

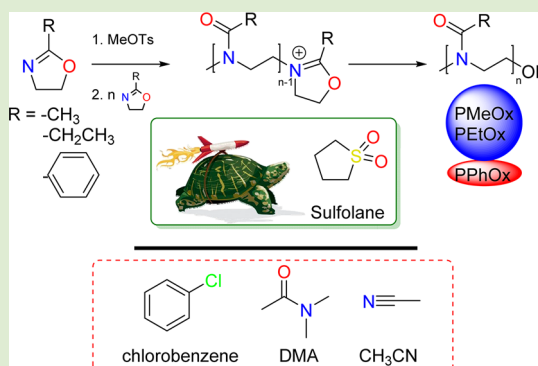
Sulfolane as Common Rate Accelerating Solvent for the Cationic Ring-Opening Polymerization of 2-Oxazolines

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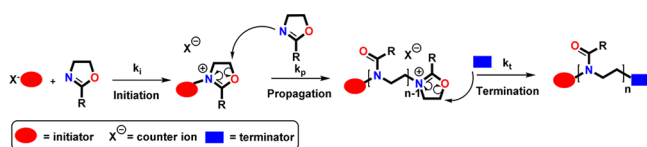
Supporting Information

ABSTRACT: The search for alternative solvents for the cationic ring-opening polymerization (CROP) of 2-methyl-2-oxazoline (MeOx) is driven by the poor solubility of P(MeOx) in polymerization solvents such as acetonitrile (CH₃CN) and chlorobenzene as well as in MeOx itself. In this study, solvent screening has revealed that especially sulfolane is a good solvent for P(MeOx). Unexpectedly, an increased propagation rate constant (k_p) was found for the CROP of MeOx in sulfolane. Further extended kinetic studies at different temperatures (60–180 °C), revealed that the acceleration is due to an increase in frequency factor, while the activation energy (E_a) of the reaction is hardly affected. In order to explore the versatility of sulfolane as polymerization solvent for the CROP of 2-oxazolines in general, also the polymerization kinetics of other 2-oxazoline monomers, such as 2-ethyl-2-oxazoline (EtOx) and 2-phenyl-2-oxazoline (PhOx), have been studied, revealing a common acceleration of the CROP of 2-oxazoline monomers in sulfolane. This also enabled more controlled synthesis of P(MeOx)-*block*-P(PhOx) block copolymers that otherwise suffers from solvent incompatibility.



During the past decades, researchers have been searching for alternative biocompatible polymers, that “outperform” the gold standard in the field, poly(ethylene glycol).^{1–3} In this respect, poly(2-alkyl/aryl-2-oxazoline)s (PAOx), more specifically, poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx), have been widely investigated for their use in biomedical applications.^{1,4–6} PAOx are prepared by living cationic ring-opening polymerization (CROP) of 2-oxazolines, and their polymerization mechanism has been studied widely (Scheme 1).⁷ One of the main advantages of the CROP is that

Scheme 1. General Scheme of the Cationic Ring-Opening Polymerization of 2-Oxazolines, Following a Three-Step Mechanism, Including Initiation, Propagation, and Termination



its living nature provides good control over the molar mass distribution, that is, narrow dispersity (\mathcal{D}), and very high end-group fidelity.^{8,9} Additionally, a broad range of structures and polymer properties are easily accessible by variation of the monomer structures.^{10–13} The CROP of 2-oxazolines consists of three steps, namely, the initiation, propagation, and termination.

