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Protocol for Automated Kinetic Investigation/Optimization of the RAFT Polymerization of Various Monomers

Caglar Remzi Becer[a,b], Andrew M. Groth[c], Richard Hoogenboom[a], Renzo M. Paulus[a,b] and Ulrich S. Schubert[a,b]*

[a] Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology and Dutch Polymer Institute (DPI), P. O. Box 513, 5600 MB Eindhoven, The Netherlands, E-mail: u.s.schubert@tue.nl
[b] Laboratory of Organic and Macromolecular Chemistry, Friedrich-Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany
[c] CSIRO Molecular and Health Technologies, Bag 10, Clayton South, Clayton, Victoria 3169, Australia

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Abstract

A standard protocol for the parallel optimization of Reversible Addition–Fragmentation Chain Transfer (RAFT) polymerization conditions using an automated synthesizer is described in this report. Experimental design based on the knowledge obtained from previous screening experiments and the literature is the most effective initial step of the High-Throughput Experimentation (HTE) cycle. In this paper, the polymerization procedure is explained step-by-step including preparation of stock solutions, inertization of the reactors and synthesizer environment, liquid transfers to or from the reactor vessels including sampling, as well as termination of the polymerization. Automated characterization techniques for the determination of monomer conversion and the molecular weight distribution of the polymers are discussed to complete the HTE cycle. Consequently, analysis of the data obtained from parallel screening of reactions and their products will result in the design of the next experimental cycle.

1 Introduction

Successful synthesis of macromolecules with desired compositions, topologies, and functionalities has been a source of great interest and curiosity to polymer researchers for many decades [1–4]. Numerous heterogeneous or homogeneous reaction mechanisms have been reported by employing specially designed catalysts for the polymerization of monomeric units [5–8]. The efficiencies of those catalysts or Chain Transfer Agents (CTAs) [9, 10] to sustain control over the polymerization were limited within a class of monomers or to specific reaction conditions. Each catalyst requires specific selection of polymerization parameters including, type of monomer [11], initiator [13, 14], co-catalyst [15, 16], and solvent [17], polymerization temperature, reaction time, and stirring speed. The list of important parameters may be extensive and their effect on the polymerization has to be investigated in order to produce well-defined polymers. It is possible to select some relatively important reaction parameters and investigate their effect with a limited number of experiments. However, this classical approach provides a narrow window to evaluate the actual effect of a certain parameter on the reaction. Combination of modern tools and High-Throughput Experimentation (HTE) methodologies can provide a better understanding based on numerous automated parallel experiments all performed under the exact same conditions and in the absence of any handling errors.

Automated synthesis platforms have been used in various fields of chemistry because of their advantages over classical methodologies such as faster, unattended, and more reliable experimentation. These platforms are not only used in materials science for research and development of polymers or catalysts but also extensively used in pharmaceuticals, agrochemicals, and specialty chemicals. Nevertheless, our main interest is creating a universal protocol for the application of controlled/"living" radical polymerization reactions on one of the most advanced automated synthesis platforms commercially available.

Atom Transfer Radical Polymerization (ATRP) [5, 6], Nitroxide Mediated radical Polymerization (NMP) [7], and Reversible Addition–Fragmentation Chain Transfer (RAFT) [8, 12] polymerization have attracted great attention since they provide well-defined polymers under certain reaction conditions without the need for stringent purification of monomers and solvents. Therefore, many independent research groups conducted kinetic studies by

Supporting information for this article is available on the WWW under www.qcs.wiley-vch.de

using different monomers, initiators [13, 14], catalysts [15, 16], solvents [17], polymerization temperatures, and reaction times to understand the effect of those parameters. On the other hand, the evaluation and comparison of the results obtained by independent laboratories remained questionable because of the unavoidable difference in experimentation procedure and assessment of different researchers. A fair comparison of the experimental results is not easy unless they are performed by following the same procedure and under the same conditions using the same purity of reagents. To minimize and overcome these unavoidable variations in manual experiments, using automated parallel synthesizer platforms might be beneficial. Combinatorial synthesis and evaluation provides the researcher a possibility to obtain a better overview and deeper understanding of the effect of any parameter on the experiment [18, 19]. This is possible in a timely fashion by using HTE and characterization tools that provide fast synthesis, characterization, and also analysis with comparable results [20–24].

