Evaluation of Automated Synthesis for Chain and Step-Growth Polymerizations: Can Robots Replace the Chemists?

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ABSTRACT: This article explores current challenges in the use of automated parallel synthesizers in polymeric materials research. Four types of polymerizations were investigated: carbodiimide-mediated polyesterification, diphenol phosgenation, free radical, and reversible addition-fragmentation chain-transfer (RAFT). Synthetic challenges of condensation polymerization, such as liquid and solid dispensing accuracy, dropwise addition, and toxic chemical handling, were successfully met using the automated synthesizer. Both solid and liquid dosing of the diphenol and diacid were successful for polyarylate synthesis. The high precision of liquid dispensing made it possible to achieve stoichiometric balance using reagent stock solutions. For all reactions, molecular weights and their reproducibility were comparable to those obtained with manual synthesis. For RAFT polymerizations, solvent and mol ratio of chain transfer reagent to initiator were successfully optimized on the automated synthesizer and a library of over 60 polymethacrylate copolymer compositions was generated. Considerable savings in time relative to manual methods were achieved when generating polymer libraries (e.g., 4.5× faster for 96 polymethacrylates and 20× faster for 45 for polycarbonates). © 2008 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 47: 49–58, 2009

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INTRODUCTION

Modern polymer science takes advantage of known structure-property relationships and new synthesis methods to assist in the creation of new materials. An emerging strategy in polymeric materials research is the use of robotic platforms that can accelerate the creation of structurally related polymer libraries. Automated parallel synthesizers can accelerate the optimization of synthetic procedures through simultaneous exploration of reaction conditions.[1] As a result, acceleration of throughput is obtained, leading to the effective exploration of polymer space. Ultimately, this can result in the identification of new and useful material compositions for diverse applications and even promote the discovery and development of new technologies.

Recent reviews advocate the use of combinatorial and high-throughput approaches in macromolecular science, but they include only a few isolated cases that describe automated technologies used instead of traditional polymerizations.[2–5] Only a handful of publications describe the success of translating manual polymer synthesis methods to automated procedures.[6–15] Studies by Schubert and coworkers, mostly describe chain-

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growth polymerizations,[16] and a single case describing the step-growth synthesis of polyurethanes compares a single automated synthesis to manual procedure without emphasis on the exploration of polymer space.[8] Additional research is needed to develop automated procedures for more types of industrial-relevant reactions and polymer compositions and to validate them relative to manual syntheses. Challenges include toxic chemical handling, the accuracy of liquid and solid dispensing, and the reproducibility that can be achieved in both degree of polymerization and specific copolymer composition.

In this article, we examine four types of polymerization using a commercially available robotic platform, focusing on the different challenges encountered in each. First, the condensation of diphenol and diacid under mild conditions requires accurate dispensing to achieve the strict stoichiometric balance necessary for high-molecular weight polyarylates.[17–19] Second, the condensation of triphosgene with a diphenol[20] involves both safety and dispensing challenges, such as ensuring adequate isolation of a toxic chemical, triphosgene, inside the automated synthesizer and finding a suitable automated process for dropwise addition to reactions in parallel. Lastly, two types of chain-growth polymerizations require inert atmosphere and accurate liquid dispensing. For such free-radical reactions, we expand on previous investigations[13] by placing special emphasis on investigating reliability and reproducibility of generating target polymer compositions, relative to manual synthesis.

An additional focus of our work is to obtain a general perspective on the advantages and challenges of operating automated synthesizers. Potential advantages include rapid optimization of reaction conditions, accelerated throughput, standardization of methods, and retention of expertise. Challenges include the substantial amount of time required for automation of manual protocols and the inherent limitations of the instrument used. As far as we are aware, ours is the first study that uses a comprehensive and systematic methodology to compare manual and automated procedures, particularly in the case of polycondensation reactions.

EXPERIMENTAL

Chemicals and Reagents

All chemicals were high purity, reagent-grade, or HPLC-grade and used as received except as noted: (i) AIBN was recrystallized from MeOH, (ii) Monomers were purified through a column of alumina to remove inhibitors, and (iii) Solvents, solutions, and monomers were degassed with nitrogen or argon before use in free radical or RAFT polymerizations.

