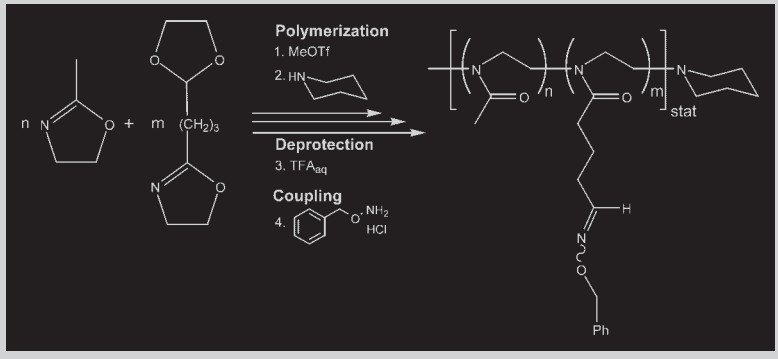
Summary: A protected aldehyde-functionalized 2-oxazoline, 2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline (**DPOx**), was synthesized from commercially available compounds in high yields. The polymerization of **DPOx** with different initiators proceeds via a living ionic mechanism; thus, the polymers were of low polydispersity and the degree of polymerization could be precisely adjusted. Copolymerization with 2-methyl-2-oxazoline gave water-soluble statistical copolymers. Hydrolysis of the homo- and copolymers resulted in well-defined, aldehyde-bearing poly(2-oxazoline)s. The aldehyde side functions reacted quantitatively with an amino-oxy compound to form the corresponding oxime.



First Aldehyde-Functionalized Poly(2-oxazoline)s for Chemoselective Ligation

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Introduction

Currently, multi-functional polymers are discussed for use as *polymer therapeutics*.[1] The polymeric motif allows multiple functionalization which provides selective cell-polymer binding sites to improve targeting in drug delivery[2] as well as increase the payload of the synthetic vehicle (e.g., cell toxins, radioactive nuclides). Furthermore, the polymeric carrier can be specifically designed in terms of size, solubility and architecture to modify the biodistribution and pharmacokinetics[3] or to modulate the immunoresponse[4] One of the candidates for the development of polymer therapeutics is poly(2-substituted-2-oxazoline). This water-soluble[5] and 'biocompatible'[6] polymer (for a 2-substitution of either methyl- or ethyl-) is prepared by living cationic polymerization and is, thus, of low polydispersity and high structural and chemical definition. We demonstrated numerous variations of poly(2-oxazoline)-based polymers in which a direct structure-property relationship is required.[7]

Besides the crucial criteria for a polymer drug delivery system such as water solubility and nontoxicity, the chemistry and architecture of the polymer has to be as defined as possible in terms of functionality and polydispersity. Ideally, homo- and heterofunctionalization should be realizable for the accommodation of diverse functions in the delivery system. Some of these coupling sites may be introduced by copolymerization; however, reactive sites are often incompatible with controlled or living polymerization

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reactions. Consequently, polymer analog conversions have to be used. To ensure highly defined polymeric products, the polymer analog reaction has to be quantitative as well as specific.

In contrast to the popular poly(ethylene glycol) (PEG), poly(2-oxazoline) provides a broader variability in terms of the chemical functionalization of the polymer side chains and, at the same time, compatibility with complex biological matrices. Very recently, novel 2-substitutions were introduced into the polymer to vary the steric need and H-bonding sites of 2-oxazoline-based lipopolymers.[8] Chemical groups such as hydroxyl,[9,10] phenyl,[11] carboxyl,[9,12] carbazol-functionalities,[13] iodaryl,[14] bipyridyl[15,16] as well as furan and maleimide modifications[17] have been reported for poly(2-oxazoline) side chains. Other side groups are either alkyl, perfluoroalkyl or aryl functions to control the (block co-) polymer solubility or the aggregation behavior. Hydroxyl or carboxyl functions are introduced by the polymerization of the protected monomer (ester) and consecutive polymer analog deprotection and conversion of the side functions. This strategy enables the formation of tailored (block) copolymers to define the number and loci of the side functions along the polymer chain, providing that the polymer analog reactions are defined and quantitative.

Since the concentrations of reactive groups tend to be low for high-molecular weight compounds and, at the same time, the conversion of multiple groups is intended, it is crucial to achieve a high degree of conversion. To tackle this problem, effective chemoselective reactions can be used. Ten years ago, Rose[18] showed that, for example, peptides having multiple aldehyde functions are quantitatively coupled in a defined manner with amino-oxy-bearing peptides. Since then, many monodisperse peptides or oligonucleotides[19–24] and other examples like hydrogels[25] have been functionalized with good success. Here we present the synthesis of a novel 2-functionalized-2-oxazoline bearing a dioxolan-protected aldehyde function, its polymerization into a homopolymer, copolymerization with 2-methyl-2-oxazoline (**MeOx**) and, after its deprotection, coupling with an amino-oxy compound as a model reaction. We analyzed the respective conversions and compared the reactivity of the new monomer with **MeOx** in a copolymerization reaction. To the best of our knowledge, this is the first example of a polymer analog aldehyde-amino-oxy reaction on a synthetic polymer. This approach combines the advantages of the living polymerization of 2-oxazolines with the powerful tool of a chemoselective couplings classified as 'click-chemistry'.[26]

Experimental Part

Materials and General Methods

All substances were purchased from Aldrich and were used as received unless otherwise stated. Reagents for the monomer and polymer synthesis, 2-(2-bromoethyl)-1,3-dioxolan, 2-methyl-2-oxazoline (**MeOx**), tetramethylethylendiamine (TMEDA), methyl triflate (**MeOTf**) and piperidine, were freshly destilled under a dry argon atmosphere prior to use. Solvents used for the polymerization were dried by refluxing over CaH_2 for approx. 3 h and subsequent destillation.

NMR spectra were obtained on a Bruker ARX 300 (^{1}H: 300.13 MHz and ^{13}C: 75.47 MHz) with TMS as internal standard at $T = 300$ K in $CDCl_3$. FT-IR spectra were recorded on a Bruker IFS 55s spectrometer with a ATR sampling accessory from Harrick (single bounce, diamond crystal) and MCT detector. Elemental analysis was performed on a Elementar Vario EL. Gel permeation chromatography (GPC) was performed on a Waters system (pump mod. 510, RI-detector mod. 410, columns PLgel 5 μm MIXED-C and PLgel 3 μm MIXED-E) with dimethyl acetamide (DMAc) as the eluent and calibrated against poly(methyl methacrylate) (PMMA) standards. Gas chromatography (GC) was performed on a Varian GC-3380 with a Chrompack CP-8 column and FID detector. For dialysis of polymeric products, a Roth ZelluTrans V Serie was used (nominal molar mass cut-off: ca. 1 000 g/mol).

