10152 *Macromolecules* **2010**, *43*, 10152–10156
DOI: 10.1021/ma1019736

Macromolecules
NOTE

Application of Time-Dependent MALDI-TOF Mass Spectral Analysis To Elucidate Chain Transfer Mechanism during Cationic Polymerization of Oxazoline Monomers Containing Thioethers

Mallory A. Cortez and Scott M. Grayson*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118, United States

Received August 26, 2010; Revised Manuscript Received October 22, 2010

Introduction

Since its first application toward macromolecular characterization, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS)[1−3] has proven to be a valuable tool for the characterization of polymers. This soft ionization technique enables the measurement of the absolute molecular weight of each discrete macromolecule represented in the polymer distribution, allowing for the calculation of the sample's number-average molecular weight (M_n) and polydispersity index (PDI), as well as determination of the exact mass of the repeat units and accurate calculation of the combined end-group mass of the polymer.[4,5] Mass spectral characterization is particularly powerful for larger polymers because unlike traditional end-group identification techniques, the signal from the end groups does not diminish (e.g., relative to those of the repeat unit for nuclear magnetic resonance (NMR) spectroscopy) as molecular weight increases. In addition, because such detailed data can be obtained from sub-microgram sample quantities, MALDI-TOF MS has been used for the qualitative elucidation of polymeric architecture,[6−8] polymer degradation,[7,9−12] and end-group transformations.[4,13] While the elucidation of polymer mechanisms and possible side reactions have been studied extensively using end-product characterization,[14−17] the investigation of the change of end groups with respect to time, in order to provide more detailed mechanistic information, has not. The cationic polymerization of thioether-functionalized oxazoline monomers offered an ideal case study to test this methodology for verifying the chain transfer mechanism suggested in our recent investigations.[18]

Traditionally, a number of techniques can be used to provide evidence for the occurrence of chain transfer events during a polymerization. Perhaps the most common involves monitoring the increase in polymer molecular weight with respect to monomer conversion, as measured by gel permeation chromatography (GPC),[18,19] NMR,[20] or Fourier transform infrared (FTIR) spectroscopy.[21,22] While these approaches can provide evidence for the occurrence of chain transfer, they offer limited utility in verifying the mechanism for chain transfer. The chain transfer event occurs at the propagating end of the polymer; therefore, identification of byproducts by end-group analysis is the most attractive technique for understanding the chain transfer mechanism. This approach has been confirmed by end-group analysis of the product using ^{1}H NMR,[20,23] MALDI-TOF MS,[24] electrospray ionization mass spectrometry (ESI MS),[25] or gas chromatography mass spectrometry (GC MS).[26] Theoretical calculations and modeling have also been used to elucidate mechanistic events in polymerizations.[21,22,27,28] Because MALDI-TOF MS is one of the most sensitive techniques for analyzing a polymer's end group, it provides perhaps the best tool for ascertaining the mechanism of a polymerization, chain transfers events, and other byproduct-generating side reactions. However, such mechanistic investigations have not been explored in much detail in the published literature. Herein, we examine a time-dependent analysis of the polymer end groups at different time points throughout the polymerization as a means of determining the chain transfer mechanism.

The general cationic ring-opening polymerization reaction of 2-oxazolines leads to well-defined poly(*N*-acylethylenimine) polymers (PNAIs) with low polydispersities[29] and easily modifiable end groups and side chains.[30−33] The polymerization of oxazoline is thermodynamically driven due to the favorable isomerization of the imino ether group to the amide functionality and elimination of monomer ring strain (Scheme 1). The cationic ring-opening polymerization of 2-oxazolines can follow either ionic or covalent mechanisms depending on the relative nucleophilicity of the counteranion derived from the initiator versus the monomer. For the tosylate counterions investigated in this study, polymerization is expected to follow the ionic route, where the propagating species is an oxazolium cation with an associated tosylate anion.[34] Termination occurs following the addition of a strong nucleophile or adventitious reactions with water. Polymers of oxazoline are particularly versatile systems because the *N*-acyl side chain enables diverse functionalization along the polymer backbone, enabling the chemical and physical properties to be readily tuned.[29,31,35−40]

