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Report

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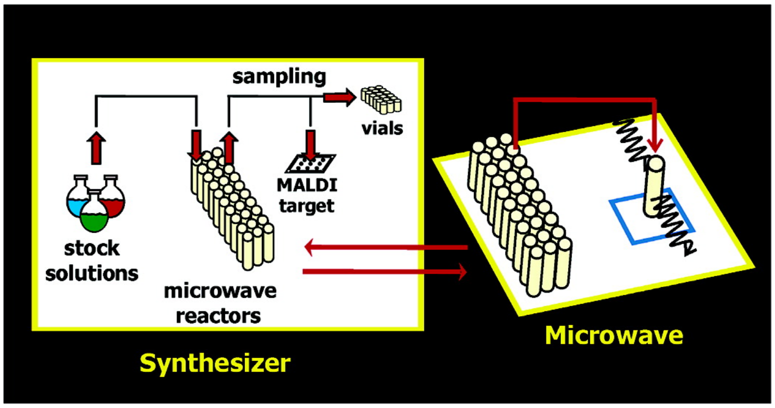

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Accelerating the Living Polymerization of 2-Nonyl-2-oxazoline by Implementing a Microwave Synthesizer into a High-Throughput Experimentation Workflow

Richard Hoogenboom, Frank Wiesbrock,
Mark A. M. Leenen, Michael A. R. Meier, and
Ulrich S. Schubert*

Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology and Dutch Polymer Institute (DPI), PO Box 513, 5600 MB Eindhoven, The Netherlands

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Introduction. During the past decade, the field of high-throughput and combinatorial polymer research has grown rapidly.[1−3] Many different polymerization techniques, varying from polycondensation to anionic polymerizations, have been performed in an automated parallel fashion. To analyze the increasing amount of samples, various characterization techniques have been automated[4] or accelerated, as well.[5] Another very recent development in organic chemical research is the introduction of (monomodal) microwave synthesizers.[6] Performing reactions under microwave irradiation instead of conventional heating results in increased reaction speeds and reduced occurrence of side reactions; however, the driving force (thermal or nonthermal microwave effects) for these improvements is still under debate.[6−9] Microwave synthesizers were also applied for combinatorial approaches in organic chemistry.[10,11] The commercially available microwave synthesizers for combinatorial and high-throughput synthesis from the major suppliers were described recently in equipment reviews.[12−14] Although microwave-assisted synthesis is quite common in organic synthesis nowadays, its application in polymer chemistry is only in its infancy.[15,16] The effect of microwave irradiation has been mainly investigated for step-growth polymerizations,[17,18] ring-opening polymerizations,[19,20] and for both free and controlled radical polymerizations;[21,22] however, many of the reported investigations were performed utilizing domestic microwave ovens without full temperature and pressure control, making the reproducibility doubtful.[16]

In this contribution, we describe the implementation of a monomodal microwave synthesizer into a high-throughput workflow (including high-throughput screening (HTS) with GC, GPC and MALDI-TOF MS) for combinatorial material research for the first time. This setup was utilized to screen solvent mixtures of acetonitrile and dichloromethane for the accelerated cationic ring-opening polymerization of 2-nonyl-2-oxazoline under microwave irradiation.[23] In addition, detailed kinetic investigations were performed for the polymerization of 2-nonyl-2-oxazoline in dichloromethane.

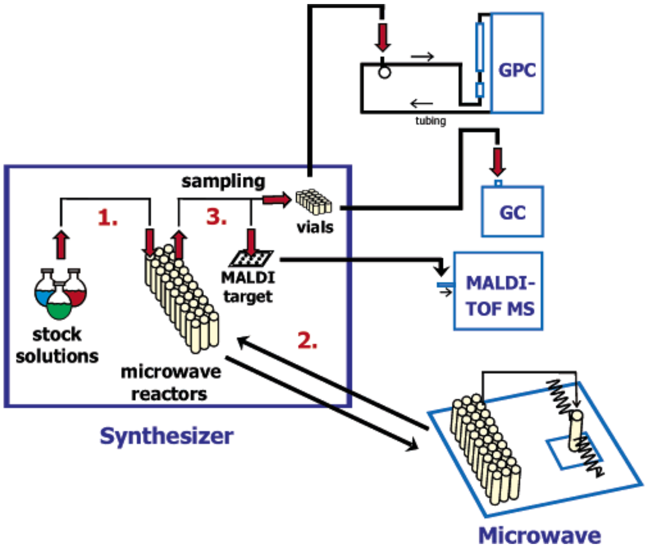

Figure 1. Schematic representation of the automated workflow, including the microwave synthesizer and the peripheral characterization equipment. All arrows going outside or inside the ASW2000 synthesis robot (synthesizer) represent manual steps.

