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A Facile Procedure for Controlling Monomer Sequence Distribution in Radical Chain Polymerizations

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Sequence-controlled polymerizations play a key role in nature. Although formed from a rather modest library of monomers, sequence-defined macromolecules such as proteins or nucleic acids are largely responsible for the complexity and diversity of the biological world. By analogy, one may predict that synthetic sequence-defined polymers could play an important role in modern applied materials science. However, paradoxically, very little effort has been spent within the last decades for developing sequence-specific polymerization methods. So far, step-by-step solid-phase synthesis is the only widespread synthetic process, allowing the preparation of sequence-defined macromolecules.[1] Other elegant bio-inspired methods such as genetic engineering or the polymerase chain reaction allow sequence control but are, by essence, only applicable for biopolymers.[2,3]

Chain copolymerizations (i.e., polymerizations consisting of initiation and propagation steps) such as ionic or radical copolymerizations are statistical processes leading generally to random microstructures.[4,5] However, in some particular cases (e.g., alternating comonomer pairs), sequences may be controlled to some degree.[6,7] Additionally, the discovery of living anionic polymerizations in the 1950s and more recently of controlled radical polymerization techniques allowed the preparation of unprecedented microstructures such as multiblock copolymers or gradient copolymers.[5,8−10] Nevertheless, the degree of sequence control in chain polymerizations remains rather low.

Herein, a novel pathway for preparing macromolecules with tailor-made microstructures was studied. This concept relies on the controlled sequential addition of various functional comonomers during the atom transfer radical polymerization (ATRP) of styrene (Scheme 1). The latter is a controlled radical polymerization in which all the polymer chains grow simultaneously.[5] However, the present concept may fail with most of the conventional radically polymerizable comonomers (e.g., (meth)acrylates, styrene derivatives, (meth)acrylamides), because they generally do not exhibit marked differences in copolymerization reactivity with styrene. Maleic anhydride and *N*-substituted maleimides are fascinating exceptions, which have a very low tendency for homopolymerization and an extremely favored cross-propagation with styrene. Hence, these monomers are consumed extremely fast in the presence of styrene, even when used in default in the comonomer feed (see Figure S2 in the Supporting Information).[11,12] Moreover, *N*-substituted maleimides may carry various functional groups (e.g., reactive, apolar, or protected polar substituents). Table S1 (Supporting Information) illustrates that ATRP is an efficient and versatile method for controlling the copolymerization of styrene with various functionalized maleimides.

To demonstrate the feasibility of the sequential concept depicted in Scheme 1, the bulk ATRP of styrene was studied at 110 °C in the presence of four *N*-substituted maleimide comonomers, which were added sequentially during the reaction: *N*-propyl maleimide (PMI, **2**), *N*-benzyl maleimide (BzMI, **3**), *N*-methyl maleimide (MMI, **1**) and *N*-[3,5-bis(trifluoromethyl) phenyl] maleimide (TFMPMI, **6**). 1-Bromoethyl benzene, copper(I) bromide, and 4,4′-dinonyl-2,2′-bipyridine were selected respectively as initiator, transition metal catalyst, and ligand, since the kinetics of styrene ATRP in the presence of this particular combination have been described in details in the literature.[13−15] The initial ratio styrene/initiator (i.e., the targeted degree of polymerization for complete conversion) was arbitrarily chosen to be 100. Ideally, the present sequential method is designed for adding discrete amounts of maleimide comonomers (i.e., 1 mol equiv as compared to initiator, which would lead to 1 unit in average per chain at each addition). However, in the present work, slightly larger amounts (i.e., 3 mol equiv) of the comonomers were used to ensure a reliable NMR monitoring of the copolymerization.

Scheme 1. Concept of the Sequential Atom Transfer Radical Copolymerization of Styrene and Various N-Substituted Maleimides

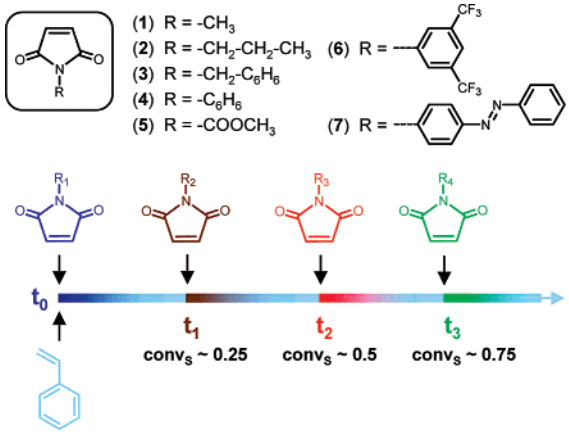

Figure 1 displays NMR spectra recorded at different stages of the reaction. The ATRP of styrene was first started in the presence of a small quantity of PMI. After 1 h of polymerization, ^{1}H NMR indicated that PMI was quantitatively incorporated in the growing polymer chains, whereas styrene was only partially consumed (Figures 1A and B). Thus, BzMI was successively added in the polymerization mixture (all the *N*-substituted maleimides are solids and were therefore dissolved in small amounts of toluene prior to each addition). Shortly after addition, a ^{1}H NMR signal of unpolymerized BzMI could be clearly seen at 4.67 ppm (Figure 1B). Yet, 1 h and 45 min later (2 h 45 min′ of reaction) this signal disappeared and was replaced by a broad signal at 4.6−4.1 ppm (Figure 1C). Moreover, the experimental molecular weight increased with conversion, which confirmed the living behavior of the reaction and therefore that the *N*-substituted maleimides are sequentially incorporated in the growing chains.[16,17] However, although the consumption of the *N*-substituted maleimides is kinetically favored,

