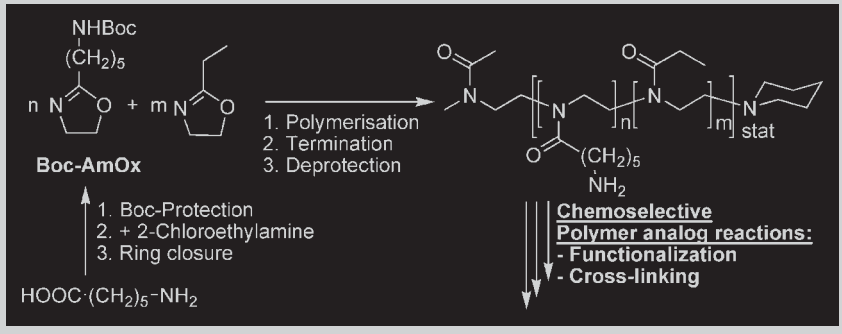
Summary: A new 2-oxazoline monomer with a Boc protected amino function, 2-[*N*-Boc-5-aminopentyl]-2-oxazoline; (**Boc-AmOx**), was synthesized from commercially available compounds. With an initiator salt system (*N*-methyl-2-methyl-2-oxazolinium triflate; **MeOxOTf**), the monomer could be converted via living cationic ring-opening polymerization to well-defined homopolymers with narrow molar mass distributions and targeted polymer chain length. After a quantitative deprotection, poly(2-oxazoline)s with pendant amino functions were obtained. In order to vary the polymer functional group density and solubility of the polymer, copolymerization with different monomer ratios of **Boc-AmOx** and 2-ethyl-2-oxazoline (**EtOx**) was performed. Ex-situ NMR spectroscopy studies verified the randomness of the cationic copolymerization. The accessibility of the pendant amino side functions was confirmed in polymer analog thiourea formation with different isothiocyanates, such as benzyl isothiocyanate (**BzNCS**), or a fluorescence dye, tetramethyl rhodamine isothiocyanate (**TRITC**). A cross-linking reaction with a bifunctional isothiocyanate (**Ph(NCS)$_2$**) resulted in poly(2-oxazoline) hydrogels.



First Poly(2-oxazoline)s with Pendant Amino Groups

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Introduction

Polymerization of 2-oxazolines yields structurally well-defined well polymers of narrow molar mass distribution, tailored composition and functionalization.[1] For example, telechelic poly(2-oxazoline)s are directly accessible by quantitative end-functionalization via the initiation[2–7] and/or the termination method.[3,8–12] Side chain functionalities can be introduced, either by direct polymerization of the respective substituted 2-oxazoline monomers, or by polymer analogous conversions of a suitable polymer precursor. In most cases, the latter is advisable, since many reactive chemical groups are not compatible with the living cationic ring-opening polymerization. The poly(2-oxazoline) system is especially intriguing for the preparation of multi-functional polymers, since most 2-oxazoline monomers can be combined by block, random or gradient polymerization into one polymer. The side chain functionalization can not only accommodate various reactive groups, but also determine the overall physical properties of

the polymer. In the simplest case, the length of an attached alkyl group determines the thermal properties and solubility.[13,14] In particular, with a methyl substitution, the polymer is highly water soluble; poly(2-ethyl-2-oxazoline) is the only amorphous polymer of this class,[14] which is still water soluble, but already displays a slight amphiphilic behavior of each monomer unit.[15] Longer saturated chains, such as *n*-nonyl- groups, result in a strong amphiphilic motif and the polymer can be characterized as a non-ionic polysoap. A combination of hydrophilic and amphiphilic monomer units via block copolymerization leads to amphiphilic polysoaps that are aggregating into defined micelles at very low critical micelle concentrations (CMC $\approx 10^{-5}$ mol/L).[16] An additional introduction of chemical groups into the hydrophobic polymer segment allows the formation of polymer ligands for micellar catalysis in aqueous media. This was successfully applied for the synthesis of poly(2-oxazoline) terpolymers containing bipyridine ligands for atom transfer radical polymerization (ATRP)[17,18] and *N*-heterocyclic carbene units for Heck reactions.[19,20] Ligands or catalysts that interfere with the polymerization mechanism were introduced into the polymer, not via the direct monomer route, but rather by modification of the polymer. A typical example is the reaction of poly(iodoaryl modified 2-oxazoline) with diphenyl phosphane yielding a polymer with pendant triphenyl phosphane units.[21–23]

Poly(2-oxazoline) with bulkier side groups, or mesogenes, have also been prepared to realize supramolecular polymer architectures.[24,25]

Recently, we investigated self-association and gelation of the polymer by a combination of end-functionalization of the polymer with a lipid moiety (lipopolymer) and by a variation of the steric demands and hydrogen bonding sites in the polymer side group.[26] By a double end-functionalization with a lipid and a coupling group, surface-bond lipopolymer scaffolds for the construction of biomimetic membranes can be produced.[27–32]

Since amphiphilicity, as well as the chemical functionality can be combined by copolymerization of the various 2-oxazoline monomers, the solubility and the chemistry of the polymer can be fine-tuned to a desired application. This renders the poly(2-oxazoline) system as a good alternative to the well-known poly(ethylene glycol) (PEG), dominantly used in biomedical applications such as drug-delivery systems (e.g. liposomes[33]) or polymer therapeutics.[34,35] Keeping the chemical functionality and simultaneously, fine-tuning the solubility of the polymer may be crucial for the successful development of a polymer therapeutic, because by this, the biodistribution and pharmacokinetics[36] as well as the immunoresponse[37] can be optimized. In this context, it is noteworthy that both homopolymers and copolymers of 2-methyloxazoline and 2-ethyloxazoline are reported to be non-toxic.[38]

Besides the above-mentioned chemical side functions of poly(2-oxazoline), several others have been reported. These include ester functionalities to generate versatile carboxyl[39–41] and hydroxyl[39,42] groups; siloxane groups;[43,44] carbazol-functionalities;[45] furan- and maleimide modifications,[46] and, very recently, we reported on the introduction of an aldehyde function into the poly(2-oxazoline) side chain.[35] As, this group would interfere with the cationic polymerization, a protected 2-oxazoline (2-(3-[1,3]dioxolan-2-ylpropyl)-2-oxazoline) molecule was synthesized, polymerized and quantitatively deprotected in a polymer analogous step.