Though it has been shown that the cationic polymerization of 2-oxazoline monomers can follow a living mechanism, recent research by Kempe et al.[41] and our laboratories[18] suggests that polymerizations of thioether containing 2-oxazoline monomers are not living. This is believed to be a result of chain transfer caused by a nucleophilic attack of the thioether on the propagating oxazolium species, generating a sulfonium ion, followed by elimination to generate a thio ether end group. Initial GPC studies confirmed the nonliving character, as the molecular weight plateaued with increase in conversion.[18] In order to verify the proposed mechanism of the chain transfer, MALDI-TOF MS end-group characterization was carried out at a variety of time points during the polymerization of the thiophenol-functionalized 2-isopropenyl-2-oxazoline monomer, 4,5-dihydro-2-(1-(phenylthio)propan-2-yl)-oxazole (**1**) (Scheme 1), and the methyl thioglycolate-functionalized 2-isopropenyl-2-oxazoline monomer, methyl 2-(2-(4,5-dihydro-oxazol-2-yl)propylthio)acetate (structure in the Supporting Information).

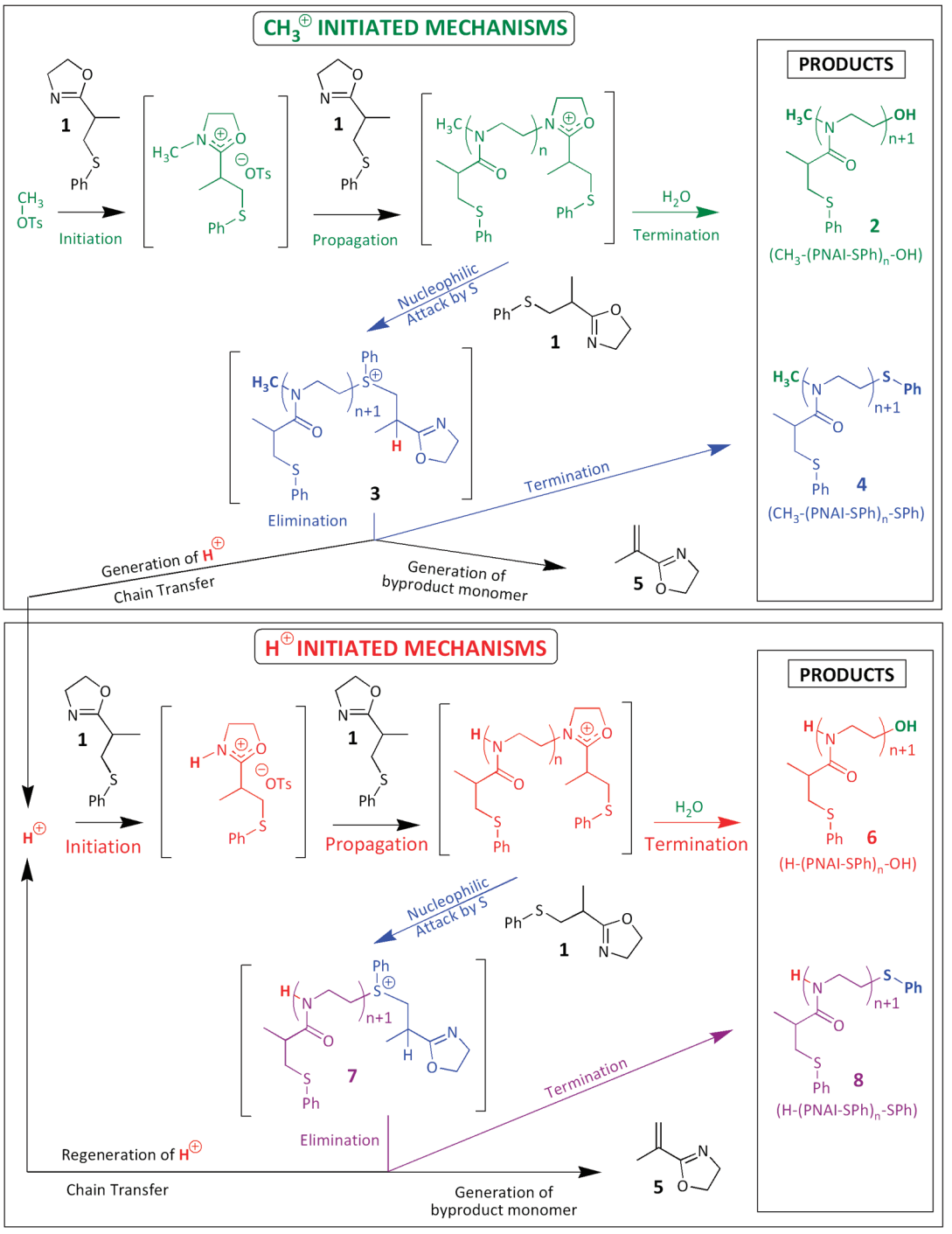
Results and Discussion

The monomer, **1**, was prepared as previously reported[18] and polymerized to yield PNAI-SPh using a methyl tosylate initiator

*Corresponding author. E-mail: sgrayson@tulane.edu.

 Published on Web 11/10/2010

Scheme 1. Proposed Chain Transfer Mechanism



