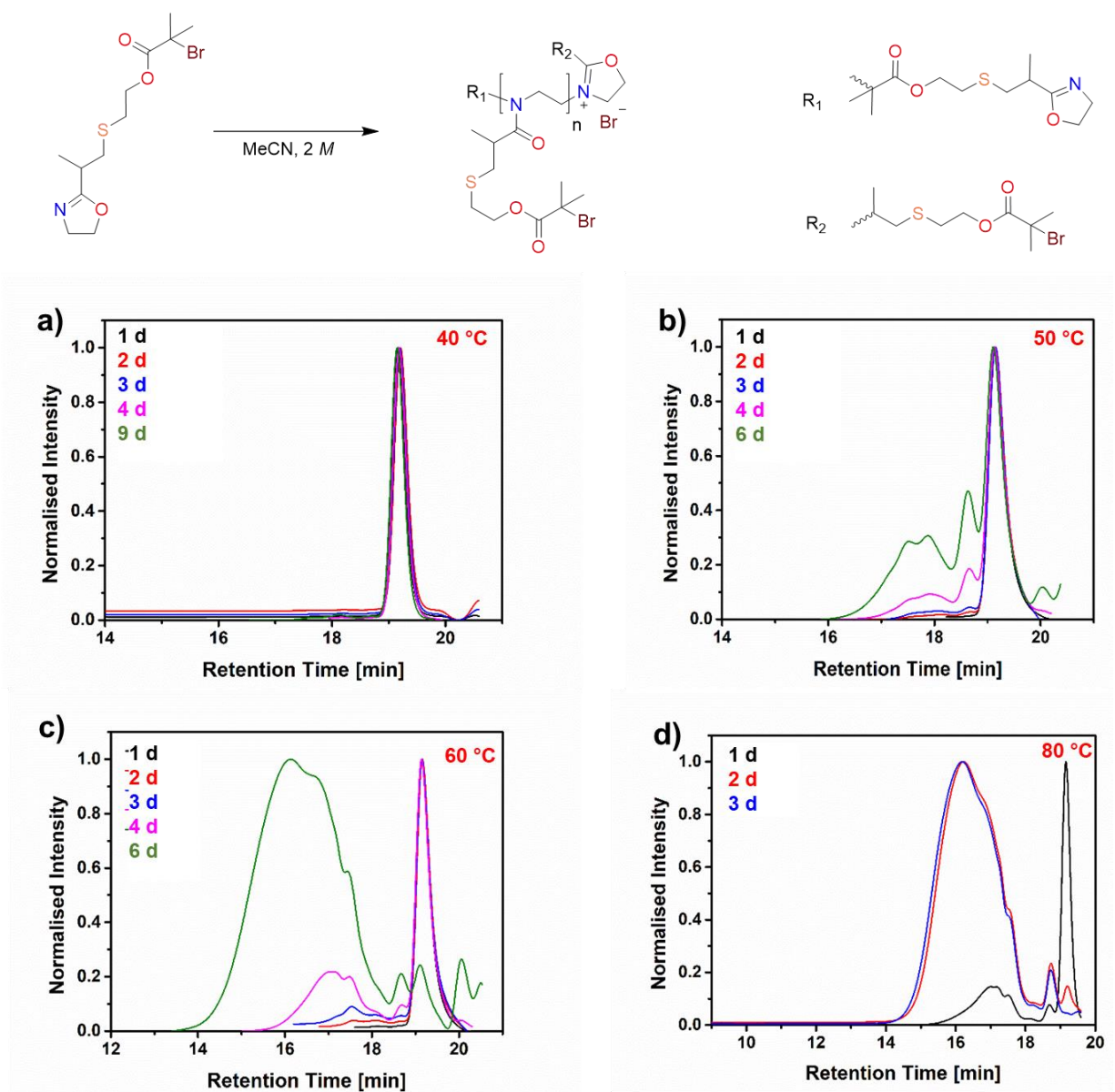


Figure 4: SEC traces of a 2 M solution of the 2-oxazoline inimer in MeCN at different polymerization temperatures of (a) 40 °C, (b) 50 °C, (c) 60 °C, and (d) 80 °C. The peak at 19.2 minutes corresponds to the inimer compound and at 40 °C there is no polymer formation observed over 9 days.

Consequently, the cationic ring-opening polymerization of the inimer was conducted at 50 °C since the initiation by a CROP initiator is much faster compared to the tertiary alkyl bromide.

