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Anionic Ring-Opening Polymerization of *N*-(tolylsulfonyl)azetidines To Produce Linear Poly(trimethylenimine) and Closed-System Block Copolymers

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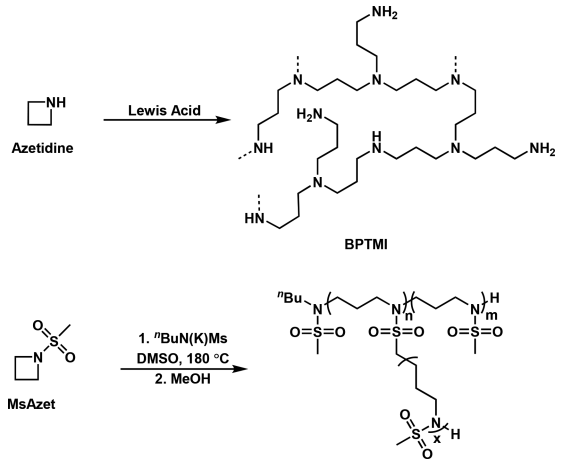
Supporting Information

ABSTRACT: The anionic ring-opening copolymerization of *N*-(*p*-tolylsulfonyl)azetidine (***p*TsAzet**) and *N*-(*o*-tolylsulfonyl)azetidine (***o*TsAzet**) produces poly(*p*TsAzet-*co*-*o*TsAzet) as a statistical copolymer. The ***p*TsAzet**/***o*TsAzet** copolymerization is living and allows for the synthesis of poly(sulfonylazetidine) of target molecular weights with narrow dispersities. ^{1}H NMR spectroscopy was used to monitor the kinetics of the polymerization and estimate the monomer reactivity ratios. It was found that the reactivity ratios for ***o*TsAzet** and ***p*TsAzet** at 180 °C are 1.66 and 0.60, respectively. The tosyl groups of p(*p*TsAzet-*co*-*o*TsAzet) were reductively removed to produce linear poly(trimethylenimine) (LPTMI). This represents the first route to LPTMI of controlled molecular weight and low dispersity. Finally, the slow kinetics of the sulfonylazetidine polymerization facilitated the synthesis of a block copolymer without requiring the sequential addition of monomer. Specifically, ***p*TsAzet**, ***o*TsAzet**, and (*N*-*p*-toluenesulfonyl-2-methylaziridine) (***p*TsMAz**) were combined in solution. ***p*TsMAz** selectively polymerizes to form the first block at moderate temperature. After consumption of ***p*TsMAz**, the temperature was increased to copolymerize ***p*TsAzet** and ***o*TsAzet** and produce the block copolymer p(*p*TsMAz)-*b*-p(*p*TsAzet-*co*-*o*TsAzet).

Despite the structural similarities between cyclic imines and cyclic oxides, their polymerizations are very different. For example, ethylene oxide can be polymerized by both cationic ring-opening polymerization (CROP)[1] and anionic ring-opening polymerization (AROP)[2,3] to produce a linear polymer with high degrees of control. In contrast, aziridine can only be polymerized by CROP to produce a hyperbranched polymer.[4−8] This has led to the development of indirect routes to linear polyimines, the most prominent being the polymerization of oxazolines, despite the difficulties in this approach.[5] However, controlled routes to polyimines continue to be highly sought after due to their use in high value applications (i.e., antimicrobial and antifouling coatings,[9] chelation and polymer-assisted deposition,[10] CO_2 capture,[11] and nonviral gene transfection[5]).

Poly(trimethylenimine) (PTMI) [−$CH_2CH_2CH_2NH$−] is among the least studied of the simple polyimines. This is due to the complexity of azetidine polymerization which exclusively forms hyperbranched PTMI (BPTMI, Scheme 1, TOP).[4,7,8,12−17] Initial work on linear PTMI (LPTMI) was reported by Kobayashi.[18] Recently, Jones utilized this oxazine based route to LPTMI and showed that its CO_2 capture ability is superior to linear polyethylenimine (LPEI) [−CH_2CH_2NH−].[19] However, to date, there are no known routes to LPTMI that have demonstrated control over molecular weight and dispersity.

