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High-throughput synthesis equipment applied to polymer research

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To speed up synthetic polymer research, a workflow dedicated to automated polymer synthesis and characterization was developed. The workflow consists of several synthesis robots with online and offline analytical equipment. For screening of reaction parameters and for library synthesis, robots equipped with glass reactors and vortex agitation are applied that match very well the classical (small-scale) laboratory experiments. For the screening and library preparation also a microwave synthesizer can be used. For upscaling purposes and process development, a robot containing 100 mL tank reactors with mechanical stirring is utilized. This robot also offers the possibility to continuously feed reagents to the reactor and to operate in batch, semibatch or continuous mode.

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I. INTRODUCTION

To accelerate chemical synthesis and to determine structure-property relationships, high-throughput and combinatorial approaches are widely used in organic and pharmaceutical research.^{1–3} Stimulated by this success, scientists from other fields like inorganic materials,^{4–6} catalysis,^{4,7,8} and polymer research^{4,9,10} began to explore the implementation of those techniques as well. Especially in the field of polymer research, high-throughput experimentation (HTE) is a promising technique since many parameters can be varied during synthesis (e.g., monomers, catalysts, initiators, end-cappers, and many reaction conditions). However, the characterization techniques for polymer research are numerous concerning the determination of, e.g., molecular weight, polydispersity index, viscosity, hardness, and stiffness, whereas the required high-throughput screening techniques only became available during the last years. Therefore, high-throughput experimentation is still relatively new in polymer research.

To gain optimal productivity from high-throughput experimentation, the entire workflow should be optimized and accelerated. In our laboratory, the high-throughput workflow consists of the following steps (see also Fig. 1):

- (1) Design of Experiments (DoE);
- (2) Automated polymer synthesis;
- (3) High-throughput screening;
- (4) Data analysis.

If necessary, these steps can be iterated until the desired polymer properties are obtained.

In this contribution, we will discuss some of the available high-throughput equipment for polymer synthesis [step (2)] and we will address the online characterization equipment [step (3)]. The applicability of the different polymer-

ization robotics will be discussed on the basis of the living cationic ring-opening polymerization of 2-oxazolines of which the general polymerization mechanism is depicted in Fig. 2.¹¹

II. AUTOMATED SYNTHESIZERS

The most important automated synthesis robots for polymer synthesis can be divided into two classes (the examples are chosen due to the presence in the Eindhoven Laboratories): Synthesizers for small scale reactions for screening of reaction parameters as well as for library synthesis and a synthesizer for up-scaling and process development. The main difference of the up-scaling and process development synthesizer is its mechanical stirring and continuous feed possibility that closer match industrial scale polymerizations. The different types of synthesizers available for automated polymer synthesis will be described in detail in the following sections.

A. ASW2000 platform

The Chemspeed ASW2000 synthesis robot is an automated parallel synthesis platform. Figure 3 shows a picture of the machine with one reactor block and, at the bottom, a schematic overview of the workspace of the synthesis robot as it is shown in the programming software. The pictures also show the modular approach of this robot with five positions for reactor arrays (bottom left of the scheme), two positions to place microtiter plates or custom racks (top left of the scheme; here a rack for 2 mL vials is programmed), one position for a large vial rack (here for 8 mL vials) and the stock solution rack (right of the scheme). Moreover, the synthesizer is equipped with a xyz-liquid handling system and agitation is achieved by a vortex movement of the reactors (up to 1400 rpm). During this vortex movement, the needle of the xyz-liquid handling can still reach the bottom of the reactors and thus samples can be taken during the polymerizations without interrupting the agitation. Moreover, the synthesizer is covered with a glove box to retain an inert

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FIG. 1. (Color online) Schematic representation of the high-throughput experimentation (HTE) cycle that starts with design of experiments (DoE), followed by automated polymer synthesis and characterization and ends with data analysis.

atmosphere for oxygen and moisture sensitive polymerizations. In addition to this inert environment in the hood, argon and vacuum can be applied to the reactors directly. The vacuum can be used for evaporation of solvents or to create an inert atmosphere by vacuum/argon cycles. The automated parallel polymerizations can be performed in 13 mL reactors (maximum 80 parallel), 27 mL reactors (maximum 40 parallel), 75 mL or 100 mL reactors (both maximum 20 parallel). The reactions can be cooled or heated with a cryostat ($-70\text{ }^{\circ}\text{C}$ to $145\text{ }^{\circ}\text{C}$) that pumps its oil through the double jacket heating mantles of the reactors. On top of the reactors an array of cold finger reflux condensers can be placed for higher temperature reactions. The temperature of these condensers ($-5\text{ }^{\circ}\text{C}$ to $50\text{ }^{\circ}\text{C}$) can be controlled *via* a second cryostat. The possibility of heating the condensers is a valuable tool for evaporating solvents from the reactors. The final part in assembling the reaction arrays is the placement of a metal reaction block on top of the reflux condensers. This reaction block has a ceramic drawer inside that can switch between opening the reactors, opening the reactors under argon, closing the reactors under argon or vacuum and closing the reactors independently. To reduce solvent evaporation, the reactors are only opened when liquid handling is required in the reactors. All described parts of the synthesis robots are controlled by the ASW2000 software implying that the polymerizations in the synthesis robot can be performed completely automated.