Triethylene glycol ethyl ether methacrylate, cyclohexyl methacrylate, and undecyl methacrylate were purchased from Polysciences. The 2,2,2-trifluoroethyl methacrylate was purchased from Matrix Scientific. Potassium carbonate and 2-hydroxypropyl methacrylate (HPMA) were purchased from Acros. Diisopropylcarbodiimide (DIPC) was purchased from Tanabe. Anhydrous, inhibitor-free tetrahydrofuran (THF), sebacic acid, succinic acid, methyl methacrylate (MMA), hydroxyethyl methacrylate (HEMA), and 2,2′-Azobis(2-methylpropionitrile) (AIBN) were purchased from Aldrich. Toluene, 1,4-dioxane, dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), isopropanol (IPA), methanol (MeOH), methyl ethyl ketone (MEK), and 1-methyl-2-pyrrolidinone (NMP) were purchased from Fisher.

Desaminotyrosyl-tyrosine alkyl esters, 4-(dimethylamino)pyridinium 4-toluenesulfonate (DPTS), and bis(thiobenzoyl) disulfide were synthesized following literature procedures.[17,21,22] Synthesis of the RAFT agent, 2-Cyanoprop-2-yl dithiobenzoate (CTA) was slightly modified from the literature procedure[22]: A mixture of AIBN (24.6 g, 0.15 mol) and bis(thiobenzoyl) disulfide (30.6 g, 0.1 mol) in EtOAc (800 mL) was heated in a round bottom flask equipped with a magnetic stirrer, reflux condenser, and heating mantle. After 18 h, the solvent was evaporated under vacuum, and the crude material was isolated with column chromatography (silica gel 60, 240–400 mesh) with EtOAc:Hexanes (4:1) as the mobile phase. After evaporation of the solvents, the 2-cyanoprop-2-yl dithiobenzoate was obtained as a red oil (yield 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm; 1.96 (s, 6*H*, 2 × C*H*$_3$); 7.38 (m, *m*-Ar*H*, 2*H*); 7.55 (m, *p*-Ar*H*, 1*H*); 7.90 (d, $J = 8.7$ Hz, *o*-Ar*H*, 2*H*).

Instrumentation

The automated parallel synthesizer was a Chemspeed Accelerator SLT100 equipped with four solvent reservoirs and four syringes (2 × 25, 10, and 1-mL). The reactor blocks were equipped with septa and reflux condensers and could be used with either simple or oil-jacketed reactors (13 mL). For the latter, temperatures could be

controlled from −20 to 150 °C (Huber Unistat Tango control unit).

Proton NMR spectroscopy was performed on a Varian 300 or 400 MHz spectrometer to determine copolymer compositions. Samples were dissolved in either DMSO-d_6 or $CDCl_3$. Gel Permeation Chromatography (GPC) was performed using a 5 μm gel precolumn and two PL columns with pore size of 10^3–10^5 Å (Polymer Labs) on a Waters 510 HPLC equipped with a Waters 410 Differential Refractometer. The mobile phase and flow rate was either THF at 1.0 mL min^{-1} or *N,N*-dimethylformamide (DMF) containing 0.1% trifluoroacetic acid (TFA) at 0.8 mL min^{-1}. Molecular weights (number-average) and polydispersity index (PDI) were determined relative to polystyrene calibration standards.

Step-Growth Case 1: Syntheses of Polyarlyates Via Carbodiimide-Mediated Coupling of Desaminotyrosyl-Tyrosine Butyl Ester (DTB) and Sebacic Acid

Manual Synthesis Protocol

DTB (215.8 mg, 0.56 mmol), sebacic acid (113.2 mg, 0.56 mmol), DPTS (70 mg, 0.24 mmol), DIPC (0.28 mL, 1.80 mmol), and CH_2Cl_2 (4.0 mL) were charged into 8 × 7-mL glass vials with Teflon-lined caps and mixed on a shaker for 48 h at RT. The reactions were precipitated in IPA and dried under vacuum for ≥24 h at 60 °C. The scale was the same as that used in the automated parallel synthesizer.

Automated Parallel Synthesis Protocol

The oil-jacketed reactors were rendered inert by five cycles of evacuation under vacuum at 120 °C for 10 min, backfilled with argon, and cooled to room temperature (RT).

