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High-Throughput Experimentation in Polymer Chemistry

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Abstract: Combinatorial and high-throughput methods have revolutionized pharmaceutical research in the last decade. This has encouraged researchers to extend these techniques to many other fields including polymer chemistry. In this paper, we mainly describe the progress we made in polymer research by utilizing an automated parallel synthesizer. The equipments and methodologies that are used in our experiments are described. The application of high-throughput experimentation or automated parallel synthesis in different polymerization techniques such as atom transfer radical polymerization, cationic ring-opening polymerization, and emulsion polymerization as well as automated matrix-assisted laser desorption/ionization time-of-flight mass spectrometry sample preparation is demonstrated in detail.
Key words: High-throughput experimentation, combinatorial chemistry, atom transfer radical polymerization, cationic ring-opening polymerization, emulsion polymerization, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

1. INTRODUCTION

The successful application of the combinatorial and high-throughput methods in pharmaceutical research has attracted great attention in the last few years.[1] These techniques allow one to explore a variety of parameters quickly and parallelly and thus can significantly accelerate the research and dramatically reduce the time-to-market for new materials in comparison with traditional approaches. In addition, their parallel characteristics make the obtained results highly comparable and therefore can help to draw more comprehensive structure-property relationships. The essential parts of the combinatorial chemistry (CombiChem) and high-throughput experimentation (HTE) include design of experiment (DoE, library design), parallel chemical synthesis, high-throughput screening, and data management. Recent years have witnessed a rapid extension of these techniques in many areas of the discovery of new materials (inorganic materials, catalysts, and organic polymers).[2] This can be partly attributed to the fast development of the automated synthesis and characterization workstations.[3] HTE seems to be perfectly suitable for polymer research due to the fact that many parameters can be varied during synthesis (e.g., monomers, catalysts, initiators, solvents, and many other reaction conditions), processing, blending, and compounding.

HTE and parallel synthesis have become a flourishing area in polymer chemistry nowadays. Significant progress have been made in synthetic polymer chemistry (including conventional free radical polymerization,[4] controlled radical polymerizations,[5] cationic ring-opening polymerization,[6] condensation polymerization,[7] and supramolecular polymerization[8]), discovery of catalysts for polyolefins,[9] coating formulations,[10] and polymer characterization techniques.[2d,3] A prominent example is the Symyx polyolefin discovery tool that has been commericalized.[11] Recently several Reviews and Feature Articles on the application of HTE in polymer chemistry have been published.[2d,e,10,12] In this paper, we will mainly focus on our recent progress in introducing automated parallel synthetic approaches to various polymerization methods (atom transfer radical polymerization (ATRP), cationic ring-opening polymerization (CROP), emulsion polymerization) and automated matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) sample preparation.

2. EQUIPMENT AND METHODOLOGY

All the experiments described in this paper were performed in a commercially available automated synthesizer (Chemspeed ASW 2000, Figure 1). Five reactor blocks can be used in parallel and each block has 4 to 16 reaction vessels depending on their volumes (100 to 13 mL). Each reaction vessel can be heated or cooled through a jacketed oil bath and is equipped with a cold-finger reflux condenser. The temperature of the oil bath was controlled by a Huber Unistst 390 W Cryostat and can be varied from –70 to +150 °C. The temperature of the reflux liquid was controlled by a Huber ministat compatible control and can be varied from –5 to +50 °C.

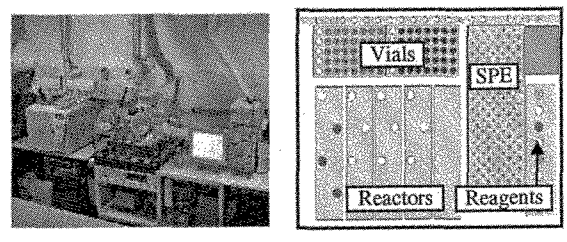


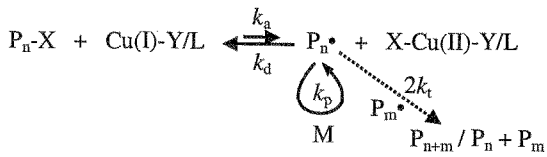
Figure 1. Left: Picture of Chemspeed ASW 2000 fully automated synthesizer with attached GPC and GC. Right: Schematic set-up of the automated synthesizer.