To prove the applicability of such a synthesis robot for polymer synthesis, the reproducibility and livingness of the cationic ring-opening polymerization of 2-ethyl-2-oxazoline was investigated.¹² 40 parallel polymerization were performed at eight different monomer to initiator ratios (each five times) including automated precipitation and isolation of the poly(2-ethyl-2-oxazoline)s. After proving the reproducibility of the polymerizations, combinations of four 2-oxazoline monomers, four initiators, four monomer to ini-

FIG. 3. Top, picture of the ASW2000 synthesis robot; bottom, a schematic overview of the workspace of the synthesis robot as it is used in the programming software.

tiator ratios and two temperatures were investigated (total 128 reactions). At defined times, samples were taken from the reaction mixtures to 2 mL vials in order to investigate the polymerization kinetics utilizing offline gas chromatography (GC) and gel permeation chromatography (GPC), which were both equipped with autosamplers. The synthesis robots allowed kinetic investigations over 20 hours polymerization time with no large time gaps between subsequent samples, which would normally occur during nights or weekends. A selected example of the obtained polymerization kinetics is shown in Fig. 4. This conversion (represented by $\ln([M]_0/[M]_t)$) against time plots for the polymerization of 2-ethyl-2-oxazoline with four different initiators (benzyl bromide, methyl triflate, methyl tosylate and methyl iodide with a monomer to initiator ratio of 40) at both $80\text{ }^{\circ}\text{C}$ and $100\text{ }^{\circ}\text{C}$ revealed the linear first order kinetics for all investigated polymerizations.

The 2-oxazoline polymerization screening was performed with offline GC and GPC analysis meaning that the analysis was performed after the polymerizations were finished. To further accelerate the kinetic investigations, GC

FIG. 2. General polymerization mechanism for the living cationic ring-opening polymerization of 2-oxazolines.

FIG. 4. Kinetic results obtained for automated kinetic investigations of the polymerization of 2-ethyl-2-oxazoline utilizing four different initiators with a monomer to initiator ratio of 60 at both 80 °C and 100 °C.

and GPC were both connected online to the synthesis robot as depicted in Fig. 5. Besides the increased time-efficiency, online characterization also provides direct feedback from the polymerization offering the possibility to adjust reaction conditions like reaction time and temperature during the experiments. For coupling the GPC to the ASW2000, the closed loop liquid system of the GPC was extended into the robot and, additionally, an injection port was integrated in the workspace of the xyz-liquid handling system of the synthesis robot (Fig. 5, left-hand side). As a result, samples taken from the parallel polymerization reactions can be directly injected into the GPC injection port. As soon as the sample is injected, a trigger signal is sent to the GPC software to start collecting the data. The GC was more difficult to integrate since it does not work with a closed loop system that can be extended. Therefore, a flow-cell located in the working area of the GC autosampler was connected to the injection port inside the automated synthesizer. The polymerization sample was injected and then flushed to the flow cell by the injection of additional solvent. When the sample is located in the flow cell, the GC autosampler receives a trigger to start injecting a sample from the flow cell (Fig. 5, right-hand side). Figure 6 shows the kinetic results obtained from both online and offline GC monitoring of the polymerization of 2-ethyl-2-oxazoline at different concentrations.¹³ These experiments clearly prove the reliability of the online characterization method. Next to the online GC and GPC

FIG. 5. (Color online) Schematic representation of the online GPC and GC instruments connected to the ASW2000 robotic systems.