Synthesis

2-[3-(1,3)-Dioxolan-2-ylpropyl]-2-oxazoline, **DPOx**

In a Schlenk flask, TMEDA (3.82 g, 32.8 mmol, 1.2 eq) was dissolved in 150 mL of dry THF and cooled to −78 °C. During 30 min, 12.6 mL (31.5 mmol, 1.15 eq) of a 2.5 M butyl lithium solution in hexane was added under vigorous stirring. The yellowish solution was stirred for 1 h at −78 °C. Subsequently, 2.82 g (33.1 mmol, 1.20 eq) of **MeOx** in 15 mL THF was added dropwise. After 2 h stirring at −78 °C, 2-(2-bromoethyl)-1,3-dioxolan (4.99 g, 27.6 mmol, 1.00 eq) in 15 mL THF was added slowly. The mixture was allowed to equilibrate to room temperature (RT) under stirring over night. The reaction was terminated by the addition of 20 mL methanol before the solvent was removed under reduced pressure. The residual yellow-orange oil was dissolved in a mixture of 100 mL chloroform and 100 mL of a saturated $NaHCO_3$ solution. The aqueous phase was extracted twice with 50 mL chloroform. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The yellowish raw product (pale-yellow liquid) was purified by flash chromatography (silica, mobile phase: ethylacetate/hexane/triethylamine = 10:5:1) and distilled to give 4.28 g (84%) of a colorless liquid.

^{1}H NMR: $\delta = 4.81$ (t, 1H, $^3J = 4.2$ Hz, –CH_2–C<u>H</u>(–O–)$_2$), 4.15 (t, 2H, $^3J = 9.4$ Hz, –N–CH_2–C<u>H</u>$_2$–O–), 3.89–3.77 (m, 6H, –N–C<u>H</u>$_2$–CH_2–O–/–O–C<u>H</u>$_2$–C<u>H</u>$_2$–O–), 2.26 (t, 2H, $^3J = 7.0$, –NOC–C<u>H</u>$_2$–CH_2–), 1.68 (m, 4H, –CH_2–C<u>H</u>$_2$–C<u>H</u>$_2$–CH–).

^{13}C NMR: $\delta = 168.3$ (–NO<u>C</u>–CH_2–), 104.3 (–CH_2–<u>C</u>H(–O–)$_2$), 67.3 (–N–CH_2–<u>C</u>H_2–O–), 65.0 (–O–<u>C</u>H_2–<u>C</u>H_2–O–), 54.5 (–N–<u>C</u>H_2–CH_2–O–), 33.2 (–NOC–<u>C</u>H_2–CH_2–), 27.8 (–CH_2–CH_2–<u>C</u>H_2–CH–), 20.5 (–CH_2–<u>C</u>H_2–CH_2–CH–).

IR: 2 963 (m), 2 880 (m), 2 653 (w), 1 666 (s), 1 482 (w), 1 459 (w), 1 435 (w), 1 412 (w), 1 391 (w), 1 362 (w), 1 304 (w), 1 235 (m), 1 196 (w), 1 166 (m), 1 133 (s), 1 088 (m), 1 050 (m), 1 028 (m), 982 (s), 954 (s), 903 (m), 820 (w), 710 (w) cm^{-1}.

$C_9H_{15}NO_3$ (185.22): Calcd. C 58.36, H 8.16, N 7.56; Found C 58.60, H 8.29, N 7.73.

N-Methyl-2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazolinium triflate, **DPOxOTf**

Reaction of **MeOTf** (638 mg, 3.89 mmol) with **DPOx** (710 mg, 3.83 mmol) was performed according to Kobayashi et al.[27] Yield: 1.29 g (3.69 mmol, 96%).

^{1}H NMR: $\delta = 4.91$ (t, $^3J = 9.8$ Hz, 2H, –N–CH_2–C$\underline{H}_2$–O–), 4.79 (t, $^3J = 4.2$ Hz, 1H, –CH_2–C$\underline{H}$(–$OR)_2$), 4.22 (t, $^3J = 9.9$ Hz, 2H, –N–C$\underline{H}_2$–CH_2–O–), 3.89–3.63 (m, 4H, –O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 3.30 (s, 3H, –N–C$\underline{H}_3$), 2.74 (t, $^3J = 7.3$ Hz, 2H, –NOC–C$\underline{H}_2$–CH_2–), 1.82 (pseudo-quin, 2H, $^3J = 7.3$ Hz, –CH_2–C$\underline{H}_2$–CH_2–CH–), 1.71 (dt, 2H, –CH_2–CH_2–C$\underline{H}_2$–CH–).

^{13}C NMR: $\delta = 178.3$ (–NOC–CH_2–), 120.8 (q, $^1J_{C,F} = 320$ Hz, F_3C–SO_3^-), 103.7 (–CH_2–C$\underline{H}$(–$OR)_2$), 71.3 (–N–CH_2–C$\underline{H}_2$–O–), 65.1 (–O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 52.3 (–N–C$\underline{H}_2$–CH_2–O–), 34.3 (–N–C$\underline{H}_3$), 32.2 (–NOC–C$\underline{H}_2$–CH_2–), 26.2 (–CH_2–CH_2–C$\underline{H}_2$–CH–), 18.2 (–CH_2–C$\underline{H}_2$–CH_2–).

$C_{11}H_{18}F_3NO_6S$ (349.32): Calcd. C 37.80, H 5.19, F 16.32, N 4.01; Found C 37.82, H 5.28, F 14.80, N 4.2.

MS (ESI): $m/z = 200.1$ $(M - OTf^-)^+$, 218.1 $(M + H_2O - OTf^-)^+$, 548.9 $(2M - OTf^-)^+$, 566.8 $(2M + H_2O - OTf^-)^+$, 585.0 $(2M + 2H_2O - OTf^-)^+$, 756.9 $(2M + 3H_2O + Na^+)^+$, 951.8 $(3M + 3H_2O - OTf^-)^+$.

N-Methyl-2-methyl-2-oxazolinium triflate, **MeOxOTf**

The reaction of **MeOTf** with **MeOx** to the initiator salt was performed accordingly. Yield: 93%.

