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SYNTHESIS OF A NOVEL α, ω-DIEPOXY-POLY(2-ETHYL-2-OXAZOLINE) OLIGOMER

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In the present paper, we report several methods of post-modification reactions to synthesize a new diepoxy-terminated poly(2-ethyl-2-oxazoline) oligomer, from α, ω-dihydroxy oligo 2-ethyl-2-oxazoline and epichlorohydrin. A comparison between phase transfer catalysis (PTC) and metalation method is made. Moreover, the influence of several factors affecting the epoxidation yield like: catalyst nature, base concentration, and temperature were investigated. The metalation method was very sensitive to water traces and therefore the yield was lower due to the very hygroscopic character of the poly(2-ethyl-2-oxazoline). The PTC method is more suitable for the synthesis of diepoxy oligomers and the optimal ratio between the reactants was determined.

Keywords: 2-ethyl-2-oxazoline, cationic polymerization, epichlorohydrin, phase-transfer catalyst

1. Introduction

Since their discovery in 1966 [1, 2], the class of 2-oxazolines has received great interest due to its versatility in enabling the preparation of materials with tailor-made properties, such as: fluorescent azo-polymers [3], light-responsive azo-polymers [4], thermo-responsive [5] polymers, and so on. The living cationic ring-opening polymerization (CROP) of 2-oxazolines provides easy and direct access to a wide variety of well-defined polymers [6, 7], in which the endgroup

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functionality can be controlled during the initiation and termination steps. Furthermore, the properties of poly(2-oxazoline)s can be tuned simply by varying the side chain of the 2-oxazoline monomer [6, 8, 9]. Recently, the particular focus has been to apply these materials for biomedical applications [8], whereas it is essential that the temperature responsiveness to be consistently at physiologically relevant temperatures and the polymer to be biocompatible.

Monofunctional and telechelic poly(2-oxazoline) prepolymers are excellent candidates for block [10] and graft copolymers [11, 12]. They can be synthesized with reasonable control over molecular weights and their distributions, and they can also be functionalized. Functional poly(2-oxazoline) oligomers can be used as macromonomers in free radical polymerizations to obtain graft polymers [12, 13], prepolymers [14, 15], and macroinitiators for block copolymer synthesis [16-18]. Multifunctional initiators were also used to prepare difunctional [19, 20] and star-shaped polymers [21-24]. Termination reactions of the cationic polymerization of 2-oxazolines with various nucleophiles like amines [25] or carboxylic acids [26, 27] also allows the introduction of functionalities to the chain-ends. Thus, difunctional polyoxazoline oligomers can be prepared by combining functional initiators and/or terminating agents or by quantitative post-modifications reactions. Difunctional poly(2-oxazoline) prepolymers can potentially be incorporated into cross-linked networks and have applications in the field of polymeric membranes, or as hydrogels for tissue engineering matrices. The preparation of the prepolymers with controllable molecular weights and quantitative endgroup functionality is the key factor to obtain the desired structures. Poly(2-oxazoline)s with hydroxyl endgroups are commonly synthesized because they can be further functionalized and utilized as ideal prepolymers for incorporation into block copolymer and network structures [28, 29]. In the literature there are few reports of controlled molecular weight poly(2-oxazoline)s with precise endgroup functionality. Poly(oxazoline)s have the beneficial key properties of poly(ethyleneglycol) [30, 31] that meet all the necessary requirements to be used in medical applications, but also have characteristics that are novel and unique, like side-chain functionality and end-group versatility.

This paper describes a detailed investigation of the level of control over the endgroup functionality of oligomeric poly(2-ethyl-2-oxazoline). The aim is to prepare prepolymers for further incorporation into tridimensional structures. α, ω-Diepoxy-poly(2-ethyl-2-oxazoline) oligomers were synthesized by reacting α, ω-dihydroxy-poly(2-ethyl-2-oxazoline) oligomers with epichlorohydrin using both phase transfer catalysis and the metalation method. Optimization of the reaction parameters was also performed in order to maximize the epoxidation yield.