To further broaden the chemistry of poly(2-oxazoline)s, we hereby report on our recent results of the synthesis of the first poly(2-oxazoline) with pendant amino groups. To the best of our knowledge, only poly(2-oxazoline)s with terminal amine groups have been described so far.[16] Our interest in the reactivity of this group is focused on the possibility of synthesizing polymer-peptide conjugates. Through the linking groups introduced in the side chain or as end functionalization, the polymers can be coupled to peptides by means of standard amide coupling reactions or, alternatively, via chemoselective ligation with isothiocyanate groups to the corresponding thiourea.[16,47–54]

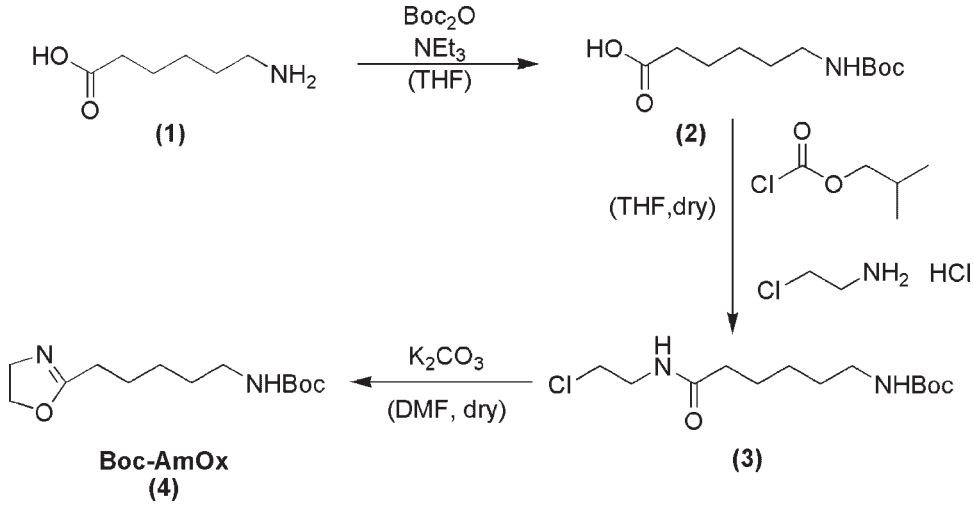
In order to develop a compatible construction kit to create multi-functional polymers, we synthesized 2-[*N*-Boc-5-aminopentyl]-2-oxazoline (**Boc-AmOx**), a protected monomer that can be directly converted via living cationic polymerization. A free amine group would interfere with the polymerization. In fact, primary and secondary amines are commonly used to terminate the polymerization of 2-oxazolines.[3,55,56] The new monomer was successfully polymerized and finally deprotected yielding homo- and copolymers with pendant amino functions. The reactivity and accessibility of the side function was investigated by coupling reactions with different isothiocyanates.

Results and Discussion

*Monomer Synthesis (**Boc-AmOx**)*

One of the advantages of the 2-oxazoline system is the direct synthesis of new monomers with desired functionalities. Various routes have been reported, including the ring-closure reaction used for the synthesis of **Boc-AmOx**, as developed by Levy and Litt [39] and recently modified by Weberskirch et al.[40] Scheme 1 outlines the reaction steps. 6-Aminohexanoic acid (**1**) was treated with Boc anhydride to give the corresponding Boc-protected compound **2** in high yields. **2** was coupled with 2-chloroethylammonium chloride in tetrahydrofuran (THF). The ring closure of **3** results in the desired monomer **Boc-AmOx**.

The monomer was characterized using NMR spectroscopy, elemental analysis and mass spectrometry. In



Scheme 1. Synthesis of 2-[*N*-Boc-aminopentyl]-2-oxazoline (**Boc-AmOx**, **4**).

Figure 1, the ^{1}H NMR spectrum of the purified Boc-protected monomer is displayed.

All of the signals could be unambiguously assigned. The signals of the two methylene groups at 4.09 ppm (a: t, 2H) and 3.68 ppm (b: t, 2H), originated from the 2-oxazoline and confirmed the successful ring formation. The methylene signals (c-g) of the spacer, as well as those from the *tert*-butyl group (i: 9H, at 1.4 ppm) corroborated the displayed structure. Additionally, the broad signal of the amidic proton, at around 4.6 ppm, is visible.

Polymerization

Our first attempts to polymerize **Boc-AmOx** with methyl triflate (**MeOTf**) as the initiator failed. A mixture of undefined low molar mass products was obtained. Presumably, the initiator does not only attack the 2-oxazoline ring, but mainly attacks the secondary amide group in the monomer side chain. Only when the salt, *N*-methyl-2-methyl-2-oxazolinium triflate (**MeOxOTf**), was used as the initiator, was the monomer readily converted to the corresponding polymers. In this case, good agreement between $[M]_0/[I]_0$ and the obtained degree of polymerization, as well as the small polydispersity index, indicate a living (stoichiometric) cationic polymerization. Apart from the different initiator, all of the polymerization reactions were performed according to a previously described procedure.[3,16,21,35] All polymerizations were terminated with an excess of piperidine.[55]

Analogous to our recent account on poly(2-oxazoline)s featuring pendant aldehyde functions, a selection of homo- and copolymers were prepared in order to vary the polymer functional group density and molar mass, only here, **Boc-AmOx** was copolymerized with 2-ethyl-2-oxazoline (**EtOx**). Regarding the structures of both monomers, it is justified to assume that their polymerization proceeds with a similar rate.[35,57] Therefore, a random copolymerization behavior can be assumed. To prove this assumption, ex situ kinetic studies of the copolymerization of **Boc-AmOx** with **EtOx** were carried out. The NMR analysis of the composition of the resulting copolymers revealed a similar conversion of both monomers over the entire reaction time.[a]