Polymerization

All polymerizations and work-up procedures were carried out after a general procedure described previously.[7,8,14]

Poly{2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline}, **PDPOx$_{25}$**, **MeOx-PDPOx$_{31}$**, **PDPOx$_{34}$**

For **PDPOx$_{34}$**: **MeOTf** (22 mg, 0.13 mmol, 1.0 eq) and 835 mg of **DPOx** (4.51 mmol, 34 eq) were dissolved in acetonitrile (ca. 9 mL) and polymerized using 42 mg piperidine (0.49 mmol, 3.7 eq) as the terminating agent to give 712 mg (86%) of a colorless powder. **PDPOx$_{25}$** and **MeOx-PDPOx$_{31}$** were synthesized accordingly using the respective $[M]_0/[I]_0$ ratio and initiator (for analytical values see Table 1).

PDPOx$_{34}$

^{1}H NMR: $\delta = 4.78$ (br, 31H, –CH_2–C$\underline{H}$(–$OR)_2$), 3.9–3.7 (m, 128H, –O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 3.37 (br, 126H, –N–C$\underline{H}_2$–C$\underline{H}_2$–N–), 2.95/2.88 (m, 3H, –N–C$\underline{H}_3$), 2.5–2.2 (m, br, 67H, –N–CO–C$\underline{H}_2$–CH_2–/–C$\underline{H}_2$–^{piperazine}), 1.9–1.4 (m, br, 134H, –N–CO–CH_2–C$\underline{H}_2$–C$\underline{H}_2$–CH–/–C$\underline{H}_2$–^{piperazine}).

^{13}C NMR: $\delta = 174$–172 (–N–C$\underline{O}$–CH_2–), 104.4 (–CH_2–C$\underline{H}$(–$OR)_2$), 64.9 (–O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 48–42 (–N–C$\underline{H}_2$–C$\underline{H}_2$–N–), 34–32 (–N–CO–C$\underline{H}_2$–CH_2–C$\underline{H}_2$–CH–), 20–19 (–N–CO–CH_2–C$\underline{H}_2$–CH_2–).

IR: 2 950 (w), 2 880 (w), 2 767 (w), 1 634 (s), 1 452 (m), 1 416 (m), 1 365 (w), 1 247 (m), 1 133 (s), 1 030 (m), 943 (m), 829 (w) cm^{-1}.

GPC: PDI = 1.08, $\bar{M}_n = 5\,220$ g/mol.

Poly[(2-methyl-2-oxazoline)-*co*-{2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline}], **P(MeOx$_{19}$DPOx$_6$)$_{stat}$**

MeOTf (102 mg, 0.622 mmol, 1.0 eq), 1.01 g **MeOx** (11.87 mmol, 19.1 eq) and 678 mg **DPOx** (3.66 mmol, 5.9 eq) were dissolved in ~15 mL acetonitrile and polymerized with 144 mg (1.69 mmol, 2.7 eq) of piperidine as the terminating agent to yield 1.66 g (91%) of a colorless powder.

^{1}H NMR: $\delta = 4.78$ (br, 5H, –CH_2–C$\underline{H}$(–$OR)_2$), 3.9–3.7 (m, 23H, –O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 3.38 (br, 95H, –N–C$\underline{H}_2$–C$\underline{H}_2$–N–), 2.97/2.88 (m, 3H, –N–C$\underline{H}_3$), 2.5–2.2 (m, br, 15H, –N–CO–C$\underline{H}_2$–CH_2–/–C$\underline{H}_2$–^{piperazine}), 2.2–1.9 (m, br, 55H, –N–CO–C$\underline{H}_3$/–C$\underline{H}_2$–^{piperazine}), 1.8–1.6 (m, br, 24H, –N–CO–CH_2–C$\underline{H}_2$–C$\underline{H}_2$–CH–/–C$\underline{H}_2$–^{piperazine}), 1.49 (m, br, 2H, –C$\underline{H}_2$–^{piperazine}).

^{13}C NMR: $\delta = 174$–173 (–N–C$\underline{O}$–CH_2–), 172–170 (–N–C$\underline{O}$–CH_3), 104.4 (–CH_2–C$\underline{H}$(–$OR)_2$), 64.9 (–O–C$\underline{H}_2$–C$\underline{H}_2$–O–), 49–42 (–N–C$\underline{H}_2$–C$\underline{H}_2$–N–), 34–32 (–N–CO–C$\underline{H}_2$–CH_2–C$\underline{H}_2$–CH–), 21.3 (–N–CO–C$\underline{H}_3$), 19.7 (–N–CO–CH_2–C$\underline{H}_2$–CH_2–).z

IR: 2 933 (w), 2 851 (w), 1 627 (s), 1 478 (m), 1 416 (s), 1 362 (m), 1 325 (w), 1 258 (m), 1 208 (m), 1 141 (m), 1 031 (m), 944 (w), 830 (w), 751 (m) cm^{-1}.

GPC: PDI = 1.12, $\bar{M}_n = 3\,390$ g/mol.

*GC Investigation of **MeOx** and **DPOx** Conversion in Copolymerization*

Under strict inert and dry conditions (glove box), 702 mg (8.25 mmol, 20 eq) **MeOx** and 381 mg (2.06 mmol, 4.9 eq) **DPOx**

Table 1. Homopolymerization of **DPOx** with **MeOTf** or **MeOxTf** as the initiator.

Initiator	$\frac{[M]_0}{[I]_0}$ [a]	$\bar{P}_n$ [b]	Yield	$\bar{M}_n$, theor.	$\bar{M}_n$ [b]	$\bar{M}_n$ [c]	PDI[d]	Polymer
			%	g/mol	g/mol	g/mol		
MeOxOTf	31	33	87	5 930	6 300	5 860	1.11	**MeOx-PDPOx$_{31}$**
MeOTf	25	28	67	4 730	5 290	3 980	1.09	**PDPOx$_{25}$**
MeOTf	34	32	86	6 300	6 020	5 220	1.08	**PDPOx$_{34}$**

[a] Initial monomer/initiator ratio.
[b] Determined by end group analysis from ^{1}H NMR spectra.
[c] Determined by gel permeation chromatography (GPC).
[d] Polydispersity index; PDI = $\bar{M}_w/\bar{M}_n$ calculated from GPC traces.

were dissolved in 8 mL acetonitrile and 0.5 mL chlorobenzene (as internal standard), and 69 mg MeOTf (0.42 mmol, 1.0 eq) was added. The GC test tube was sealed and the reaction mixture was transferred to a pre-heated (85 °C) agitator. Samples were automatically taken at $t = 0$ min and subsequently every 30 min. Monomer conversions were calculated from the decay of the respective peak integrals of the GC traces using the internal standard.