Solid Dispensing. Monomers (DTB and sebacic acid) and catalyst (DTPS) were dispensed as solids using optimized dispensing parameters (final dosing amount, initial dosing speed, mass flow, filter coefficient, and oscillation periods) and extruder. The diphenol was dispensed first, and the amount was weighed as part of the automated workflow. Based on this information, the amount of diacid needed was calculated and programmed for each individual reactor. DIPC was transferred as a solution in chloroform.

Liquid Dispensing. Monomer stock solutions, [0.4 M DTB in THF (1.4 mL, 215.8 mg, 0.56 mmol) and 0.316 M sebacic acid in THF (1.77 mL, 113.1 mg, 0.56 mmol)], were charged by syringe transfer to eight reactors using the 4-needle tool with various syringe sizes. The transferred stock solutions were evaporated to remove THF. The reactors were cooled to 20 °C, and 0.136 M DPTS in CH_2Cl_2 (1.8 mL, 72 mg, 0.25 mmol), CH_2Cl_2 (2.2 mL), and DIPC (0.28 mL, 1.80 mmol) were transferred by syringe. The reactors were then vortexed at 600 rpm for 48 h at RT. The polymers were precipitated manually in IPA and were dried under vacuum for ≥24 h at 60 °C.

Step Growth Case 2: Synthesis of Polycarbonates Via Diphenol Phosgenation of Desaminotyrosyl-Tyrosine Ethyl Ester (DTE)

Caution: Triphosgene is a hazardous (toxic and corrosive) chemical. A phosgene detector was installed into the hood of the automated synthesizer so that the absence of phosgene could be verified at the end of the reaction before opening the robot's hood to the laboratory. Additionally, two vials (8-mL) containing ammonium hydroxide sealed with septa and an empty vial (8-mL) to transfer the ammonia were placed in the instrument in case any residual phosgene (from the triphosgene breakdown) needed to be quenched, as further discussed in Results and Discussion.

Manual Synthesis Protocol

DTE (2.5 mL, 0.6 g DTE, 1.68 mmol, 0.67 M) in pyridine/CH_2Cl_2 (3.45 equivalents of pyridine/DTE) was transferred via syringe into two 50-mL round bottom flasks, each equipped with magnetic stir bar and septa with Teflon tubing connected to a 2-syringe infusion pump. Triphosgene solution (19 wt %, 1 mL, 0.2 g, 0.67 mmol) was delivered dropwise (50 μL min^{-1}) to the two reactions using the syringe pump. The reactions were stirred an additional 45 min before quenching with 5-mL THF:H_2O.

Automated Parallel Synthesis Protocol

A 25-mL stock solution of 0.67 M DTE in pyridine/CH_2Cl_2 was prepared using 6.0-g DTE (16.78 mmol) and 4.7-mL (57.6 mmol) pyridine. The DTE stock solution (2.5 mL, 0.6 g DTE, 1.68 mmol) was transferred to four of the simple (non-jacketed) reactors equipped with septa. The reactions were

vortexed at 600 rpm at RT. A stock solution of triphosgene in toluene (20 wt %, 1 mL, 0.2 g, 0.67 mmol) was dispensed to each reaction (i.e., 10 aliquots of 100 μL dispensed at 1 mL min^{-1}) using the 1 mL syringe equipped with a ceramic-coated needle. After the addition was complete, the reactions were vortexed for 45 min at RT, quenched with a 1:1 mixture of THF/H_2O, and then vortexed for 30 additional minutes. The reactions were precipitated manually in IPA and dried under vacuum for $\geq$24 h at 60 °C. [Note: Precipitation also removes low molecular weight polymer fractions.]

Chain-Growth Cases: Syntheses of Polymethacrylates Via Free Radical Solution (FRS) and Reversible Addition-Fragmentation Transfer (RAFT) Polymerization of Isobutyl Methacrylate

Manual Synthesis Protocol

Purified isobutyl methacrylate (3 g), toluene, AIBN stock solution ($[iBuMA]_0/[AIBN]_0 = 400$) for FRS or AIBN stock solution ($[CTA]_0/[AIBN]_0 = 4$) for RAFT, RAFT chain transfer reagent stock solution ($[iBuMA]_0/[CTA]_0 = 1000$), and a magnetic stir bar were charged in a 50-mL round-bottomed flask before sealing with a septa. The reactions were degassed by bubbling nitrogen through the solutions. The reactions were then stirred for 6 h (or 20 h for RAFT) at 70 °C, cooled to RT, precipitated in MeOH, and dried under vacuum for $\geq$24 h at 60 °C. Ten reactions were run in parallel.