Results and Discussion. To combine the advantages of both microwave-assisted polymer synthesis and high-throughput polymer synthesis, the implementation of a microwave synthesizer (Emrys Liberator, Biotage)[24] into a high-throughput workflow was investigated. Even though this microwave system comprises a liquid handling system, a more modular approach was needed to fulfill the different automated filling and sampling tasks. In addition, for many reactions it is required to handle the stock solutions under an inert atmosphere. Both the inert atmosphere and the flexible modular approach were found in an ASW2000 synthesis robot.[25] The standard racks for the microwave synthesizer were programmed as customized rack in the ASW2000 software, enabling the incorporation of the microwave vials into the previously established high-throughput workflow around the ASW2000 robot.[4,25] The extended workflow with the microwave synthesizer is schematically depicted in Figure 1, where all arrows going outside or inside the synthesis robot represent manual transportation of the racks to the appropriate equipment. The new workflow consists of three major steps, as depicted by the numbers in Figure 1: (1) Automated preparation of the reaction mixtures by dispensing stock solutions with the ASW2000 (under inert atmosphere, if required). (2) Transportation of the microwave vials to the microwave synthesizer and subsequent polymerization of the reaction mixtures utilizing the microwave robot arm for automated sequential irradiation of the vials (quenching can also be done automatically if required). When all polymerizations are finished, the rack is placed back into the ASW2000 robot. (3) Samples for, for example, gas chromatography (GC) and gel permeation chromatography (GPC) can be taken automatically from all polymerization mixtures. After manual transportation of

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* To whom correspondence should be addressed. E-mail: u.s.schubert@tue.nl.

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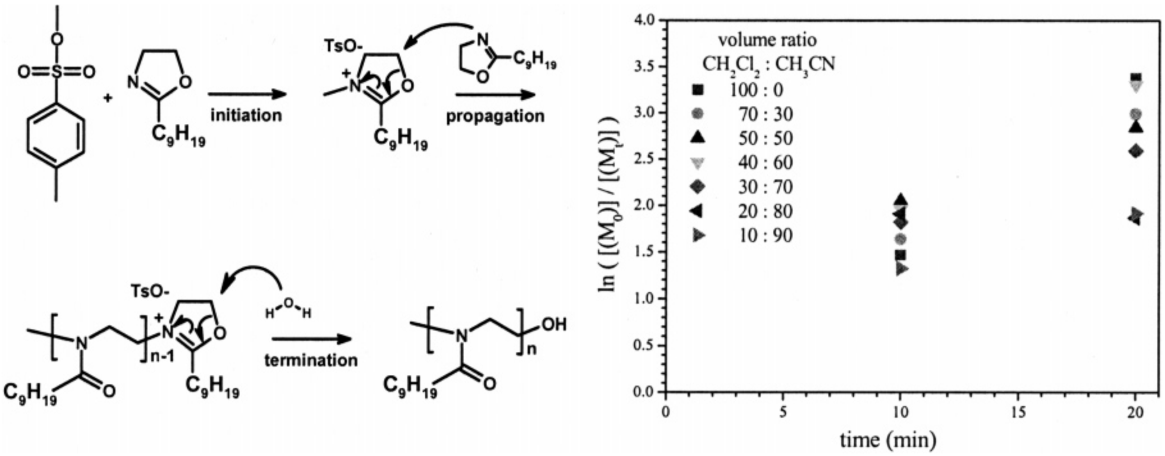

Figure 2. Left: Synthetic scheme for the polymerization of 2-nonyl-2-oxazoline initiated with methyl tosylate. Right: Kinetic results obtained for the microwave-assisted polymerization of 2-nonyl-2-oxazoline in different solvent mixtures containing acetonitrile and dichloromethane ([NonOx] = 2 M; [M]/[I] = 60; I = methyl tosylate; T = 140 °C).