2. Experimental

2.1 Materials

2-Ethyl-2-oxazoline (EtOx, Merck) was purified by distillation over calcium hydride then stored under argon. Epichlorohydrin (ECH, Aldrich, 99%), tetra-N-butylammonium bromide (TBAB, Aldrich, 99%), 18-crown-6-ether (TCI, 98%), sodium hydride (NaH, Acros Organics, 80% dispersion in mineral oil) were used as such; α,α′-dibromo-p-xylene (BrXy, Aldrich, 97%) was further purified by sublimation. Acetonitrile (ACN, Merck) was dried over CaH_2 for 24h, distilled and stored under argon. Tetrahydrofuran (THF, Merck) was distilled over Na/benzophenone, and then stored under argon in a schlenk flask. Chloroform (Chemical Company) was freshly distilled before use.

2.2. Characterization

FT-IR spectra were recorded on a Bruker Vertex 70 spectrometer fitted with a Harrick MVP2 diamond ATR device. NMR spectra were recorded on a Gemini-300BB Spectrometer in $CDCl_3$ at 25°C.

2.3. Titration experiments

Titration of hydroxyl groups was performed to determine the number average molecular weight of poly(2-ethyl-2-oxazoline) oligomer by endgroup analysis. The hydroxyl index was determined by the phtalation method in pyridine. Two solutions were prepared in advance, reactive solution (phthalic anhydride in pyridine - 1mol/L) and titration solution (sodium hydroxide in water – 0.5 mol/L). 0.2 g of PEtOx-OH was introduced in a round bottom flask together with 12.5 mL of phthalic anhydride solution and stirred magnetically until complete dissolution. The reactive mixture was then heated at 115°C for 1 h. The flask was left to cool at room temperature before adding 7.5 mL of pyridine. The carboxylic groups resulted from the excess of phthalic anhydride were titrated with a solution of sodium hydroxide, using phenolphthalein as indicator. Two runs of each titration was carried out and one blank.

The epoxidation extent of the synthesized PEtOx-epoxy was titrimetrically determined by the addition of $HClO_4$ to the epoxy ring, in glacial acetic acid, at room temperature [32]. A standard 0.1 N solution of perchloric acid was done by mixing 8.5 mL of 72% $HClO_4$, with 300 mL of glacial acetic acid and adding 20 mL of acetic anhydride. Then, the mixture was diluted to 1000 mL with glacial acetic acid and allowed to stand overnight. The solution was standardized against potassium acid phthalate, using crystal violet as indicator. 0.2 g PEtOx-epoxy and 0.8 g of cetyltrimethylammonium bromide were weighted in an Erlenmeyer flask and 20 mL of glacial acetic acid was added. Immediately after dissolution, a few drops of crystal violet solution in acetic acid were added and the sample was titrated with standardized $HClO_4$ solution until the bright-green color persisted. Two blank tests were additionally performed, one without the PEtOx-epoxy oligomer and one with PEtOx-hydroxy oligomer. The titrations were done in duplicate.