Automated Parallel Synthesis Protocol

The 13-mL oil-jacketed reactors equipped with septa and reflux condensers were inertized before reagent addition as described above. The reactors were cooled to RT and the degassed reagents (purified monomers, stock solution of either AIBN ($[iBuMA]_0/[AIBN]_0 = 400$) (conventional free radical) or a co-solution of AIBN with 2-cyanoprop-2-yl dithiobenzoate (RAFT chain transfer reagent) ($[CTA]_0/[AIBN]_0 = 4$), and ($[iBuMA]_0/[CTA]_0 = 1000$)) and solvent were charged by syringe transfer using the 4-needle tool while being purged with argon. Volumes $\leq$1 mL were transferred using the 1 mL syringe to maximize the accuracy. The reactions were vortexed at 600 rpm at 70 °C for 6 h (FRS) or 20 h (RAFT) under argon. The reactions were cooled to 20 °C and precipitated manually. The polymers were dried under vacuum for $\geq$24 h at 60 °C.

RESULTS AND DISCUSSION

Stoichiometric Balance: Investigation of Solid Versus Liquid Dispensing

Automated synthesis of condensation polymers with high molecular weight is only feasible when automated reagent dispensing is accurate to ~2%. In other words, the mol ratio of the monomers must be $\geq$0.98 to achieve a degree of polymerization (DP) in excess of 99. A reaction based on 100-mg diphenol and 60-mg diacid requires accuracy within 2 and 1 mg, respectively. Scaling up to 0.5-g diphenol increases the acceptable variability five-fold, but it also increases the chances of clogging the extruders during solid dispensing.

To achieve accurate and reproducible solid dosing, we focused on both materials preparation (e.g., grinding and sieving the reagents into a uniform powder, vacuum drying, and storing in a dehumidifier) and on adjustable parameters of the parallel synthesizer (e.g., type of extruder and the rate of oscillation toward the end of the dispensing). However, for desaminotyrosyl-tyosine benzyl ester (DTB), despite these efforts to improve fine dosing, the standard deviations were outside of the acceptable range to maintain stoichiometric balance within 2%. The typical result obtained for 20 replicates was 223 $\pm$ 10.9 mg, which is ~5%, whereas 2% is needed. In contrast, the synthesizer could successfully dispense diacids with the requisite precision (see Table 1).

One possible "work-around" is to make the diphenol the first reagent dispensed and use the automatically generated recordings of the exact amount delivered to the vial to re-calculate the amount of second reagent needed for exact stoichiometric balance. This work-around requires that the workflow be temporarily stopped so that the necessary amounts of second reagent can be calculated for each individual reactor, followed by restarting the automated workflow. The average molecular weight of poly(DTB sebacate), which was synthesized in this way in three repetitions by automated synthesis, was 174 $\pm$ 46 kg mol^{-1} (Table 2), when compared with 118 $\pm$ 44 kg mol^{-1} for manual synthesis. The degree of polymerization was 200 for the manual method and 288 for the automated. Without this work around, the average molecular weight achieved in three repetitive syntheses of poly(DTB sebacate) was beyond

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Table 1. Determination of Liquid and Solid Dispensing Accuracy on the Chemspeed SLT100

Solid Transfer	Solid Type	Extruder	Programmed Value (mg)	Experimental Average (mg)	Standard Deviation[a]
DTB	Powder	Type 4, cone	215.80	222.89	10.90
Sebacic acid	Beads	Modified type 2	113.20	113.19	0.40
Adipic acid	Fine powder	Modified type 2	81.84	81.95	0.36
Liquid Transfer	**Reservoir Solvent**	**Syringe Size**	**Programmed Value (mL)**	**Experimental Average (mL)**	**Standard Deviation[a]**
THF reactor to vial	CH_2Cl_2	1 mL	0.500	0.463	0.008
Toluene reactor to vial	Toluene	1 mL	0.500	0.496	0.002
THF vial to vial	THF	1 mL	0.500	0.496	0.001
Toluene reactor to vial	Toluene	25 mL	3.930	3.900	0.010

[a]Based on n = 10–20.

the lower limits of our standard curve, indicative of oligomer formation of less than 20 repeating units. It is important to emphasize that this work-around only works when one of the two reagents that need to be in stoichiometric equivalence presents facile solid dispensing (in this case, the diacid, as evidenced by the data for accuracy and repeatability of extruder in Table 1).