The polymerization is initiated by the attack of the nitrogen lone pair of the monomer onto an electrophilic initiator, such as methyl *p*-toluenesulfonate (MeOTs), methyl trifluoromethanesulfonate, or alkyl halides, leading to a cationic oxazolium species.^{14–17} Propagation occurs via subsequent attack of the next monomer onto the five-position of this oxazolium species, resulting in ring-opening, with the new monomer ending up as the reactive cationic oxazolium chain end. Finally, the living polymerization is terminated by adding a nucleophilic terminating agent, such as water, amines, or carboxylates.^{18–21} The CROP of 2-oxazolines is often proposed to occur in an ideal living manner, assuming that no chain transfer and termination reactions occur during the polymerization.^{10,22,23} The propagation rate of the CROP of 2-oxazolines determines the rate of the overall polymerization and is influenced by different parameters such as the type of monomer, initiator, and solvent.^{24–29} In earlier research by, among others, the groups of Litt and Nuyken, already a variety of parameters have been discussed.^{8,23,30} Litt explored the effect and possible interference of solvents with different functional groups on the CROP of 2-oxazolines in order to explain the mechanism of polymerization. In this research, 2,4-dimethyl sulfolane was already mentioned among the noninterfering

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solvents, which was proven by a normal infrared spectrum for the CROP of 2-(*n*-pentyl)-2-oxazoline.³¹

The CROP of 2-oxazolines is commonly performed in CH₃CN^{31,32} using MeOTs as initiator. However, CH₃CN seems to be less suitable for the polymerization of MeOx due to the poor solubility of higher molar mass PMeOx (>~20 kDa) in CH₃CN, resulting in reduced control over the CROP of MeOx when aiming for higher degrees of polymerization (DPs). This can be explained by a significant change in hydrophilicity upon polymerization due to the isomerization of the cyclic imino ether structure (MeOx) to a tertiary amide structure (PMeOx). The same reasoning can be applied to explain the poor solubility of PMeOx in other common polymerization solvents, including chlorobenzene and even its own monomer, obstructing bulk polymerization.

In the search for more polar solvents for the CROP of MeOx, we identified *N,N*-dimethylacetamide (DMA) and sulfolane. Sulfolane is an alternative dipolar aprotic solvent, which is mostly used as an industrial solvent but, recently, also used as a universal solvent for ATRP.³³ Apart from the extremely high dipole moment (4.7 D), high boiling point, and high chemical stability, it has a high solvency power for cations (i.e., high Hildebrand solubility parameter), which is favorable for the CROP of 2-oxazolines.³⁴ In both DMA and sulfolane, MeOx and PMeOx are found to be soluble (Table 1), whereby PMeOx readily dissolved (++) in sulfolane and more slowly in DMA (+), making them promising candidates for the CROP of MeOx.

Table 1. Overview of the Tested Polymerization Solvents with Corresponding Dipole Moments, Hildebrand Parameters, and Solubility of PMeOx in Each Solvent

solvent	dipole moment ³⁴	Hildebrand solubility parameter ³⁴	P(MeOx) solubility ^a
chlorobenzene	1.54	9.5	—
DMA	3.73	23.3	+
CH ₃ CN	3.44	11.9	+/-
sulfolane	4.69	27.2	++
MeOx	n.d. ^b	n.d. ^b	—

^aExperimentally determined. ^bNot determined.

After the solvent screening, a series of kinetic studies was performed for the CROP of MeOx, with a target DP of 100, in DMA and sulfolane at 140 °C, and under microwave conditions, in order to compare the results with the conventional polymerization of MeOx in CH₃CN. Note that PMeOx with a DP of 100 is still soluble in CH₃CN, enabling the kinetic study, but higher DP MeOx is no longer well-soluble in CH₃CN. All polymerizations showed linear first-order kinetics (Figure 1, left), whereby it should be mentioned that the microwave heating ramp to reach 140 °C is not included in the plotted reaction time, and therefore, the origin is not intercepted for very faster polymerizations. Remarkably, the microwave polymerization in sulfolane revealed a 3-fold increase of the k_p ($k_p = 393 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$) compared to the polymerization in CH₃CN ($k_p = 133 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$) and DMA ($k_p = 103 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$), as determined from the slope of the first order kinetic plot assuming fast and complete initiation as is commonly true for the CROP of 2-oxazolines with MeOTs as initiator.³² The size exclusion chromatography (SEC) traces of the final polymers reveal that DMA offers relatively poor control over the CROP of MeOx