Scheme 1. (TOP) CROP of Azetidine To Produce BPTMI;[7] (BOTTOM) AROP of MsAzet[37]



Inspired by recent breakthroughs in the AROPs of *N*-sulfonyl aziridines[20−33] as a way to access linear polyimines,[34−36] we recently reported on the AROP of *N*-(methanesulfonyl)azetidine (**MsAzet**) (Scheme 1, bottom).[37] The polymerization kinetics of **MsAzet** were notably slower than *N*-sulfonylaziridines, and, surprisingly, the resulting p(MsAzet) had a branched structure. The branching, which arose due to transfer to the methanesulfonyl groups during

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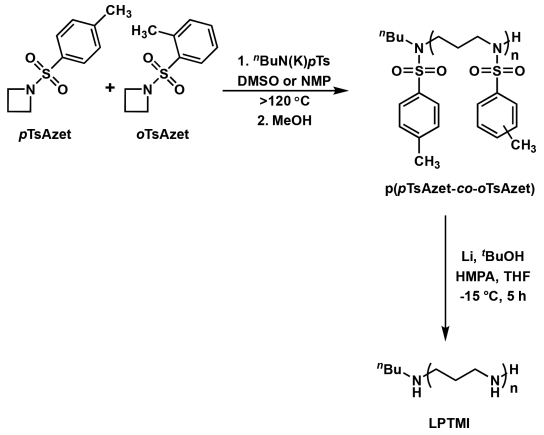
polymerization, precluded **MsAzet** as a precursor to LPTMI. However, the fact that AROP of **MsAzet** did occur, suggests that a suitable *N*-sulfonylazetidine could be used to form a linear polymer and provide a controlled route to LPTMI.

We turned our attention to the polymerization of *N*-(tolylsulfonyl)azetidines as their protons are less likely to be activated under the polymerization conditions. We initially attempted to use AROP to convert *N*-(*p*-tolylsulfonyl)-azetidine (***p*TsAzet**) and *N*-(*o*-tolylsulfonyl)azetidine (***o*TsAzet**) to the corresponding homopolymers, however, both monomers only formed low molecular weight homooligomers. The poor solubility of p(*N*-(tolylsulfonyl)azetidine) homopolymers is not completely unexpected as related poly(*N*-sulfonylaziridine) homopolymers are often similarly insoluble.[26,31,34]

We next attempted the copolymerization of the two *N*-(tolylsulfonyl)azetidine monomers (Scheme 2). This was

Scheme 2. Polymerization of TsAzet Monomers to Soluble p(*p*TsAzet-*co*-*o*TsAzet) and Transformation to LPTMI



motivated by prior work showing that the solubility of poly(*N*-sulfonylaziridine) random copolymers are greatly improved compared to the corresponding homopolymers.[34] Copolymerization of ***p*TsAzet** with ***o*TsAzet** in a 1:1 ratio produced p(*p*TsAzet-*co*-*o*TsAzet), which is soluble in DMF, DMSO, NMP and HMPA. The weakly basic nature of the propagating anion[24] allows this copolymerization to proceed in NMP without any apparent reaction with NMP. For the polymerizations performed in DMSO, small amounts of transfer to solvent is likely occurring,[37,38] although we were unable to observe and quantify this. DMF was also a suitable solvent for the AROP of sulfonyl azetidines.