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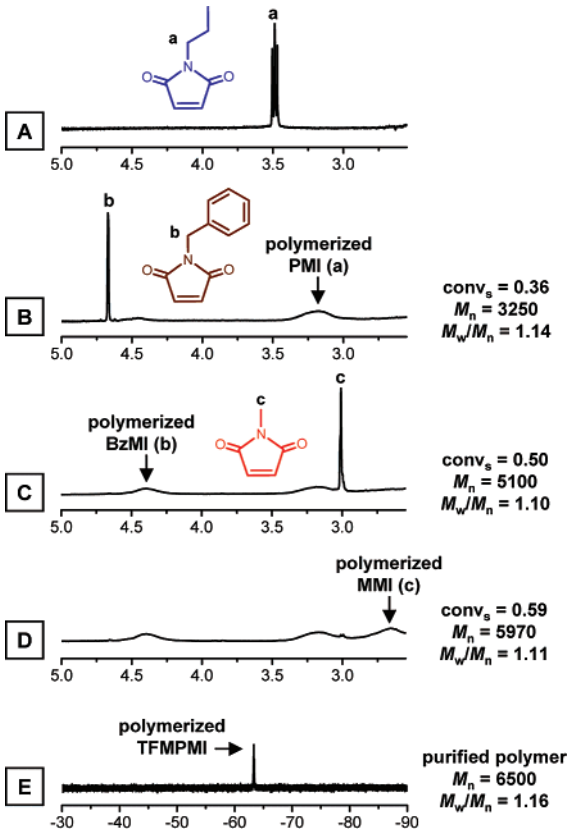

Figure 1. NMR spectra recorded in $CDCl_3$ at different stages of the sequential copolymerization: (A) ^{1}H spectrum (zoom of the region 2.55−5.0 ppm) of the initial reaction mixture, (B) ^{1}H spectrum recorded shortly after the addition of BzMI (t = 1 h), (C) ^{1}H spectrum recorded shortly after the addition of MMI (t = 2 h 45 min′), (D) ^{1}H spectrum recorded 15 min before the addition of TFMPMI (t = 5 h 45 min′), (E) ^{19}F spectrum recorded for the final purified copolymer (isolated after 21 h of polymerization).

their copolymerization with styrene is probably not strictly alternating in the present sequential process.[11] After each addition, because of the differences in concentrations between styrene and the added maleimides, the copolymerization remains to some degree statistical.[16,17]

After full polymerization of BzMI, MMI was added in the copolymerization medium. Immediately after addition, a sharp singlet, due to the methyl protons of MMI, could be observed by ^{1}H NMR at 3 ppm (Figure 1C). These particular protons disappeared with time, indicating a successful controlled radical copolymerization of MMI and styrene. After 5 h 45 min′ of reaction (i.e., 3 h after addition), ^{1}H NMR indicated complete incorporation of MMI in the copolymer chains (Figure 1D). Thus, the last comonomer TFMPMI was added, and the reaction was continued for several additional hours. After this last addition, the kinetics of polymerization became significantly slower. This behavior is due to the dilution of the experiment with the repeated toluene additions. Nevertheless, although slower, the polymerization progressed after the addition of TFMPMI.

After reaction, the copolymer was isolated by selective precipitation in methanol (all the comonomers were verified to be soluble in methanol). Size exclusion chromatography indicated that the final polymer is well-defined (M_n = 6500 g·mol^{-1}; M_w/M_n = 1.16). Furthermore, the purified sample was studied by ^{19}F NMR, which confirmed the presence of fluorinated monomer units in the copolymer (Figure 1E). As described previously in the literature, a peak corresponding to the fluoro atoms of the polymerized TFMPMI could be observed at −63.5 ppm.[18]

These experimental results indicate that PMI, BzMI, MMI, and TFMPMI could be sequentially incorporated in living copolymer chains. Indeed, the formed copolymer is not strictly sequence-defined at the molecular level. However, it possesses a pre-programmed distribution of functional side groups (i.e., propyl, benzyl, methyl, and 3,5-bis(trifluoromethyl)phenyl) along the polymer backbone. This first proof of concept suggests that the present sequential method is a promising route for preparing copolymers with tailor-made microstructures. The technique can be kinetically optimized for incorporating more than four different maleimides in each chain, eventually automatized, and moreover potentially applied to a wide range of *N*-substituted maleimides.

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Supporting Information Available: Full experimental part, model kinetic studies, and additional copolymerizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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