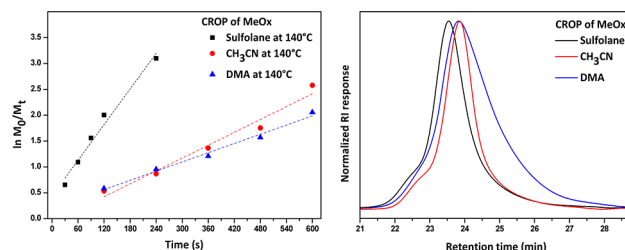


Figure 1. Comparison of the linear first order plots of the monomer consumption vs time for the living CROP of MeOx in sulfolane ($M_n = 16.9$ kDa; $\bar{D} = 1.17$), CH₃CN ($M_n = 13.6$ kDa; $\bar{D} = 1.16$), and DMA ($M_n = 11.5$ kDa; $\bar{D} = 1.35$) with MeOTs as initiator, at 140 °C with a DP of 100 (left); corresponding SEC traces with DMA/LiCl as SEC eluent (right).

(Figure 1, right), most likely due to trace impurities that are very difficult to remove from DMA, whereas the SEC traces for the polymers obtained in CH₃CN and sulfolane are quite well-defined, with \bar{D} values lower than 1.2.

In order to gain further insight in the CROP of MeOx in sulfolane, the CROP was investigated at different temperatures, that is, 60, 80, 100, 120, and 140 °C (Figure 2A). From the

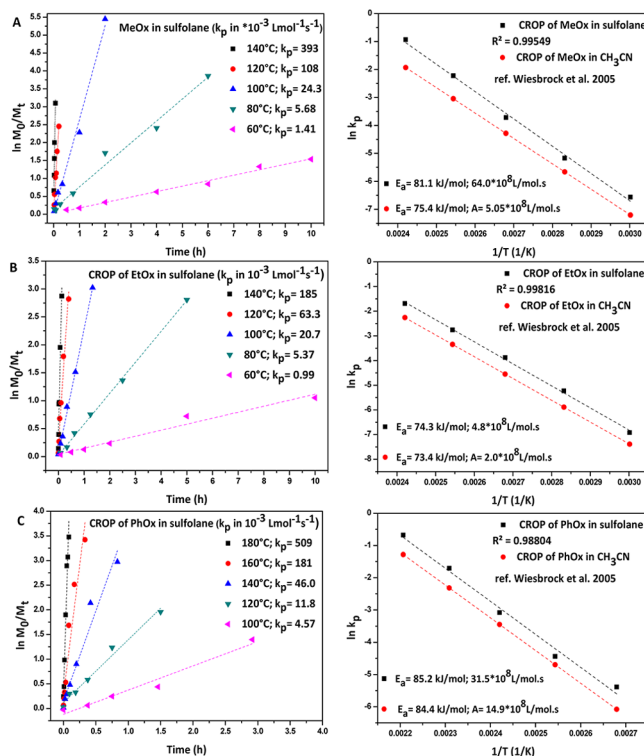


Figure 2. First-order kinetic plots for the cationic ring-opening polymerization of MeOx (A), EtOx (B), and PhOx (C) in sulfolane at 3 M monomer concentration, with MeOTs as initiator and target DP of 100 (left), and the corresponding Arrhenius plots together with Arrhenius plots for the polymerization of the corresponding monomers in CH₃CN (right).¹⁰

Arrhenius plot ($\ln k_p$ vs $1/T$), the respective Arrhenius parameters with regard to eq 2 could be derived, revealing an activation energy (E_a) of 81.1 kJ/mol, somewhat higher than the reported E_a for the CROP of MeOx in CH₃CN (Wiesbrock et al., $E_a = 75.4$ kJ/mol), indicating that the likelihood for reaction upon collision is mildly reduced in sulfolane.³² The

frequency factor (A), however, shows a significant 10-fold increase, with a value of $6.40 \times 10^9 \text{ s}^{-1}$ for the CROP of MeOx in sulfolane versus $5.05 \times 10^8 \text{ s}^{-1}$ for the CROP of MeOx in CH_3CN . The frequency factor, A , can be interpreted as the rate or number of collisions between the reactants. Altogether, this leads to a higher k_p value for the CROP of MeOx in sulfolane as the rate of successful collisions, that is, the product of A and the E_a term (1), is defined as the k_p .