Polymer Analog Reactions

Deprotection of Side Chain Aldehyde

The polymer was dissolved in 4 mL of 5% aqueous TFA solution (v/v) and transferred into a dialysis membrane and dialyzed for 2–3 h against 400 mL of a pure 5% aqueous TFA. Then, the polymer solution was dialyzed twice against 2 L deionized water (2 h) and subsequently freeze-dried (water) to yield the following polymers.

Poly[2-(4-oxobutyl)-2-oxazoline], **POBOx$_{34}$**

145 mg (94%) of a colorless powder was obtained from 202 mg (0.0316 mmol) of **PDPOx$_{34}$**.

^{1}H NMR: $\delta = 9.69$ (s, 33H, –CH$_2$–C$\underline{\text{H}}$O), 3.38 (br, 133H, –N–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–N–), 2.96/2.89 (m, 3H, –N–C$\underline{\text{H}}_3$), 2.5–2.2 (m, br, 140H, –N–CO–C$\underline{\text{H}}_2$–CH$_2$–C$\underline{\text{H}}_2$–CHO/–C$\underline{\text{H}}_2$–$^{\text{piperazine}}$), 2.0–1.7 (m, br, 76H, –CH$_2$–C$\underline{\text{H}}_2$–CH$_2$–CHO/–C$\underline{\text{H}}_2$–$^{\text{piperazine}}$).

^{13}C NMR: $\delta = 204$–201 (–CH$_2$–$\underline{\text{C}}$HO), 173–172 (–N–$\underline{\text{C}}$O–CH$_3$), 47–41 (–N–$\underline{\text{C}}$H$_2$–$\underline{\text{C}}$H$_2$–N–/–CH$_2$–$\underline{\text{C}}$H$_2$–CHO), 34–31 (–N–CO–$\underline{\text{C}}$H$_2$–CH$_2$–), 18–15 (–N–CO–CH$_2$–$\underline{\text{C}}$H$_2$–CH$_2$–).

IR: 2 929 (w), 2 830 (w), 2 725 (w), 1 719 (m), 1 637 (s), 1 450 (m), 1 420 (m), 1 389 (w), 1 322 (w), 1 246 (w), 1 198 (m), 1 169 (m), 1 125 (w), 1 068 (w), 943 (w), 798 (w) cm^{-1}.

GPC: PDI = 1.17, $\overline{M}_n = 5\,550$ g/mol.

P(MeOx$_{19}$OBOx$_6$)$_{stat}$

192 mg (87%) of a colorless powder was obtained from 243 mg (0.0862 mmol) **P(MeOx$_{19}$DPOx$_6$)$_{stat}$**.

^{1}H NMR: $\delta = 9.69$ (s, 5H, –CH$_2$–C$\underline{\text{H}}$O), 3.39 (br, 96H, –N–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–N–), 2.98/2.89 (m, 3H, –N–C$\underline{\text{H}}_3$), 2.6–2.2 (m, br, 24H, –N–CO–C$\underline{\text{H}}_2$–CH$_2$–C$\underline{\text{H}}_2$–CHO), 2.2–1.7 (m, br, 75H, –N–CO–C$\underline{\text{H}}_3$/–N–CO–CH$_2$–C$\underline{\text{H}}_2$–CH$_2$–/–C$\underline{\text{H}}_2$–$^{\text{piperazine}}$).

^{13}C NMR: $\delta = 202$–201 (–CH$_2$–$\underline{\text{C}}$HO), 173–172 (–N–$\underline{\text{C}}$O–CH$_2$–), 172–170 (–N–$\underline{\text{C}}$O–CH$_3$), 48–41 (–N–$\underline{\text{C}}$H$_2$–$\underline{\text{C}}$H$_2$–N–/–CH$_2$–$\underline{\text{C}}$H$_2$–CHO), 34–31 (–N–CO–$\underline{\text{C}}$H$_2$–CH$_2$–), 21–20 (–N–CO–$\underline{\text{C}}$H$_3$), 18–15 (–N–CO–CH$_2$–$\underline{\text{C}}$H$_2$–CH$_2$–).

IR: 2 999 (w), 2 927 (w), 2 854 (w), 2 723 (w), 1 720 (w), 1 691 (w), 1 629 (s), 1 478 (m), 1 415 (s), 1 361 (m), 1 323 (w), 1 291 (w), 1 255 (m), 1 236 (m), 1 197 (m), 1 163 (m), 1 125 (w), 1 071 (w), 1 035 (w), 1 010 (w), 973 (w), 923 (w), 827 (w), 745 (m) cm^{-1}.

GPC: PDI = 1.18, $\overline{M}_n = 3\,210$ g/mol.

Amino-Oxy Ligation[28]

Under a dry N_2 atmosphere, 50–75 mg of polymer, *O*-benzylhydroxylamine hydrochloride (1.2 eq per aldehyde) and dry sodium acetate (2–3 eq per aldehyde) were suspended in dry methanol. In an ultrasonic bath, the mixture was heated slowly (over 1–2 h) to ~50 °C and stirred at RT for 2–8 h. The solvent was removed and the residue dissolved in 6 mL chloroform. The solid constituents were removed by centrifugation and decantation. The polymer was purified by precipitation (chloroform/ether) and freeze-dried (H_2O or benzene).

Poly[2-(4-benzyloxyiminobutyl)2-oxazoline]$_{34}$, **PBnOBOx$_{34}$**

To a suspension of 54 mg (0.011 mmol, 1 eq) **POBOx$_{34}$** and 74 mg BnONH$_2$ · HCl (0.46 mmol, 42 eq), 86 mg of NaOAc (1.1 mmol, 95 eq) were added. After the procedure described in ref.,[28] 61 mg (65%) were obtained as a colorless solid.

^{1}H NMR: $\delta = 7.37$ (br, 21H, –N=C$\underline{\text{H}}$–CH$_2$–), 7.27 (m, br, 166H, –CH$_2$–C$_6\underline{\text{H}}_5$), 6.63 (br, 12H, –N=C$\underline{\text{H}}$–CH$_2$–), 5.01/4.95 (br, 67H, =N–C$\underline{\text{H}}_2$–C$_6$H$_5$), 3.38 (br, 142H, –N–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–N–), 2.97/2.88 (m, 3H, –N–C$\underline{\text{H}}_3$), 2.5–1.7 (m, br, 260H, –N–CO–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–CH=/–C$\underline{\text{H}}_2$–$^{\text{piperazine}}$).

