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Multihydroxy Polyamines by Living Anionic Polymerization of Aziridines

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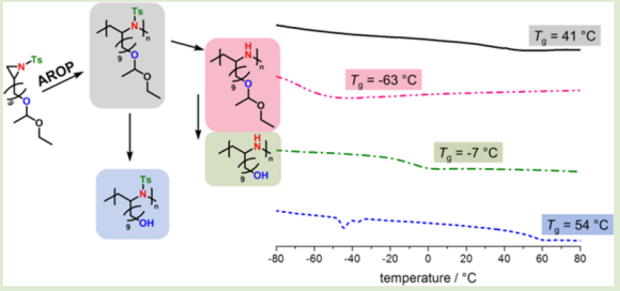
Supporting Information

ABSTRACT: Acetal-protected and sulfonamide-activated aziridines (Az) have been prepared and polymerized by living anionic polymerization with molecular weight dispersities in most cases below $Đ < 1.2$ and controlled molecular weights. Three new monomers have been prepared varying in the length of the pendant chain. The resulting double protected polymers can be selectively deprotected in order to release the polyamine or the polyol structures. Detailed structural characterization was performed for all polymers, and chain extension proves their living polymerization behavior and the formation of block copolymers. Thermal analysis can be used in order to follow the deprotection steps. These new protected monomers broaden the scope of the azaanionic polymerization of aziridines and may find useful applications as well-defined functional poly(ethylene imine) derivatives.



After 60 years of its discovery, living anionic polymerization (LAP) is still the polymerization technique with the highest control over molecular weight and distribution and has the highest precision for the synthesis of block copolymers, end-functionalized polymers, and other well-defined architectures.[1−4] Besides the classic vinyl- and acrylate-monomers, also anionic ring-opening (AROP) strategies for epoxides are standard procedure today.[4−6] Due to the high reactivity of the living anion toward most functional (electrophilic) groups, protective groups are common in LAP to generate (poly)-functional materials.[7] In the last years linear polyglycerol (linPG) as a multifunctional analogue of poly(ethylene glycol) (PEG) gathered a lot of attention in the biomedical field. It is accessible by AROP of several protected glycidyl ethers.[8] Especially the acetal-protected ethoxy ethyl glycidyl ether (EEGE), which was developed already in 1987,[9] became a standard monomer for oxyanionic polymerization today (cf. Figure 1).[6,8,10,11]

Poly(ethylene imine) derivatives are an important gene transfection agent today, which are only available by uncontrolled cationic polymerization of aziridine or living cationic polymerization of oxazolines with subsequent hydrolysis.[12−14] The ring opening of aziridine derivatives is attractive as it allows direct access to branched polymers or materials functionalized at the nitrogen.[15−17] The synthesis of well-defined poly(ethylene imine) derivatives by anionic polymerization carrying additional functional groups has not been accomplished to date.

Herein, we present the first acetal-protected and sulfonamide-activated aziridines for the living azaanionic polymerization. These monomers can be regarded as aziridine analogues of EEGE and double-protected precursors to polyhydroxyl-PEI-derivatives. *N*-Sulfonyl aziridines represent a rather new monomer class for the AROP. To date, mainly the uncontrolled cationic polymerization of various aziridines is used for synthesis of polyamines and -imines. The anionic polymerization of aziridines, however, is not found in textbooks. It was a single report by the group of Toste,[18] showing the feasibility of the AROP of sulfonamide-activated