with acetonitrile as the solvent in a flame-dried round-bottom flask under nitrogen gas to reduce contamination by water. Aliquots were removed (using care to prevent introduction of water into the polymerization vessel) at different time intervals and worked up by quenching any live polymer chains with an excess of water. The MALDI-TOF mass spectra of each aliquot exhibited multiple distributions each separated by 221.1 Da, the repeat unit mass of PNAI-SPh (for a representative example, see the four different color-coded distributions in Figure 1). For each distribution, if the counterion mass is subtracted from the observed mass and the repeat unit number extrapolated to 0, the mass of the end groups can be approximated and compared with the theoretical values (Figure S1, Supporting Information).[4] For this particular polymerization, the expected product, in the absence of any chain transfer events, would be the hydroxyl-terminated CH_3-(PNAI-SPh)$_n$-OH (**2**) (green, end-group mass = 32.037 Da, Figure 1). However, because of its nucleophilicity, the thioether in the monomer is expected to compete with the nitrogen in the monomer in reacting with the propagating cation. The resulting byproduct, **3**, could then undergo elimination to yield a polymer with a phenylsulfide end group, CH_3-(PNAI-SPh)$_n$-SPh (**4**) (blue, end-group mass = 124.080 Da, Figure 1). As byproducts of this proposed termination, 1 equiv of the eliminated monomer, 2-isopropenyl 2-oxazoline (**5**), and 1 equiv of H^+ are also generated. The H^+ generated could then initiate polymerization, which is expected to be terminated either by an analogous chain transfer reaction or