2.4. Synthesis

2.4.1. Synthesis of the α, ω-dihydroxy-poly(2-ethyl-2-oxazoline) oligomer (PEtOx-OH)

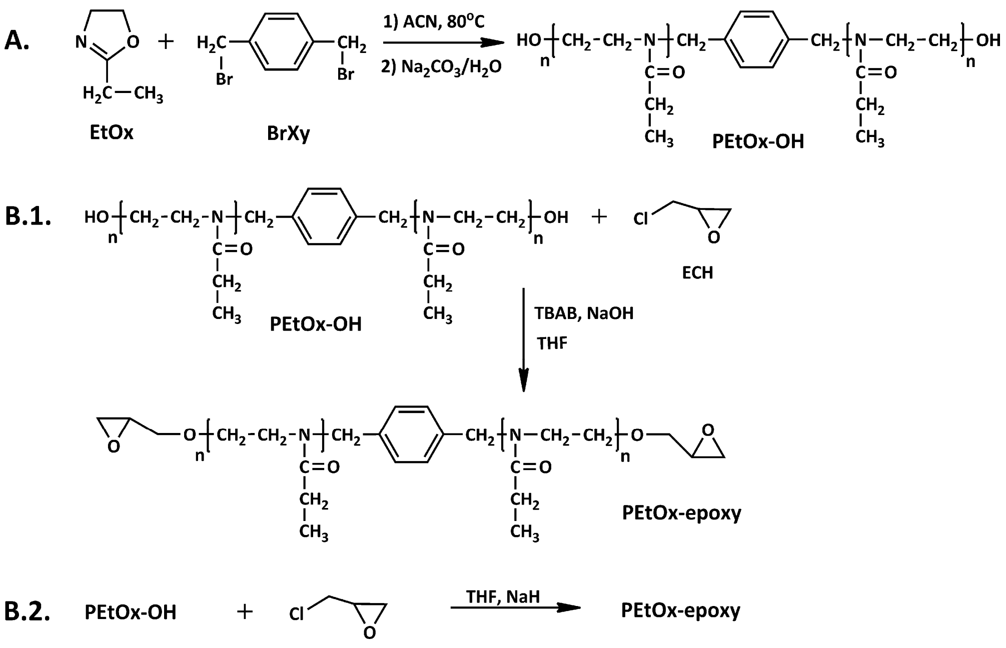
The α, ω-dihydroxy-poly(2-ethyl-2-oxazoline) difunctional oligomer was prepared by living cationic ring opening polymerization (CROP) as sketched in Scheme 1.A. In a Schlenk flask, under dry and inert conditions, a solution of 0.7801 g (2.95 mmol) of initiator (BrXy) and 23 mL of ACN was prepared in advance. Then 6 mL (59 mmol) of EtOx was added. The final mixture was left to react for 5 hours at 80 °C in an oil bath, under continuous stirring. After being cooled at room temperature (20 °C), the Schlenk flask was opened and the polymerization was terminated by the addition of a solution of 3.2 g (30.2 mmole) sodium carbonate in 8 mL of distilled water. The flask was again sealed and the mixture was heated at 80 °C for 20 h. The Schlenk was opened and the solvent evaporated under reduce pressure on a rotary evaporator. Then, the residue was dissolved in 30 mL of water and extracted with (3x100 mL) chloroform. The organic layer was dried over magnesium sulphate, followed by filtration and evaporation of the solvent. The residue was dissolved in 30 mL of chloroform and precipitated in cold diethyl ether. The polymer material was collected and dried in vacuo at 50 °C to give 5.5 g of white foamy PEtOx-OH oligomer (yield 93%).

2.4.2. Synthesis of the α, ω-diepoxy-poly(2-ethyl-2-oxazoline) oligomer (PEtOx-epoxy)

The α,ω-diepoxy-poly(2-ethyl-2-oxazoline) difunctional oligomer (PEtOx-epoxy), was synthesized using two different methods in which we obtained different epoxidation degrees.

Method 1 (see Scheme 1.B.1.) The optimized recipe is given below. Different parameters were varied and they are indicated later together with the experimental results in Table 1. To a stirred solution of 0.5 g (5.05 mmoles) α,ω-hydroxy - poly(2-ethyl-2-oxazoline) in 5 mL THF, under argon were added successively 7.06 mg (0.022mmol) phase transfer catalyst, 0.105 g (2.63 mmoles) NaOH as powder and 0.21 mL (2.63 mmoles) ECH. The -OH endgroups:ECH:NaOH mole ratio was 1:6:6. The reaction mixture was vigorously stirred at 40 °C for 9 h, cooled down to room temperature (20 °C) and the solvent was removed in vacuo.

The residue was dissolved in 5 mL of water, a small portion of NaCl (0.1-0.15 g) was added and the aqueous phase was extracted with (4x15 mL) $CHCl_3$. The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and the solvent evaporated. The residue was dissolved in $CHCl_3$ and the solution added dropwise to a large excess of cold diethyl ether to precipitate the α, ω-diepoxy-poly(2-ethyl-2-oxazoline) oligomer. The resulting white foamy oligomer was dried under vacuum overnight at 50 °C (yield: 82%).



Scheme 1. Synthesis routes for diepoxy-terminated poly(2-ethyl-2-oxazoline) oligomer (PEtOx-epoxy)

Method 2 is also described in Scheme 1.B.2. In a Schlenk flask, under dry and inert conditions, a solution of 0.5 g (5.05 mmoles) of PEtOx-OH in 5 mL THF at room temperature was prepared. After complete dissolution of the polymer, the appropriate amount of NaH powder was added in the system. The resulting mixture was sealed off under nitrogen cushion, and vigorously stirred for 2 h at 30°C. Then, 0.16 ml (2.06 mmoles) of ECH were injected to prepare the final mixture. The -OH endgroups:ECH mole ratio was 1:4. The reaction was allowed to continue for 24 h at 30°C, and then the solution was cooled down to room temperature (20 °C) and filtrated. The polymer was separated by evaporation of the solvent using a rotary evaporator connected to a vacuum source. The obtained residue was dissolved in 20 ml of $CHCl_3$ and washed with (3x5 mL) brine. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum on a rotary evaporator. The polymer was further dissolved in 5 ml of $CHCl_3$ and precipitated into cold diethyl ether. The oligomer was obtained as a white foam, which was dried overnight under vacuum at 50°C (yield: 85%).