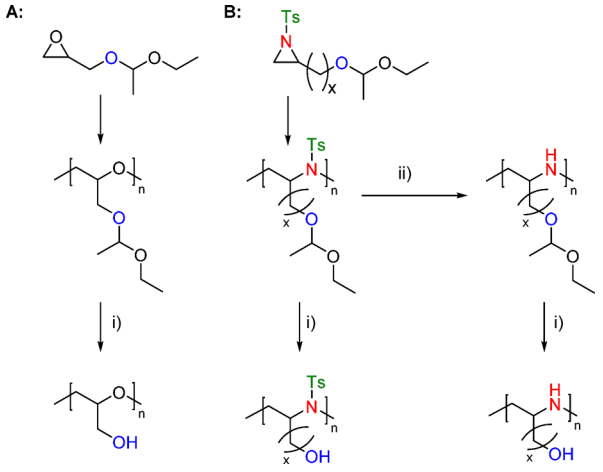


Figure 1. Synthesis of A: linear poly(glycerol) by anionic polymerization of ethoxy ethyl glycidyl ether with subsequent acidic hydrolysis. B: Acetal-protected poly(sulfonamide)s and selective deprotection with (i) diluted HCl and (ii) Red-Al, x = 1, 2, 9, Ts = *p*-toluenesulfonyl).

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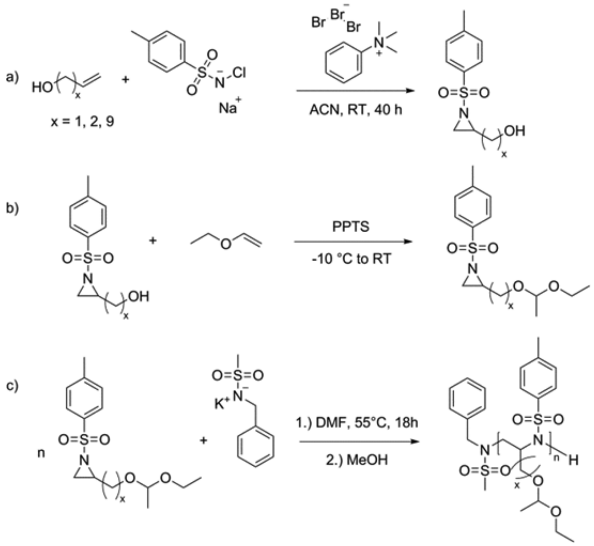
aziridines. Our group has recently expanded the family of sulfonyl aziridines for the termination of carbanionic polymerization or the synthesis of polyvinyl poly(aziridine) (PAz).[19,20] The general "trick" for enabling anionic ROP is to activate the aziridine ring for other nucleophiles. This can be achieved by amidation at the ring nitrogen with electron-withdrawing substituents, such as tosyl or mesyl groups. These electron-deficient aziridines can be ring-opened by strong nucleophiles and allow the polymerization of a variety of substituted aziridines mostly in a living manner to produce poly(aziridine)s (PAz - the abbreviation PAz is used herein to differentiate their origin from the typical polyamines made by cationic polymerization, such as poly(ethylene imine) (PEI)).[19,20]

In this paper a family of double-protected aziridines (**1**, **2**, **3**, Scheme 1) is synthesized and polymerized by LAP. The

Scheme 1. Synthesis of the Acetal-Protected, Sulfonamide-Activated Aziridines: (a) Aziridination of α-Hydroxy-ω-alkenes; (b) Acetalization (ACN = Acetonitrile, PPTS = Pyridinium *p*-toluenesulfonate); and (c) Anionic Polymerization of Acetal-Protected, Sulfonamide-Activated Aziridines



resulting acetal- and sulfonamide-protected polymers can be selectively and/or consecutively treated to release either hydroxyl or amine groups (Figure 1).

A new class of bifunctional aziridines has been designed that can be synthesized by a convenient two-step protocol: the first step is the aziridination of the double bond in an α-hydroxy-ω-alkene via the bromine-catalyzed addition of chloramine-T (Scheme 1a).[21] The alcohol is then protected by the reaction with ethyl vinyl ether to introduce the ethoxy ethyl group (Scheme 1b).[9]

Three novel monomers with varying side-chain lengths have been synthesized: 2-((1-ethoxyethoxy)methyl)-*N*-tosylaziridine (MEETsAz, **1**), 2-((1-ethoxyethoxy)ethyl)-*N*-tosylaziridine (EEETsAz, **2**), and 2-((1-ethoxyethoxy)nonyl)-*N*-tosylaziridine (NEETsAz, **3**) (Scheme 1).