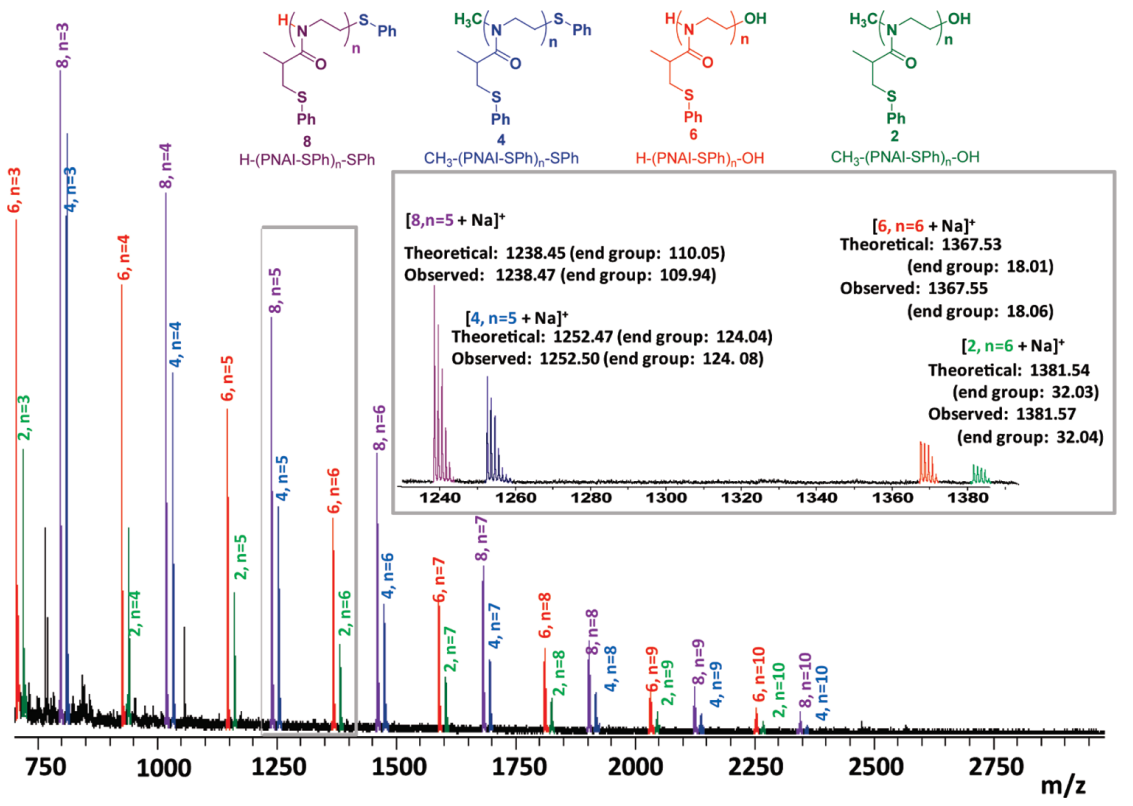


Figure 1. MALDI-TOF MS spectrum of PNAI-SPh after 1 h (monoisotopic exact mass used in calculations for all distributions).