The polymerization kinetics of the AROP of *N*-(tolylsulfonyl)azetidines in DMSO-d_6 were studied by real-time ^{1}H NMR spectroscopy.[27,29,37] The plot of natural log of total monomer concentration with respect to time is linear, suggesting it is first order with respect to total monomer concentration and that the number of active chain ends remains constant during the polymerization (Figure S1 and Table S2).[39] Compositional drift was observed during the course of the copolymerization, with ***o*TsAzet** being incorporated at a faster rate (Figure S3). The monomer reactivity ratios were estimated using Lynd's nonterminal model.[40] This model assumes that the identity of the active chain end does not impact subsequent monomer additions, which is usually a valid assumption in ionic polymerizations.[41,42] Lynd's nonterminal model is attractive as it allows determination of reactivity ratios through the observation of a single copolymerization. This model calculated the reactivity ratios to be 1.66 and 0.60 for ***o*TsAzet** and ***p*TsAzet**, respectively, at 180 °C (Table S2).[43] We also determined the reactivity ratios for ***o*TsAzet** and ***p*TsAzet** by the Kelen–Tüdös method and there were found to be similar (Figure S4 and Table S3).[44]

In order to determine the possibility of controlling the AROP of the *N*-(tolylsulfonyl)azetidines, a series of copolymerizations were performed where the monomers to initiator ratio was varied (the ratio of the monomers was kept 1:1). The D_p, as measured by ^{1}H NMR spectroscopic end-group analysis closely matched the theoretical values (Table S4) and the plot of M_n vs monomer: initiator was linear (Figure 1). All SEC

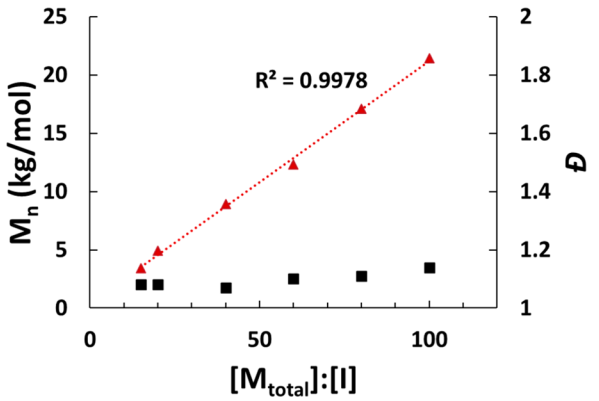


Figure 1. M_n determined by ^{1}H NMR end-group analysis vs $[M_{total}]$:[I] (▲). Dispersity vs $[M_{total}]$:[I] (■).

traces are monomodal with narrow *Đ* (Figure S20 and Table S4) and a decrease in retention time was observed with increasing monomer to initiator ratio. MALDI-TOF mass spectrometric (MS) analysis of the polymers revealed signals consistent with each polymer chain containing the ^{n}Bu(N)Ts initiator (Figure S22). Additionally, upon complete consumption of the monomers, additional equivalents of monomers could be added to the reaction mixture, and chain extension was observed (Figure S21). This data shows that, as with sulfonylaziridines, the copolymerization of ***p*TsAzet** and ***o*TsAzet** appears to be living and controlled.

WAXS data revealed that p(*p*TsAzet-*co*-*o*TsAzet) was crystalline, but the crystalline peaks are distinct from those of the p(*p*TsAzet) and p(*o*TsAzet) homooligomers (Figure S28). This suggests that p(*p*TsAzet-*co*-*o*TsAzet) does not have blocky domains. DSC presents a well-defined T_g of 68 °C and T_m of 140 °C and TGA reveals a T_d of 360 °C (Table S5, entry 6). The difference between the T_m of the copolymer and the homooligomers (213 and 190 °C for ***p*TsAzet** and ***o*TsAzet** homooligomers, respectively, Table S5) further suggests an absence of blocky segments.

In order to convert p(*p*TsAzet-*co*-*o*TsAzet) into LPTMI, the tosyl groups were removed using Li (Scheme 2).[34,45] ^{1}H NMR spectra (Figure S17) of the resulting polymer was consistent with the formation of LPTMI.[19] MS was used to confirm that chain scission had not occurred during the deprotection. MALDI-TOF mass spectrum of LPTMI (Figure S24) derived from low molecular weight p(*p*TsAzet-*co*-*o*TsAzet)$_{15}$ revealed a D_p = 14.8 with *Đ* = 1.04. The observed MALDI-TOF MS data of LPTMI implies that no chain scission is occurring during the removal of the tosyl groups.