Methyl tosylate (MeOTs), methyl triflate (MeOTf) and propargyl tosylate (propargyl-OTs) were investigated to find the most suitable initiator for the CROP of InOx (**Figure 5**). The molar mass and dispersity of the polymers obtained using MeOTf, propargyl-OTs and MeOTs as initiators were calculated as 2000 Da and 1.69, 4000 Da and 1.33, and 2300 Da and 1.23, respectively. The best result was obtained when reacting the InOx (DP=10) with MeOTs at 50 °C at a 2 M monomer concentration, yielding a dispersity value of 1.23, which was in a good agreement between experimental and theoretical molar mass. Due to the decreased reaction temperature, the polymerization reactions were allowed to proceed for 18 h, showing full monomer conversion, as observed *via* ^1H NMR spectroscopy.

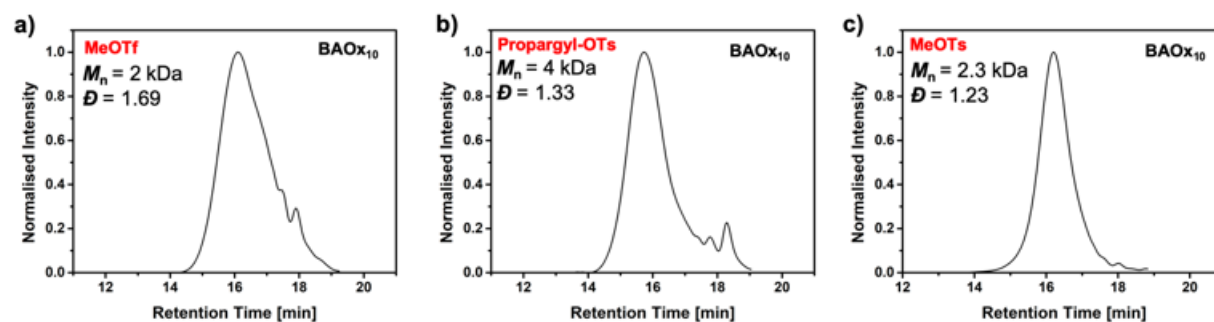


Figure 5: SEC analysis of poly(2-oxazoline inimer) prepared by cationic ring opening polymerization performed at 2 M concentration in MeCN at 50 °C and initiated with (a) MeOTf, (b) Propargyl-OTs, and (c) MeOTs for a target DP = 10. Samples for SEC analysis were taken after 18 h.

Furthermore, MeOTs was applied to target higher degrees of polymerization (DP = 20, 50, 100) (**Figure 6**). The InOx inimer shows a controlled polymerization behavior for DP values of less than 50. However, at higher DPs, a broadening of the MWD was observed due to longer reaction times and potential self-initiation from the tertiary bromide in the side chains. Furthermore, reaction times increased considerably, requiring 60 h and 65 h for DP = 50 (**P3**) and

DP = 100 (**P4**), respectively. When higher DPs were targeted, the MWD increased significantly and the theoretical molecular weight was much higher in comparison with the determined molecular weight by SEC. It has to be noted, that the quality of the polymers in terms of dispersity and achieving the expected molecular weights was enhanced by storing the InOx in a Schlenk tube over molecular sieves. Residual water acts as a terminating agent in cationic ring opening polymerization and therefore, the monomers should be dried carefully and kept under an inert environment to avoid any termination reaction during the polymerization. By doing so, the dispersity for low molecular weight InOx polymers was improved to 1.16 (**P1**). Furthermore, MALDI-ToF MS analysis was carried out for **P1**, in order to confirm the polymer composition. Unfortunately, the InOx polymer failed to ionize sufficiently under the applied conditions, resulting in a poor resolution. The high density of alkyl bromide functionalities might be responsible for this observation (**Figure S6**).