Reaction vessels were connected with a membrane pump, which could be utilized for inertization or evaporation processes. Mixing was performed by a vortex process (0 to 1400 rpm). A glovebox ensured an argon atmosphere outside the reaction system. The automated synthesizer was connected to an online size exclusion chromatograph (SEC), which can determine the molecular weights of the polymers. An offline gas chromatograph (GC) was utilized to measure monomer conversions. A Gilson liquid handling system was used in the automated synthesizer.

A program has to be written before performing a reaction in the automated synthesizer, which will translate all the reaction procedures into computer-understandable language. For the controlled/living polymerizations such as ATRP and CROP, an inertization process including several cycles of vacuum and argon filling under certain high temperature is needed to remove the oxygen and moisture from the reaction vessels. This together with many other steps (such as switching on reflux and stirring, dispensing certain amount of reagents into specific reaction vessels, setting reaction temperatures, turning on vortex, rinsing needles, taking samples, and so on) will be programmed step by step. In order to avoid the cross-contamination and small bubbles in the tubes in the liquid-handling systems, it is important to program several additional rinsing steps between the steps of transferring reagents.

3. ATRP

In the last years, the field of free radical polymerization has been revolutionized with the advent of controlled/"living" radical polymerization techniques, which provide polymers with predetermined molecular weights, low polydispersities, specific functionalities, and various architectures under relatively mild reaction conditions.[13] One of the most versatile systems is atom transfer radical polymerization (ATRP) due to the easy availability of many kinds of catalysts, initiators, and monomers.[14] The success of an ATRP system depends largely on a reversible dynamic equilibrium established between the dormant species (alkyl halides) and the active radicals (Scheme 1), which determines the radical



Scheme 1

concentrations in the system and subsequently the polymerization rate and radical termination. Many parameters in ATRP such as the utilized monomers, catalysts (metal salts/ligands), initiators, solvents, reactant ratios, and reaction temperatures can significantly influence the equilibrium and thus the controllability of the polymerization, which makes the optimization of reaction conditions very time-consuming, in particular when a new reaction system is investigated. Moreover, the identification of the best catalytic system for a certain ATRP system is rather difficult due to the different polymerization conditions described. Therefore, new techniques such as HTE, which allow a fast and efficient optimization of the reaction conditions in an automated parallel synthesizer under comparable and reproducible conditions, are highly suitable for this research direction.

An important prerequisite for the successful application of HTE techniques in a specific experiment is that each chain in the entire experimental process ("workflow") must be high-throughput so that the whole process is not hampered by bottlenecks at certain steps. This must be taken into account when designing a high-through experiment. One of the main issues in ATRP is the separation of the obtained polymers and catalysts, which was usually carried out by manually passing the polymer solution through a column of aluminium oxide or silica. The development of a high-throughput procedure for ATRP requires the fast online purification of the polymers, allowing an online SEC to determine the molecular weights and polydispersities of the obtained polymers. Therefore, we firstly developed an automated purification method, where a hand-made aluminium oxide column in a solid phase extraction (SPE) cartridge (length = 5.6 cm, diameter = 0.6 cm) including porous polyethylene frit and an ASPEC cap (Chemspeed Ltd.) was used.[5d] The reaction mixture was automatically transferred to the column and THF was used as the eluent to wash down the polymer. The efficient removal of the catalysts by using this technique was verified by both UV-Vis and atomic absorption spectroscopy measurements.

Another important issue for performing ATRP in an automated synthesizer is to test whether the automated synthesizer can provide reproducible as well as comparable results with those obtained from the conventional laboratory experiment. Therefore, a well-known ATRP system, i.e., the CuBr-catalyzed ATRP of methyl methacrylate (MMA) utilizing ethyl 2-bromoisobutyrate (EBIB) as the initiator, *N*-(*n*-hexyl)-2-pyridylmethanimine (NHPMI) as the ligand, and *p*-xylene as the solvent at 90 °C, was chosen for this purpose.[5d] Figure 2 shows the high reproducibility of the results obtained in the synthesizer (open symbols) and their good comparability with those obtained in the conventional experimental set-up (filled symbol).