FIG. 6. Comparison of online and offline GC monitoring of the cationic ring-opening polymerization of 2-ethyl-2-oxazoline at different concentrations (reprinted with permission from Ref. 13).

characterization methods, a method for online MALDI-TOF MS sample preparation was developed. A tailor made MALDI-target holder was constructed that fits into a micro-titer plate position in the synthesizer. The samples from the reaction mixture were spotted onto prespotted matrix and salt. After the reaction was finished, the MALDI samples could be measured directly.¹⁴

B. Accelerator SLT100 platform

The Chemspeed Accelerator SLT100 automated synthesizer combines the flexibility of the ASW2000 synthesizer platform with more sophisticated tools for liquid and solid handling. The accelerator is also designed for small scale synthesis and screening with vortex agitation (13 mL, 27 mL, 75 mL, and 100 mL reactors). The automated synthesizer and a schematic overview of its workspace as used in programming (different from the ASW2000 software) are depicted in Fig. 7. The reaction arrays and peripherals are similar to those of the ASW2000, but the working area of the accelerator is larger (up to 192 reactors can be placed in parallel). The main difference for the accelerator is its overhead robot arm that can pick up different modules. In our laboratories we have both a four needle head (4-NH) and a solid dosing unit (SDU) available. The 4-NH has four needles in parallel that can be used simultaneously (or separately) to accelerate all liquid handling tasks. The sampling of 16 reactors could be accelerated by a factor of 3 if compared to the ASW2000.¹⁵ Even though the aspiration and dispensing is four times faster (four needles compared to one), picking up the 4-NH and the movement through the synthesizer are slower than moving the xyz-liquid handler of the ASW2000 resulting in three times faster sampling. The SDU is a module that can pick up containers of solids to dispense the solids directly into the reactors. The containers are equipped with microextruders inside and by rotating the containers solids are dispensed down to submilligram accuracy. Moreover, the SDU has an internal microbalance and

FIG. 7. Top, picture of the Accelerator SLT100 synthesis robot; bottom, a schematic overview of the workspace of the synthesis robot as it is used in the programming software.

measures the amount of solid that is added into the reactors. In a first test, the SDU was applied to dispense sodium iodide in the reactors to investigate the conversion of benzyl chloride into benzyl iodide, which is a more active initiator for the cationic ring-opening polymerization of 2-oxazolines.¹⁵ The benzyl iodide is unstable when stored and, therefore, the *in situ* generation in *N,N*-dimethylacetamide (the polymerization solvent) was studied with different sodium iodide to benzyl chloride ratios at three different temperatures. During these investigations it was found that solid dosing of sodium iodide could be performed with 4 mg accuracy due to the very hygroscopic and sticky nature of this solid.

Next to the standard glass reactors as described in the ASW2000 section, individually heatable reactors and pressure reactors are available for the accelerator.¹⁶ The individually heatable reactor array consists of 16 parallel 13 mL reactors that all have a ceramic heating mantle. As a result, the separate reactors can be electrically heated from ambient temperature to 230 °C. In addition, all reactors have a PT100 temperature sensor and thus the reaction temperature can be controlled with an internal or an external reference. Those individually heatable reactors were applied to optimize the polymerization temperature of both the cationic ring-opening polymerization of 2-ethyl-2-oxazoline (Ref. 17) and 2-phenyl-2-oxazoline.¹⁵ The potential of the individually heatable reactors for temperature optimization is demonstrated by Fig. 8 that shows the different polymerization mixtures of the polymerization of 2-ethyl-2-oxazoline at differ-

FIG. 8. Reaction mixtures of the cationic ring-opening polymerization of 2-ethyl-2-oxazoline after polymerization at different temperatures utilizing the individually heatable reactors.

ent temperatures: The color of the reaction mixtures designate the occurrence of side reactions and provides a visual indication of the livingness of the polymerization. The pressure reactors that are available for the accelerator synthesis robot can be operated with pressures up to 90 bar. This pressure is controlled by a separate gas cylinder that can be manually set to a certain pressure. When this pressure is available, the robot system can automatically apply this pressure to the reactors and release it too. The pressure reactors were successfully applied for the cationic ring-opening polymerization of 2-ethyl-2-oxazoline in acetonitrile, whereby the reaction mixture could be easily superheated to 140 °C under 15 bar nitrogen pressure.¹⁸

C. Microwave synthesizer

A different type of automated synthesizer is the Emrys Liberator microwave synthesizer from Biotage (formerly PersonalChemistry). Figure 9 shows a picture and schematic representation of the microwave synthesizer. In contrast to the parallel operating Chemspeed synthesis robots, it irradiates the different reaction vials in a serial fashion. However, the main difference is the microwave heating compared to thermal heating. The (single-mode) microwaves directly transfer their energy to all dipoles present in the reaction mixture. As a result, very fast and efficient heating can be obtained compared to thermal heating where heat transfer from the reactor wall into the reaction mixture is required. However, the use of microwave reactors in polymer chemistry is still in its infancy.¹⁹

The computer controlled Emrys Liberator microwave system is equipped with a robot arm to move the reaction vials in and out the microwave cavity and to dispense reagents or quenchers into the vials as well. The utilized reaction vials (0.2 to 2.0 mL or 2.0 to 5.0 mL) are capped and can be operated up to 20 bar pressures. During the reactions, agitation is performed with a stirring bar and the reaction temperature and pressure are monitored and visualized online. The possibility of going to 20 bar pressure also provides the possibility of going to superheated conditions as is also possible with the pressure reactors in the accelerator. The fast heating and the temperature control of the system make it a