In this report, we describe an experimental protocol for the high-throughput investigation of RAFT polymerization kinetics for acrylates, acrylamides, and styrenics. However, the type of monomer or catalyst can be varied and an analogous version of this protocol can equally be applied for other polymerization reactions, *i.e.*, ATRP [25], NMP [24], anionic [26], and cationic ring opening polymerization [27], with some additional precautions depending on the oxygen and water sensitivity of the polymerization technique. This protocol is a step-by-step procedure that is applicable in the automated parallel synthesizer platform. The synthesis as well as automated characterization techniques for the determination of monomer conversion and molecular weight distribution will be discussed in order to calculate the important kinetic parameters of the polymerization procedure that are required to evaluate the control over and the rate of the polymerizations. This automatic synthetic protocol was already successfully applied for optimizing the RAFT polymerization of various acrylates and methacrylates using 2-cyanobutyl dithiobenzoate as a CTA [23, 28, 29]. In addition, we have demonstrated that the resulting optimized polymerization procedure can be applied for the synthesis of copolymers [23, 29, 30] and that it can be directly scaled to a ten times larger volume using mechanically stirred reactors [22].

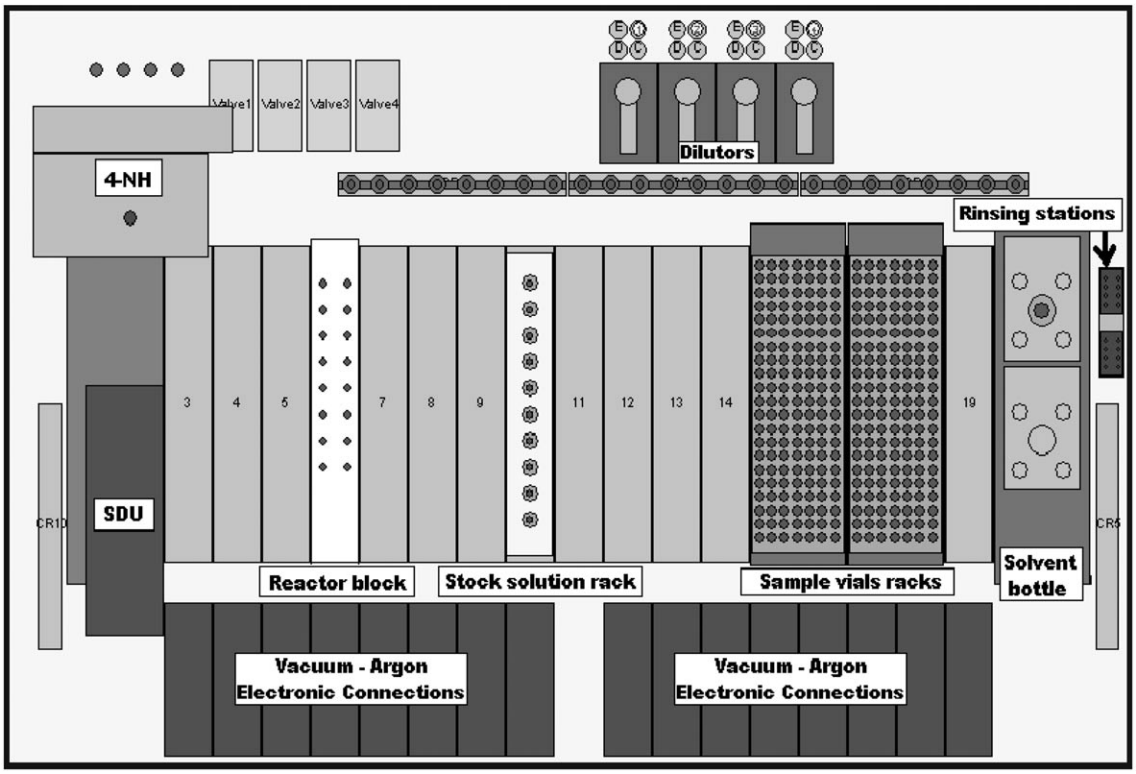
2 Materials and Methods

2.1 Chemicals

(i) Acrylic Acid (AA, Aldrich 99%), (ii) hydroxyethyl acrylate (HEA, Aldrich 96%), (iii) hydroxypropyl acrylate (HPA, Aldrich 95%, mixture of isomers), (iv) *n*-butyl acrylate (*n*-BA, Aldrich 99 + %), (v) octadecyl acrylate (ODA, Aldrich 97%), (vi) *N*,*N*-dimethyl acrylamide (DMAc, Aldrich 99%), (vii) *N*-isopropyl acrylamide (NIPAM, Aldrich 99%), and (viii) *p*-methyl styrene (*p*-MS, Aldrich 96%) were purified by passing over a basic alumina column. Azoisobutyronitrile (AIBN, Aldrich 98%) was recrystallized from methanol. Cumyl phenyldithioacetate (CTA-1) and *S*-dodecyl-*S*′-cyanomethyl trithiocarbonate (CTA-2) were synthesized according to the procedure described elsewhere [31, 32]. *N*,*N*-Dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) were purchased from Biosolve.

2.2 Instrumentation for Automated Synthesis and Characterization

The polymerizations reported in this protocol were performed in a Chemspeed Accelerator™ SLT106 automated synthesis platform. The schematic overview of the platform is illustrated in Scheme 1 and each unit will be explained in detail below. The platform is equipped with a glass reactor block which consists of 16 reaction vessels each with a volume of 13 mL. The reaction vessels are equipped with a heating jacket for sufficient