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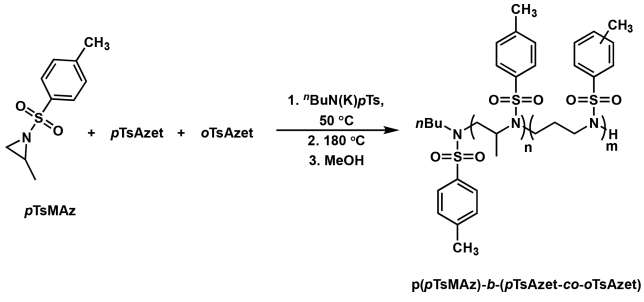
Lastly, we set out to produce block copolymers utilizing *N*-(tolylsulfonyl)azetidine monomers, as this would provide a route to novel polyimine block copolymers. Because ***p*TsAzet** and ***o*TsAzet** do not polymerize at temperatures <100 °C, we proposed that a third monomer, which polymerizes at lower temperatures, could do so in the presence of the sulfonyl azetidines, and allow for a closed-system block copolymer synthesis in which all monomers are present at initiation. After this first monomer is consumed, the reaction mixture could then be heated to higher temperature to facilitate the copolymerization of the azetidines.

We chose to create a block copolymer using *N*-(*p*-tolylsulfonyl)-2-methylaziridine (***p*TsMAz**) as ***p*TsMAz** readily polymerizes at lower temperatures and its propagating chain end could likely initiate the *N*-(tolylsulfonyl)azetidines. To accomplish the block copolymer polymerization, ***p*TsMAz**, ***p*TsAzet**, ***o*TsAzet** and ^{n}BuN(K)*p*Ts were dissolved in DMSO-d_6 (Scheme 3). The reaction mixture was heated to 50 °C for 4 h, during which time ***p*TsMAz** was consumed (Figure 2A). Next, the reaction mixture was heated to 180 °C to polymerize the second block, resulting in the formation of the desired block copolymer p(*p*TsMAz)$_{20}$-*b*-p(*p*TsAzet-*co*-*o*TsAzet)$_{40}$.

Scheme 3. Block Copolymerization of *p*TsMAz with *o*TsAzet and *p*TsAzet To Produce p(*p*TsMAz)-*b*-p(*p*TsAzet-*co*-*o*TsAzet)



Monitoring the polymerization by ^{1}H NMR showed no evidence of sulfonylazetidine consumption at lower temperature (Figure 2A). As such, the resulting block copolymer is believed to have a sharp transition between the two domains, with no region of sulfonylaziridine and sulfonylazetidines mixing. In addition, the SEC trace of the resulting polymer showed no evidence of lower molecular weight p(*p*TsMAz) homopolymer (Figure 2B). Subsequent sulfonyl group removal of this block copolymer would allow for the synthesis of a LPPI-*b*-LPTMI block copolymer.

This ability to produce block copolymers in a closed-system provides a solution to a common issue with the synthesis of block copolymers, especially high-performance block copolymer materials. Traditionally, upon addition of the second monomer, there is often a small amount of chain termination which leads to the presence of homopolymer impurity.[46] This homopolymer impurity can affect the properties of the block copolymer material. This problem can be mitigated by the use of strenuous purifications, as well as high vacuum and break-seal techniques.[47−50] Sumerlin reported block copolymers by RAFT polymerization synthesized in a closed system where individual monomers were segregated in the reaction mixture by temporarily freezing one monomer in a high melting point solvent.[51] Recently, Wurm has utilized a similar closed-system