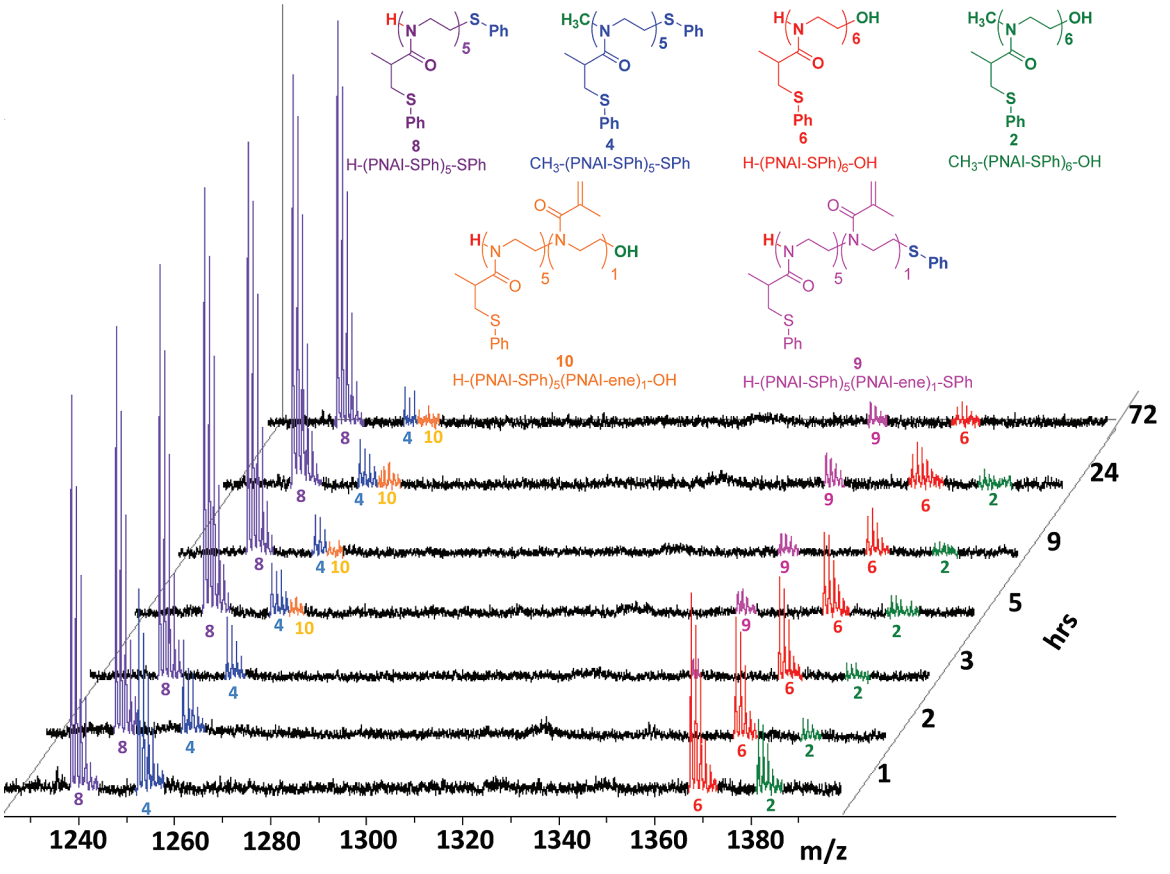


Figure 2. MALDI-TOF MS of chain transfer products at various time intervals (signal counts normalized relative to compound **8** at each time point).

by quenching with water when the reaction is worked up. The initiation by H^+ is not thought to come from water due to the various steps taken to reduce contamination by water prior to the quenching step. In addition, the prevalence of chain transfer is only noted in the described thioether monomers, but not oxazoline monomers that would be susceptible to water contamination without nucleophilic side chain functionalities. If the polymer is still living when the sample is quenched, the product is expected to have hydrogen and hydroxyl end groups H-(PNAI-SPh)$_n$-OH, **6** (red, end-group mass = 18.057 Da, Figure 1). However, if these H^+ initiated chains also undergo termination via a nucleophilic attack by sulfur (**7**), a phenyl sulfide-terminated polymer chain (H-(PNAI-SPh)$_n$-SPh (**8**) (purple, end-group mass = 109.940 Da, Figure 1) plus an additional equivalent of monomer **5** and H^+ are produced. Finally, because each chain transfer event releases the monomer **5** into the reaction mixture, this monomer is expected to be incorporated into the polymer, especially as its concentration builds up late in the polymerization, resulting in copolymers **9** and **10** (pink and orange, Figure 2). It should also be noted that chain transfer to monomer, in which the monomer abstracts a proton from the living chain end via an elimination, has been reported for other oxazoline monomers,[42,43] but this byproduct is not observed in a measurable quantity in the mass spectra reported herein, perhaps due to the large steric bulk of the substituents on the side chain which would inhibit the proton abstraction.

Examination of the time-dependent MS data provided strong support for the proposed mechanism (Figure 2). Though this method is not quantitative, it can be used to qualitatively determine which side reactions contribute to the observed chain transfer events, which were apparent from previous GPC studies.[18] Analysis of the end groups was carried out using a linear regression protocol previously developed in our laboratories[4] which takes into consideration each *n*-mer present within a given distribution. The observed end-group masses matched the theoretical end-group masses closely, with a deviation of less than 0.08 Da for each of the distributions identified (Figure S1, Supporting Information). As predicted by the proposed mechanism, the polymer chains initiated by the methyl tosylate initiator (green and blue, Figure 2) exhibited the strongest signal at the first time point, though even after only 1 h polymers initiated by chain transfer (H^+) dominated the distribution. In addition, the proportion of hydrogen-initiated polymer chains (red and purple, Figure 2) increased consistently throughout the course of the reaction, particularly compound **8**, which in theory should be the major product late in the polymerization. Finally, only in the later mass spectra is evidence seen of the incorporation of the elimination byproduct monomer **5** and predominantly with the H^+-initiated polymer chains which are still living late in the polymerization, e.g., H-(PNAI-SPh)$_n$(PNAI-ene)$_1$-SPh (pink (**9**), Figure 2) and H-(PNAI-SPh)$_n$(PNAI-ene)$_1$-OH (orange (**10**), Figure 2). Analysis of the monomer with the thioglycolate side chain yielded very similar results, and these data are detailed in the Supporting Information.