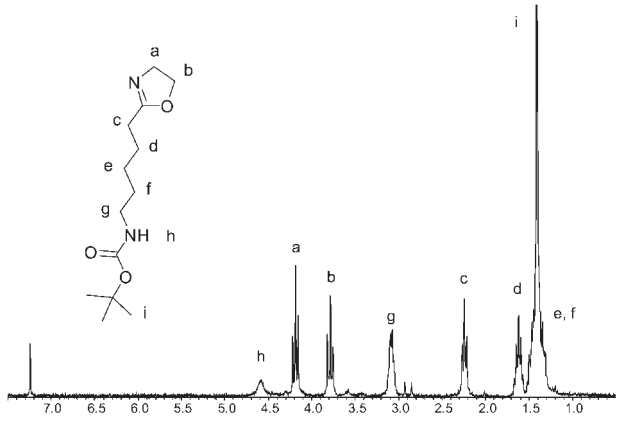
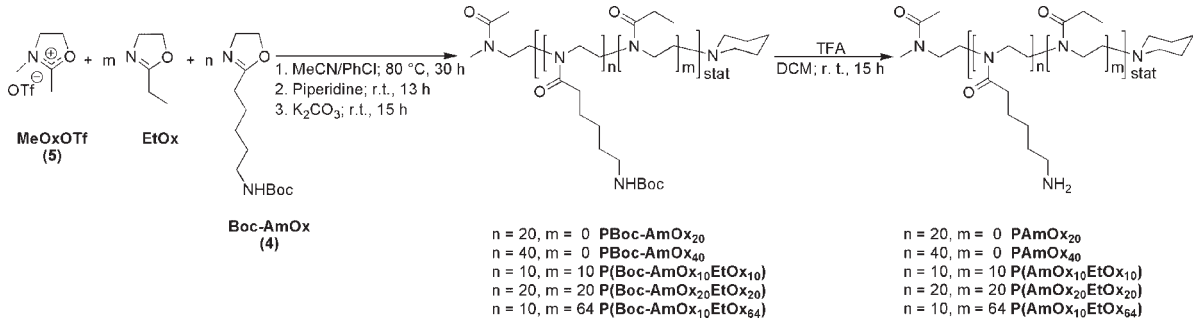


Figure 1. ^{1}H NMR spectrum (in $CDCl_3$), and chemical structure, of the **Boc-AmOx** monomer along with its peak assignments. The signals between 2.8 and 3.0 ppm are from residual DMF.

[a] Ex situ monitoring of the EtOx and Boc-AmOx copolymerization was performed with MeOxOTf as the initiator, analogous to the herein described polymerization procedure (see experimental part). After different polymerization times, fractions of the reaction solution were collected, the polymer precipitated and analyzed by ^{1}H NMR spectroscopy. The ratios of the characteristic signals of the monomers were used to determine the content of the respective monomer in the product. Additionally, GPC analysis was performed to check the monomodal distribution of each fraction. In all cases only one type of polymer could be identified. Hence, simultaneous homopolymerization of both monomers can be excluded. Over the entire monitored reaction time (2–42 h) the Boc-AmOx/EtOx ratio was found to be constant with approximately 1.2 (55:45).



Scheme 2. Homopolymerization of **Boc-AmOx** and random copolymerization with **EtOx** using **MeOxOTf** as the initiator salt and piperidine as the terminating agent. The deprotection of the pendant amino group was performed with trifluoroacetic acid (TFA) in dichloromethane.

Scheme 2 outlines the homopolymerization reaction of **Boc-AmOx** as well as its copolymerization with **EtOx** to polymers of different length and monomer ratios. The corresponding analytical values are summarized in Table 1. In all cases, the polydispersity index (PDI $= \overline{M}_w/\overline{M}_n$) was found to be low, except for the longest copolymer, **P(Boc-AmOx$_{10}$EtOx$_{64}$)**, PDI = 1.38, (see Table 1). Here, the growing influence of a known cross-linking side reaction is noticeable.[43,58] As an example, the ^{1}H NMR spectrum of the copolymer **P(Boc-AmOx$_{10}$EtOx$_{64}$)** is shown in Figure 2a. Although the assignment was straightforward, a reliable end group analysis using the signals of the terminal methyl group, *a*, or of the piperidine methylene groups (*m*, *n*, *o* in Figure 2) could not be performed due to signal overlapping. Hence, the polymer composition was determined from the ratio of the characteristic signals of the two monomers (for **Boc-AmOx**: signals e, f, g, p; 15H; for **EtOx**: signal l; 3H). The analysis showed no or minor differences between the initial monomer feed ratio and the monomer content in the polymers ([**Boc-AmOx**]$_0$:[**EtOx**]$_0$

Table 1. Analytical values and nomenclature of the synthesized polymers. Differences between the experimental and expected molecular weights can be explained on the basis of the different hydrodynamic volume of the polymers and their interaction with the stationary phase as compared to the PMMA standard used for GPC calibration (also see ref.[21, 35]).