heating. These heating jackets are connected to a Huber Unistat Tango (−5–145 °C). Besides, all reaction vessels are equipped with finger type reflux condensers to prevent evaporation during liquid transfers from the reactor block to the vials. Reflux condensers are connected to a Huber Ministat (−5–40 °C). Agitation was performed by vortex mixing at a rate of 600 rpm. The reactor platform is also equipped with a stock solution rack with ten flask attachment positions and connected to an argon line to keep the stock solutions under an inert atmosphere. It is also possible to use a Solid Dosing Unit (SDU) that has accuracy within 0.1 mg; however, it was not necessary to use that tool for the RAFT polymerizations that are discussed in this report. Furthermore, two sample vial racks with 147 positions in each of them were placed in the platform to store the polymerization samples that were used to study the polymerization kinetics. Liquid transfers were handled by using the 4-Needle Head (4-NH) which is capable of transferring four samples from four different reactor vessels to four sample vials simultaneously. The 4-NH is connected to a reservoir solvent bottle to rinse the needles after each liquid transfer step. The liquid transfer between the reservoir and the 4-NH is supplied by four dilutors, which are placed at the back of the platform (Scheme 1). Three separate Teflon rinsing stations are available in the different positions within the synthesizer hood. The connections which are necessary for the vacuum and argon flow are present in front of the platform. A solvent bottle with a volume of 500 mL is placed to a rack in the platform to fill the sample vials with GPC eluent. The number of reactor blocks, sample vial racks, solid bottles, stock solution racks can be altered according to the need in this flexible synthesis platform. A step-by-step program is prepared in the Application Editor module (Product version 1.8.2.18)



Scheme 1. Typical layout of the automated synthesis platform. SDU: Solid Dosing Unit, 4-NH: 4-Needle Head.

of the Chemspeed software and the completed program was run in the Application Executor module. Additionally, a webcam is mounted adjacent to the platform to monitor the experiments online with conventional web browsing software on any computer. It is also crucial that HTE should be followed by High-Throughput Characterization (HTC), which can be performed by online monitoring [33–35] or using autosamplers on offline characterization tools.

Monomer conversions were determined by Gas Chromatography (GC). An Interscience Trace GC instrument with a Trace Column RTX–5 connected to a PAL autosampler was used. For the injection of polymerization samples, a special Interscience injector liner with additional glass wool was used.