IR: 3 088 (w), 3 063 (w), 3 032 (w), 2 925 (m), 2 853 (w), 1 738 (w), 1 724 (w), 1 639 (s), 1 496 (w), 1 453 (m), 1 416 (s), 1 365 (m), 1 306 (w), 1 260 (m), 1 157 (m), 1 096 (m), 1 012 (s), 878 (m), 754 (s), 697 (s), 645 (s) cm^{-1}.

GPC: PDI = 1.26, $\overline{M}_n = 7\,760$ g/mol.

P(MeOx$_{19}$BnOBOx$_6$)$_{stat}$

To a suspension of 75 mg (0.029 mmol, 1 eq) **POBOx$_{34}$** and 31 mg BnONH$_2$ · HCl (0.19 mmol, 6.6 eq), 26 mg of NaOAc (0.32 mmol, 11 eq) were added. After the procedure described in ref.,[28] 52 mg (56%) were obtained as a colorless solid.

^{1}H NMR: $\delta = 7.37$ (br, 4H, –N=C$\underline{\text{H}}$–CH$_2$–), 7.27 (m, br, 27H, –CH$_2$–C$_6\underline{\text{H}}_5$), 6.63 (br, 2H, –N=C$\underline{\text{H}}$–CH$_2$–), 5.01/4.95 (br, 11H, =N–C$\underline{\text{H}}_2$–C$_6$H$_5$), 3.38 (br, 94H, –N–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–N–), 2.97/2.88 (m, 3H, –N–C$\underline{\text{H}}_3$), 2.5–1.7 (m, br, 93H, –N–CO–C$\underline{\text{H}}_3$/–N–CO–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–C$\underline{\text{H}}_2$–CH=/–C$\underline{\text{H}}_2$–$^{\text{piperazine}}$).

IR: 2 932 (w), 2 860 (w), 1 627 (s), 1 478 (m), 1 414 (s), 1 362 (m), 1 323(w), 1 290 (w), 1 254 (m), 1 208 (m), 1 080 (w), 1 038 (m), 1 011 (m), 922 (w), 834 (w), 754 (m), 700 (w) cm^{-1}.

GPC: PDI = 1.12, $\overline{M}_n = 3\,530$ g/mol.

Results and Discussions

To verify the reported incompatibility of the cationic polymerization of 2-oxazolines with aldehydes,[29] we performed standard polymerizations of the **MeOx** monomer (M) using **MeOTf** (I^1) or **MeOxTf** (I^2) as initiators in the presence of propionaldehyde (A) ($[M]_0/[I^1]_0/[A]_0 = 27{:}1{:}5$ and $[M]_0/[I^2]_0/[A]_0 = 29{:}1{:}5$). Shortly after heating, the reaction mixture turned yellow and in no case was a polymer formed. The numerous low molar mass products were not further analyzed.

Numerous protective groups such as cyclic and acyclic acetals and their thio-derivatives are known for aldehydes.[30] The thio-derivatives are not suitable for our purposes, since *S*,*S*-acetals are not stable against strong electrophiles (e.g., methyl iodide or triflates). Acyclic *O*,*O*-acetals are easy to hydrolyze, and dioxan derivatives are surprisingly stable under acidic conditions. A good

compromise between stability and reactivity might be a dioxolan derivative that hydrolyzes under acidic conditions to yield the aldehyde function and is presumably inert under the polymerization conditions. Although unsubstituted 1,3-dioxolan can undergo cationic ring-opening polymerization with Lewis acids,[31,32] similar to 2-oxazolines, it is believed that in a preliminary initiation step, H-abstraction is needed to start the polymerization.[33] Regarding the different nucleophilicity of the ring heteroatom, a competitive propagation reaction of 2-oxazoline and the 1,3-dioxolan moiety is possible but rather unlikely. Thus, with alkylating initiators such as triflates and the propagating oxazolinium cation, a selective ring-opening polymerization of the 2-oxazoline in the presence of a dioxolan might be possible.

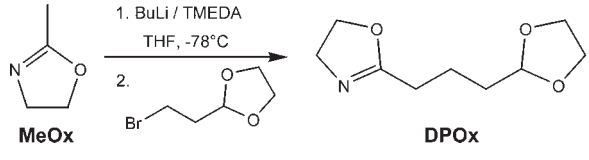
Monomer Synthesis

According to our previously described procedure,[14] 2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline (**DPOx**) could be directly synthesized in a one-pot reaction from commercially available compounds. Use of BuLi/TMEDA instead of lithium diisopropylamide (LDA) increased the yield of **DPOx** to 84% (Scheme 1). The monomer was characterized by ^{1}H and ^{13}C NMR, ATR-FTIR spectroscopy and elemental analysis. The NMR spectra are displayed along with the assignment in Figure 1. The IR spectrum of **DPOx** (not shown) features the characteristic C=N stretching mode at 1 666 cm^{-1} for the 2-oxazoline ring, as well as the C–O stretching mode of the 1,3-dioxolan moiety at 1 133 cm^{-1}.

Polymerization

To test the reactivity differences of the two ring systems, **DPOx** was reacted with the initiator **MeOTf** (1:1 eq.). The reaction was quantitative and resulted in a *N*-methyl-2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazolinium cation. Analysis by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis and mass spectrometry confirmed the selective alkylation of the 2-oxazoline ring. The 1,3-dioxolan moiety was unchanged (see Experimental Part; spectra not shown).[34] The selective conversion of **DPOx** into the initiator salt (**DPOxOTf**) offers the possibility to place a functional group for later coupling at the very beginning of a poly(2-oxazoline) chain by the so-called 'initiator method'.[27]

With either **MeOTf** or **MeOxOTf** as the initiator and piperidine as the terminating agent,[35] **DPOx** was homopolymerized (see Scheme 2). The results are summarized in Table 1.



Scheme 1. Synthesis of 2-[3-(1,3)-dioxolan-2-ylpropyl]-2-oxazoline (**DPOx**).