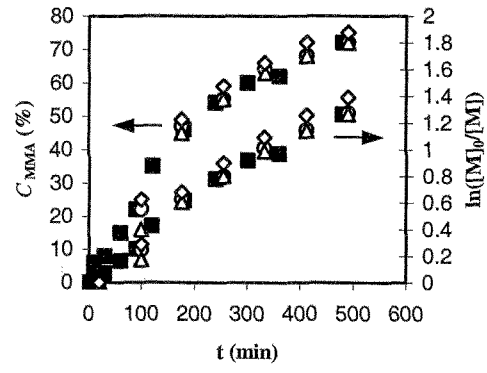


Figure 2. Plots of monomer conversions and $\ln([M]_0/[M])$ versus reaction time t of three parallel reactions in the automated synthesizer (empty symbols) and the same reaction in the conventional set-up (filled symbols) (see ref 5d).

With these results in hand, we performed the homogeneous ATRP of MMA mediated by CuBr/NHPMI utilizing the described automated synthesizer.[5e] The effects of initiators, solvents, and reactant ratios on the polymerization were investigated. Three different kinds of initiators, namely EBIB, (1-bromoethyl)benzene (BEB), and *p*-toluenesulfonyl chloride (TsCl) were utilized to initiate the polymerization. EBIB revealed to be the best initiator for the studied system in terms of molecular weight control and polydispersities of the obtained polymers, while BEB-initiated polymerization provided polymers with polydispersity indices (PDIs) close to 1.6 and molecular weights determined by SEC ($M_{n,SEC}$) much higher than the theoretical ones (Figure 3). Each reaction was also performed two times in parallel, and the results showed very good reproducibility. The solvents used (i.e., toluene, *p*-xylene, and *n*-butylbenzene) showed a strong influence on the polymerization. The reactions in toluene and *p*-xylene were well controlled and proceeded at almost the same rates. However, a dramatic increase in the polymerization rate was observed in *n*-butylbenzene and polymers with higher polydispersities were obtained. This phenomenon needs further investigation. The initiator and Cu(I) concentrations were found to have a positive effect on the polymerization.

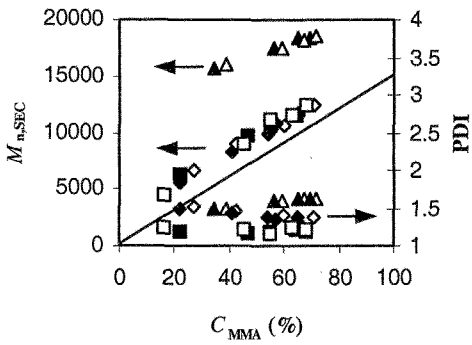


Figure 3. Dependence of $M_{n,SEC}$ and PDIs of the polymers on monomer conversions of the ATRP of MMA in *p*-xylene at 90 °C using EBIB (■,□), BEB (▲,△), and TsCl (◆,◇) as initiators. $[MMA]_0/[initiator]_0/[CuBr]_0/[NHPMI]_0$ = 150/1/1/3. The line in the figure represents the theoretical molecular weights.

A high-throughput experimentation of 100 different reactions has also been carried out in the automated synthesizer.[15] Four different kinds of initiators (EBIB, methyl 2-bromopropinate (MBP), BEB, and TsCl), five different metal salts (CuBr, CuCl, CuSCN, $FeBr_2$, and $FeCl_2$), and five bipyridine-type ligands [2,2'-bipyridine, 4,4'-dimethyl 2,2'-bipyridine (dMbpy), 4,4'-dihexyl 2,2'-bipyridine (dHbpy), 4,4'-dinonyl 2,2'-bipyridine (dNbpy), and 4,4'-ditridecanyl 2,2'-bipyridine (dTbpy)] were utilized in the ATRP of MMA in *p*-xylene at 90 °C. The optimal reaction conditions for Cu(I) halide, CuSCN, and Fe(II) halide-mediated ATRP systems were determined. The best results obtained for Cu(I) halide-mediated ATRP systems (Table I) were in good agreement with those described in the literatures. The Cu(I)-mediated ATRP systems were usually controlled, while Fe(II) halide-mediated ones lost their control in most cases. The only one acceptable result for the Fe(II) halide-mediated ATRP systems was obtained from the combination of $FeBr_2$, dTbpy, and EBIB (Table I). In addition, dHbpy showed the best performance in Cu(I)-mediated systems among all the ligands used.