Polymer	Theoretical molecular weight	$\overline{M}_{n,GPC}$[a)]	PDI_{GPC}[a)]	Yield
				%
Protected polymers				
PBoc-AmOx$_{20}$	5 310	5 400	1.11	43
PBoc-AmOx$_{40}$	10 437	8 000	1.14	54
P(Boc-AmOx$_{10}$EtOx$_{10}$)	3 738	4 700	1.14	75
P(Boc-AmOx$_{20}$EtOx$_{20}$)	7 290	7 400	1.20	83
P(Boc-AmOx$_{10}$EtOx$_{64}$)	9 091	8 200	1.38	56
Deprotected polymers				
PAmOx$_{20}$	3 310	–	–	91
PAmOx$_{40}$	6 437	–	–	86
P(AmOx$_{10}$EtOx$_{10}$)	2 738	–	–	92
P(AmOx$_{20}$EtOx$_{20}$)	5 290	–	–	88
P(AmOx$_{10}$EtOx$_{64}$)	8 091	–	–	88
Coupled with benzyl isothiocyanate				
PBz-AmOx$_{20}$	6 290	6 900	1.17	83
PBz-AmOx$_{40}$	12 397	7 300	1.17	76
P(Bz-AmOx$_{10}$EtOx$_{10}$)	4 228	6 600	1.29	83
P(Bz-AmOx$_{20}$EtOx$_{20}$)	8 270	10 600	1.20	81
P(Bz-AmOx$_{10}$EtOx$_{64}$)	9 581	8 300	1.44	83
Coupled with TRITC:				
PTRITC-AmOx$_{20}$	12 177	5 800	1.08	73
PTRITC-AmOx$_{40}$	24 173	–	–	58
P(TRITC-AmOx$_{10}$EtOx$_{10}$)	7 174	6 600	1.15	77
P(TRITC-AmOx$_{20}$EtOx$_{20}$)	14 161	6 200	1.14	75
P(TRITC-AmOx$_{10}$EtOx$_{64}$)	12 525	9 800	1.40	70

[a)] Values for the deprotected polymers and for **PTRITC-AmOx$_{40}$** could not be measured because of poor solubility.

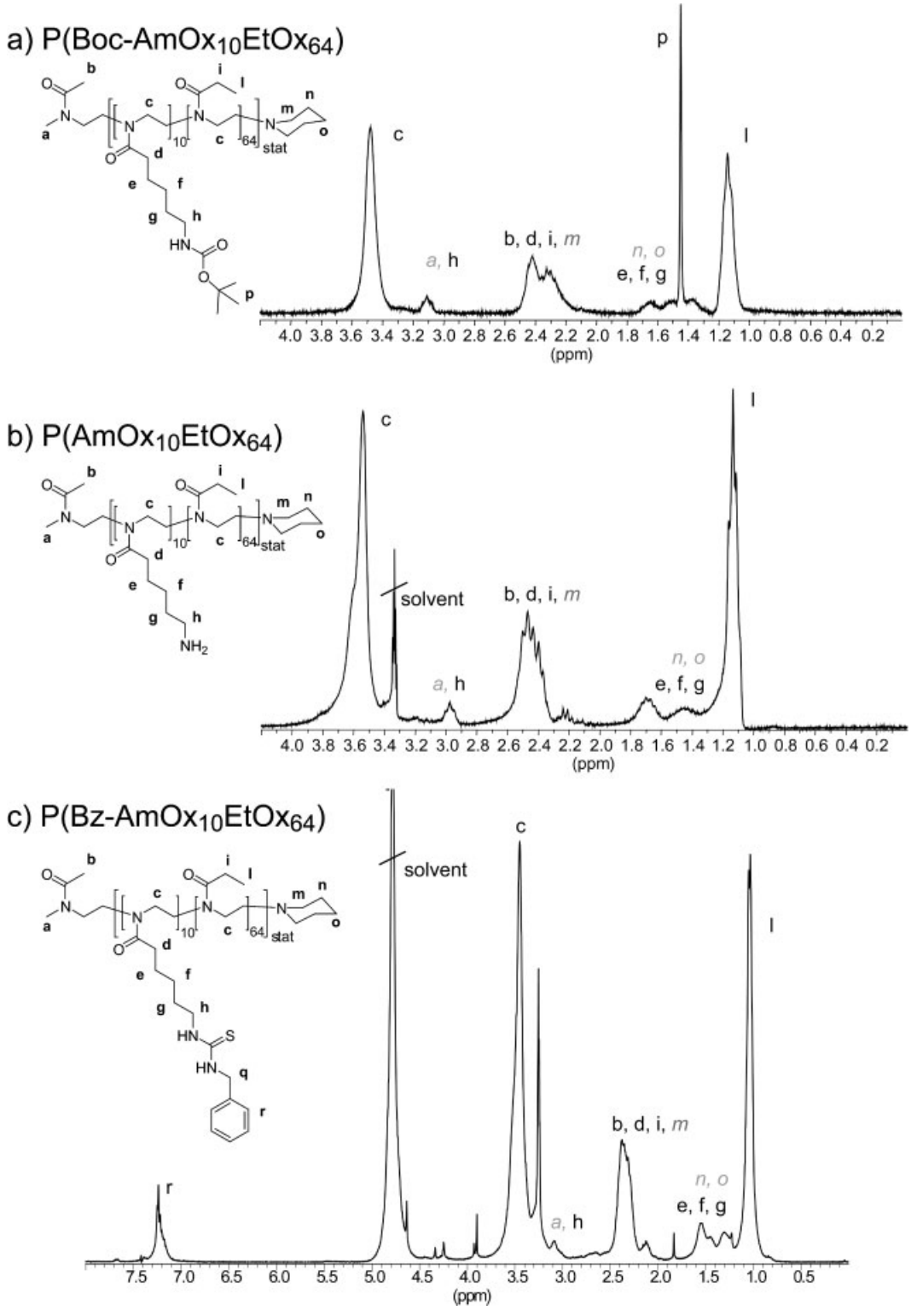
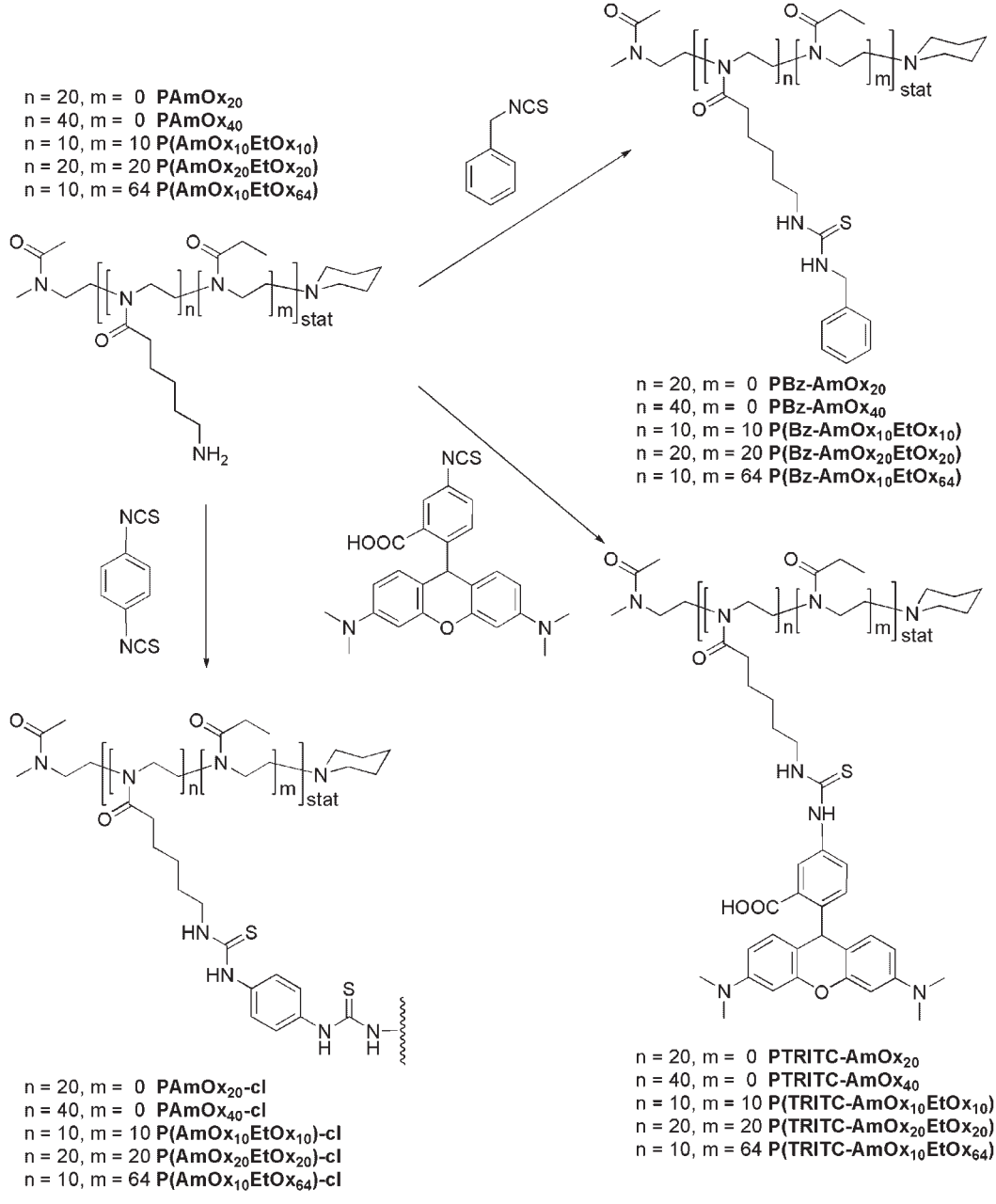


