Synthesis and microwave assisted polymerization of fluorinated 2-phenyl-2-oxazolines: the fastest 2-oxazoline monomer to date†

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The living cationic ring-opening polymerization of 2-oxazolines with fluorinated aromatic substituents was found to be strongly accelerated by *o*-fluoro substituents.

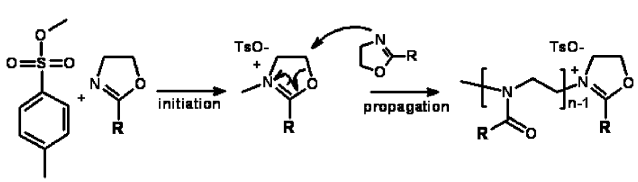
2-Oxazolines are known as versatile monomers in living cationic ring-opening polymerizations (CROP) since 1966/1967.[1–5] The polymerization, schematically shown in Scheme 1, starts with a nucleophilic attack of the lone pair of the ring nitrogen of the 2-oxazoline onto an initiator such as methyl tosylate (or other electrophiles such as benzyl bromide).[6,7] The nucleophilic attack of a second monomer unit onto the formed oxazolinium species leads to a rearrangement of the ring causing the cleavage of the C–O bond. Due to the absence of chain-transfer or termination reactions under the appropriate conditions, the polymerization occurs in a living manner until all monomer is consumed or a terminating agent such as water is added.

The resulting polymer consists of a polyethylenimine chain with narrow molecular weight distributions (PDI < 1.20) which bears the 2-substituent of the starting oxazoline monomer as amidic side chains. The properties of the polymers are strongly dependent on the 2-substituent and therefore easily tunable by using various 2-substituents, R.[5,8] Due to its manifold properties, (co)poly(2-oxazoline)s are of wide interest in chemical and medicinal research.[9,10] During the last forty years, the long polymerization time of 2-oxazolines to reach full conversion (between hours and weeks)[9] was a major drawback. Since 2004 this drawback has been overcome by using a single mode microwave reactor as heat source (advantageous non-contact heating) and closed reaction vessels (superheated conditions, *i.e.* $T > b_p$ solvent) which decreased the polymerization time down to a few minutes.[11] The use of ionic liquids as solvent further increased the polymerization rate.[12]

This development was thought to enable the expansion of the possible monomer range to 2-oxazolines, which were expected to feature very low polymerization rates. Here one can think about 2-phenyl-2-oxazolines which are substituted with electron-withdrawing substituents which lower the electron density of the aromatic system, and hence from the conjugated oxazoline ring, resulting in reduced nucleophilicity of its nitrogen atom. To prove this hypothesis, we synthesized and polymerized four fluorinated 2-phenyl-2-oxazolines starting with all three possible monofluorinated monomers to investigate the influence of the substitution position onto the polymerization. In addition to the three monofluorinated aromatic monomers, the polymerization of *o*-difluoro-2-phenyl-2-oxazoline was investigated. Here, we discuss the synthesis of these fluorinated monomers and discuss the unexpected differences of the polymerization kinetics in detail. These fluorinated 2-oxazoline monomers were chosen to address the possible polymerization of low reactive monomers since they are interesting candidates for the preparation of (multi)-block copoly(2-oxazoline)s that combine hydrophilic, lipophilic and fluorophilic segments into one polymer chain.

Although the synthesis of *o*-fluoro[13,14] and *m*-fluoro[15] 2-phenyl-2-oxazoline were already reported starting from the corresponding aromatic acid or acid chlorides, we synthesized the monofluorinated oxazolines **2a–c** from the corresponding benzonitriles according to a modified one-step synthesis procedure (Scheme 2).[16] The monofluoro-benzonitriles **1a–c** were treated with 2-ethanolamine in the presence of a Lewis-acid catalyst, namely $Zn(OAc)_2$, to yield the desired oxazolines **2a–c** in moderate yields. Due to the undesired side product formation during the synthesis of **2a** (see ESI†) we changed our synthetic strategy to synthesize the *ortho*-difluoro analogue **5** *via* a two-step procedure which is slightly different from the previously reported synthetic method for this compound using ethanol amine.[17] Starting from the acid chloride **3** one can obtain amide **4** *via* a modified one-step procedure in a good yield.[18] Finally, the desired oxazoline **5** can be obtained by basic elimination of hydrogen chloride.