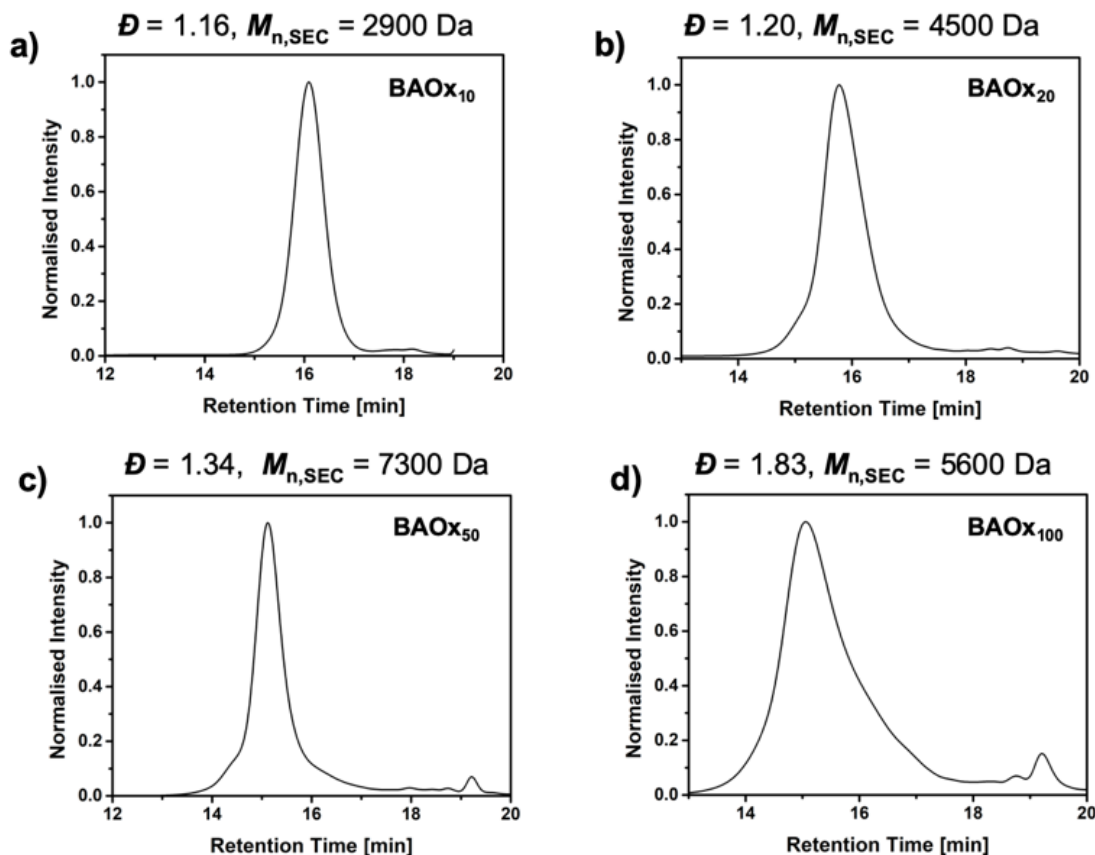


Figure 6: SEC analysis of poly(2-oxazoline inimer) prepared by cationic ring opening polymerization performed at 2 M concentration in MeCN at 50 °C and initiated with MeOTs at DP values of (a) 10 (**P1**, 20 h), (b) 20 (**P2**, 20 h), (c) 50 (**P3**, 60 h), and (d) 100 (**P4**, 65 h).

Synthesis of InOx macroinitiators for brush copolymerization

In order to increase the scope of the oxazoline brush backbone, the inimer was investigated for its copolymerization behavior with water soluble 2-ethyl-2-oxazoline (EtOx), 2-isopropyl-2-oxazoline (*i*PrOx) and lipophilic and double bond containing fatty acid derived 2-oxazoline (FAOx) monomers.

Table 1. Optimization of cationic ring opening polymerization of InOx based homo, random and block copolymers.

| Run | | M1 / M2 | DP M1/M2 | Temp (°C) | Time (h) | $M_{n,theo}$ (kDa) | $M_{n,SEC}$ (kDa) | \bar{D} |
|------------|---------------|---------------------|-------------|--------------|-------------|-----------------------|----------------------|-----------|
| P1 | HOMO | InOx | 10/0 | 50 | 20 | 3.5 | 2.9 | 1.16 |
| P2 | | InOx | 20/0 | 50 | 20 | 6.8 | 4.5 | 1.20 |
| P3 | | InOx | 50/0 | 50 | 60 | 16.9 | 7.3 | 1.34 |
| P4 | | InOx | 100/0 | 50 | 65 | 33.8 | 5.6 | 1.83 |
| P5 | RANDOM | InOx/EtOx | 10/10 | 40 | 45 | 4.4 | 2.8 | 1.51 |
| P6 | | InOx/EtOx | 5/45 | 60 | 50 | 6.2 | 5.6 | 1.29 |
| P7 | | InOx/ <i>i</i> PrOx | 10/10 | 60 | 20 | 4.5 | 3.9 | 1.15 |
| P8 | | InOx/FAOx | 10/10 | 60 | 20 | 6.4 | 5.4 | 1.24 |
| P9 | BLOCK | InOx/EtOx | 5/45 | 60 | 60 | 6.2 | 5.3 | 1.33 |
| P10 | | InOx/EtOx | 10/90 | 50 | 84 | 12.4 | 12.7 | 1.35 |
| P11 | | InOx/EtOx | 10/40 | 50 | 84 | 7.6 | 9.6 | 1.30 |