$$k = Ae^{-E_a/RT} \quad (1)$$

$$\ln k = \ln A - \frac{E_a}{RT} \quad (2)$$

To understand the higher pre-exponential factor A in sulfolane, we should consider that A can be expressed as the product of the collision factor (Z) and the steric factor (ρ). Even though these factors are very difficult to determine, it may be speculated that the amphiphilic structure of sulfolane leads to preferential solvation of MeOx and PMeOx by the polar sulfone group. As a result, the chances of collision increase as both reagents have enhanced local concentration in the sulfone part of the solvent, leading to higher Z . Moreover, the orientation of the molecules will be altered as the hydrophilic cationic imino ether part of the oxazolinium living chain end will orient toward the sulfone groups, thereby exposing the C5-carbon where the next monomer will attack, potentially leading to an increase in ρ .

To examine the scope of sulfolane as rate accelerating polymerization solvent for the CROP of 2-oxazolines, kinetic studies for the CROP of EtOx (hydrophilic) and PhOx (aromatic and hydrophobic) were also performed at different temperatures. (Figure 2B,C) Both the k_p s for the CROP of EtOx ($k_p^{140^\circ\text{C}} = 185 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$) and PhOx ($k_p^{140^\circ\text{C}} = 46 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$) at 140°C in sulfolane revealed faster polymerizations compared to the CROP of the respective monomers in CH_3CN , that is, EtOx ($k_p^{140^\circ\text{C}} = 104 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$) and PhOx ($k_p^{140^\circ\text{C}} = 32 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$). Although all polymerizations are accelerated in sulfolane compared to CH_3CN , the relative order in k_p remains unchanged with the CROP of MeOx being faster than EtOx, followed by PhOx. From the Arrhenius plots (Figure 2) it can be concluded that for all three 2-oxazoline monomers the E_a for the CROP in sulfolane remains more or less unchanged compared to the E_a in CH_3CN . On the contrary, the CROP of the 2-oxazolines shows a higher A value in sulfolane compared to the CROP in CH_3CN , which demonstrates clearly the solvent-induced acceleration by sulfolane, as discussed above for MeOx.

DMA-SEC analyses demonstrated that all synthesized PAOx polymers have a \bar{D} of <1.2 – 1.3 (Figure 3), which is similar to the previous reported results for the CROP of 2-oxazolines in CH_3CN ³² and is acceptable for PMeOx, PEtOx, and PPhOx, synthesized at elevated temperatures, inevitably leading to minor chain transfer and coupling reactions as is also evident from the double molar mass shoulder. A slight increase in the \bar{D} is observed when lowering the polymerization temperature, which could be an indication of slower initiation. Furthermore, the linear relationship between the degree of conversion and the experimental M_n demonstrates the livingness and controlled character of the CROP of MeOx, EtOx, and PhOx. It is important to note that the experimental M_n values are calculated against poly(methyl methacrylate) (PMMA) standards. Therefore, the experimental M_n values are overestimated