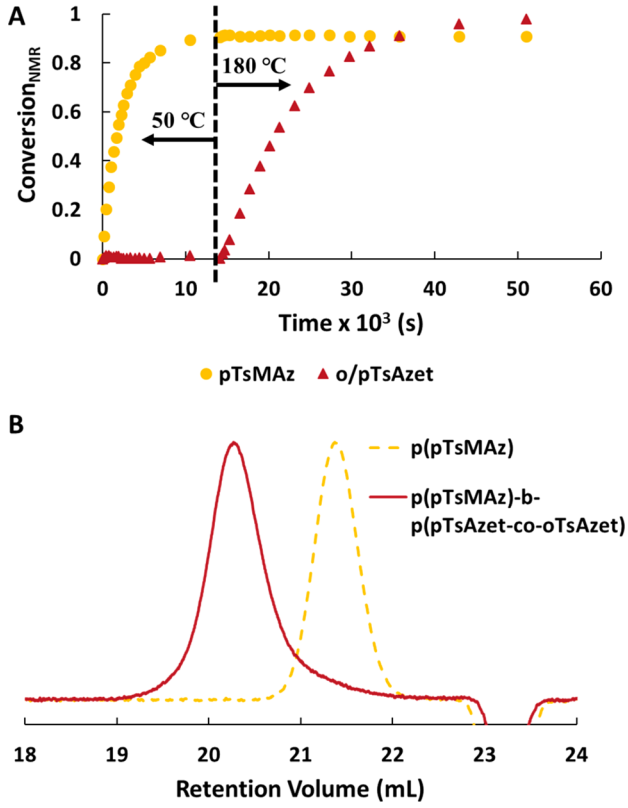


Figure 2. (A) Plot of conversion vs time for the copolymerization of ***p*TsMAz**,***p*TsAzet** and ***o*TsAzet** in DMSO-d_6 to produce p-(*p*TsMAz)$_{20}$-*b*-p(*p*TsAzet-*co*-*o*TsAzet)$_{40}$. The reaction is kept at 50 °C for 4 h, then 180 °C for 10.25 h. The NMR measured conversion of ***p*TsMAz** appears to not reach 100% due to signal overlap between the monomer and polymer resonances in ^{1}H NMR spectra of the reaction mixture as the polymer signal grows in intensity. (B) SEC trace of p(*p*TsMAz)$_{20}$ prior to block copolymer chain extension (yellow ---). SEC trace of p(*p*TsMAz)$_{20}$-*b*-p(*p*TsAzet-*co*-*o*TsAzet)$_{80}$ (red —). Block copolymerization to produce p(*p*TsMAz)$_{20}$-*b*-p(*p*TsAzet-*co*-*o*TsAzet)$_{80}$ was performed with [***p*TsMAz**]:[***o*TsAzet**]:[***p*TsAzet**]:[I] of 20:40:40:1 in NMP at 70 °C for 12 h, then 205 °C for 16 h.

to synthesize p(*p*TsMAz)-PEO block copolymers, although there is some gradient in the transition between the blocks.[52]

In conclusion, we have shown that the copolymerization of ***p*TsAzet** with ***o*TsAzet** produces a soluble, statistical copolymer, p(*p*TsAzet-*co*-*o*TsAzet), and reported the kinetics of the polymerization as well as the reactivity ratios of the two monomers in the copolymerization. The polymerization is living and controlled and can be converted to LPTMI. This allows, for the first time, the synthesis of LPTMI by a controlled, living anionic ring-opening polymerization, an important finding due to the potential high value of this polymer in nonviral gene transfection; studies have shown that the length of the carbon spacer between the nitrogens (i.e., ethyl vs propyl) influences nucleotide binding.[53] Additionally, the high barrier to ring-opening of *N*-sulfonylazetidines can be exploited to produce block copolymers in a closed-system process.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, NMR spectra, MALDI-TOF mass spectra, SEC, WAXS, kinetic and compositional drift data, and thermal analysis plots (PDF)

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Notes

The authors declare no competing financial interest.

Unprocessed, experimental data can be found online via Open Science Framework at: https://dx.doi.org/10.17605/OSF.IO/PFJE6.

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