InOx: Inimer oxazoline, **EtOx:**2-Ethyl-2-oxazoline, ***i*PrOx:**2-Isopropyl-2-oxazoline, **FAOx:**2-Fatty acid derived 2-oxazoline. All polymerizations were performed at 2 M concentration in MeCN.

$M_{n,theo}$ values were calculated based on the conversion values, which was quantitative in all cases. $M_{n,SEC}$ was determined *via* SEC (THF + 2% TEA) using linear PMMA calibration standards.

A series of homopolymers, as well as random and block copolymers of InOx were prepared as listed in **Table 1**. Homopolymerization of InOx at various DP proceeded smoothly up to DP = 50 but increased dispersity has been observed at DP = 100. This may be due to extended reaction time (65 h) and the impact of impurities on the polymerization. The appearance of a tail in the SEC trace of **P4** (**Figure 6d**) indicates the initiation of new chains at a later stage of polymerization, which greatly reduces the number average molar mass and increases the dispersity of the sample. When *i*PrOx and FAOx were employed, well-defined polymers **P7** and **P8** were obtained reaching full monomer conversion. However, the utilization of EtOx as a co-monomer resulted in an increased dispersity, which is believed to occur due to the higher reactivity of EtOx

and therefore, higher rates of side-initiation from the tertiary alkyl bromides of InOx monomers (**P5-P6**). Furthermore, block copolymers of EtOx and InOx (**P9-P10**) were synthesized by polymerizing the EtOx segment first, followed by chain extension with InOx, producing the desired block copolymer with slightly increased MWD. These preliminary findings underpin the versatility of this novel functional monomer to open avenues to the synthesis of dense-, less dense- and blocky brush copolymers.

Synthesis of POx-brush-PAc copolymers

The obtained InOx derived homo, random and block polymers were reacted with ethyl acrylate (EA), oligo(ethylene glycol) methyl ether acrylate (OEGA) and 2-ethylhexyl acrylate (EHA) under typical Cu(0)-RDRP conditions in order to form brush polymer architectures (**Table 2**). The following conditions were applied for Cu(0)-RDRP in organic media (IPA or DMSO as a solvent), $[\text{Monomer}] / [\text{InOx}] / [\text{Me}_6\text{TREN}] / [\text{CuBr}_2] = \text{DP} / 1 / 0.18 / 0.05$ and 5 cm of preactivated copper wire. When InOx homopolymers (DP=10) were reacted with EA (DP=10 or 30), highly dense brush polymers **BP1** and **BP2** with ethyl acrylate chains on every third backbone atom were obtained as the backbone is formed of 2-oxazoline based polymers. The high reactivity of EA and the high density of polymer chains resulted in increased MWD values due to potential polymer-polymer coupling. However, when InOx copolymers were utilized as grafting from polymer initiators, less dense brush polymers **BP3** and **BP4** were obtained, showing less chain-chain coupling and therefore lower MWD values. The utilization of OEGA in the brush polymerization yielded the highly dense brush polymer **BP5** with an extremely low MWD of 1.06, reaching full conversion for OEGA. Due to the relatively lower reactivity compared to EA, the reaction of OEGA occurs more smoothly. It should also be noted that the disagreement between theoretical and measured molecular weight is a result of the brush polymer architecture. With the intention to

broaden the scope of possible 2-oxazoline-*brush*-acrylate copolymers, non-polar EHA was employed in the Cu(0)-mediated polymerization, using iso-propanol (IPA) as a solvent. For all investigated DPs of EHA, ranging from 5-20, and InOx ranging from 10-50, well defined polymers with MWDs between 1.11-1.33 were obtained with full monomer conversion yielding hydrophobic acrylate brushes grafted from a polar POx backbone (**BP6-BP11**).

