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Writing on Polymer Chains

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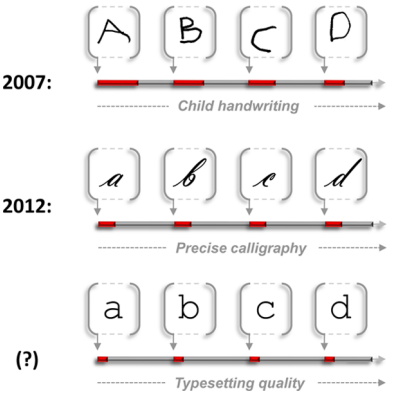
CONSPECTUS

Synthetic polymer materials are currently limited by their inability to store information in their chains, unlike some well-characterized biopolymers. Nucleic acids store and transmit genetic information, and amino acids encode the complex tridimensional structures and functions within proteins.



To confer similar properties on synthetic materials, researchers must develop "writing" mechanisms, facile chemical pathways that allow control over the primary structure of synthetic polymer chains. The most obvious way to control the primary structure is to connect monomer units one-by-one in a given order using iterative chemistry. Although such synthesis strategies are commonly used to produce peptides and nucleic acids, they produce limited yields and are much slower than natural polymerization mechanisms. An alternative strategy would be to use multiblock copolymers with blocks that have specified sequences. In this case, however, the basic storage element is not a single molecular unit, but a longer block composed of several repeating units. However, the synthesis of multiblock copolymers is long and tedious. Therefore, researchers will need to develop other strategies for writing information onto polymer chains.

In this Account, I describe our recent progress in the development of sequence controlled polymerization methods. Although our research focuses on different strategies, we have emphasized sequence-regulation in chain-growth polymerization processes. Chain-growth polymerizations, particularly radical polymerization, are very convenient methods for synthesizing polymers. However, in most cases, such approaches do not lead to controlled monomer sequences. During the last five years, we have shown that controlled/living chain-growth polymerization mechanisms offer interesting advantages for sequence regulation. In such mechanisms, the chains form gradually over time, and therefore the primary structure can be tuned by using time-controlled monomer additions. For example, the addition of small amounts of acceptor comonomers, such as N-substituted maleimides, during the controlled radical polymerization of a large excess of donor monomer, such as styrene, allows the writing of information onto polymer chains in a robust manner. Even with these advances, this strategy is not perfect and presents some of the drawbacks of chain-growth polymerizations, such as the formation of chain-to-chain sequence defects. On the other hand, this approach is experimentally easy, rapid, scalable, and very versatile.

Introduction

One of the most fascinating properties of biological polymers is their capacity to store information at the molecular level. Nucleic acids, in particular DNA, utilize for example a simple set of 4-monomers to encode the replication, development and functions of biological organisms. Nature however does not utilize, properly speaking, a writing mechanism to encode nucleic acids chains in the sense that all modifications occur through complex mutation and evolution processes.[1] In biological polymerizations, such as replication, translation, and transcription, the molecular information contained in DNA chains is just copied from an existing model. However, recent progress in biochemistry has provided synthetic routes to literally "write" intentional messages on nucleic acid chains. For instance, solid-phase phosphoramidite-protocols allow synthesis of sequence-defined oligonucleotides,[2] which can be ligated, copied, amplified, and used in materials science or in a biological context. The most spectacular application of synthetically encoded nucleic acids was perhaps the fabrication of an artificial bacterium genome reported three years ago by Venter and co-workers.[3] More recently, Church and

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co-workers have revolutionized the field of data-storage by describing that a full biology text-book could be written, stored, and read on nucleic acids chains.[4] Although having very different scientific implications, these two examples show the importance of encoded polymer chains in future technologies.

Yet, an important question arises at this stage: does classical polymer chemistry have a role to play in this emerging technological context? In other words, are these new opportunities only constrained to existing sequence-defined biopolymers? Challenges in biology, such as the design of artificial Life as described by Venter, are indeed (so far) strictly restricted to biological polymers. On the other hand, materials science applications such as molecular data storage are certainly not limited to DNA and would most probably benefit from more chemical diversity. In this context, the search for synthetic sequence-controlled polymerization methods is a valid scientific goal. However, such an objective implies a major research effort in fundamental polymer science.[5] Besides semibiological approaches, such as PCR or protein engineering, there is at present no known polymerization process that allows preparation of synthetic macromolecules comparable with natural nucleic acids or proteins. Classical large-scale polymerization methods such as chain-growth and step growth polymerizations lead in general to ill-defined primary structures, whereas sequence-defined approaches, such as solid-phase chemistry and enzyme-free template replication, are experimentally demanding and limited in scale and molecular weight.[6,7]