3. Results and discussion

The synthesis of α, ω-dihydroxy PEtOx2000 oligomer was done using a modified procedure of Kobayashi [23], by living cationic ring opening polymerization. The desired number average molecular weight (Mn) was obtained by adjusting the molar ratio between EtOx and initiator. The hydroxyl number determined by the phtalation method was 57.84 mg KOH/g corresponding to 1940 Da.

The synthesis of α, ω-diepoxy PEtOx2000 oligomers took place in solid-liquid system. Tetrahydrofurane was chosen as solvent due to the chemical stability towards alkali and sodium hydride. In addition, THF is a theta solvent for PEtOx oligomer [33]. The first approach to synthesize α,ω-diepoxy-poly(2-ethyl-2-oxazoline) oligomers was based on the reaction of PEtOx-OH with ECH under solid – liquid phase transfer catalysis conditions (PTC), while the second synthetic strategy was performed through the alkali-metalation of hydroxy group followed by the reaction with ECH.

3.1. Synthesis of PEtOx-epoxy oligomers using phase transfer catalysis method

In order to find the optimal conditions under PTC we studied the influence of three factors on the epoxidation extent: (i) the mole ratio between OH groups and sodium hydroxide and ECH, ii) PTC nature and (iii) temperature. The epoxidation extent was titrimeticically determined as well as by ^{1}H-NMR spectroscopy by comparing the areas of the peaks corresponding to the epoxy ring methylene proton (δ=2.78 ppm, Fig. 1) and methylene protons from the benzyl initiator fragment (δ=4.54 ppm).

3.1.1. The influence of ECH and alkali hydroxide concentration

The amount of sodium hydroxide used varied from 2 to 8 moles. From Table 1 one can notice that the yield of epoxidation increased gradually from 23.5 to 75.6% with increasing amount of the added epichlorohydrin from 2 to 6 mole. At 60 °C the extent of epoxidation determined by the titrimetric method exhibited over 120%. However, the epoxidation extent calculated from ^{1}H-NMR spectrum was 72.7% (see Table 1). This discrepancy can be explained by the occurrence of side reactions. The possible side reactions are: i) the attack of hydroxide ions toward oxirane ring with the generation of glycerol, ii) the attack of the hydroxide ion toward the epoxidized polymer with the formation of diols iii) possible hydrolysis of the amide group followed by the reaction of amino groups with the ECH. Titration with perchloric acid is affected by the presence of epoxidized hydroxyl groups, of epoxidized amino groups and of eventually free amino groups, which are all titrated with perchloric acid, and this method is approximate. In all other cases, the correlation between the two methods (titrimetric and ^{1}H-NMR) is very good indicating lack of side reactions.

Table1

The effect of the reactants and temperature factors on the formation of α, ω-diepoxy PEtOx$_{2000}$ oligomers

Run	Reactants molar ratio (mole)						Temperature (°C)	Epoxidation extent (%)	
	OH[a]	NaOH	KOH	NaH	ECH	PTC		Titration	^{1}H-NMR
1	1	2	-	-	2	0.05[b]	30	23.5	23.7
2	1	4	-	-	4	0.05[b]	30	48	47.2
3	1	6	-	-	6	0.05[b]	30	67.4	65.3
4	1	8	-	-	8	0.05[b]	30	81.2	75.6
5	1	-	6	-	6	0.05[c]	30	63.1	63.8
6	1	6	-	-	6	0.05[b]	40	99.8	99.5
7	1	6	-	-	6	0.05[b]	60	120	72.7
8	1	-	-	1	4	-	30	40.2	41.3
9	1	-	-	1.5	4	-	30	42.3	42.9
10	1	-	-	2	4	-	30	56.2	55.8
11	1	-	-	1	4	-	50	40.7	41.4
12	1	8	-	-	8	-	60	20.4	25.6
13	1	6	-	-	6	-	40	0	