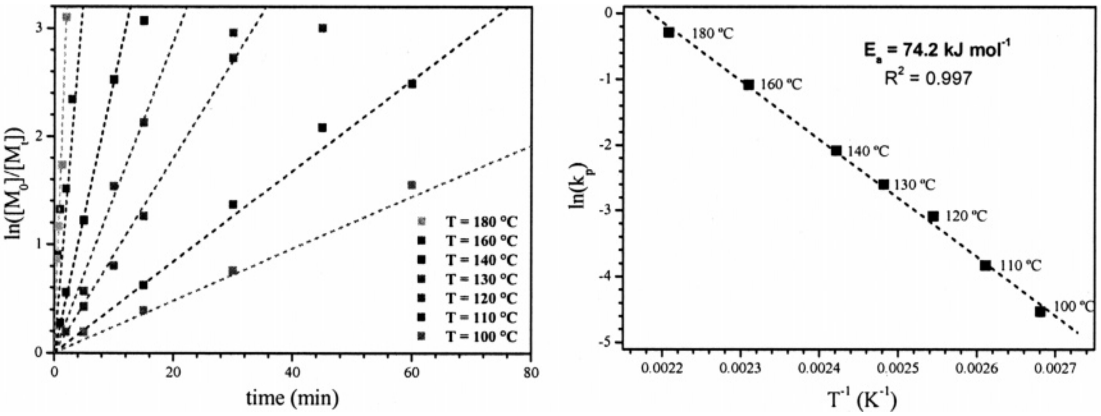

Figure 3. Left: Monomer conversion (represented by ln{[M_0]/[M_t]}) against time plot for the microwave-assisted polymerization of 2-nonyl-2-oxazoline in dichloromethane at different temperatures ([NonOx] = 2 M; [M]/[I] = 60; I = methyl tosylate). Right: Arrhenius plot for this polymerization system.

the samples, the analyses are performed (most of the equipment operates with autosamplers).

In addition, the extended workflow provides the possibility to perform multistep reactions utilizing combinations of microwave irradiation and conventional heating for the different reaction steps.

This high-throughput workflow was utilized for investigating the microwave-assisted cationic ring-opening polymerization of 2-nonyl-2-oxazoline as depicted in Figure 2, left.[26] Preliminary polymerizations in acetonitrile resulted in a white precipitate after the polymerization.[27] It was not clear whether the polymer precipitated during polymerization or upon cooling the vial after the favored reaction time. For industrial applications, direct precipitation might be advantageous to collect the solid polymer after the polymerization without additional workup procedures, but for the preparation of block copolymers or for endcapping, precipitation is generally undesirable. Commonly, high-boiling chlorinated solvents are added to 2-oxazoline polymerization mixtures in order to prevent the precipitation of the polymer;[28,29] however, the microwave-assisted polymerizations can be performed up to pressures of 20 bar, and thus, high temperatures are not limited to high boiling solvents. Therefore, a solvent screening for the microwave-assisted polymerization of 2-nonyl-2-oxazoline at 140 °C was performed by gradually changing the solvent composition from acetonitrile to dichloromethane. The reaction temperature of 140 °C was chosen, since this was previously found to be the optimal polymerization temperature for 2-ethyl-2-oxazoline.[23] The polymerization mixtures for the solvent screening were prepared in the ASW2000 robot and zero-time GC samples were taken from the mixtures. Subsequently, two vials with the same composition were heated under microwave irradiation for 10 and 20 min, respectively. After all reactions were finished, the rack was placed back in the ASW2000 robot for automated sampling to GC vials. The kinetic results obtained from this solvent screening are shown in Figure 2, right, demonstrating that the polymerizations in all different solvent mixtures have similar polymerization rates and, more importantly, that the polymerizations proceed significantly faster than polymerizations performed under conventional heating at ambient pressure.[26] In addition, only the polymerizations performed with 80 or 90% acetonitrile did not reach conversions higher than 85%, which could be due to precipitation of the polymer during the polymerization process. These results also demonstrate the possibility to perform the cationic ring-opening polymerization of 2-nonyl-2-oxazoline in dichloromethane for the first time. To further investigate the livingness of the polymerization in dichloromethane, 42 polymerizations were

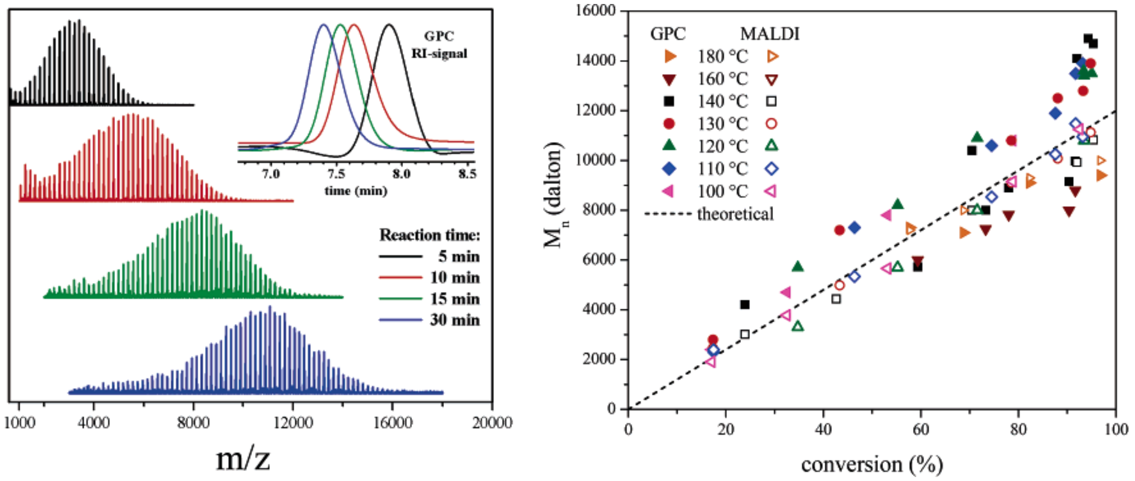

Figure 4. Left: Obtained MALDI-TOF MS spectra and GPC traces in time for the polymerization of 2-nonyl-2-oxazoline at 120 °C. Right: Increase in number average molecular weights, obtained from both GPC (solid symbols) and MALD-TOF MS (open symbols), against monomer conversion (PDI values are around 1.1).