The high purity of the monomers was achieved after thorough chromatographic purification, which was verified by ^{1}H and ^{13}C NMR spectroscopy. In Figure 2 the ^{1}H NMR spectrum of **3** is shown exemplarily (the spectra for **1** and **2** are to be seen in the Supporting Information). The characteristic

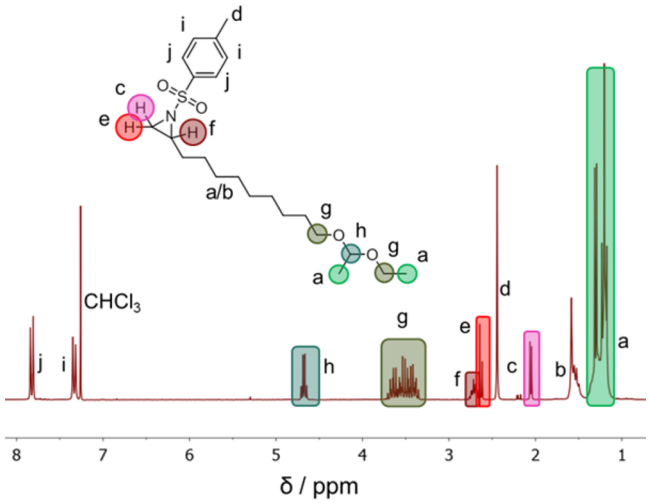


Figure 2. ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) of 2-((1-ethoxyethoxy)nonyl)-*N*-tosylaziridine (**3**).

resonances of the three protons at the substituted aziridine ring are detectable as a multiplet (f) at 2.78−2.65 ppm for the methine and two doublets at 2.63 ppm (e) and 2.05 ppm (c) for the methylene protons. Furthermore, the resonances (g) with a multiplet at ca. 3.76−3.33 ppm and (h) with a quartet at 4.68 ppm can be assigned to the methylene groups next to the oxygen center in the ethoxy ethyl protection groups. All other resonances can be assigned as indicated in Figure 2.

All monomers were successfully polymerized at 55 °C in dry DMF over a period of 18 h with full conversion. The initiator was generated by deprotonation of *N*-benzyl methanesulfonamide (BnNHMs) with bis(trimethylsilyl)amide (KHMDS) prior to the addition of the monomer (Scheme 1). KHMDS can also be used as the initiator itself; however, initiation kinetics are not optimal (data not shown). The living polymerizations—with the typical yellow/orange color of the azaanion—were terminated by the addition of degassed methanol and then precipitated into methanol.

All polymers were characterized by ^{1}H NMR spectroscopy, size exclusion chromatography (SEC), and differential scanning calorimetry (DSC) (see Table 1, all details are listed in the Supporting Information). The SEC elugrams of all polymers exhibit a monomodal and narrow molecular weight distribution with M_w/M_n < 1.25 in all cases, indicating a living mechanism under the applied conditions as reported for other sulfonyl-aziridines.[19,20] To prove the living character, chain extension experiments were performed, using the monomers **1** and **3** as first block. After 13 h, monomer **1** was added to both reactions. ^{1}H NMR and SEC data demonstrate the increasing molecular weight of P1-4(**1**+**1**) and P4(**3**+**1**), including the successful formation of the block copolymer P4 (cf. Figures S33−36). In addition, the polymerization kinetics of **1** with two different initiators (BnNHMs and 1-pyrenemethylmethane-sulfonamide (PyNHMs)) were studied to prove the high control over the molecular weight distribution (see Supporting Information for all data). Figures S28 and S31 show the plots of $\ln([M]_0/[M])$ versus time, and both P1-2 and P1-3 reveal a linear behavior for a living polymerization. In Figures S27 and S30 the plots of the number-average molecular weight (M_n) versus conversion are shown, also increasing linearly. Both data sets indicate a constant concentration of the growing chains, thus a living character of the polymerizations.