Gel Permeation Chromatography (GPC) was measured on two different Shimadzu systems with different configurations and eluents. One system (GPC1), which has chloroform/triethylamine/isopropanol (94:4:2) as eluent at a flow rate of 1 mL/min, is equipped with an SCL-10A system controller, an LC-10AD pump, an RID-10A refractive index detector, and a PLgel 5-mm mixed-D and the column oven set to 50 °C. Each measurement on GPC1 takes 15 min *per* sample which is a relatively short measuring time in comparison to other GPC systems. The other system (GPC2), which has DMA with 5 mmol LiCl mixture as eluent at a flow rate of 1 mL/min, is equipped with an SCL-10A system controller, an LC-10AD pump, an RID-10A refractive index detector, an SPD-10A UV detector, and both a PSS Gram30, and a PSS Gram1000 column in series and the column oven was set to 60 °C. The GPC measurement using GPC2 takes approximately 35 min for each injection. The necessity of using two different GPC systems is caused by the different solubility of the polymers in the eluents or interactions of the polymers with the column material, *i.e.*, poly(AA) is not soluble in chloroform and poly(NIPAM) interacts with the column material of GPC1.

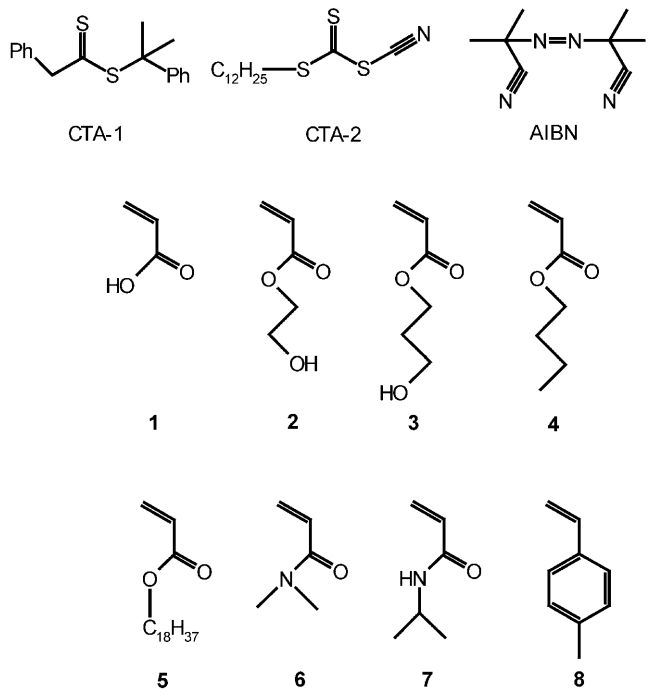
3 Results and Discussion

3.1 Typical Polymerization Protocol in the Automated Synthesizer Platform

Design of experiments is the first and most important step of the any HTE protocol and must be done carefully. In this study, experiments are designed to study the polymerization kinetics of eight different monomers using two different CTAs which will result in 16 experiments in one automated synthesis run. Eight different stock solutions of the monomers AA, NIPAM, HEA, HPA, DMAc, *n*-BA, ODA, and *p*-MS in appropriate solvents and also two stock solutions for two different CTAs and, in addition, a stock solution with an initiator (AIBN) in the solvent (preferably in the same solvent used for the monomer)

have to be prepared. The chemical structures of the used monomers, CTAs, and initiator are depicted in Scheme 2. The required amounts of the relevant stock solutions of monomer, initiator, CTA, and solvent were be prepared 10% in excess. This slight excess is required to ensure that only liquid is drawn into the needle during aspiration since the end of the needle is cut on an angle and may also aspirate gas from within the stock solution flask at low solution levels. The prepared stock solutions were be bubbled with argon to remove the oxygen, not less than 30 min, either in a fume hood or in the synthesizer platform by using needles connected to the argon line of the robot with specifically designed tubing.

A total reaction volume of 4 mL and a monomer concentration of 2M (with the exception of NIPAM due to limited solubility) were used for each of the reaction vessels when the 16×13 mL double jacket reactor block was utilized. The ratio [CTA]/[monomer]/[AIBN] can be varied to optimize the RAFT polymerization conditions. The experiment was programmed to transfer samples with a volume of 100 μL from each reactor vessel at predefined times to study the monomer conversion, molecular weight, and polydispersity indices in time. The transferred samples were also diluted with 1 mL of an appropriate solvent prior to the injection to GC or GPC instruments. In order to quench the polymerization reaction, the samples were cooled down by adding a ten-fold volume excess of GPC eluent into the sample vials. To ensure sufficient places for the sample vials, two sample vial racks each with 147 positions were placed in the platform. The layout of the utilized synthesis platform as described for sixteen parallel polymerizations using eight different monomers, and two CTAs is shown in Scheme 1.