Table 2. SEC and ¹H NMR analysis of P(InOx)-brush-P(Acrylate/Acrylamide) copolymers.

| Code | <i>Oxazoline brush macroinitiator backbone composition</i> | | | Acrylic brush Monomer and DP | <i>Oxazoline/Acrylic Brush copolymer</i> | | |
|-------------|--|------------------|-----------|---|--|------------------|-----------|
| | Macroinitiator | $M_{n,SEC}$ (Da) | \bar{D} | | $M_{n,theo}$ (Da) | $M_{n,SEC}$ (Da) | \bar{D} |
| BP1 | InOx ₁₀ | 2900 | 1.16 | EA ₁₀ | 13 400 | 5400 | 1.31 |
| BP2 | InOx ₁₀ | 3500 | 1.17 | EA ₃₀ | 33 600 | 21 500 | 1.60 |
| BP3 | InOx _{10-r-iPrOx10} | 3900 | 1.15 | EA ₂₀ | 24 600 | 4500 | 1.37 |
| BP4 | InOx _{10-r-FAOx10} | 5400 | 1.24 | EA ₂₀ | 26 400 | 5800 | 1.27 |
| BP5 | InOx ₁₀ | 2900 | 1.16 | OEGA ₁₀ | 51 400 | 26 900 | 1.06 |
| BP6 | InOx ₁₀ | 2900 | 1.16 | EHA ₅ | 12 100 | 10 700 | 1.11 |
| BP7 | InOx ₅₀ | 6800 | 1.35 | EHA ₅ | 62 900 | 19 400 | 1.33 |
| BP9 | InOx ₁₀ | 2900 | 1.16 | EHA ₁₀ | 21 400 | 15 900 | 1.10 |
| BP10 | InOx ₂₀ | 3800 | 1.23 | EHA ₂₀ | 80 400 | 33 600 | 1.14 |
| BP11 | InOx ₅₀ | 7300 | 1.34 | EHA ₂₀ | 200 900 | 47 700 | 1.25 |
| BP12 | InOx ₁₀ | 2700 | 1.12 | OEGA _{10-b} -EHA ₁₀ | 69 800 | 33 900 | 1.30 |
| BP13 | InOx _{5-b} -EtOx ₄₅ | 5300 | 1.35 | HEAM ₂₀ | 14 900 | 32 000 | 1.47 |
| BP14 | InOx _{10-b} -EtOx ₄₀ | 9600 | 1.30 | NIPAM ₁₀ | 18 700 | 22 000 | 1.38 |
| BP15 | InOx _{10-b} -EtOx ₄₀ | 9600 | 1.30 | NIPAM ₅₀ | 63 900 | 84 000 | 1.50 |

EA (Ethyl acrylate), OEGA (oligo (ethylene glycol)acrylate), EHA (2-ethylhexyl acrylate), HEAM (2-hydroxyethyl acrylamide), NIPAM (*N*-isopropyl acrylamide). eAll polymerizations were performed by employing the following Cu(0) mediated polymerization conditions: [Monomer] / [InOx] / [Me₆TREN] / [CuBr₂] = DP / 1 / 0.18 / 0.05 and 5 cm of preactivated copper wire. $M_{n,theo}$ values were calculated based on the conversion values, determined *via* ¹H NMR spectroscopy. $M_{n,SEC}$ was determined by SEC in THF + 2% TEA or DMF with 5 mM NH₄BF₄ for water-soluble polymers calibrated with linear PMMA standards.

The grafting from approach was further investigated in a chain extension experiment. Hence, InOx (DP=10) was utilized as a brush initiator for the Cu(0)-RDRP of OEGA (DP=10). After full monomer conversion (4 h), chain extension was induced by adding non-polar EHA (DP=10). However, the polymerization stopped at 60% monomer conversion after 18 h to yield a highly dense, amphiphilic and well defined brush copolymer (\mathcal{D} =1.27) with a number average molecular weight of 22,800 Da (**Figure 7a**). In order to increase the monomer conversion for the second block, the experiment was repeated by adding the second portion of monomer (EHA, DP = 10) with an additional amount of ligand and deactivator (0.18 equiv. of Me₆TREN and 0.05 equiv. of CuBr₂). The additional ligand and deactivator resulted in an increased conversion of >90% after 18 h, maintaining good control over the polymerization (\mathcal{D} = 1.21, M_n =30,800 Da) (**Figure 7b**).