Next, we explored the alternative approach of using liquid stock solutions. Experimental variables that had to be optimized were (i) syringe size and delivery rate and (ii) solvent choice. Liquid dispensing was performed with a high degree of accuracy and precision when the solvent lines were primed and an appropriately nonvolatile solvent was chosen (i.e., it was necessary to use THF, toluene, or DMF instead of the highly volatile CH_2Cl_2) (Table 1). The precision was further improved from ±30 μL to ±4 μL by dispensing with a 1 mL syringe instead of a 25 mL one.

Solvent Optimization

For carbodiimide-mediated polycondensations, the CH_2Cl_2 is the preferred solvent, but cannot be used with the available liquid dispensers due to its high volatility and because it is a poor solvent for the monomers used in this study. However, as

Table 2. Comparison of Automated and Manual Synthesis of Step and Chain Polymerization

Polymer	Type of Polymerization	Automated Dispensing	M_w[a] (kg mol^{-1})		n[b]
			Automated	Manual	
Poly(DTB sebacate) by condensation	Step	Solid	174 ± 46	118 ± 44	3,8
		Liquid	95 ± 38	–	8
Poly(DTE carbonate) by phosgenation	Step	Liquid, dropwise (25 mL)	374 ± 218	297 ± 92	4
		Liquid, dropwise (1 mL)	218 ± 86	–	4
		Liquid, 25 μL	137 ±134	–	4
		Liquid, 50 μL	84 ± 8	–	4
		Liquid, 100 μL	194 ± 40	–	4
Poly(isobutyl methacrylate) by free radical polymerization	Chain	Liquid	125 ± 13	127 ± 18	10
Poly(isobutyl methacrylate) by RAFT polymerization	Chain	Liquid	49 ± 4	110 ± 5 (46 ± 0)[c]	10

[a]Measured by SEC, values relative to polystyrene standards.
[b]Number of repetitions.
[c]Higher MW when degassing was final step.

Table 3. Solvent Effect on Polymerization of Poly(DTB sebacate)

Solvent	Polarity Index	$r = N_A/N_B$	M_w[a] (kg mol^{-1})
DMSO	7.2	1.00	6
NMP	6.7	1.00	10
DMF	6.4	0.99	12
EtOAc	4.4	0.98	51
THF	4.0	0.99	12
CH_2Cl_2	3.1	1.00	111

[a]Measured by THF SEC, values relative to polystyrene standards.

the reaction progresses with the fraction of the monomer molecules in solution the solubility is not longer an issue as the polymer is soluble in CH_2Cl_2. On the other hand, all of the polar, aprotic solvents that work well with the liquid dispensing system and were good solvents for the monomers, interfered with the carbodiimide-mediated polycondensation reaction and produced only low molecular weight products. Previously, it was reported that addition of 3% pyridine to the reaction mixture, reduced the molecular weight of the product by one-half.[18] These results are consistent with reports that polar solvents decrease the reaction rate of carbodiimide with acids by improving solvation of the acid.[23]

Thus, we had to address the significant challenge of selecting a solvent system that would dissolve the monomers, be suitable for liquid dispensing, and be suitable for the polymerization. Because none of the solvents that exhibited good monomer solubility were suitable to obtain high molecular weight polymers (see Table 3), it was necessary to use different solvents for dispensing of the monomers and for performing the polycondensation reactions. Of the solvents listed in Table 3, THF was identified as the preferred dispensing solvent. Once the reagents were dispensed, THF was removed by evaporation, and CH_2Cl_2 was added into the reactors as the polymerization solvent.

These extra steps would have been very inconvenient in manual synthesis, but in the context of an automated workflow, the solvent exchange steps did not cause any additional work for the operator. The polymers obtained by manual synthesis and automated synthesis using THF stock solutions in eight repetitions resulted in similar weight-average molecular weights and standard deviations: 118 ± 44 kg mol^{-1} for manual (using solid dispensing and CH_2Cl_2 as reaction medium) and 95 ± 38 kg mol^{-1} for automated synthesis (THF for dispensing and CH_2Cl_2 for reaction) (Table 2).