Scheme 2. Schematic presentations of the chemical structures of the CTAs, monomers, and initiator.

Before starting the automated synthesis run, the reactor block has to be mounted in the robot system and a sufficiently large solvent reservoir has to be placed in the robot followed by flushing the tubing extensively. Subsequently, the stock solution vials were be placed in the stock solution rack, the labeled sample vials are positioned in the sample racks, the hood of the platform is closed, and the robot is flushed with argon for at least 60 min to create an inert atmosphere in the robot system. It should be mentioned that argon is preferred over the use of nitrogen based on the higher density of argon in combination with the loss of inert gas through the opening connections of the hood for, *e.g.*, the waste lines. During this flushing period, the program to run the robot can be prepared in the Application Editor software module of the Chemspeed system. Note that less experienced users might want to prepare the program in advance to make sure it is ready to use when the hardware is ready. In the Application Editor software, all available tasks (*i.e.*, transfer liquid, transfer solid, wait, heat or cool, reflux, vacuum, *etc.*) in the programming software are on the left side of the window and they can be added to the program by dragging and dropping to the right side (Figure S1 of Supporting Information). After adding a generic step to the program, the necessary settings have to be adjusted, *i.e.*, the amount of liquid or solid that is to be transferred, the period of waiting time, the required temperature for the heater, cooler, *etc.*

The first three steps of the program are the common ones which should be performed prior to any experiment in this platform. First, a liquid transfer from the valve ports to the waste which is necessary to fill and rinse all the tubing prior to any liquid transfers to remove air bubbles from the tubing to ensure accurate volume transfers. The following step is another wait step of 60 min to develop a positive pressure of argon to maintain an inert atmosphere in the hood. When the robot system is equipped with a glove-box hood, the positive pressure can be directly seen by the upward positioning of the gloves. The last step of the three is possibly the most important step in the program and is labeled as "inertization". This step is a macrotask and consists of numerous steps and even sub-macrotasks. Each step of the inertization macrotask is listed with short descriptions in Table 1. The macrotask starts with heating the reactor block and reflux condensers to 140 and 40 °C, respectively (steps 3 and 4). As soon as the set temperature is reached it continues with the next sub-macrotask which is applying vacuum to the reactor vessels for 2 min and flushing them with argon for 1 min and repeating this cycle for ten times while vortexing (steps 5.1 – 5.5). After the completion of this sub-macrotask the reactor block is cooled to 20 °C and the reflux condensers to 0 °C, respectively (steps 7 – 9). By finalizing this macrotask, an inert atmosphere is being provided in the hood and also in

Table 1. Steps of the inertization macrotask.

Step	Substep	Task	Description
1		Wait	Wait 1 min
2		Vortex	Agitation ON (600 rpm) on zone reactors
3		Heating/cooling	Thermostat ON (140 °C) on zone reactors
4		Reflux	Reflux temperature ON (40 °C) on zone reactors
5		Macrotask	Loop ten times
	5.1	Set drawer reaction block	Closed under vacuum on zone reactors
	5.2	Vacuum	Vacuum ON on zone reactors (10 mbar)
	5.3	Wait	Wait 2 min
	5.4	Set drawer reaction block	Closed under inert gas (Ar) on zone reactors
	5.5	Wait	Wait 1 min
6		Set drawer reaction block	Open under inert gas (Ar) on zone reactors
7		Heating/cooling	Thermostat ON (20 °C) on zone reactors
8		Reflux	Reflux temperature ON (0 °C) on zone reactors
9		Heating/cooling	Thermostat ON (20 °C) on zone reactors
10		Vortex	Agitation OFF on zone reactors
11		Vacuum	Vacuum OFF on zone reactors

Table 2. Step-by-step protocol for the RAFT polymerization in the automated platform.