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Table 1. Characterization Data for All Polymers and All Deprotected Polymers

polymer	M_n [a]	M_n [b]	M_w/M_n [b]	T_g/°C [c]
P1-1	9200	2200	1.23	+61
P1-2	15100	3700	1.18	n.d.
P1-3	10200	2800	1.19	n.d.
P1-4	12300	5000	1.25	n.d.
P1-1-OH	7000	2300	1.25	+132
P2-1	9600	2900	1.09	+79
P2-2	15900	6400	1.10	+78
P2-3	15900	4600	1.12	n.d.
P2-4	15900	3700	1.12	n.d.
P2-3-OH	12300	5100	1.15	+92
P3-1	6400	1700	1.18	+41
P3-2	6400	1400	1.14	n.d.
P3-2-OH	13600	2000	1.20	+54
P3-3	6400	2300	1.15	n.d.
P3-4	6400	2600	1.17	n.d.
P3-4-NH	4100	700	1.53	−63
P3-4-NH-OH	3000	900	2.01	−7

[a]Theoretical number-average molecular weight (in g/mol). [b]Number-average molecular weight and molecular weight dispersity determined via SEC in DMF (vs PEO standards). [c]Glass transition temperature determined via DSC.

In Figure 3 the ^{1}H NMR spectrum of P3-2 is depicted as a representative example. All signals are detected as broad

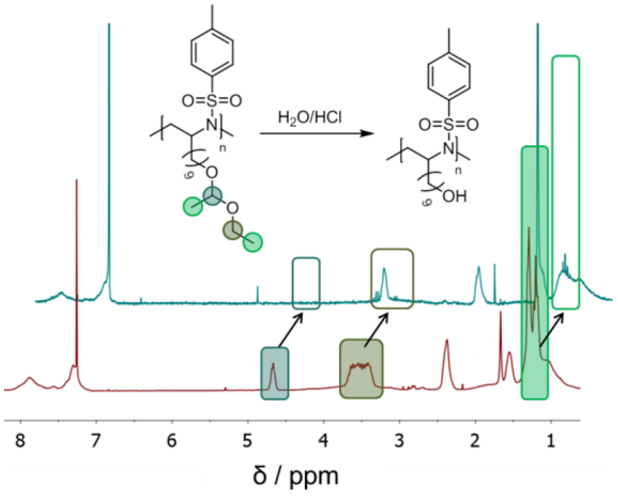

Figure 3. ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) of poly(2-((1-ethoxyethoxy)nonyl)-*N*-tosylaziridine) (P3-2) and poly(*N*-tosyl-2-aziridinenonanol) (P3-2-OH).

polymer resonances, and the aziridine ring resonances disappeared and turned into the backbone of the polymer (4.38−2.72 ppm). The two methylene groups of the acetal-protected side chain overlap with these signals and cannot be differentiated exactly (3.74−3.29 ppm). The broad signal between 1.45 and 0.61 ppm can be attributed to the two methyl groups of the acetal substituent and to the alkyl side chain, whereas the methyl group of the tosyl substituent evolves at 2.53−2.23 ppm.

To release the pendant hydroxyl groups, the polymer was dissolved in ethanol and stirred with concentrated hydrochloric acid at 70 °C overnight. As an example for this reaction, both ^{1}H NMR spectra of the polymer-protected P3-2 and the P3-2-OH are shown in Figure 3. After the acidic hydrolysis, no acetal protons are detectable in the characteristic regions (highlighted in green) proving quantitative hydrolysis and release of the hydroxyl groups (equal to the degree of polymerization).