In summary, the use of accurately prepared reagent stock solutions made it possible to achieve the stoichiometric balance required to obtain high molecular weight polymers via automated synthesis. Additional steps for the evaporation of the dispensing solvent were needed, but were readily incorporated into the automated workflow.

Dropwise Addition of Reagent and Use of Hazardous Materials During Diphenol Phosgenation Towards Polycarbonate Synthesis

Triphosgene is a versatile phosgene substitute useful in a myriad of chemical transformations, such as chlorination, chloroformylation, carbonylation, and dehydration. Often, manual procedures using triphosgene solutions call for slow and dropwise addition to the reaction mixture; thus, the development of an automated protocol mimicking the "drop-wise" addition of a triphosgene solution would be beneficial in a wide range of synthetic procedures, not only polycarbonates synthesis.[24]

The first step towards automating this process was to determine if triphosgene could be safely used in the automated synthesizer. For the liquid transfer, a ceramic-coated needle was required to handle the corrosive triphosgene stock solution. Teflon tubing was used during all procedures. The use of ammonia (dispensed from vials of ammonium hydroxide, as outlined in the Experimental section) worked well to quench phosgene in the air space of the hood. Unused triphosgene solution was quenched with equal volumes of 10% triethylamine in ethanol.

The major challenge with automating the phosgenation reaction was defining dispensing parameters that could mimic the dropwise addition of triphosgene solution over 30 min to 1 h in the manual protocol and allow for multiple reactions to be run in parallel. Specifically, the synthesis of poly(DTE carbonate) was investigated as a model reaction. First, we tried to mimic dropwise addition directly by reducing the dispensing rate to 0.05 mL min^{-1}. Both 25 mL and 1 mL syringes were evaluated, and the triphosgene solution was dispensed dropwise in four cycles of 250 μL each to four reactors. The resulting polymers had weight-average molecular weights of 374 ± 218 kg mol^{-1} and 218 ± 86 kg mol^{-1} for the 25

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and 1 mL syringes, respectively, which compares with 292 ± 92 kg mol for the manual syntheses (Table 2). Although the average molecular weight was greater than 200 kg mol^{-1} for both the automated and manual phosgenations, the variability was very high when the 25 mL syringe was used for the triphosgene addition.

The obvious approach was to investigate the effect of increasing the size of the aliquot of triphosgene solution dispensed. Specifically, we wanted to determine if the same results could be obtained when triphosgene solution was delivered at a faster dispensing rate and in larger aliquots of 25, 50, or 100 μL. Additions with aliquots of 25 or 50 μL at 1 mL min^{-1} failed to provide either high molecular weight polymer or reproducible results (137 ± 134 kg mol^{-1} and 84 ± 8 kg mol^{-1}, respectively). We expect this is due to quenching of the triphosgene solution by moisture inside the hood of the automated synthesizer.

By using a larger aliquot of 100 μL, we could minimize the exposure of the solution in the needle and in the stock solution vial to the atmosphere of the automated synthesizer and accelerate the rate of addition. Specifically, 10 cycles of 100 μL of triphosgene solution were dispensed at 1.0 mL min^{-1} to four reactions and yielded polymers with weight-average molecular weights of 194 ± 40 kg mol^{-1}. Although there was a slight decrease in molecular weight moving from dropwise addition to dispensing 100 μL aliquots of triphosgene solution, the addition can be completed in a time frame (i.e., 30 min) amenable to parallel reactions. Based on these results, we expect that with two needles working in parallel, we will be able to run eight reactions in parallel. Because the total reaction time is only 1 h, 48 reactions could be performed overnight. Comparatively, manual synthesis of 48 polycarbonates could at best be performed in 2 to 3 weeks by running four reactions a day, or 20 reactions per week; thus, the automated synthesis of polycarbonates is a preferred approach to accelerate output and explore polymer space.

Reproducibility of Automated Free Radical and RAFT Polymerizations Through Synthesis of Poly(isobutyl methacrylate)

Automated synthesis of polymethacrylates by RAFT polymerization, using 2-cyanoprop-2-yl dithiobenzoate as the chain transfer reagent, has previously been reported.[13] We developed similar protocols without purging the automated synthesizer hood with argon, as first trials indicated that we could omit this step from the published method and still get reproducible high-molecular weights. Specifically, the purified monomers, stock solutions, and solvent were degassed and transferred by syringe to the reactors, which had been thrice evacuated and refilled with argon. The manual synthesis was executed by degassing the reaction after reagents were charged and the flask was sealed with a septum.