FIG. 9. Top, picture of the Emrys Liberator microwave synthesizer; bottom, schematic representation of the microwave synthesizer.

very suitable tool to screen different reaction temperatures: A large stock solution can be divided over different vials that will be heated to different temperature (from 60 °C to 250 °C). Moreover, after the programmed reaction time, the vials are actively cooled by a nitrogen stream which provides a reliable basis for kinetic investigations. To further optimize the flow through of the microwave synthesizer, the vial rack was programmed in the ASW2000 software offering the possibility of automatically filling the microwave vials with different ratios of reagents for library synthesis.²⁰

FIG. 10. Number average molecular weight (M_n) and polydispersity indices (PDI's) against monomer conversion for the cationic ring-opening polymerization of 2-ethyl-2-oxazoline at different temperatures in the microwave synthesizer; the dotted line represents the theoretical M_n (reprinted with permission from Ref. 21).

FIG. 11. Top, picture of the Autoplant A100 up-scaling and process development robot; bottom, a schematic overview of the workspace of the synthesis robot as it is used in the programming software. In both figures only one-half of the synthesis robot is shown for clarity.

Moreover, after a kinetic screening of reaction conditions (e.g., temperature, time or solvent) the irradiated microwave vials can be placed back into the ASW2000 for automated sample preparation.

Kinetic investigations of the cationic ring-opening polymerization of four different 2-oxazolines in acetonitrile were performed in this microwave synthesizer up to temperatures of 200 °C.^{21,22} The polymerization could be accelerated by a factor of 400 without losing the living and controlled nature of the polymerization. Control experiments in the accelerator and a high-pressure NMR-tube revealed that the increased reaction speed solely resulted from the higher temperatures and not from so-called nonthermal microwave effects. Figure 10 shows the increase of the number average molecular weight (M_n) against monomer conversion. The linear dependence of M_n on conversion, the good correspondence between obtained and theoretical (dotted line) M_n and the low polydispersity indices ($PDI < 1.20$) clearly demonstrated that the living nature of the polymerization is retained at high temperatures in the microwave synthesizer.

D. Accelerator autoplant process development platform A100

The Chemspeed Accelerator Autoplant A100 is an up-scaling and process development synthesis robot on the basis of the Accelerator SLT100 platform meaning that all periph-

FIG. 12. Different polymerization setups that can be achieved with the continuous feed pumps in the Autoplant A100, semibatch (with one or two continuous feeds), continuously stirred tank reactor (CSTR) and cascade.

eral equipment and the overhead robot arm with the four needle head are similar. A picture and the schematic overview from the software (both showing only one-half of the machine) are depicted in Fig. 11. The picture shows the Autoplant A100 with two reactor modules. Each module consists of two sets of two reaction vessels (100 mL), one stock solution vessel (50 mL) and two continuous feed pumps. Heating is performed electrically, whereby the temperature is controlled by a valve that opens the connection to the cooling liquid. This separate cooling circuit also allows for very fast cooling rates to be obtained. Moreover, the two reaction vessels can be heated and cooled individually from $-70\text{ }^{\circ}\text{C}$ to $300\text{ }^{\circ}\text{C}$ and reflux is obtained by pumping cooling liquid through the reactor head. Agitation is performed by overhead anchor stirrers, which makes the reactions more comparable to industrial scale processes. The continuous feeds can be used in many different ways as depicted in Fig. 12. If the feeds are not used or are only used to fill the reactions before heating, batch reactions can be performed. However, also semibatch (with one or two continuous feeds), continuously stirred tank (CSTR) and cascade reactions can be performed with the same apparatus by only changing the connection of the tubings. So far, the cationic ring-opening polymerization of 2-oxazolines has not been tested yet in the Autoplant A100. Nevertheless, the influence of continuous addition of monomer, initiator or monomer and initiator on the molecular weight and molecular weight distribution of polymers prepared *via* free radical polymerization could be investigated successfully.¹⁸ Figure 13 demonstrates the effect of continuous feeding initiator (over 10 hours polymerization time) to the free radical polymerization of methyl methacrylate in *N,N*-dimethylacetamide. The depicted GPC traces show broadening of the distribution and an increase of the molecular weight when more of the initiator [azodiisobutyronitrile (AIBN)] is continuously fed into the reactor.

FIG. 13. (Color online) GPC traces obtained for the free radical polymerization of methyl methacrylate utilizing batch or semibatch reactor setups on the Autoplant A100.

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