After the hydrolysis of the acetals, all polymers retained their narrow molecular weight distributions; however, the apparent molecular weights of most polyhydroxy sulfonamides from SEC shifted to higher values, i.e., to lower elution times (Figures S12, S18, and S20). This is attributed to the change in polarity of the polyols. No change in the molecular weight dispersity excludes possible side reactions in analogy to PEEGE.[22]

As SEC is a relative method, no absolute molecular weights were determined, and all molecular weights are apparent vs PEG standards. Presumably, the hydrodynamic radius of PAz is smaller than PEG in DMF due to the higher hydrophobicity. Compared to the theoretical molecular weight (compare Table 1), and assuming a living polymerization mechanism, and full monomer conversion, the absolute molecular weight should be higher than measured in SEC under these conditions.[20] For the chain extension experiments PyNHMs was employed as the initiator allowing NMR end group analysis for molecular weight determination. These polymers exhibit molecular weights two to three times higher compared to the apparent SEC values. The molecular weight of P1-4 was about 14 400 g/mol, compared to 5000 g/mol (SEC analysis) (more data are shown in the Supporting Information). Herein, polymers with molecular weights (SEC data) between 1700 and 6400 g/mol were synthesized, but this should not be regarded as an upper limit.

The sulfonamide groups along the polymer backbone were removed by treatment of the acetal-protected polymers with sodium bis(2-methoxyethoxy)aluminum hydride. Under these conditions ca. 76% of the amino groups can be released (compare Figure 4 and Figures S23 and S24). Subsequent treatment of these polymers with hydrochloric acid releases also the pendant hydroxyl groups. For both deprotection steps the NMR spectra prove successful reaction; however, SEC traces

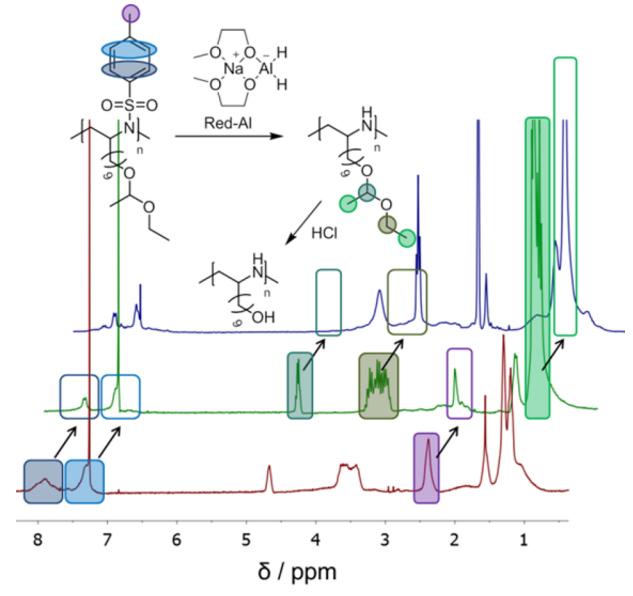

Figure 4. ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K) of poly(2-((1-ethoxyethoxy)nonyl)-*N*-tosylaziridine) (P3-4), poly(2-((1-ethoxyethoxy)nonyl)aziridine) (P3-4-NH), and poly(2-aziridinenonanol) (P3-4-NH-OH).

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reveal a broadening in the molecular weight dispersity. This is, however, probably attributed to interactions of the polyamine with the column material under the applied conditions, which was reported earlier for amine-containing polyethers.[23] We do not claim that no chain scission occurs during the relatively harsh deprotection step. Nevertheless, diffusion-ordered (DOSY) ^{1}H NMR data of P3-4-NH and P3-4-NH-OH (see Figures S23b and S25b) show that all ^{1}H NMR resonances can be assigned to the same diffusion signal, proving the existence of an intact polymer chain.

All polymers are amorphous materials, showing glass transition temperatures (T_g) between ca. 40 and 80 °C in the protected form (determined by DSC measurements: T_g(P1) = 61 °C, T_g(P2-1) = 79 °C, T_g(P3-1) = 41 °C) independent of the molecular weights synthesized herein. After deprotection of the acetals, all hydroxyl-functional polymers showed higher T_g than the starting compounds (T_g(P1-OH) = 132 °C, T_g(P2-3-OH) = 92 °C, T_g(P3-2-OH) = 54 °C). When the sulfonamide was removed first, the polyamine (with acetals) showed a glass transition temperature of T_g(P3-4-NH) = −63 °C, which increased after the acetal deprotection to T_g(P3-4-NH-OH) = −7 °C.