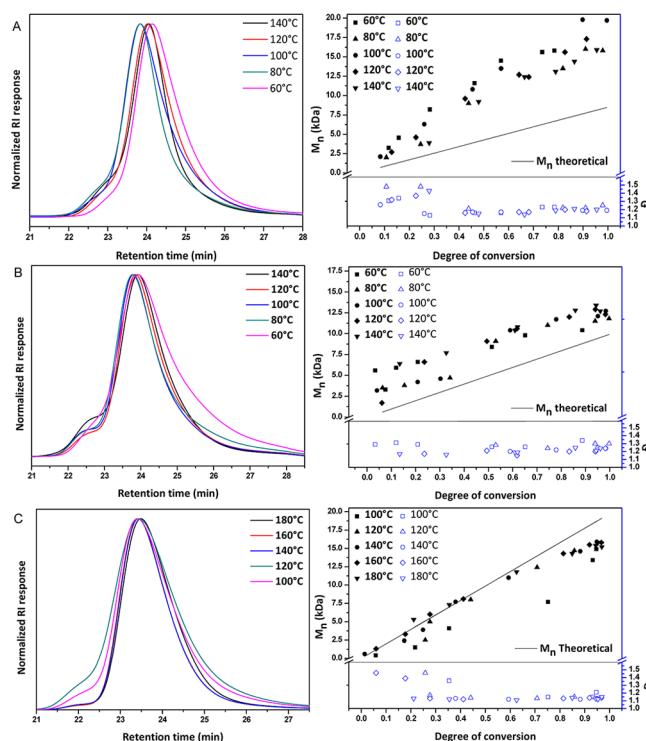


Figure 3. Size-exclusion chromatography traces for PMeOx (A), PEtOx (B), and PPhOx (C). For comparison, the polymers with conversion over 90% at the different temperatures are shown (left). The experimental and theoretical number-average molecular weights and dispersities are plotted vs conversion for the CROP of MeOx, EtOx, and PhOx (right).

for the hydrophilic polymers PMeOx and PEtOx (Figure 3). Importantly, we recently reported a correction factor for the M_n of PEtOx versus PMMA standards in DMA of 0.5876,³⁵ which indeed appears to be in line with the overestimation of the M_n values in Figure 3 for PEtOx, confirming near 100% initiation efficiency, as we also speculated above for PMeOx.

As a final proof for the livingness of the CROP of 2-oxazolines in sulfolane, a block copolymer has been synthesized consisting of a first block of PMeOx, followed by a second block of PPhOx. Here, the PMeOx block was synthesized first to ensure fast initiation of the second PPhOx block after sequential addition of the PhOx monomer. The SEC analysis (Figure 4) shows the first PMeOx block, sampled before addition of the second monomer, and the resulting PMeOx-block-PPhOx copolymer, both with \bar{D} values of 1.1. The ^1H NMR analysis further confirmed the desired structure.

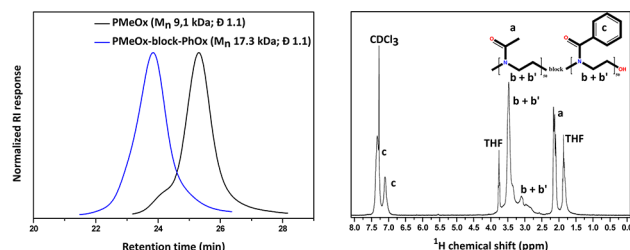


Figure 4. Size exclusion chromatography trace of first PMeOx₅₀ block and resulting PMeOx₅₀-block-PPhOx₅₀ copolymer (left). Corresponding NMR analysis of block copolymer after precipitation in tetrahydrofuran (right).

Importantly, the prepared diblock copolymer has a significantly lower \bar{D} than the previously reported analogue that was prepared in CH_3CN ($\bar{D} = 1.25$), which may be a result of improved solvent compatibility of both hydrophilic (MeOx) and hydrophobic blocks (PhOx) in sulfolane.¹⁰

In conclusion, it is clearly shown that sulfolane can be used as a polymerization solvent for the CROP of hydrophilic and aromatic (hydrophobic) 2-oxazoline monomers, such as MeOx, EtOx, and PhOx. In general, the CROP is faster in sulfolane, compared to the standard polymerization solvent, CH_3CN , which opens tremendous possibilities toward further optimization of the CROP of 2-oxazolines with regard to decreasing reaction times for the synthesis of PAOx. Specifically, the synthesis of high molar mass PMeOx will be targeted and investigated in further research facilitated by the good solubility of PMeOx in sulfolane, enabling further use of PMeOx in biomedical applications.

■ ASSOCIATED CONTENT

■ Supporting Information

Materials, equipment, and experimental data for the synthesis of the homopolymers and PMeOx-*block*-PhOx copolymer. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00392.

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■ Notes

The authors declare no competing financial interest.

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