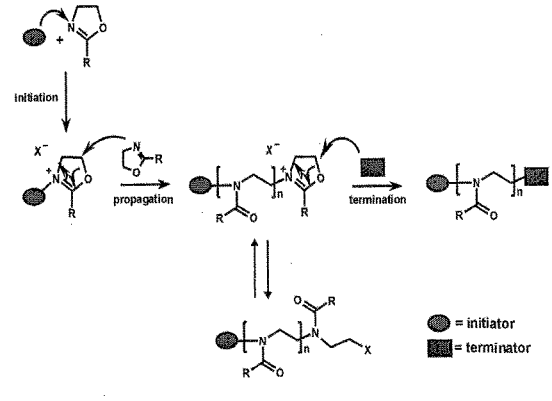
Table I. Selected results for the ATRP of MMA obtained by the automated synthesizer. [a]

Metal salt	Ligand	Initiator	C_M[b] (%)	$M_{n,SEC}$	f[c]	PDI
CuBr	dHbpy	TsCl	55	9320	0.91	1.12
CuCl	dHbpy	TsCl	52	9830	0.82	1.11
CuBr	dNbpy	TsCl	41	7830	0.81	1.14
CuCl	dNbpy	TsCl	28	7190	0.61	1.12
CuBr	dTbpy	TsCl	41	9600	0.66	1.10
CuCl	dTbpy	TsCl	40	9460	0.66	1.09
CuSCN	dHbpy	EBIB	71	11430	0.94	1.30
CuSCN	dNbpy	EBIB	65	10790	0.93	1.33
CuSCN	dTbpy	EBIB	65	11530	0.87	1.29
$FeBr_2$	dTbpy	EBIB	50	10570	0.72	1.28

[a] $[MMA]_0/[initiator]_0/[metal\ salt]_0/[ligand]_0$ = 150/1/1/2, MMA/*p*-xylene = ½ v/v, 90 °C, Reaction time was 215 and 284 min for TsCl and EBIB-initiated systems, respectively.
[b] Monomer conversion.
[c] Initiation efficiency $f = M_{n,th}/M_{n,SEC}$.

4. CROP

The living cationic ring-opening polymerizations (CROP) of 2-substituted-2-oxazolines were also performed in the automated synthesizer in our laboratory. Since its discovery in 1966,[16] the CROP of 2-substituted-2-oxazolines has been extensively studied because of its broad range of specific applications.[17] The polymerization of 2-substituted-2-oxazolines is initiated by a strong electrophile, which attacks the endocyclic nitrogen of 2-substituted-2-oxazoline to form an oxazolinium ring. The C-O bond in this oxazolinium ring is weakened and propagation occurs by the nucleophilic attack of the next monomer on this carbon atom. The polymerization could be terminated by the addition of a strong nucleophile (Scheme 2).[16,17] As in the ATRP system, many parameters in CROP will significantly influence the polymerization, e.g, monomer, initiator, solvent, reaction temperature, and so on. Therefore, automated parallel synthesis is also very suitable for this research direction.



Scheme 2. Reaction mechanism of the CROP of 2-substituted-2-oxazolines (see ref. 12c).

The reproducibility of the results obtained in the automated synthesizer and their comparability with those from the conventional set-up were also checked in the beginning for CROP.[6d] The benzyl bromide initiated-CROP of 2-ethyl-2-oxazoline with acetonitrile as the solvent and piperidine as the terminating agent at 80 °C was chosen for this purpose, and the molar ratio of monomer to initiator ([M]/[In]) was 20, 30, 40, 50, 60, 70, 80, and 100, respectively. These polymerizations were performed in the automated synthesizer at a 500 mg (8 × 1 parallel reaction) and 150 mg (8 × 5 parallel reactions) scales, respectively. All the reaction procedures, including the addition of monomer, solvent, initiator, and terminating agent, sampling during the reactions, precipitation of the polymers into diethyl ether, and transfer of the polymers from reaction vessels into vials, were done automatically. The polymerizations were carried out for 24 h and they provided similar amount of polymers with those carried out in the conventional set-up in most cases. The molecular weights of the obtained polymers determined with ^{1}H NMR, MALDI-TOF MS, and SEC techniques were close to the theoretical ones. Most importantly, good reproducibility was achieved for the parallel reactions.