For conventional free radical polymerization, the reproducibility for the manual and automated synthesis of poly(isobutyl methacrylate) was excellent (Table 2). In the case of RAFT polymerization, the polymer molecular weights obtained by automated synthesis were lower than those prepared by manual synthesis. Oxygen has been shown to retard radical polymerizations.[25] Therefore, for direct comparison of the automated procedure, manual synthesis of the RAFT procedure was performed using syringe transfer of degassed reagents to a flask while purging with nitrogen. The molecular weights of the polymers obtained by manual synthesis without the final degassing step were comparable to the products of the automated protocol, suggesting that the oxygen incorporated during the syringe transfer was sufficient to affect the polymerization. Thus while our results show that purging of the automated synthesizer is not needed for conventional free radical reactions, stringent exclusion of oxygen may be needed to optimize RAFT polymerizations, for example by purging with argon while transferring the reagents.

Reaction Optimization: A Case Study of a Polymethacrylate Library Synthesis

Solvent effects on initiator efficiency, monomer reactivity ratio, and polymerization rate have been reported.[22,26] Usually, these experiments take considerable amount of time, as reactions are executed one at a time. We wanted to prove the advantages of automated parallel synthesis for the reaction optimization of different polymethacrylates in a single experiment. In particular, we evaluated the effect of solvent on the synthesis of several homopolymers and copolymers (Table 4). Comparison of copolymerization reactions of benzyl and hydroxypropyl methacrylate (MA) with MMA revealed that lower molecular weight polymers with high polydispersities were obtained when toluene or DMF was used as the solvent, but well-defined high-molecular weight

Table 4. Solvent Effect on Polymethacrylate Polymerizations

Solvent	Monomer Polymerized	$[CTA]_0/[AIBN]_0$	M_n[a] (kg mol^{-1})	PDI
Dioxane	Methacrylic acid	10	221	1.5
DMF	Methacrylic acid	10	48	1.5
DMF	Methacrylic acid	4	98	1.6
DMF	Tetrahydrofurfuryl MA	4	137	1.6
DMF	HPMA-MMA (75-25)	10	54	1.8
DMF	Tetrahydrofurfuryl MA	10	44	1.8
EtOAc	*t*-Butyl MA	10	32	1.5
MEK	Benzyl MA-MMA (25-75)	10	97	1.4
MEK	HPMA-MMA (75-25)	10	154	1.4
MEK	Benzyl MA-MMA (50-50)	4	144	1.5
MEK	*t*-Butyl MA	10	49	1.6
MEK	Undecyl MA	4	85	1.6
None	Undecyl MA	4	185	1.8
Toluene	Undecyl MA	4	19	1.8
Toluene	Benzyl MA-MMA (25-75)	10	22	1.9
Toluene	*t*-Butyl MA	4	31	2.0
Toluene	Benzyl MA-MMA (50-50)	10	43	2.1

[a]Measured by SEC, values relative to polystyrene standards.

polymers could be obtained using MEK. Also, polymerization of methacrylic acid in dioxane was significantly faster than in DMF, even when the mol ratio of CTA to AIBN was reduced to four. In the case of undecyl methacrylate, bulk polymerization provided the highest molecular weight product. Additionally, control of the polymerization depends on the chain transfer efficiency of the RAFT chain transfer reagent.[27] The molecular weight of a benzyl MA-MMA copolymer and poly(tetrahydrofuryl methacrylate) were successfully increased when the mol ratio of CTA to AIBN was reduced from 10 to 4. For poly(*t*-butyl methacrylate), the combination of the low mol ratio of CTA to AIBN and the use of toluene as the reaction solvent resulted in a polymer with a broad PDI. By changing the reaction solvent to either EtOAc or MEK and increasing the CTA to AIBN mol ratio to 10, the polymerization of *t*-butyl methacrylate resulted in a product with a lower PDI. In short, parallel synthesis allows for rapid optimization of reaction conditions by analyzing several parameters at once.