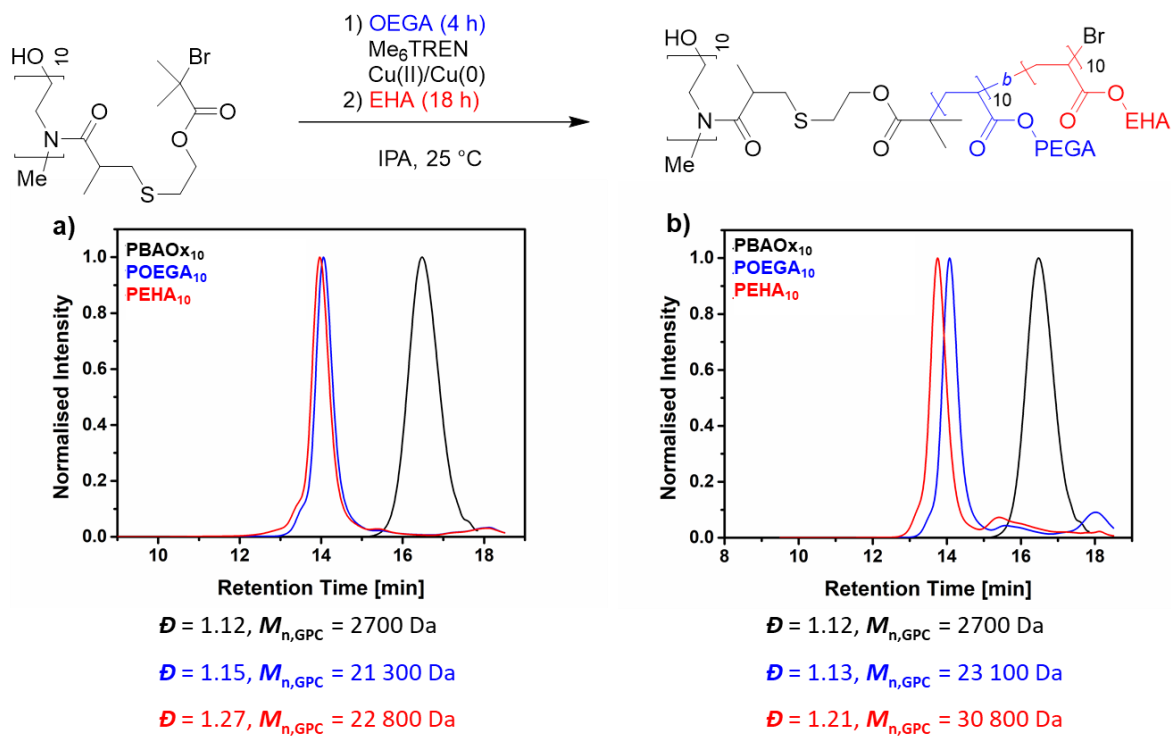


Figure 7: SEC analysis of InOx₁₀ initiated Cu(0)-RDRP with OEGA (DP=10) and chain extension with EHA (DP=10) by adding no additional catalyst with the second block (a) or adding additional catalyst (b).

The small shift of the SEC traces was thought to result from the drastic change in polarity of the chain extended brush polymer causing a decrease in hydrodynamic volume. These findings clearly demonstrate a robust method for synthesizing well-defined amphiphilic brush copolymers by combining a functional POx backbone with the powerful features of Cu(0)-mediated RDRP.

As mentioned above, block copolymers of InOx and EtOx are also accessible, allowing the synthesis of water-soluble blocky brush copolymers. Herein, the 2-oxazoline polymer **P11** was utilized in aqueous Cu-mediated RDRP of the water-soluble acrylamides such as *N*-hydroxyethyl acrylamide (HEAM) (**BP13**) and *N*-isopropylacrylamide (NIPAM) (**BP14-BP15**). Polymerizations proceeded to full monomer conversion within less than 2 h, yielding water soluble

brush copolymers with slightly increased MWDs (\mathcal{D} =1.38-1.50). The moderate dispersity values result from the less defined starting material and the highly reactive polymerization system.