performed at seven temperatures ranging from 100 to 180 °C utilizing the high-throughput workflow.[30] For each temperature, six polymerizations were performed for different times. After cooling to room temperature, the polymerizations were automatically quenched by the addition of water with the microwave liquid handling system. The microwave rack was placed back in the synthesis robot after all polymerizations were finished. Samples were taken automatically from the reaction mixtures to GC vials and GPC vials. In addition, samples for matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) were prepared by automated spotting of the polymerization mixtures onto a MALDI target.[5] GC analysis of the samples yielded the monomer conversion in time, as depicted in Figure 3, left. The monomer conversion is represented by $\ln\{[M_0]/[M_t]\}$, which should result in a linear behavior for first-order kinetics. For all investigated temperatures, indeed, first-order kinetics were obtained, suggesting a living polymerization. Moreover, the polymerization times were reduced from more than 10 h for conventional heating to 2 min under microwave irradiation. The slopes of the kinetic plots divided by the initiator concentration resulted in the polymerization rates, k_p. The corresponding Arrhenius plot (Figure 3, right) yielded an activation energy of 74.2 kJ·mol^{-1} for this system, which is in good agreement with the previous reported activation energies for similar polymerizations of 2-methyl-2-oxazoline (80.0 kJ·mol^{-1}, conventional heating)[31] and 2-ethyl-2-oxazoline (73.4 kJ·mol^{-1}, microwave heating)[23] with methyl tosylate in acetonitrile. The similar activation energies for microwave-assisted and conventionally heated polymerizations indicate that the acceleration of the 2-nonyl-2-oxazoline polymerization under microwave irradiation is primarily a temperature effect. In addition, for the polymerization of 2-ethyl-2-oxazoline in acetonitrile, it was previously verified that the acceleration under microwave irradiation resulted only from temperature effects: microwave polymerization at 140 °C and thermal polymerization at 140 °C in a pressure NMR tube revealed the same polymerization rates.[23] Therefore, it might be assumed that the acceleration of the 2-nonyl-2-oxazoline polymerization under microwave irradiation is also merely a temperature effect. Figure 4, left depicts the MALDI-TOF MS spectra and GPC traces obtained at different reaction times for the microwave-assisted polymerization of 2-nonyl-2-oxazoline in dichloromethane at 120 °C. Narrow monomodal distributions with polydispersity indices around 1.1 were obtained with both techniques, demonstrating the very good control over the polymerization. Similar narrow distributions were obtained for all investigated reaction times at all different temperatures. The development of the number average molecular weight (M_n from both GPC and MALDI-TOF MS) with monomer conversion is linear, as depicted in Figure 4, right. Moreover, these M_n values are close to the theoretical molecular weight (Figure 4 right, dotted line). The combination of linear first-order kinetics and linear increase of molecular weight (close to the theoretical molecular weight) with monomer conversion clearly proves that 2-nonyl-2-oxazoline was polymerized in a living manner in dichloromethane at the investigated temperatures, ranging from 100 to 180 °C.

Conclusions. In this Report, we have demonstrated the successful implementation of a microwave synthesizer into a high-throughput workflow. The resulting workflow was utilized to screen different solvent mixtures (ranging from 100% acetonitrile to a solvent mixture with a dichloromethane/acetonitrile ratio of 90:10) for the microwave-assisted cationic ring-opening polymerization of 2-nonyl-2-oxazoline at 140 °C to prevent precipitation of the polymer during the polymerization process. Polymerizations in solvent mixtures containing more than 20% dichloromethane were found to proceed to full monomer conversion, whereas a lower dichloromethane content led to a maximum conversion of only 85%. In addition, kinetic investigations of the microwave-assisted polymerizations of 2-nonyl-2-oxazoline in dichloromethane revealed a living polymerization mechanism for all investigated temperatures (100 to 180 °C). The polymerizations under microwave irradiation proceeded significantly faster than conventionally heated polymerizations (at ambient pressure). The successful living polymerization of 2-oxazolines in dichloromethane under microwave irradiation was demonstrated for the first time.

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Supporting Information Available. Experimental details are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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