The benzyl bromide-initiated CROP of 2-ethyl-2-oxazoline was further performed in an automated synthesizer with an individually heatable reactor block (13 mL reaction vessels).[6e] *N,N*-dimethylacetamide (DMAc) was used as the solvent in this case in order to allow a broader temperature range, (i.e., 50 to 130 °C). The kinetic plots of $\ln([M]_0/[M])$ against reaction time t were all linear throughout the reactions (up to 95% monomer conversion), indicating that the concentrations of the active species were constant (Figure 4). The polymerization rate increased with the reaction temperature. The activation energy of the studied system was determined to be 68.7 kJ/mol, which is very close to the value for the CROP of 2-methyl-2-oxazoline (72.9 kJ/mol). The optimal reaction temperature for the studied system was found to be 100 °C in terms of the polymerization rate and molecular weight control. Some parallel polymerizations were performed at this optimized temperature, which indeed provided well-controlled polymers.

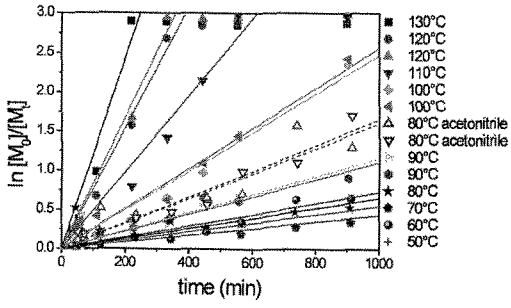


Figure 4. Kinetic plots of $\ln([M]_0/[M])$ versus reaction time t for the different reactions in DMAc (Solid lines) and acetronitrile (dashed lines) (The colored figure can be found in ref. 6e).

Recently, a high-throughput experimentation was designed for the CROP of 2-substituted 2-oxazolines,[18] where four different monomers (namely 2-methyl, ethyl, nonyl, and phenyl-substituted 2-oxazoline), four initiators [benzyl bromide (BB), methyl triflate (MeOTf), methyl tosylate (MeOTs), and methyl iodide (MeI)], four different [M]/[In] (20, 40, 60, and 80), and two reaction temperatures (80 and 100 °C) were utilized. The combination of all these parameters provided a library of 128 polymerizations, which were carried out in the automated parallel synthesizer with 16 polymerizations (one monomer, four initiators, four [M]/[In], and one reaction temperature) each time. Linear kinetic plots were obtained for most of the systems, where the polymerization rates were derived (Figure 5). The results showed that polymerizations at 100 °C were much faster than those at 80 °C for all different monomers and that the polymerizations of 2-alkyl-2-oxazolines were much faster than 2-phenyl-2-oxazoline polymerizations. The obtained order in polymerization rates for the different initiating species for all monomers was in total agreement with the general statement that the lower the nucleophilicity of the counterions, the higher the polymerization rates: MeOTf > MeOTs > MeI > BB. However, polymerizations initiated with MeOTf or MeOTs were much more sensitive to residual moisture or other small contaminations, resulting in loss of control over the polymerization.

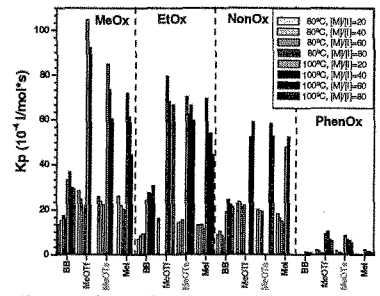


Figure 5. Polymerization rates for different combinations of monomer, initiator, [M]/[In], and reaction temperature.

5. EMULSION POLYMERIZATION

We also successfully performed emulsion polymerization in the described automated synthesizer.[19] Emulsion polymerization is a free-radical polymerization process that involves the emulsification of monomers in a continuous aqueous phase and stabilization of the initial droplets and final latex particles by a surfactant. Surfactants have a large influence on the latex product properties, e.g., particle size distribution, molecular weight, and rheological properties. The optimization of emulsion polymerization conditions is often very time-consuming (e.g., type of surfactants, concentration, and stirring speed).

To investigate the potential applications of combinatorial and high-throughput methods in emulsion polymerization, automated emulsion polymerizations in five parallel reactors with well-defined systems of styrene or vinyl acetate were studied. It was shown for the first time that an automated parallel synthesizer could be applied to emulsion polymerizations utilizing industrially relevant polymer recipes. Visual emulsification experiments for the automated synthesizer utilizing vortex stirring revealed that the critical stirring speed had a lower and an upper limit and that the vortexing speed must be higher for decreased

reaction vessel volumes. The emulsion polymerization carried out in the automated synthesizer with the optimized vortex rate provided results comparable with those from classical stirred batch reactors; i.e., the conversion/time histories for both conventional and automated systems were almost identical in both cases of styrene and vinyl acetate and comparable latex particles were produced (Figure 6). However, a limitation regarding solid content was observed in the automated synthesizer.

