Sequence-Controlled Polymerization

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Polymer-Chain Encoding: Synthesis of Highly Complex Monomer Sequence Patterns by Using Automated Protocols**

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Automated procedures have lately attracted chemists working in a wide range of fields because of the opportunity to generate significant amounts of data within short timeframes. For instance, automated platforms used for combinatorial chemistry and high-throughput experiments are highly valuable for the parallel synthesis of bio-oligomers and for screening of new molecules for drug discovery or catalysis.[1] Recently, automated synthesizers have also gained interest among polymer chemists, thus leading to the design and construction of synthesis workstations adapted to perform polymerization reactions.[2] Various chain-growth and step-growth polymerizations have been explored using automated protocols to demonstrate the feasibility to translate traditional polymerization methods into automated syntheses.[3] In many cases, it has been evidenced that robotic approaches simplify and broaden the synthetic possibilities of these polymerizations.

Among modern techniques of polymerization, controlled radical polymerizations (CRP), such as nitroxide-mediated polymerization (NMP), atom-transfer radical polymerization, and reversible addition–fragmentation chain-transfer polymerization, have become increasingly important in academic and industrial research.[4] Indeed, these approaches provide polymers with well-controlled molecular weights and narrow molecular-weight distributions under mild experimental conditions. Moreover, polymers with controlled end functionality, composition, and tailored architectures, such as linear, grafted, cyclic, and hyperbranched polymers, are readily accessible using these techniques. On the other hand, CRP approaches still offer limited opportunities for controlling important molecular parameters, such as tacticity and monomer sequences. The control of these molecular parameters is highly challenging but has received growing interest in the polymer chemistry community in the search for methods to access the sequence precision that exists in natural macromolecules, such as proteins and DNA.[5] Thus, various sequence-controlled concepts have been proposed; these methods include iterative monomer addition, template chemistry, catalysis, and kinetic approaches.[6]

Our research group has previously introduced a CRP-based sequence-controlled strategy that permits the precise positioning of functional N-substituted maleimides (MIs) on styrene-based backbones.[7] The concept is based on the unique kinetic behavior of the copolymerization of donor/acceptor comonomer pairs when performed in nonequimolar quantities and under controlled/living conditions.[8] This approach is very versatile and allows the synthesis of either hydrophobic[7,9] or hydrophilic[10] polymers with controlled sequence patterns. However, our strategy remains experimentally demanding and requires numerous successive monomer additions and sample withdrawals. Thus, only a limited number of MIs can be added on the polymer chains when manual conditions are used. For instance, we have described that four different functional MIs can be incorporated on polystyrene chains using manual procedures.[7] Herein we demonstrate that this upper-limit can be remarkably improved by using automated polymerization protocols.

A Chemspeed SLT II automated platform (see the Supporting Information, Figure S1 for the configuration) was tested for the synthesis of sequence-controlled copolymers. A first series of model experiments involving the incorporation of two MIs only (see the Supporting Information, Figures S2 and S3) was studied to compare the copolymerization kinetics obtained in automated and manual conditions. It was indeed important to verify that the use of a robotic synthesizer, which uses different stirring, heating, and degassing methods than those available to a researcher working in a fume hood, does not lead to significant kinetic deviations, as compared to the use of manual chemistry methods. The model polymers were synthesized by NMP using the alkoxyamine BlocBuilder MA (2-{*N*-*tert*-butyl-*N*-[1-(diethoxy-phosphoryl)-2,2-dimethyl-propyl]-aminooxy}-2-methyl-propionic acid) at 120 °C in an anisole solution. In these experiments, *N*-(*n*-propyl)maleimide (PrMI) was added at the beginning of the polymerization (i.e. in the presence of a large excess of styrene) and *N*-benzylmaleimide (BzMI) at half styrene conversion. For the automated experiments, a program was designed for mimicking the tasks performed under standard conditions, by using the Autosuite software of the synthesizer. This method involved various steps including transfer of the reagents into the reactor, purging of the reactor by three vacuum/argon cycles, control of the temperature of

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the polymerization, timely precise additions of N-substituted maleimides diluted in anisole, and timely precise withdrawal of aliquots from the reaction mixture. The kinetic behaviors of the automated and manual polymerizations were similar (see the Supporting Information, Figures S2 and S3), thus validating the feasibility of polymerization by using an automated protocol and the accuracy of the program created. Additional model experiments, in which BzMI was incorporated at other chain locations (i.e. after 20% or 70% of styrene conversion) were also performed (data not shown) and these experiments confirmed that the robotic platform is viable for performing sequence-controlled copolymerizations.