Both initiators are suitable for starting the homopolymerization of **DPOx** in a defined manner. The high conversion, the good agreement between $[M]_0/[I]_0$ and the obtained degree of polymerization as well as the very narrow molar mass distribution indicate a living (stoichiometric) polymerization mechanism and a fast initiation reaction ($k_i \gg k_p$). The 1,3-dioxolan moiety remained intact throughout the polymerization reaction at 85 °C in acetonitrile. To exemplify the successful reaction, the ^{1}H and ^{13}C NMR spectra of **PDPOx$_{34}$** are shown in Figure 3a. All expected signals could be unambiguously assigned. Especially in the ^{13}C NMR spectrum, the intensive signals (i, j) of the intact 1,3-dioxolan ring along with the typical poly(2-oxazoline) backbone signals (b, k) proved a selective polymerization by ring-opening of the 2-oxazoline system.

Besides other applications, a defined tuning of the number of functional moieties along a polymer chain is interesting for the preparation of polymer therapeutics. The density and loci of binding sites at a polymeric carrier could be tailored to the polymer-cell recognition process. With the initiator method, we already have a tool for placing a function at the proximal chain end, and the homopolymerization of **DPOx** allows high loading of the polymer; thus, the question remains if a copolymerization of **DPOx** with **MeOx** results in statistical copolymerization. This would yield hydrophilic poly(2-oxazoline) copolymers in which the number of functional sites for consecutive coupling of peptides as cell binding motifs could be easily adjusted by the ratio of two monomers. Therefore, we performed the copolymerization of **DPOx** with **MeOx** according to the reaction displayed in Scheme 2.

Again, calculation of the peak integral ratios of the terminal methyl group to the integrals of the backbone and the dioxolan ring in ^{1}H NMR spectrum (not shown) resulted in a degree of polymerization, which was in good agreement with the adjusted initial initiator to monomers ratio. The ratio of the integrals of dioxolan to side chain methyl integral is also in accordance with the expected values. Additional identification of the dioxolan ring in the ^{13}C NMR and IR spectra verified the successful copolymerization. Finally, the product of this and other copolymerization reactions showed only one monomodal trace in GPC analysis and the solubility (precipitation) gave no indication of the formation of different homopolymers.

The two monomers are quite different in the steric need and solubility. In copolymerization, both monomers would form the propagating ionic chain end in which **DPOx** might show a different reactivity. All this might cause a non-statistical polymerization behavior, which prefers the (temporal) polymerization of one monomer and results in gradient or block copolymers. To investigate the reactivity of the monomers, the monomer consumption in a copoly-

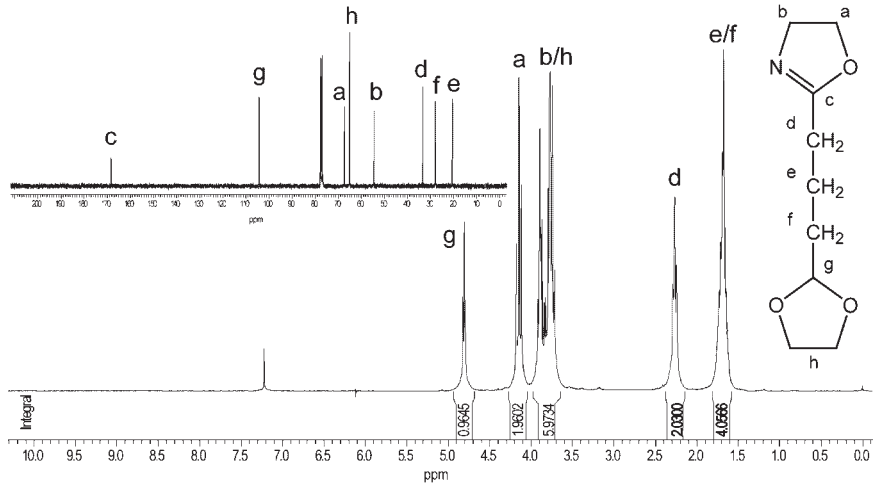
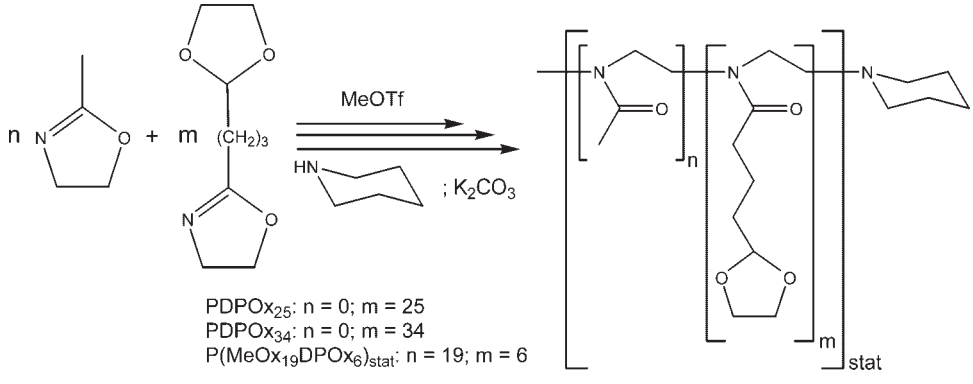


Figure 1. ^{1}H and ^{13}C NMR spectra (insert) of **DPOx**. All signals could be assigned; residual side products were not detected after purification. Signals h and g are characteristic for the 1,3-dioxolan ring (for details see Experimental Part).



Scheme 2. One-pot preparation of poly(2-oxazoline)s with different amounts of protected side chain aldehyde.

merization was monitored by GC. The polymerization was performed in a GC sample vial; samples of the polymerization mixture were taken every 30 min over a period of 8 h. As seen in Figure 2, both monomers were converted at approximately the same rate where **DPOx** shows a slightly slower consumption. Moreover, during the entire polymerization, both monomers are converted at similar rates. Hence, no block or gradient copolymers are formed and the protected aldehyde functionality is statistically distributed along the copolymer chain.

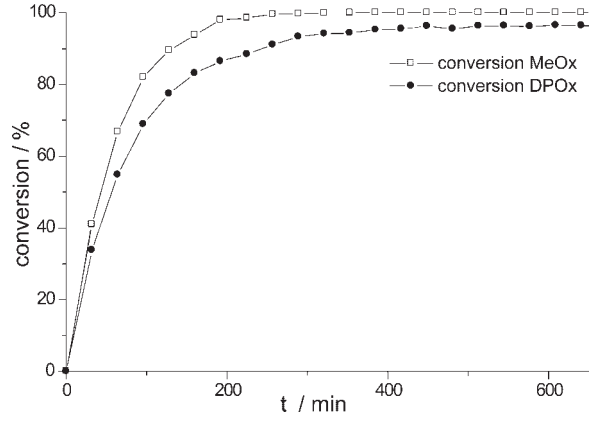


Figure 2. Conversion of **MeOx** and **DPOx** with time as monitored by on-line GC sampling. Conversion of **DPOx** appears to be slightly slower; however, the rate of conversion is comparable for both monomers. (Note: Final conversion is $<100\%$ due to contamination by the multiple sample collection.)