Figure 2. Examples of ^{1}H NMR spectra of a synthesized copolymer a) with Boc-protected **AmOx** units (**P**(**Boc-AmOx$_{10}$EtOx$_{64}$** in $CDCl_3$); b) after the deprotection using TFA in DCM (**P**(**AmOx$_{10}$EtOx$_{64}$**); and c) after the reaction with benzyl isocyanate (**P**(**Bz-AmOx$_{10}$EtOx$_{64}$**) (both in CD_3OD). Assignments in italics could not be directly assigned and are based on previously published data (ref.[3,15,16,35]).

feed = 10:10 (signal ratio 1:1); 20:20 (signal ratio 1:1) and 10:64 (signal ratio 1:8.2)).

Scheme 2 also outlines the polymer analogous deprotection by a treatment of the polymers with trifluoroacetic acid (TFA) in dichloromethane (DCM) to yield poly(2-oxazoline)s with pendant amino functions. According to the ^{1}H NMR data (Figure 2b), the signal corresponding to the *tert*-butyl group (signal p, 1.4–1.5 ppm in Figure 2a) disappeared completely, thus indicating a quantitative conversion. The high amino group content of the deprotected polymers significantly lowered their solubility. In particular the poly(5-amino pentyl-2-oxazoline) homopolymers (**PAmOx$_n$** with $n = 20$, 40) were nearly insoluble. The copolymerization with **EtOx** to poly[(5-amino pentyl-2-oxazoline)-*co*-(2-ethyl-2-oxazoline)] (**P(AmOx$_n$-EtOx$_m$)**) resulted in an improved solubility in water and polar organic solvents. However, gel permeation chromatography (GPC) analysis of the polymers with free amino groups was still not possible, due to the presence of the ammonium trifluoroacetate salt.



Scheme 3. Polymer analogous reactions of different isothiocyanates with the amino functionalized poly(2-oxazoline)s.

Coupling Reactions

After deprotection, all of the polymers were subjected to a polymer analogous reaction with isothiocyanates of different steric demand. In order to test the accessibility and reactivity of the polymer-bound amine groups, reactions with benzyl isothiocyanate (**BzNCS**) and a fluorescence dye, tetramethyl rhodamine isothiocyanate (**TRITC**), were performed. The reactions are summarized in Scheme 3.