[a] oligomer OH end groups
[b] the PTC used was TBAB
[c] the PTC used was 18-crown-6-ether

3.1.2. The influence of PTC nature

We performed the reaction also in the presence of 18-crown-6-ether. In this case, we used potassium instead of sodium hydroxide, due to a better complexation of the potassium ion by the crown ether. The PTC catalysts were chosen based on previous reports for the synthesis of glycidyl ethers [34]. When we used 18-crown-6 ether as PTC a lower epoxidation yield was registered, when TBAB was replaced by 18-crown-6 ether as PTC. These can be explained in terms of a lower complexation, of chlorine anion by the crown ether as compared to TBAB [35]. Consequently, reaction with crown ether is much slower than the onium salt-catalyzed reaction. Therefore, we concentrated in finding the optimal conditions for the method with TBAB.

3.1.3. The temperature influence

Under the optimized molar ratio of reactants as mentioned above, the reaction temperature was varied from 30 to 60°C. For PTC reaction increasing the temperature leads to increased reaction yield, but also accelerates the side reactions. Therefore, we determined that the optimal temperature for the PTC method is 40 °C (run 6).

3.2. Synthesis of PEtOx-epoxy oligomers using the metalation method

Epoxidation of α, ω-dihydroxy PEtOx2000 oligomers was performed also through the alkali-metalation of hydroxy group followed by the reaction with ECH. The metalation method leads to lower epoxidation extent than expected based on literature reports for diepoxy poly(ethylene glycols), i.e. an excess of 4 moles of ECH should lead to a quantitatively conversion of the OH groups [36], probably due to the presence of water in the system. The water is most likely introduced by the PEtOx oligomer, which is highly hygroscopic and very difficult to dry, taking into account that THF was distilled over sodium/benzophenone. With excess of NaH against the hydroxyl groups, the extent of epoxidation increased. However, if we compare the experiments 2 and 8 we can observe that we have obtained similar yields, therefore the excess of ECH could be another factor affecting the epoxidation yield when using metalation method, due to its influence upon the reaction rate. The reaction temperature scarcely affected the epoxidation extent (see Table 1, runs 8-11).

3.3. FT-IR/ ^{1}H-NMR characterization

The α, ω-dihydroxy PEtOx2000 and α, ω-diepoxy PEtOx2000 oligomers were characterized by means of FT-NMR and FT-IR spectroscopy. The formation of the α, ω-dihydroxy PEtOx2000 oligomer is demonstrated by the ^{1}H-NMR spectroscopy, as presented in Fig. 1, bottom. After the living CROP, the polymer displayed the characteristic signals of poly(2-ethyl-2-oxazoline) at 1.13 and 2.36 ppm, methyl and methylene protons from ethyl side group, and at 3.46 ppm the two methylene protons form the backbone. The signals corresponding to the initiator are present at 4.54 ppm methylene protons vicinal to the aromatic ring. The doublet signal from o-ArCH$_2$- is found at 7.15 ppm. The signal at 3.78 ppm is assigned to the methylene protons vicinal to the -OH endgroups.

The structure of the dihydroxy oligomer was confirmed also by FT-IR spectroscopy. The IR spectrum shows specific bands for the poly(2-oxazoline) chains at 1624 ($\nu_{C=O}$), 1196 (ν_{C-O}), 2977 (ν_{CH3}) and 2939 ($\nu_{-CH2CH3,}$) all in cm^{-1}. The absorption bands of the hydroxyl endgroup can be found at 3434 (ν_{O-H}) cm^{-1} (see Fig. 2, bottom).