The fluorinated monomers and the non-fluorinated analogue 2-phenyl-2-oxazoline (PhOx) were polymerized *via* cationic ring-opening polymerization in nitromethane at 140 °C with methyl tosylate as initiator using microwave irradiation



Scheme 1 Schematic representation of the methyl tosylate initiated cationic ring-opening polymerization of 2-substituted 2-oxazolines.

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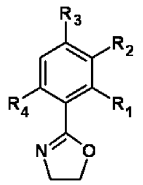

2a: R_1 = F; R_2 = R_3 = R_4 = H
2b: R_2 = F; R_1 = R_3 = R_4 = H
2c: R_3 = F; R_1 = R_2 = R_4 = H
5: R_1 = R_4 = F; R_2 = R_3 = H

Scheme 2 Overview of the investigated monofluoro-2-phenyl-2-oxazolines **2a–c** and the *o*-difluoro-2-phenyl-2-oxazoline **5**.

as heat source. Therefore, stock solutions were prepared containing solvent, monomer and initiator with [monomer] : [initiator] = 60 : 1. The initial monomer concentration $[M]_0$ was in all cases $[M]_0$ = 1.4 M. From these stock solutions, several reaction vials were prepared, which were polymerized at 140 °C for different times. After the desired time, the polymerizations were quenched by the addition of water and the monomer conversion, represented as $\ln(M_0/M_t)$, was monitored by GC. In all cases, the first-order kinetic plots of the monomer consumption in respect to the reaction time revealed a linear relationship (Fig. 1, left) demonstrating a constant amount of propagating species. A closer look at the polymerization times showed that indeed all monomers, which were expected to feature low polymerization rates, could be polymerized to full conversion in less than two hours using microwave irradiation.

Subsequent GPC analysis resulted in constantly increasing molecular weights of the polymers during the polymerizations (Fig. 1, right). The M_n values correlated reasonably linear to the monomer conversion demonstrating a living/controlled polymerization; discrepancies to the theoretical M_n might be related to the occurrence of some chain transfer reactions as well as to calculating the M_n in respect to polystyrene standards. The PDI values of all polymers are below 1.30 up to 90% conversion indicating that the polymerization takes place in a controlled manner. The higher PDI values for **2a–c** (up to 1.46) for conversions higher than 90% are presumably caused by the high viscosity of the polymerization mixture and therefore hindered diffusion of the last monomer units to the reaction center. Nonetheless, the polymerization of **5** reveals low polydispersity indices of around 1.2 up to 99% conversion. Furthermore, all four polymers could be characterized by MALDI-TOF-MS. The spectra feature monomodal mass distributions and equidistant peaks with a difference according to the mass of one monomer unit Δ = 165 Da (**2a–c**) or Δ = 183 Da (**5**), respectively (see ESI; Fig. S7–S10).†

From the slopes of the first-order kinetic plots (Fig. 1, left) the corresponding polymerization rates were determined, which are summarized in Table 1. PhOx features a polymerization rate of k_P = 0.036 L mol^{-1} s^{-1} which is a factor three slower than the polymerization rates of 2-alkyl-2-oxazolines such as 2-ethyl-2-oxazoline.[11] This is due to the +M effect of the phenyl substituent onto the oxazoline ring. The positive charge of the oxazolinium ring of the growing species is partially compensated by resonance with the aromatic system leading to a slower chain growth. This effect is slightly more distinctive for *m*FOx **2b** and *p*FOx **2c** resulting in slightly slower polymerization rates of k_P = 0.027 L mol^{-1} s^{-1} and k_P = 0.029 L mol^{-1} s^{-1}. However, the polymerization rates for *o*FOx **2a** (k_P = 0.173 L mol^{-1} s^{-1}) and *o*DFOx **5** (k_P = 0.382 L mol^{-1} s^{-1}) are surprisingly high, *i.e.* the polymerizations proceed five or ten times faster than for PhOx. In fact, the polymerization of *o*DFOx **5** is even faster than the polymerization of 2-methyl-2-oxazoline at 140 °C (k_P = 0.146 L mol^{-1} s^{-1})[7] and can be considered the fastest, "Speedy Gonzales", 2-oxazoline monomer to date.