After purification, the products were characterized by GPC, ^{1}H NMR and FT-IR spectroscopy. In Figure 2c the ^{1}H NMR spectrum of the polymer product (**P(Bz-AmOx$_{10}$-EtOx$_{64}$)**) is displayed. The successful coupling is indicated by the aromatic signal (r), appearing at 7.0–7.4 ppm. This is corroborated by the GPC analysis. The relative increase of the molar masses on addition of the isothiocyanates, and the reasonably good agreement between the theoretical and experimental molar masses for **PBzAmOx$_n$EtOx$_m$** (Table 1), indicates a successful coupling reaction. The respective polydispersity indices did not change significantly (Table 1).

While the coupling reactions with the smallest isothiocyanate (**BzNCS**) were successful and quantitative, the attachment of the much larger fluorescent dye **TRITC** was not complete for both the **PAmOx$_n$** homopolymers and the **P(AmOx$_{20}$EtOx$_{20}$)** copolymer. Only when the polymer could provide sufficient space, a quantitative conversion was obtained (with **P(Bz-AmOx$_{10}$EtOx$_{64}$)** and **P(Bz-AmOx$_{10}$EtOx$_{10}$)**). This underlines the need to tailor a suitable polymer body, by dilution of the pendant functional group concentration for consecutive polymer analogous reactions to accommodate the sterically demanding side groups.

Cross-Linking

All of the polymers were reacted with an excess of a bifunctional cross-linker (**Ph(NCS)$_2$**) to obtain polymer hydrogels of **PAmOx$_n$EtOx$_m$-cl** (for $n = 10, 20, 40$; $m = 0, 10, 20, 64$) (Scheme 3). During the reaction, the polymers either precipitated or were slowly converted into swollen gels. The products were subjected to an extraction protocol using various polar solvents (e.g. $CHCl_3$, DMF, MeOH, DMAc) for several hours. After solvent evaporation, the extracted material was collected and analyzed by NMR spectroscopy. In none of the cases, characteristic polymer signals could be identified. Hence, all of the polymers were completely converted into cross-linked gels. After the extraction experiments, the gels were investigated by ATR FT-IR spectroscopy. The characteristic NCS-band of the cross-linker at $\approx$2000 cm^{-1} could be detected in none of the gels. Instead, the appearance of the characteristic band at $\approx$1100 cm^{-1} proved the formation of the thiourea linking group. It is noteworthy that variation of the **AmOx** content in the polymer and different choices of the comonomer allows the easy preparation of a broad variety of hydrogels, or even amphiphilic gels, by this simple cross-linking reaction.

Conclusion

In a straightforward synthesis, a new 2-oxazoline monomer, bearing a Boc-protected amino function, was obtained in high yields. The monomer could be homopolymerized and copolymerized in a controlled fashion by living cationic polymerization. A simple polymer analogous deprotection step to poly(2-oxazoline)s with pendant amino groups was quantitative. The reactivity and accessibility of the amino side function was investigated by coupling reactions with different isothiocyanates. The degree of the reaction between $-NH_2$ and NCS depends on the molecular weight of the polymers, the sequence of NH_2 groups in the polymer, the steric demand of the reagent R-NCS and, last but not least, on the solubility of the modified polymers. Furthermore, it was demonstrated that reactions with bifunctional isothiocyanates ($C_6H_4(NCS)_2$) yield cross-linked hydrogels.

Currently, the novel amino-containing polymers are used for ligand attachment, to obtain macroligands for catalytic applications[59] as well as for the attachment of peptidic cell-binding motifs to develop polymer therapeutics for biomedical use, for example in cancer diagnosis and therapy.

Experimental Part

Materials and Methods

The monomers and solvents used for the cationic polymerization were purified as recently reported. Other commercially available chemicals (Aldrich) were used without further purification.[26,35] The same purification procedures were used in the NMR and ATR FT-IR spectroscopy and gel permeation chromatography (GPC) experiments. NMR spectra were recorded in $CDCl_3$, unless otherwise stated, at 250 or 300 MHz. The respective solvent signals were used as reference. Elemental analyses were measured by the Microanalytical Laboratory of the Inorganic Chemistry of the TU München (Mr. Barth). HPLC-ESI mass spectra were obtained on a Finnigan NCQ-ESI with HPLC conjunction LCQ (HPLC system Hewlett Packard HP 1100, Nucleosil 100 5C$_{18}$).

Synthesis

N-Boc-6-aminohexanoic Acid, **2**

Di-*tert*-butyl dicarbonate (25.0 g, 114 mmol) was added to a stirred mixture of 15.0 g (114 mmol) of 6-aminohexanoic acid (**1**) and 20.6 mL (150 mmol) of triethyl amine (TEA) in 160 mL dry THF. After 3 days, 300 mL water was added. The pH was adjusted to 5 with 1 M aqueous $KHSO_4$-solution, and the product was separated by extraction with ethyl acetate, which was subsequently removed under reduced pressure. The solid

residual was identified as the desired protected amino acid (yield = 22.4 g (85%)).

^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (13H, m, C(CH_3)$_3$, CH_2), 1.6 (2H, quin., J = 7.5 Hz, CH_2), 2.31 (2H, t, J = 7.2 Hz, CH_2COO), 3.07 (2H, m, CH_2N), 4.56 (1H, s, N*H*), 11.6 (1H, s, COO*H*).

ESI-MS: ($C_{11}H_{21}O_4N$, 231.30 g · mol^{-1}) $m/z = 132.1$ (m – Boc + H)$^+$, 232.2 (m + H)$^+$.

tert-Butyl 5-(2-Chloroethylcarbamoyl) Pentyl Carbamate, **3**

5.2 g (22.5 mmol) of **2** were dissolved in 70 mL of dry THF and 3.13 mL triethylamine (22.5 mmol). At 0 °C, 2.9 mL (22.5 mmol) of *iso*-butyl chloroformiate was added under nitrogen atmosphere and the mixture was stirred for 5 min at 0 °C, and a further 10 min at room temperature. After cooling to 0 °C, 2.6 g (22.5 mmol) of 2-chloroethyl amine hydrochloride, dissolved in 10 mL of dry DMF and 3.13 mL of TEA (22.5 mL), was added, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated and the residue dissolved in DCM. The solution was extracted with 10% (w/w) Na_2CO_3 and saturated aqueous NaCl solutions. The solvent was evaporated and the remaining oil dissolved in diethyl ether. The product was precipitated in *n*-hexane. 4.8 g (yield = 73%) of the product was collected.