In summary, the first azaanionic polymerization of acetal-protected, sulfonamide-activated aziridines is presented. A convenient protocol for the two-step synthesis of three novel monomers was established. All monomers were polymerized to well-defined homopolymers and exhibited full conversions with narrow molecular weight distributions ($Đ \leq 1.25$). The ethoxy ethyl protecting group can be conveniently removed, yielding linear polysulfonamides with free hydroxyl groups in every repeating unit. Also subsequent deprotection of the sulfonamides and the acetal groups proved to be possible, rendering these materials as highly interesting for novel polyelectrolytes, which are compatible with conventional anionic polymerization setups, for example.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00901.

Detailed experimental procedures as well as analytical and spectral characterization data (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Szwarc, M.; Levy, M.; Milkovich, R. *J. Am. Chem. Soc.* **1956**, *78*, 2656−2657.

(2) Tonhauser, C.; Frey, H. *Macromol. Rapid Commun.* **2010**, *31*, 1938−1947.

(3) Baskaran, D.; Müller, A. H. E. *Prog. Polym. Sci.* **2007**, *32* (2), 173−219.

(4) Hirao, A.; Goseki, R.; Ishizone, T. *Macromolecules* **2014**, *47*, 1883−1905.

(5) Higashihara, T.; Hayashi, M.; Hirao, A. *Prog. Polym. Sci.* **2011**, *36*, 323−375.

(6) Obermeier, B.; Wurm, F.; Mangold, C.; Frey, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7988−7997.

(7) Natalello, A.; Alkan, A.; von Tiedemann, P.; Wurm, F. R.; Frey, H. *ACS Macro Lett.* **2014**, *3*, 560−564.

(8) Thomas, A.; Müller, S. S.; Frey, H. *Biomacromolecules* **2014**, *15*, 1935−1954.

(9) Fitton, A. O.; Hill, J.; Jane, D. E.; Millar, R. *Synthesis* **1987**, *1987*, 1140−1142.

(10) Mangold, C.; Wurm, F.; Frey, H. *Polym. Chem.* **2012**, *3*, 1714−1721.

(11) Taton, D.; Le Borgne, A.; Sepulchre, M.; Spassky, N. *Macromol. Chem. Phys.* **1994**, *195*, 139−148.

(12) Tauhardt, L.; Kempe, K.; Knop, K.; Altuntaş, E.; Jäger, M.; Schubert, S.; Fischer, D.; Schubert, U. S. *Macromol. Chem. Phys.* **2011**, *212*, 1918−1924.

(13) Jäger, M.; Schubert, S.; Ochrimenko, S.; Fischer, D.; Schubert, U. S. *Chem. Soc. Rev.* **2012**, *41*, 4755−4767.

(14) Monnery, B. D.; Hoogenboom, R. In *Cationic Polymers in Regenerative Medicine*; Royal Society of Chemistry: London, 2015; pp 30−61.

(15) Jang, H.-J.; Lee, J. T.; Yoon, H. J. *Polym. Chem.* **2015**, *6*, 3387−3391.

(16) Suzuki, T.; Kusakabe, J.; Ishizone, T. *Macromolecules* **2008**, *41*, 1929−1936.

(17) Lava, K.; Verbraeken, B.; Hoogenboom, R. *Eur. Polym. J.* **2015**, *65*, 98−111.

(18) Stewart, I. C.; Lee, C. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17616−17617.

(19) Thomi, L.; Wurm, F. R. *Macromol. Rapid Commun.* **2014**, *35*, 585−589.

(20) Thomi, L.; Wurm, F. R. *Macromol. Symp.* **2015**, *349*, 51−56.

(21) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845.

(22) Wurm, F.; Nieberle, J.; Frey, H. *Macromolecules* **2008**, *41*, 1184−1188.

(23) Dingels, C.; Wurm, F.; Wagner, M.; Klok, H. A.; Frey, H. *Chem. - Eur. J.* **2012**, *18*, 16828−16835.

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