To understand this observed acceleration, MMFF94 calculations were performed on **2a–c**, **5** and the *N*-methylated model compounds **2a–c**$^+$, **5**$^+$ (representing the transition states during the polymerizations) to gain detailed information about the influence of the geometric structure onto their polymerization behavior (for graphical details see ESI,† Table S1 and S2).[19] The Monte Carlo simulations,[19] using MMFF94 force field, for the unsymmetrical monomers *o*FOx **2a** and *m*FOx **2b** result in two conformers with only small energetic differences, while the symmetrical monomers *p*FOx **2c** and *o*DFOx **5** exist in only one conformer as expected. In the minimum structures of *m*FOx **2b** and *p*FOx **2c** the oxazoline unit and the aromatic unit are nearly perfectly coplanar with out-of-plane angles of α = 0.11 and 0.17°, respectively. This enables in both cases unhindered mesomeric interactions between both rings leading to slightly lower polymerization rates for *p*FOx **2b** and *m*FOx **2c** than for PhOx: due to the electron-withdrawing effect of the fluorine the electron density of the phenyl ring is lowered resulting in a negative impact onto the +M effect. On the other hand, if an *ortho*-F substituent is present, the coplanarity of both rings is removed.

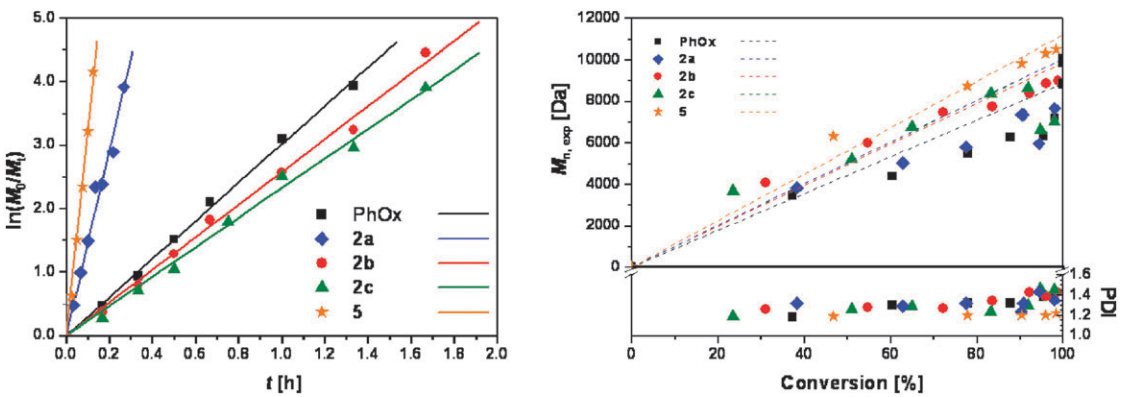

Fig. 1 Polymerizations of PhOx, **2a–c** and **5**: (left) first-order kinetics plots; (right) number-average molecular weight M_n against conversion.

Table 1 Polymerization rates

Monomer	$k_p/10^{-3}$ L mol^{-1} s^{-1}
PhOx	35.8
*m*FOx **2c**	26.7
*p*FOx **2b**	29.3
*o*FOx **2a**	173.1
*oD*FOx **5**	382.4

For *o*FOx **2a** the out-of-plane angle is about $\alpha = 3$–4° indicating only minor influence onto the mesomeric ring–ring interaction, while in the case of *o*DFOx **5** a major influence becomes visible by means of an out-of-plane angle of $\alpha = 39^\circ$.