^{1}H NMR ($CDCl_3$): $\delta = 1.25–1.50$ (13H, m, OC(CH_3)$_3$, $CH_2CH_2CH_2$NHBoc), 1.63 (2H, m, NCOCH$_2CH_2$), 2.18 (2H, q, J = 7.4 Hz, NCOCH_2CH$_2$), 3.06 (2H, m, CH_2NHBoc), 3.39 (2H, dt, J = 5.5 Hz, 3.3 Hz, ClCH$_2CH_2$N), 3.78 (2H, t, J = 4.9 Hz, ClCH_2CH$_2$N).

ESI-MS: ($C_{13}H_{25}ClN_2O_3$, 292.80 g · mol^{-1}) $m/z = 193.2$ (m – Boc – H)$^+$, 293.1 (m + H)$^+$, 315.2 (m + Na)$^+$.

2-[*N*-Boc-5-amino pentyl]-2-oxazoline, **Boc-AmOx**, **4**

5.5 g (18.7 mmol) of **3** were dissolved in 40 mL of dry DMF and 5.1 g (37.4 mmol) of dry K_2CO_3 was added. The solution was stirred for 5 h at 70 °C under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the remaining solid was dissolved in DCM and successively filtered to remove the excess K_2CO_3. The solvent was evaporated and 4.1 g (yield = 86%) of **4** was collected.

^{1}H NMR: $\delta = 1.15–1.42$ (15H, m, C(CH_3)$_3$, CH_2CH_2-CH_2NHBoc), 1.40 (2H, m, CCH$_2CH_2$), 2.12 (2H, m, CCH_2-CH$_2$), 2.97 (2H, m, CH_2NHBoc), 3.68 (2H, m, OCH_2CH$_2$N), 4.09 (2H, m, OCH$_2CH_2$N).

ESI-MS: $m/z = 157.2$ (m–Boc + H)$^+$, 201.2 (m–^{t}Bu + H)$^+$, 257.2 (m + H)$^+$.

$C_{13}H_{24}N_2O_3$ (256.34): Calculated: C 60.91, H 9.44, N 10.93; Found: C 60.60, H 9.37, N 10.86.

N-Methyl-2-methyl-2-oxazolium Triflate, **MeOxOTf**, **5**

N-Methyl-2-methyl-2oxazolium triflate, **MeOxOTf**, **5** was synthesized as reported.[35]

Polymerization

All polymerizations were performed according to our recent account.[35] Please refer to Table 1 for the analytical values of all polymers.

Poly(*N*-Boc-5-amino pentyl-2-oxazoline)$_n$, **PBoc-AmOx$_n$** ($n = 20$, 40)

PBoc-AmOx$_{20}$: **Boc-AmOx** 0.96 g (3.76 mmol), **MeOxOTf** 0.047 g (0.188 mmol), piperidine 0.047 g (0.564 mol). Yield = 0.43 g (43%).

^{1}H NMR: $\delta = 1.29–1.56$ (9H, OC(CH_3)$_3$, 2H, NCOCH$_2$-CH_2CH$_2$, 2H, CH$_2$CH_2CH$_2$NHBoc), 2.01–2.18 (2H, NCOC-H_2CH$_2$), 3.01–3.1 (2H, CH_2NHBoc), 3.4–3.6 (4H, CON-CH_2CH_2NCO).

IR: 1 166 (CO–O–$_{\text{Boc group}}$), 1 627 (C=O$_{\text{amide}}$), 1 739 cm^{-1} (CO–NH$_{\text{Boc group}}$).

Poly[(*N*-Boc-5-amino pentyl-2-oxazoline)$_{10}$(2-ethyl-2-oxazoline)$_{10}$], **P(Boc-AmOx$_m$EtOx$_n$)** ($n = 10$, 20; $m = 10$, 20, 64)

P(Boc-AmOx$_{10}$EtOx$_{10}$): Boc-AmOx 0.5 g (1.95 mmol), **EtOx** 0.193 g (1.95 mmol) of 2-ethyl-2-oxazoline, **MeOxOTf** 0.048 g (0.195 mmol), piperidine 0.049 g (0.585 mmol). Yield = 0.550 g (75%).

^{1}H NMR: $\delta = 1.08$ (3H, NCOCH$_2$CH_3), 1.29–1.56 (9H, OC(CH_3)$_3$, 2H, NCOCH$_2$CH_2CH$_2$, 2H, CH$_2$CH_2CH$_2$NHBoc), 2.01–2.18 (2H, NCOCH_2CH$_2$, 2H, NCOCH_2CH$_3$), 3.01 3.1 (2H, CH_2NHBoc), 3.4–3.6 (4H, CONCH_2CH_2NCO).

IR: 1 166 (CO–O–$_{\text{Boc group}}$), 1 627 (C=O$_{\text{amide}}$), 1 739 cm^{-1} (CO–NH$_{\text{Boc group}}$).

Deprotection

The Boc protected polymer (200–500 mg) was dissolved in 2 mL of trifluoroacetic acid and DCM (1:1) and the solution was stirred for 15 h. After solvent evaporation, the residue was precipitated with diethyl ether and isolated by centrifugation.

Poly(5-amino pentyl-2-oxazoline)$_n$, **PAmOx$_n$** ($n = 20$, 40)

^{1}H NMR (MeOH): $\delta = 1.29–1.56$ (2H, CH$_2$CH_2CH$_2$NH$_2$, 2H, NCOCH$_2$CH_2CH$_2$, 2H, CH$_2$CH_2CH$_2$NH$_2$), 2.09–2.35 (2H, NCOCH_2CH$_2$), 2.83 (2H, CH_2NH$_2$), 3.4–3.6 (4H, CON-CH_2CH_2NCO).