Aldehyde Deprotection and Chemoselective Ligation

Among the numerous possibilities to convert the 1,3-dioxolan moiety to an aldehyde function,[30,36,37] acid hydrolysis with strong protic acids such as trifluoroacetic acid (TFA) is the most straightforward one. However, several attempts failed including a variation of the deprotection reaction with, for example, PPTS,[38] $PdCl_2$,[39] DDQ[40] or

Table 2. Selected analytical data of synthesized polymers and modified samples.

Polymer	$\bar{M}_n$ [a)]	$\bar{M}_n$ [b)]	$\bar{M}_n$ [c)]	PDI[d)]	Yield[e)]
	g/mol	g/mol	g/mol		%
PDPOx$_{34}$	6 400	6 400	5 220	1.08	86
POBOx$_{34}$	4 900	4 900	5 550	1.17	94
PBnOBOx$_{34}$	8 480	8 700	7 760	1.26	65
P(MeOx$_{19}$DPOx$_6$)$_{stat}$	2 830	2 820	3 390	1.12	91
P(MeOx$_{19}$OBOx$_6$)$_{stat}$	2 560	2 560	3 210	1.18	87
P(MeOx$_{19}$BnOBOx$_6$)$_{stat}$	3 190	3 160	3 530	1.12	56

a) Calculated from initial monomer/initiator ratio and for 100% conversion for modified polymers.
b) Determined by end group analysis from ^{1}H NMR spectra.
c) Determined by GPC.
d) PDI calculated from GPC traces.
e) Yield of recovered substance. Spectroscopic analysis gave quantitative conversion of the side chain functionalities.

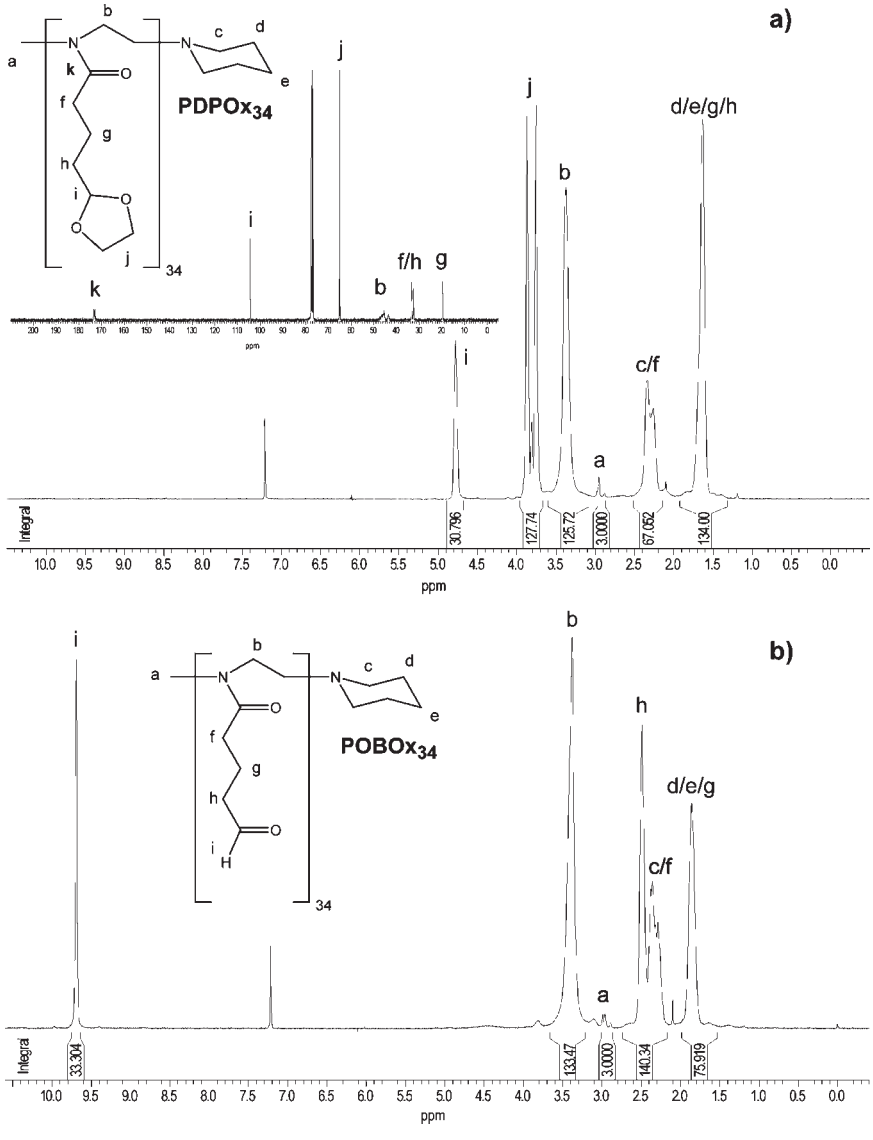


Figure 3. ^{1}H NMR spectra of (a) **PDPOx$_{34}$**. Acid hydrolysis with TFA yields quantitative conversion into the aldehyde function of **POBOx$_{34}$** (b).

$BiCl_3$.[37] Since the cleavage of *O*,*O*-acetals is an equilibrium reaction and here performed as a polymer analogous conversion, it is assumed that the reaction is equilibrated at the hemiacetal formation. This is indicated by the analysis of the respective ^{1}H NMR spectra. After treatment with the above-mentioned reagents, the polymer spectra often no longer showed signals from an intact 1,3-dioxolan ring but a strong new signal at 4.3 ppm. To avoid equilibrium, the hydrolysis of **PDPOx$_n$** was performed in a dialysis setup with aqueous TFA (5%) in the inner and outer compartment. This immediately gave a quantitative conversion of the 1,3-dioxolan to the free aldehyde function. The deprotection was confirmed by ^{1}H and ^{13}C NMR and IR spectroscopy; other analytical values (PDI, P_n) were almost unaffected by the conversion (see Table 2). Figure 3 displays the ^{1}H NMR spectra of **PDPOx$_{34}$** and of the deprotected poly[2-(4-oxobutyl)-2-oxazoline] (**POBOx$_{34}$**). In the spectrum of the hydrolysis product (Figure 3b), the signals of the 1,3-dioxolan are no longer detectable; instead, a strong signal at 9.69 ppm indicates the quantitative formation of the aldehyde side chain functionality. This conclusion is corroborated by the appearance of a new carbonyl signal of the aldehyde in the ^{13}C NMR spectrum at around 204–201 ppm. In IR, the ν(C–O) vibration at 1 133 cm^{-1} completely disappeared and two new characteristic aldehyde modes at 2 723 [ν(C–H)] and 1 720 cm^{-1} [ν(C=O)] are present (not shown).