The automated protocols were next investigated for the incorporation of larger numbers of MIs in polystyrene chains. In particular, the target of this study was to identify the maximum number of MIs that can be efficiently positioned on polystyrene backbones of different chain lengths (e.g. DP_n = 20, 50 and 100). To answer this question, a single model MI (i.e. BzMI) was added multiple times during the NMP of styrene (Figure 1). To minimize the probability of nonfunctionalized sites, two equivalents of BzMI relative to Bloc-Builder MA were employed per addition.[8] Moreover, in a perfectly-regulated sequence-controlled copolymerization process, each BzMI feed should be added after full conversion of the previous one (i.e. the feed consumptions should not overlap). A significant number of experiments were performed to reach this goal. For this purpose, the automated platform was necessary, as it allowed a rapid screening of

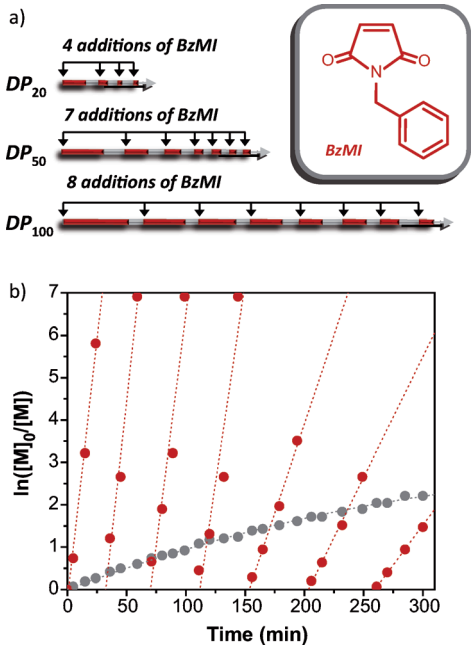

Figure 1. Automated sequence-controlled copolymerization of styrene (gray) with BzMI (red). In this approach, successive automated additions of BzMI were performed during the NMP of styrene (120 °C, anisole solution). a) The microstructures estimated experimentally for polymers of different chain length (the displayed DP_n values refer only to the number of styrene units in the chains). b) The semi-logarithmic plot of monomer conversion versus time for the DP_{50} experiment. The corresponding DP_{20} and DP_{100} data can be found in the Supporting Information. DP_n = degree of polymerization.

experimental conditions. Based on our past experience, we can conclude that it would be extremely time-consuming to perform such a screening manually. Here, optimal kinetic conditions were identified in a very short time. Figure 1, and Figures S4 and S5 (see the Supporting Information) show the semi-logarithmic plots of monomer conversion versus time obtained for these different experiments. It was found that 4, 7, and 8 discrete BzMI additions can be performed without significant overlapping on polystyrene chains of DP_n 20, 50, and 100, respectively. However, the semi-logarithmic plots of styrene conversion versus time are not linear but exhibit a slight curvature. This trend is probably a consequence of two distinct effects: 1) the slow oxidation of the reagents stored on the robotic platform, 2) the progressive dilution of the experiments owing to the repeated addition of small amounts of anisole at each MI feed. Nevertheless, the experiments reached high styrene conversions in all cases (i.e. about 85%). Moreover, plots of molecular weight versus conversion (see the Supporting Information, Figure S6) indicated that all experiments exhibited a controlled/living behavior. This aspect was also confirmed by the SEC and ^{1}H NMR analyses (see the Supporting Information, Figure S7) of the final purified polymers. In all cases, experimental molecular weights and copolymer compositions were in good agreement with theoretical values (see the Supporting Information, Table S1). In addition, narrow molecular weight distributions were measured for all copolymers.

The next step was the synthesis of complex monomer sequence patterns using different MIs at each addition. Four model maleimides were tested, namely, BzMI, PrMI, pentafluorophenyl 4-maleimidobenzoate (PFP-MI), and triisopropylsilyl-protected *N*-propargyl maleimide (TIPS-PMI). The latter two monomers were selected as they open up a range of possibilities for post-polymerization modification.[9c,11] Polystyrene chains with a targeted DP_n of 100 were considered in these syntheses. As demonstrated above, eight MI-containing zones can be potentially placed on chains of such length. In fact, when we take into account the achievable number of zones (i.e. 8) and the number of model MIs (i.e. 4) used here, 4^8 possible microstructures (i.e. 65536) can be created (assuming that the formed chains are asymmetric) on a DP_{100} polystyrene chain. Therefore, suggesting unprecedented possibilities of molecular encoding on synthetic polymer chains. It should be noted that the sequence-controlled polymers discussed here are chain-growth polymers exhibiting chain-to-chain deviations in terms of chain length and composition. Thus, the number of arrangements discussed in this paper does not reflect molecular arrangements (i.e. molecular positioning of each monomer unit in the chain) but microstructural arrangements (i.e. arrangement of functional MI zones on a polystyrene backbone). As a proof of principle, some of these possible microstructures were synthesized on the automated platform. For example, Figure 2a and Figure S8 (see the Supporting Information) show the preparation of microstructures containing alternating zones of BzMI/PFP-MI and BzMI/PrMI, respectively. The NMP conditions were the same as those described in the previous paragraphs.