Conclusion

The use of time-dependent MALDI TOF mass spectral analysis provides strong evidence to support the prevalence of chain transfer via nucleophilic addition/elimination of the thioether functional group during the cationic polymerization of thioether containing oxazoline monomers. Theoretical predictions match the observed trends for the six major products expected during this oxazoline polymerization and subsequent chain transfer reactions with theoretical and observed end-group masses exhibiting a deviation of less than 0.08 Da. While this specific study of oxazoline polymerizations is limited in scope, the time-dependent mass spectral technique described for confirming polymerization mechanisms is both broadly applicable and particularly powerful, considering the miniscule amounts of sample required for analysis.

Acknowledgment. The authors thank the Tulane University for support of this research and the Louisiana Board of Regents for a graduate fellowship (M.A.C.). The authors also acknowledge the National Science Foundation (NSF-MRI 0619770) for enabling mass spectral characterization.

Supporting Information Available: Linear regression end-group analysis and MALDI-TOF MS data for the polymerization of the methyl thioglycolate-functionalized monomer (**S1**). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Tanaka, K.; Ido, Y.; Akita, S.; Yoshida, Y.; Yoshida, T. *Proc. Second Japan-China Joint Symp. Mass Spectrom.* **1987**, 185–188.
(2) Karas, M.; Hillenkamp, F. *Anal. Chem.* **1988**, *60*, 2299–2301.
(3) Tanaka, K.; Waki, H.; Ido, Y.; Akita, S.; Yoshida, Y.; Yoshida, T. *Rapid Commun. Mass Spectrom.* **1988**, *2*, 151–153.
(4) Li, Y.; Hoskins, J. N.; Sreerama, S. G.; Grayson, M. A.; Grayson, S. M. *J. Mass Spectrom.* **2010**, *45*, 587–611.
(5) Van Rooij., G. J.; Duursma, M. C.; Heeren, R. M. A.; Boon, J. J.; de Koster, C. G. *Am. Soc. Mass Spectrom.* **1996**, *7*, 449–457.
(6) Hayashi, S.; Adachi, K.; Tezuka, Y. *Chem. Lett.* **2007**, *36*, 982–983.
(7) Hoskins, J. N.; Grayson, S. M. *Macromolecules* **2009**, *42*, 6406–6413.
(8) Hart-Smith, G.; Lammens, M.; Du Prez, F. E.; Guilhaus, M.; Barner-Kowollik, C. *Polymer* **2009**, *50*, 1986–2000.
(9) Wachsen, O.; Reichert, K. H.; Krüger, R. P.; Much, H.; Schulz, G. *Polym. Degrad. Stab.* **1997**, *55*, 225–231.
(10) Weidner, S.; Kuehn, G.; Werthmann, B.; Schroeder, H.; Just, U.; Borowski, R.; Decker, R.; Schwarz, B.; Schmuecking, I.; Seifert, I. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 2183–2192.
(11) Grayson, S. M.; Fréchet, J. M. J. *Org. Lett.* **2002**, *4*, 3171–3174.
(12) Kemp, T. J.; Berridge, R.; Eason, M. D.; Haddleton, D. M. *Polym. Degrad. Stab.* **1999**, *64*, 329–338.
(13) Li, Y.; Hoskins, J. N.; Sreerama, S. G.; Grayson, S. M. *Macromolecules* **2010**, *43*, 6225–6228.
(14) Zammit, M. D.; Davis, T. P.; Haddleton, D. M.; Suddaby, K. G. *Macromolecules* **1997**, *30*, 1915–1920.
(15) Jayakannan, M.; van Dongen, J. L. J.; Janssen, R. A. J. *Macromolecules* **2001**, *34*, 5386–5393.
(16) Suddaby, K. G.; Hunt, K. H.; Haddleton, D. M. *Macromolecules* **1996**, *29*, 8642–8649.
(17) Gies, A. P.; Geibel, J. F.; Hercules, D. M. *Macromolecules* **2010**, *43*, 952–967.
(18) Cortez, M. A.; Grayson, S. M. *Macromolecules* **2010**, *43*, 4081–4090.
(19) Phelan, M.; Aldabbagh, F.; Zetterlund, P. B.; Yamada, B. *Macromol. Theory Simul.* **2005**, *14*, 109–116.
(20) Rix, F. C.; Rachita, M. J.; Wagner, M. I.; Brookhart, M.; Milani, B.; Barborak, J. C. *Dalton Trans.* **2009**, *41*, 8977–8992.
(21) Cramer, N. B.; Davies, T.; O'Brien, A. K.; Bowman, C. N. *Macromolecules* **2003**, *36*, 4631–4636.
(22) Cramer, N. B.; Reddy, S. K.; O'Brien, A. K.; Bowman, C. N. *Macromolecules* **2003**, *36*, 7964–7969.
(23) Yang, P.; Baird, M. C. *Organometallics* **2005**, *24*, 6013–6018.
(24) van Meerendonk, W. J.; Duchateau, R.; Koning, C. E.; Gruter, G. M. *Macromolecules* **2005**, *38*, 7306–7313.
(25) Günzler, F.; Junkers, T.; Barner-Kowollik, C. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 1864–1876.
(26) Illsley, D. R.; Lehrle, R. S. *Eur. Polym. J.* **1991**, *27*, 177–184.
(27) Thickett, S. C.; Gilbert, R. G. *Macromolecules* **2008**, *41*, 4528–4530.
(28) Noda, S.; Nakamura, A.; Kochi, T.; Chung, L. W.; Morokuma, K.; Nozaki, K. *J. Am. Chem. Soc.* **2009**, *131*, 14088–14100.
(29) Aoi, K.; Okada, M. *Prog. Polym. Sci.* **1996**, *21*, 151–208.
(30) Einzmann, M.; Binder, W. H. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2821–2831.
(31) Kobayashi, S.; Tokuzawa, T.; Saegusa, T. *Macromolecules* **1982**, *15*, 707–710.
(32) Kirlibal, H.; Yağci, Y. *Turk. J. Chem.* **2004**, *28*, 477–485.
(33) Kempe, K.; Jacobs, S.; Lambermont-Thijs, H. M. L.; Fijten, M. M. W. M.; Hoogenboom, R.; Schubert, U. S. *Macromolecules* **2010**, *43*, 4098–4104.