The main purpose of the synthesis of aldehyde-functionalized poly(2-oxazoline) was the preparation of a set of defined biocompatible polymers bearing chemical coupling groups for chemoselective ligation, i.e., the selective coupling of aldehydes with amino-oxy-functionalized peptides. We chose *O*-benzylhydroxylamine hydrochloride as the amino-oxy compound to test the accessibility of the side chain aldehydes for this coupling reaction. In Figure 4, the conversion of the deprotected copolymer, **P(MeOx$_{19}$-OBOx$_6$)$_{stat}$**, to poly{(2-methyl-2-oxazoline)-*co*-[2-(4-benzyloxyiminobutyl)-2-oxazoline]} (**P(MeOx$_{19}$BnOBOx$_6$)$_{stat}$**) is shown.

Reactions with the other aldehyde-functionalized poly(2-oxazoline)s were performed in the same manner. The successful reaction can be followed in the ^{1}H NMR spectra in Figure 4. The characteristic signal of the aldehyde side group (j) in Figure 4a completely disappeared, and three new signals (i, j, k) appeared upon formation of the oxime group (Figure 4b). These signals appear twice since the coupling allows the formation of the *E* and *Z* isomer. The integrals in ^{1}H NMR spectra of the new side chain

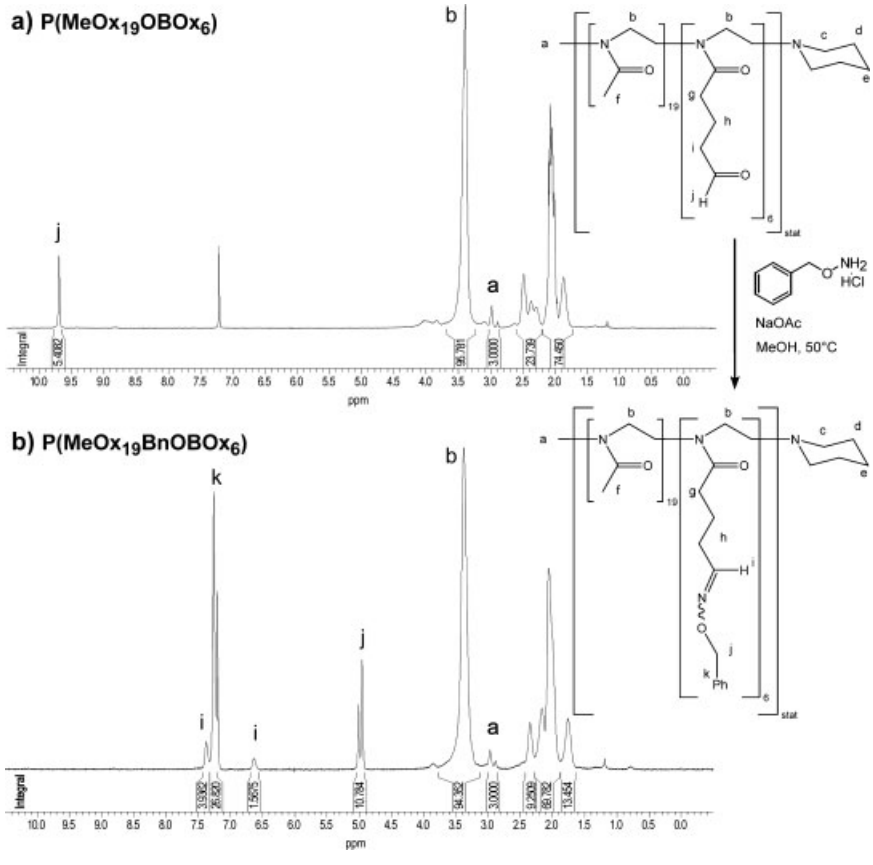


Figure 4. ^{1}H NMR spectra and reaction scheme of the chemoselective ligation of aldehyde-functionalized poly(2-oxazoline) with *O*-benzylhydroxylamine hydrochloride. The final product can have the *cis* and *trans* configuration.

phenyl moieties are in excellent agreement with the expected values, indicating quantitative conversion of all the aldehyde functions. Again, IR spectroscopy verified the complete conversion of the aldehyde to the oxime. Although the typical ν(C=N) vibration for the oxime group around 1 690–1 630 cm^{-1} is obstructed by the strong amide I band of the polymer backbone, the modes at 2 723 and 1 720 cm^{-1} disappeared upon coupling and an additional sharp band at 700 cm^{-1} appeared which can be assigned to the monosubstituted benzyl moiety. Conversion of the **POBOx$_{34}$** homopolymer was successful; characterization by ^{1}H NMR spectroscopy revealed complete conversion. However, in the corresponding IR spectra a weak signal at 1 724 cm^{-1} indicated a residual trace of unreacted aldehyde side functions. Presumably, the functional density along the polymer chain requires further optimization of the reaction. Side products were not detectable. An overview of the polymer analytical data for the homo- and copolymer after the polymer analog reactions is given in Table 2.

Conclusion

We reported a simple one-pot synthesis to prepare a 1,3-dioxolan protected aldehyde function on a 2-oxazoline monomer. Polymerization of the monomer, **DPOx**, proceeds selectively via a living cationic ring-opening mechanism of the 2-ozazoline ring. Copolymerization studies of **DPOx** with **MeOx** demonstrated the formation of statistical copolymers. By simply changing the initiator/monomer/comonomer ratios, different chain lengths and, thus, molecular weights as well as numbers of functionalities can be achieved. The polymer analog deprotection of the 1,3-dioxolan side function to the aldehyde and the chemoselective coupling with an amino-oxy compound were successful. Moreover, the quantitative conversion of the side-chain functionalities impressively underlines the value of chemoselective reactions. In ongoing studies, we will exploit this combination of a defined living polymerization yielding aldehyde-functionalized polymers with the chemoselective coupling of peptidic cell-binding motifs to develop a new class of polymer therapeutics for cancer diagnosis and therapy.

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