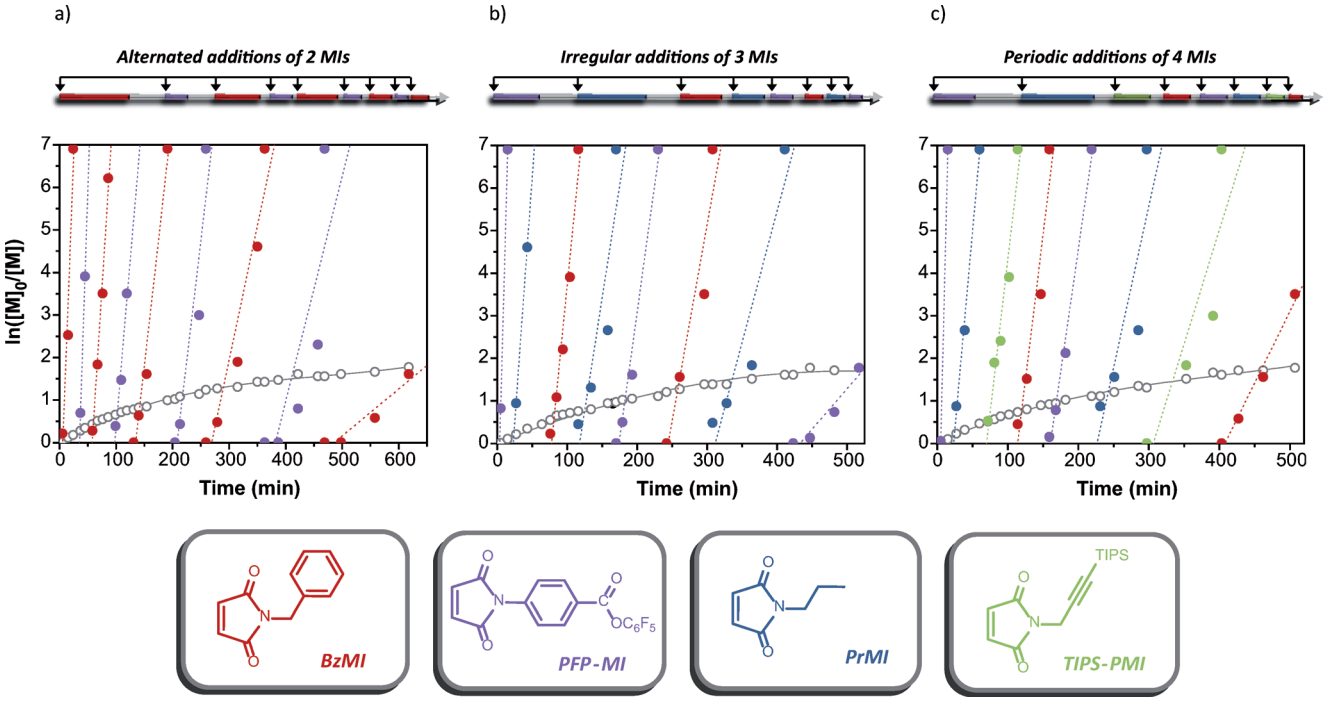

Figure 2. Automated preparation of complex monomer sequence patterns: a) microstructure containing alternated BzMI (red) and PFP-MI (purple) regions; b) microstructure containing scrambled BzMI (red), PrMI (blue), and PFP-MI (purple) regions; and c) microstructure containing periodic PFP-MI (purple), PrMI (blue), BzMI (red), and TIPS-PMI (green) regions. The graphs show the semi-logarithmic plot of monomer conversion versus time for each experiment. Experimental conditions in all cases: 120 °C, anisole, $[S]_0/[BlocBuilder]_0 = 100:1$. S = styrene.

It should be however noted that the solubility of PFP-MI in anisole is low and therefore that this MI requires a higher amount of solvent at each addition as compared to other MIs. Nevertheless, in both experiments, the kinetic monitoring of the reaction indicated that each N-substituted maleimide was well-incorporated in the polymer backbone with no noticeable superimposition of two consecutive feeds. Interestingly, owing to the fact that PFP-MI is more reactive than PrMI, it was possible to introduce one more MI feed (i.e. 9) on the polystyrene chain in the BzMI/PFP-MI experiment (Figure 2a) compared to the BzMI/PrMI one. Furthermore, SEC and ^{1}H NMR data indicated the formation of well-defined polymers with controlled chain-lengths, molecular weight distributions and compositions in both experiments (see the Supporting Information, Table S1).

More complex microstructures (i.e. irregular and periodic patterns) were prepared by using three or four different N-substituted maleimides (Figure 2b and c). Again, the semi-logarithmic plots of monomer conversion versus time indicate the local incorporation of each N-substituted maleimide feed without significant overlap. Moreover, in all cases the final polymers exhibited well-defined macromolecular structures (see the Supporting Information, Table S1 and Figure S9). The results indicate that, even when using a broader range of MIs, the automated platform remains viable for preparing well-controlled monomer sequence patterns.

In summary, as speculated in our initial work,[7] the sequence-controlled copolymerization of donor/acceptor comonomers can be considerably improved by using robotic tools. Indeed, automated procedures allow the straightforward preparation of well-defined polymer chains containing up to 8 (in some cases 9) precisely positioned functional MIs. Thus, complex chain encryption is attainable. These new results demonstrate further that the field of sequence-controlled polymers is rapidly progressing.

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