Step	Task	Description
1	Liquid transfer	From reservoir to waste port
2	Wait	1 (filling hood with Argon)
3	Inertization	Macrotask
4	Liquid transfer	From reservoir to waste port
5	Liquid transfer	From AA stock to reactors
6	Liquid transfer	From NIPAM stock to reactors
7	Liquid transfer	From HPA stock to reactors
8	Liquid transfer	From DMA stock to reactors
9	Liquid transfer	From BuA stock to reactors
10	Liquid transfer	From HEA stock to reactors
11	Liquid transfer	From ODA stock to reactors
12	Liquid transfer	From MeSty stock to reactors
13	Liquid transfer	From CTA1 + AIBN stock to reactors
14	Liquid transfer	From CTA2 + AIBN stock to reactors
15	Liquid transfer	From solvent stock to reactors
16	Vortex	Agitation ON (600 rpm) on zone reactors
17	Wait	1 min (mixing the reactors)
18	Liquid transfer	From reactors to *t*-zero sample vials
19	Liquid transfer	From solvent bottle to *t*-zero sample vials
20	Reflux	Reflux temperature ON (0 °C) on zone reactors
21	Heating/cooling	Thermostat ON (70 °C) on zone reactors
22	Set timer	Set timer = 0
23	Wait	Wait 1 h after timer = 0
24	Liquid transfer	From reactors to *t*-1 h sample vials
25	Liquid transfer	From solvent bottle to *t*-1 h sample vials tion of steps 23 – 25 with different waiting times
39	Shut down	Macrotask, shut down thermostat, cryostat, and vortex

the reaction vessels. The following steps of the program with short descriptions are listed in Table 2 and explained in detail below.

Subsequent to cooling the reactor block and reflux condensers, the robotic arm picks up the 4-NH and starts transferring liquids from the stock solution vials to the reactor vessels with the predefined values while vortex mixing is continuously performed. Subsequent to the addition of all necessary stock solutions to the reactors (steps 5 – 15), there is a waiting step for 1 min to ensure the homogeneity of the reaction mixtures (step 17) before transferring the initial (t_0) samples of the polymerization to the GC vials (step 18). Following the first sampling step, the drawer valve position is set to "closed" under argon and heating the reactor blocks is started up at the set reaction temperature (in this case 70 °C) while maintaining the reflux con-

densers at 0 °C (steps 20 and 21). The next step after reaching the desired reaction temperature is called "set timer" which will be accepted as the beginning time of the reaction (step 22). The exact time for sampling will be calculated according to this initial timing step. The rest of the program consists of several waiting and sampling steps (steps 23–25, which are repeated five times with different waiting times) until the last step which is a shut down macrotask (step 39). Importantly, after each liquid transfer from the reactor vessels to the sample vials the 4-NH will rinse the inside and also outside of the four needles by transferring 2 mL of solvent from the reservoir to the waste. Besides, 1 mL of appropriate GPC eluent will be added to the sample vials in order to quench the polymerization by cooling down the polymerization mixtures. The final shut down procedure cools down the reactors and warms up the reflux condensers to room temperature and stops vortex mixing, vacuum pump, thermostat, and cryostat.

When the program writing phase is complete, it is advised to double check each step and value in order to minimize the human errors in the programming. It is also advisable to run a simulation in the Application Executor Software module (which is also the application that actually runs this program, see Figure S2 of Supporting Information). The actual program file is included as supplementary material for this report on the webpage of this journal.

After running the automated parallel polymerizations, the hood of the synthesis robot has to be air-extracted for at least 1 h to remove any volatile monomers and solvent. After this extraction period, the robot system can be opened and the sample vials as well as the final polymers from the parallel reactors can be collected for analysis.