IR: 1 627 (C=O$_{\text{amide}}$), 796 cm^{-1} (NH$_3$).

Poly[(5-amino pentyl-2-oxazoline)$_{10}$(2-ethyl-2-oxazoline)$_{10}$], **P(AmOx$_m$EtOx$_n$)** ($n = 10$, 20; $m = 10$, 20, 64)

^{1}H NMR (MeOH): $\delta = 1.08$ (3H, NCOCH$_2$CH_3), 1.29–1.56 (2H, CH$_2$CH_2CH$_2$NH$_2$, 2H, NCOCH$_2$CH_2CH$_2$, 2H, CH$_2$CH_2CH$_2$NH$_2$), 2.09–2.35 (2H, NCOCH_2CH$_2$, 2H, NCOCH_2CH$_3$), 2.83 (2H, CH_2NH$_2$), 3.4–3.6 (4H, CON-CH_2CH_2NCO).

IR: 1 627 (C=O$_{\text{amide}}$), 796 cm^{-1} (NH$_3$).

Polymer Analogous Reaction with Isothiocyanates

The polymers and the isothiocyanates (2 fold excess to the polymer amino group content) were dissolved in 1 mL MeOH and 100 mg K_2CO_3 were added. The solution was stirred for 15 h at room temperature. The excess of K_2CO_3 was filtered and the polymers were purified either by precipitation in

diethyl ether or, in case of the TRITC coupling, by column chromatography (Sephadex G25; MeOH as eluent).

After the cross-linking reaction using phenyl diisothiocyanate, the insoluble material was purified by extraction.

PBz-AmOx$_n$ ($n = 20, 40$)

^{1}H NMR (MeOH): $\delta = 1.29–1.56$ (2H, $CH_2CH_2CH_2NH_2$, 2H, $NCOCH_2CH_2CH_2$, 2H, $CH_2CH_2CH_2NHCS$), 2.09–2.35 (2H, $NCOCH_2CH_2$, 4H, $CH_2N(CH_2)_2$), 3.4–3.6 (2H, CH_2NHCS), 3.89 (2H, $CH_2NHCSNHCH_2$), 7.23 (5H, CH_{Ar}).

The $SCNHCH_2Ar$ signal overlapped with the solvent.

IR: 1 120 ($CS–NH_{isothiocyanate}$), 1 515 (Ar), 1 646 cm^{-1} ($C{=}O_{amide}$).

P(Bz-AmOx$_m$EtOx$_n$) ($n = 10, 20$; $m = 10, 20, 64$)

^{1}H NMR (MeOH): $\delta = 1.08$ (3H, $NCOCH_2CH_3$), 1.29–1.56 (2H, $CH_2CH_2CH_2NH_2$, 2H, $NCOCH_2CH_2CH_2$, 2H, $CH_2CH_2CH_2NHCS$), 2.09–2.35 (2H, $NCOCH_2CH_2$, 2H, $NCOCH_2CH_3$), 3.4–3.6 (4H, $CONCH_2CH_2NCO$, 2H, CH_2NHCS), 3.89 (2H, $CH_2NHCSNHCH_2$), 7.23 (5H, CH_{Ar}).

The signal corresponding to $SCNHCH_2Ar$ overlapped with the solvent.

IR: 1 120 ($CS–NH_{isothiocyanate}$), 1 515 (Ar), 1 646 cm^{-1} ($C{=}O_{amide}$).

PTRITC-AmOx$_n$ ($n = 20, 40$)

^{1}H NMR (MeOH): $\delta = 1.29–1.56$ (2H, $CH_2CH_2CH_2NH_2$, 2H, $NCOCH_2CH_2CH_2$, 2H, $CH_2CH_2CH_2NHCS$), 2.09–2.35 (2H, $NCOCH_2CH_2$), 2.76 (12H, $CH_{Ar}NCH_3$), 3.4–3.6 (4H, $CONCH_2CH_2NCO$, 2H, CH_2NHCS), 3.89 (2H, $CH_2NHCSNHCH_2$), 6.5–7.5 (9H, CH_{Ar}).

The signal corresponding to $CH(C_{Ar})_3$ overlapped with the solvent.

IR: 1 081 ($CS–NH_{isothiocyanate}$), 1 598 (Ar), 1 646 cm^{-1} ($C{=}O_{amide}$).

P(TRITC-AmOx$_m$EtOx$_n$) ($n = 10, 20$; $m = 10, 20, 64$)

^{1}H NMR (MeOH): $\delta = 1.08$ (3H, $NCOCH_2CH_3$), 1.29–1.56 (2H, $CH_2CH_2CH_2NH_2$, 2H, $NCOCH_2CH_2CH_2$, 2H, $CH_2CH_2CH_2NHCS$), 2.09–2.35 (2H, $NCOCH_2CH_2$, 2H, $NCOCH_2CH_3$), 2.76 (12H, $CH_{Ar}NCH_3$), 3.4–3.6 (4H, $CONCH_2CH_2NCO$, 2H, CH_2NHCS), 3.89 (2H, $CH_2NHCSNHCH_2$), 6.5–7.5 (9H, CH_{Ar}).

The signal corresponding to $CH(C_{Ar})_3$ overlapped with the solvent.

IR: 1 081 ($CS–NH_{isothiocyanate}$), 1 598 (Ar), 1 646 cm^{-1} ($C{=}O_{amide}$).

PAmOx$_n$-cl ($n = 20, 40$)

IR: 1 124 ($CS–NH_{isothiocyanate}$), 1 587 (Ar), 1 664 cm^{-1} ($C{=}O_{amide}$).

P(AmOx$_m$EtOx$_n$)-cl ($n = 10, 20$; $m = 10, 20, 64$)

IR: 1 124 ($CS–NH_{isothiocyanate}$), 1 587 (Ar), 1 664 cm^{-1} ($C{=}O_{amide}$).

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