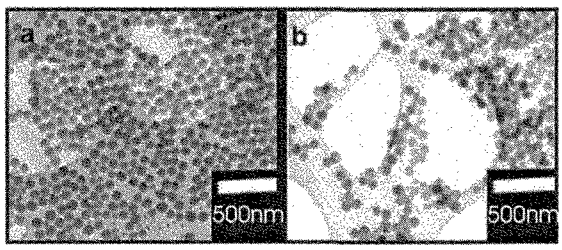


Figure 6. Transmission electron microscopy images of polystyrene emulsion latexes: (a) conventional 25 wt.-%, (b) automated synthesizer (366 rpm) 25 wt.-% (see ref. 19).

6. AUTOMATED MALDI SAMPLE PREPARATION

MALDI-TOF MS is a very powerful analytical tool for the investigation of properties of synthetic polymers, such as molecular weight, molar mass distribution, and end group analysis.[20] It is in principle also a very selective and fast analytical technique, very suitable for high-throughput screening.[21] Although MALDI-TOF MS has been used for the fast analysis of a large number of samples,[22] for the automated identification of proteins,[22b] and for the screening of peptide libraries,[23] no studies have been available regarding the screening of polymerization reactions with this technique. It should be mentioned that one of the most important parts in MALDI analysis is the sample preparation since this step is crucial for the success of the MALDI experiment.[24] Therefore, we developed a new automated MALDI sample preparation method that allows the integration of MALDI sample preparation into the workflow of combinatorial polymer research.[25]

The new MALDI sample preparation method was carried out as a multiple layer approach (from bottom to top: polymer layer, salt additive layer, and matrix layer), which offers the ability to prepare complex sample without the requirement of premixing the different components. This made it possible to obtain and spot easily a large number of samples during polymerizations. The spotting of a sample onto the MALDI target was performed using the liquid handling system in an automated synthesizer (Figure 7). The solutions of polymers, salt additive, and matrix were aspirated and subsequently spotted onto a defined position on the MALDI target. These positions were programmed into the software of the automated synthesizer on a *xyz* basis. This automated spotting technique was evaluated with polystyrene standards and also applied to the screening of the CROP of 2-ethyl-2-oxazoline in the automated synthesizer. The results from the newly developed spotting method and the manual spotting method were in good agreement in terms of molecular weights and polydispersities of the polymers.

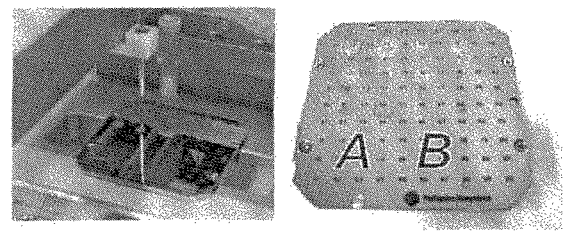


Figure 7. Left: Spotting of matrix solution onto the MALDI target in the custom-made rack with a needle attached to the robotic arm of the automated synthesizer. Right: Comparison of automatically (A) and manually (B) spotted samples (see ref. 25).

7. CONCLUSIONS

Even though combinatorial and high-throughput methods in polymer chemistry are still in their infancy, it can be expected that large numbers of new materials will be discovered more effectively with this methodology in the near future. Up to now, we have successfully carried out ATRP, CROP, emulsion polymerization, and automated MALDI sample preparation in the automated synthesizer as described above. We believe that all known polymerization techniques are possible to be performed in an automated way. However, it should be mentioned that especially very viscous systems and controlled anionic polymerizations still remain very challenging and performing these reactions in the automated synthesizer need further development of the robot system. We are currently working on automated free radical co- and ter-polymerizations, reversible addition-fragmentation chain transfer (RAFT) polymerization, ring-opening polymerization of *L*-lactides and anionic polymerization as well as database development. These activities will produce a much higher level of fundamental understanding in polymer science. In combination with DoE, modeling, and sophisticated data-handling methods, we hope, at some point, a kind of material informatics might be created.

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