3.2 Automated Characterization Techniques for Parallel Kinetic Experiments

Following the successful completion of 16 parallel polymerizations and transferring all samples for the kinetic studies, the monomer conversion in each sample vial is measured by using GC (or other analytical technique as necessary). The chromatograms thus obtained will yield the ratio between the monomer and reference solvent peaks (which is normally the reaction solvent – hence a different solvent to the reaction solvent must be used for diluting the GC samples). The conversion will be calculated by comparing these ratios with the initial ratio from the time zero sample of each reaction. Depending on the oven program of the GC, each measurement takes around 10–30 min (including cooling) by using a GC equipped with an auto sampler. The accuracy of the calculation of the monomer conversion is dependent on the peak shape of the monomer and solvent in the GC trace. For instance, AA monomer has a broad peak in GC and ODA shows no peak in GC. Therefore, the monomer conversions for AA and ODA may have to be determined by using NMR or GPC, respectively. All the other monomers that are used in this study result in narrow peak shapes with good separation providing accurate results. Semi-logarithmic kinetic plots can be drawn by using the data obtained from GC. The results of four monomers, namely *n*-BA, DMAc, HPA, and *p*-MS are shown in Figure 1 as a representative first order kinetic plot. The slopes of each set of data in the kinetic plot divided by the CTA concentration gives the apparent propagation rates of the monomers with units of L/mol·s. The apparent rate constants (k_p^{app}) calculated for *n*-BA, DMAc, HPA, and *p*-MS are 0.98×10^{-4}, 2.32×10^{-4}, 1.89×10^{-4}, and $0.17 \times 10^{-4}\ s^{-1}$, respectively. The kinetic results of other polymerizations described in this protocol will be discussed in detail and published elsewhere.

Besides the determination of the monomer conversion, the molecular weights, and polydispersity indices of the polymers represent very important data for such a kinetic study. Therefore, GPC can be used as a rapid and efficient characterization tool to obtain the molecular weight data of the polymers. Relatively short measurement times *per* sample can be achieved by using shorter or less serial chro-

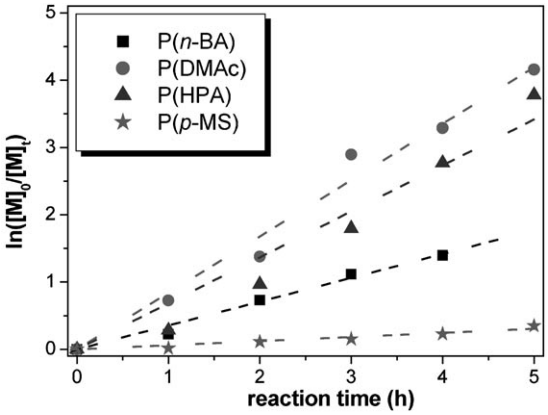


Figure 1. Semi-logarithmic first order kinetic plot of *n*-BA(■), DMAc(●), HPA(▲), and *p*-MS(★).

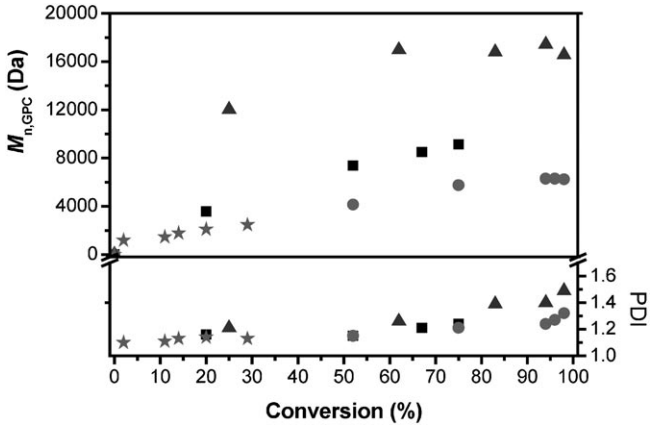


Figure 2. Molecular weight and polydispersity index *versus* monomer conversion plot of *n*-BA(■), DMAc(●), HPA(▲), and *p*-MS(★) obtained by measuring on GPC1 system.

matography columns. On the other hand, this may reduce the accuracy of the obtained results depending on the molecular weight range of the column. After the GC measurements, the same samples are placed into the autosampler of the GPC systems and are analyzed under the appropriate conditions. Number average molecular weight and polydispersity indices of the polymers *versus* monomer conversion plots can be drawn by using the data obtained from GC and GPC, as shown in Figure 2. It is also possible to compare the theoretical and obtained molecular weights of the polymers at certain monomer conversion. This typical plot provides crucial information about the control over the polymerization.

4 Conclusions

In this paper, we report a protocol for the kinetic investigation of RAFT polymerizations of various monomers that can be performed in an automated parallel synthesis platform. This standard procedure is practical in obtaining comparable kinetic data all over the world independent of the research group, technician, or student. We believe that HTE and characterization methods will be more efficient and eliminate errors and variability due to different experimentalists or laboratory conditions by employing reported standard protocols.

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