(34) Aoi, K.; Miyamoto, M.; Chujo, Y.; Saegusa, T. *Macromol. Symp.* **2002**, *183*, 53–64.
(35) Gress, A.; Völkel, A.; Schlaad, H. *Macromolecules* **2007**, *40*, 7928–7933.
(36) Gress, A.; Smarsly, B.; Schlaad, H. *Macromol. Rapid Commun.* **2008**, *29*, 304–308.
(37) Gress, A.; Heilig, A.; Smarsly, B. M.; Heydenreich, M.; Schlaad, H. *Macromolecules* **2009**, *42*, 4244–4248.
(38) Hoogenboom, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7978–7994.
(39) Hoogenboom, R. *Macromol. Chem. Phys.* **2007**, *208*, 18–25.
(40) Schlaad, H.; Diehl, C.; Gress, A.; Meyer, M.; Demirel, A. L.; Nur, Y.; Bertin, A. *Macromol. Rapid Commun.* **2010**, *31*, 511–525.
(41) Kempe, K.; Lobert, M.; Hoogenboom, R.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3829–3838.
(42) Litt, M.; Levy, A.; Herz., J. *J. Macromol. Sci., Part A* **1975**, *9*, 703–727.
(43) Weber, C.; Becer, C. R.; Baumgaertel, A.; Hoogenboom, R.; Schubert, U. S. *Des. Monomers Polym.* **2009**, *12*, 149–165.