Reproducibility of RAFT Polymerization on the Automated Synthesizer: Synthesis of a Large Methacrylate Copolymer Library

Evaluation of monomer feed versus actual composition parameters of 63 polymethacrylate copolymers synthesized twice by RAFT methods (two different experiments) on the automated synthesizer revealed that the target copolymer compositions could be achieved with excellent accuracy and repeatability. In summary, 10 reactions out of the 63 did not produce an isolable solid (indicative of low-molecular weight oligomer), but of the remaining 53 copolymers, 52 exhibited a composition within 2 mol % of the theoretically expected composition, as determined by ^{1}H NMR spectroscopy (Results not shown). The high precision in the copolymer compositions that were successfully synthesized is a direct reflection of the performance of the automated liquid dispensing. The inability to synthesize a few of the compositions was governed by the monomer reactivity ratio, as the reaction conditions were the same for all polymerizations.

Acceleration of Output: Manual Versus Automated

As with manual synthesis, preparation for a large number of repetitive experiments requires significantly more time for planning and preparation than running a single experiment. Reaction optimization is critical when a large set of polymers has to be synthesized, irrespective of the use of manual or automated synthesis. However, when using an automated parallel synthesizer, there is an extra step: The translation of a manual synthetic procedure into an automated "workflow" of

the sequence of tasks to be performed, such as heating, cooling, stirring, precipitating, filtering, etc.

This time needed to translate manual synthesis to automated is usually long (from 2 h to 2 days for the polymerization systems we studied), and it may also include making time for performing one or more dry runs with inactive "placebo" reagents before expensive or scarce reagents are used. The critical question, therefore, is when a "crossover" is achieved and the time to generate the workflow is more than compensated by savings in time, throughput, quality, etc.

As a specific example, we compared the time required for manual and automated synthesis of 10 and 45 methacrylate polymers. For 10 replicates of the RAFT polymerization of isobutyl methacrylate, the total time required from start to finish for automated synthesis was several hours longer than for manual synthesis. Furthermore, the total operator time (e.g., the time a person was engaged in performing the synthesis exclusive of waiting or idle time) was 30 min longer for automated synthesis than manual synthesis.

As one would expect, the use of an automated synthesizer became significantly more efficient than manual synthesis when 45 reactions had to be performed. The set up for 45 reaction vessels on the automated synthesizer took only 10 min more than setting up 10 reactions. The expansion of the number of polymethacrylate syntheses from 10 to 45 required almost no extra time of effort on the automated synthesizer, whereas the repetitive manual synthesis of 45 polymethacrylates required 4.5 times more operator time than the synthesis of 10 polymethacrylates.

In the case of manual polycarbonate synthesis, the dropwise addition of the triphosgene reaction required significant operator time. When synthesizing polycarbonates manually, even an experienced operator could not conduct more than six individual manual syntheses per day. Here the automated synthesizer was able to reduce the time required to synthesize 45 different polycarbonates from over 2 weeks to a single overnight procedure.

One clear advantage of the automated protocol is the ability for two different individuals to obtain the exact same results over a shorter period of time. Even with the most explicitly documented manual synthesis, subtle differences in an individual's technique affect the outcome of a complex synthetic procedure. In the case of an automated workflow, exactly the same results will be obtained each time the workflow is executed, as long as the reagent solutions are identical.

CONCLUSIONS

Successful solutions to synthetic challenges in automated synthesis, such as stoichiometric balance, dropwise addition, and handling of toxic chemicals, have been described in this article. In particular, procedures for the automated synthesis of condensation polymers (tyrosine-based polyarylates and polycarbonates) have been described for the first time. These results establish the feasibility of using automated reagent dispensers even when extremely accurate reagent ratios are needed. Comparison of automated and manual synthesis for 10 and 45 polymethacrylates demonstrated that for small sets of polymers, the advantages of automated synthesis are improved reproducibility, but not necessarily reduced labor. The ability of automated synthesis to significantly accelerate project timelines becomes more pronounced when a larger number of polymers need to be synthesized. An additional use of the automated synthesizer is to explore different reaction conditions in parallel. Finally, one of the most significant advantages of automated synthesis is the preservation of "know-how": Once a workflow has been optimized and archived, even minimally trained personnel can precisely reproduce the synthetic results obtained initially by highly trained chemists. In summary, the automated synthesizer does not replace the chemist; rather, the chemist's expertise is needed for designing an effective workflow, which is then available for indefinite reuse.

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