Additional structural information could be obtained from Monte Carlo simulations of the methylated model compounds **2a–c**$^+$, **5**$^+$ using MMFF94 force field, which gave in all cases only one energetically favored conformer. The structural occurrences avoid $N^+\cdots F$ interactions in the case of methylated **2b**$^+$ and **2c**$^+$ but for the *ortho*-substituted analogues the $N^+\cdots F$ distances with $d = 2.99$ Å (**2a**$^+$) or $d = 3.04$ Å (**5**$^+$) indicate attractive C–F$\cdots$N$^+$ interactions, also known from literature.[20–22] As such, it can be concluded that the polymerization of *o*FOx **2a** and *o*DFOx **5** is accelerated due to the $N^+\cdots F$ interactions. The donation of electron density through space of the *ortho*-F substituent to the cationic reaction center—the tetra-coordinated nitrogen atom—accelerates the polymerization tremendously. The further acceleration for the polymerization of **5** can be attributed to the higher nucleophilicity of the attacking monomer **5** resulting from the non-coplanarity of the aromatic and the oxazoline unit.

The intermolecular interaction between the fluorine and the cationic center can be evidenced by means of NMR spectroscopy: first the $^1J_{C-F}$ coupling constant decreases and second the ^{19}F signals shift to higher field.[23,24] To evidence this proposed interaction, we synthesized the cationic model compound CH_3-*oD*FOx **5**$^+$ representing the growing polymerization species of **5** during the polymerization. We prepared a 1.4 molar solution of **5** together with an equimolar amount of methyl tosylate in dry nitromethane-d_3 and heated it in the microwave to 140 °C. After the reaction, the solution was transferred to a dry NMR tube for NMR analysis (see ESI,† Fig. S1–S6). Unfortunately, the ^{13}C spectrum was non-conclusive due to the very broad signals of the carbon atoms attached to the fluorine. However, the ^{19}F NMR spectrum showed the fluorine signal of **5** at −111.7 ppm in respect to hexafluoroisopropanol as internal reference. In the ^{19}F NMR spectrum of the cationic intermediate **5**$^+$ two signals appear. One sharp singlet at −107.3 ppm, which can be assigned to the fluorine which does not participate in the interaction with the cationic center, and one multiplet shifted to higher field, −115.5 ppm, representing the C–F$\cdots$N$^+$ motif supporting the proposed fluorine–cation interaction.

In summary, the living cationic ring-opening polymerization of four fluorinated 2-phenyl-2-oxazolines was successfully performed using microwave irradiation as heat source. For the *p*FOx **2b** and *m*FOx **2c** the electron-withdrawing effect of the fluorine causes a lower polymerization rate in comparison to PhOx while *o*FOx **2a** and *o*DFOx **5** polymerize much faster than PhOx. In fact, the *o*DFOx **5** is the fastest polymerizing 2-oxazoline monomer known to date. This observed acceleration is due to an interaction of the cationic reaction center N$^+$ with the *ortho*-fluorine substituent which overcompensates the negative electron-withdrawing effect and by the increased nucleophilic character of the monomer **5** due to the non-planarity of the oxazoline and the phenyl substituent. The stabilizing C–F$\cdots$N$^+$ interaction was supported by theoretical calculations (MMFF94) and by means of ^{19}F NMR spectroscopy.

Future investigations will focus on the synthesis of all other possible fluorinated 2-phenyl-2-oxazolines ($F_2 \rightarrow F_5$) to perform a systematic study on the effect of F-substitution on the polymerizations. In addition, other *o*-substituents will be introduced to further probe the effect on the polymerization rates. Besides these detailed investigations to understand the observed acceleration, future research will strongly focus on the formation of co- and terpolymers with other non-fluorinated monomers to investigate the phase-separation and the formation of multicompartment micelles.

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