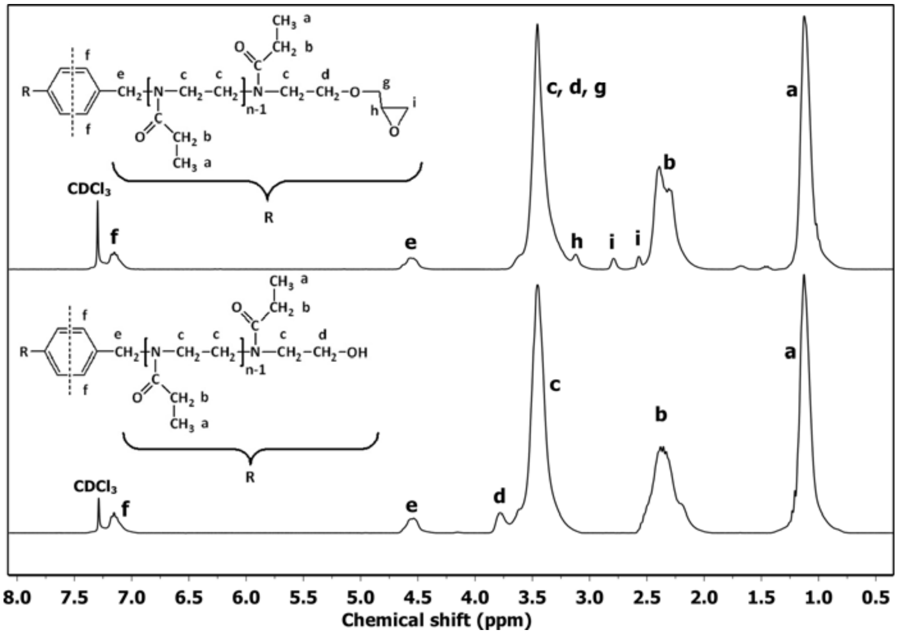


Fig. 1. ^{1}H-NMR spectra of the PEtOx-OH (up); PEtOx-epoxy difunctional oligomers (run 6) (bottom)

The chemical structure of the difunctional oligomers having epoxy groups was confirmed also by FT-IR and FT-NMR spectroscopy. As it can be noticed from Fig. 2 top, the IR spectrum displayed distinctive peaks for the epoxy groups at 750, 912 and 1110 cm^{-1}, besides those specific to the oxazoline chains, mentioned above. In the H-NMR spectrum, after the epoxidation reaction, the characteristic signals of epoxy group can be found at 2.57, 2.79 and 3.12 ppm (Fig. 1, top). One can notice also that the signal corresponding to methylene protons linked to -OH has disappeared from the spectrum evidencing the completion of the reaction. The epoxidation extent was calculated for sample 6 by comparing the areas of the peaks corresponding to the epoxy ring methine proton (3.12 ppm) and methyl proton from the oxazoline unit (1.12 ppm). The epoxidation degree found was 99.5 %, close to the one titrimetically determined (see Table 1), proving the efficiency of the functionalization method.

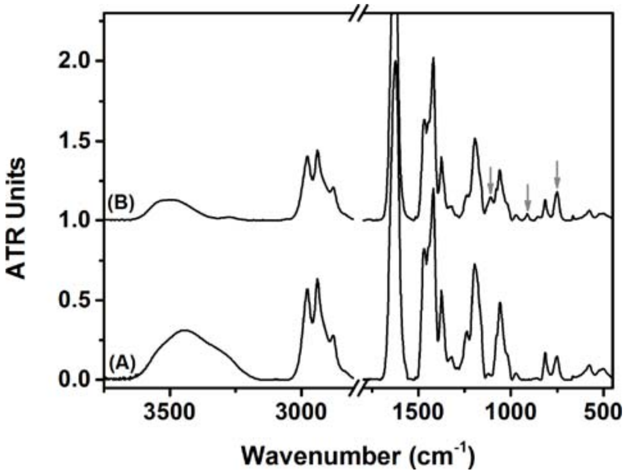


Fig. 2. FT-IR spectra of the PEtOx-OH (A); PEtOx-epoxy difunctional oligomers (run 6) (B)

4. Conclusions

We successfully synthesized a new α, ω-diepoxy-poly(2-ethyl-2-oxazoline) oligomer using the PTC or metalation method respectively. To increase the epoxidation extent of the dihydroxy oligomer we optimized the reaction conditions and we attained a 99.5% epoxidation extent by PTC and 56% by metalation. This large difference between the two results is explained by the water traces present in medium, which strongly affects the metalation method. For the optimal run via PTC, we demonstrated that the reaction should be performed at 40 °C, due to the occurrence of side reactions at higher temperatures. The chemical structure of both α, ω-dihydroxy-poly(2-ethyl-2-oxazoline) and α, ω-diepoxy-poly(2-ethyl-2-oxazoline) oligomers was put into evidence by FT-IR and ^{1}H-NMR spectroscopy.

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