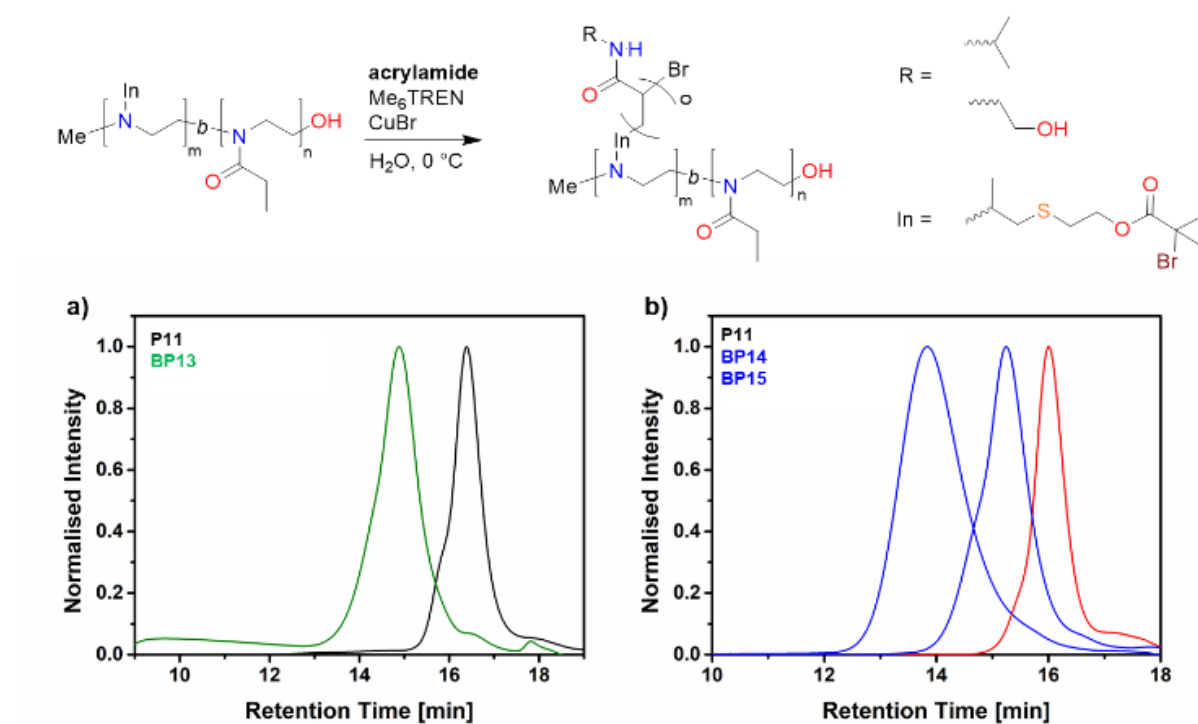


Figure 8: SEC traces of synthesized water soluble brush polymers a) HEAM (DP=20) and b) NIPAM (DP=10 and DP=50). SEC was carried out in DMF + 5 mM ammonium tetrafluoroborate to achieve solubility of hydrophilic brush polymers.

Conclusions

In conclusion, a very simple and modular synthesis method for a 2-oxazoline derived inimer structure was demonstrated. Reactivity studies were carried out in order to find optimum polymerization conditions for InOx inimer and to prevent self-initiation. Based on this understanding, a variety of random and block copolymers with EtOx, FAOx and *i*PrOx were synthesized in a controlled fashion. Brush copolymer synthesis *via* Cu(0)-mediated RDRP was

demonstrated to proceed readily with different polar and apolar monomers in DMSO or IPA as well as water soluble acrylamides in aqueous polymerization media. Therefore, an arsenal of novel dense-/less dense- and blocky brush copolymers with possible applications in the fields of bio lubrication and drug delivery become accessible with this synthetic method. The potential loss of the beneficial properties of poly(2-oxazolines) due to shielding effects of the poly(acrylate) brushes can be circumvented by reducing the grafting density or by employing 2-oxazoline block copolymers as brush initiators. In the future, we will be focusing on the elucidation of the structural properties and explore possible applications for brush copolymers from 2-oxazolines and acrylic monomers.

Supporting Information. Materials, instruments, general synthesis procedures, supporting analysis of the polymers presented in the manuscript are provided in the supporting information.

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Author Contributions

VB has performed all the experimental work. The project was designed and discussed by the contributions of all authors. The manuscript was written through contributions of all authors.

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Graphical abstract