In fact, in terms of synthetic polymer chemistry, some important fundamental aspects need to be solved over the coming years: (i) writing information on synthetic polymer chains, (ii) correlating monomer sequences with structure and functions, (iii) reading messages written on polymer chains, and (iv) erasing/rewriting polymer microstructures. For approximately five years, the first issue has been investigated by several research groups and promising routes have been described.[8−17] It is, however, important to give an accurate description of the field at this stage of the discussion. Reported methods are generally limited to either simple sequence patterns (e.g., alternating or periodic microstructures) or to small oligomer syntheses. Nevertheless, noticeable progress has been made within a very short period of time. For instance, our group has reported an original method to "write" information on synthetic polymer chains.[8,18,19] This strategy relies on the time-controlled addition of small amounts of functional acceptor monomers (e.g., N-substituted maleimides) during the living polymerization of a large excess of a donor monomer (e.g., styrenic derivatives). As a result, a wide variety of tailored polymer microstructures can be synthesized. Although, this method does not allow a perfect sequence-regulation, it opens up new avenues for the design of encoded polymer chains. This Account summarizes our recent achievements using this approach.

The Concept for Chain Encryption

The concept for monomer sequence-control that we introduced in 2007 is based on the "living" copolymerization of donor and acceptor comonomers.[8] A comprehensive analysis of the field of donor/acceptor copolymerization was reported in a previous feature article and will therefore not be described in details in this Account.[19] In brief, our concept requires two different types of unsaturated monomers, a donor and an acceptor comonomer. Because of the opposite polarity of their double bonds, these monomers exhibit usually a stronger tendency to copolymerize than to homopolymerize. Typical examples of donor monomers include isobutylene, vinyl ethers, stilbene, styrene, and many styrenic derivatives. Frequently used acceptor comonomers are, for example, maleic anhydride, MIs, and pentafluoro styrene. The radical or cationic copolymerization of a donor/acceptor comonomer pair leads in general to regular alternating microstructures. However, the obtained microstructure depends on the initial donor/acceptor comonomer feed and on the monomer conversion at which the copolymer was isolated. For instance, when a large excess of donor monomer is used in the initial feed, copolymerization is usually taking place at the beginning of the reaction (i.e., until full consumption of the acceptor comonomer) followed by the homopolymerization of the excess of donor. Such a two-stage behavior is particularly interesting in the case of a living polymerizations mechanism, for example, in CRP processes such as ATRP, NMP, or RAFT.[20,21] In such polymerizations, all chains are initiated and grown simultaneously and therefore variations in comonomer consumption are "encrypted" in the microstructure of the formed polymer. Thus, nonstoichiometric donor/acceptor living copolymerizations containing an excess of donor lead generally to the formation of block copolymers containing a donor/acceptor copolymer segment connected and a donor homopolymer segment.[22−24] The main originality of our approach was to exploit this interesting behavior in extreme conditions (Figure 1), in particular in the presence of very small amounts of acceptor comonomers (e.g., 1 molar equiv per chain). In such conditions, the zones encrypted in the polymer chains cannot be described anymore as blocks but as short functional patches

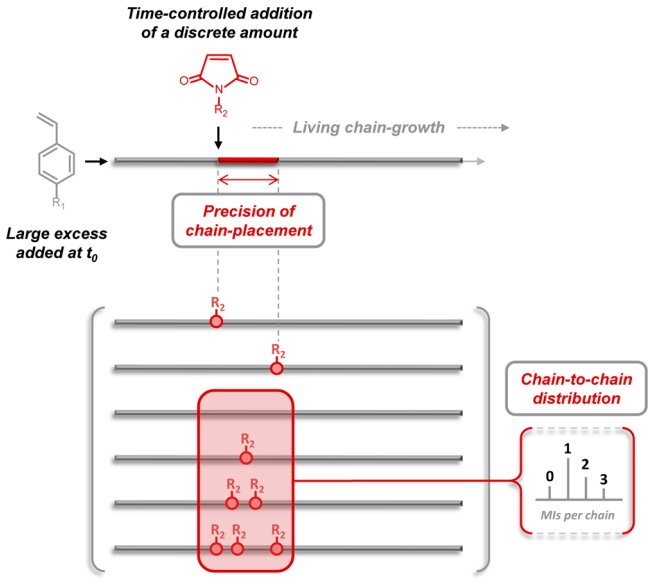

FIGURE 1. Main concept: local chain-installation of a discrete amount of an acceptor monomer during the living polymerization of a large excess of a donor monomer. The bottom part of the figure shows a simplified representation of the chain-to-chain distribution of the acceptor comonomer in the final sample.

positioned in a donor homopolymer chain. This concept was first demonstrated by ATRP using styrene as the donor monomer and various MIs as acceptor comonomers.[8] It was shown that, although tiny amounts of acceptor comonomer are used, donor/acceptor copolymerization remains kinetically favored as compared to donor homopolymerization. Consequently, the MI is rapidly consumed and included in short regions of the copolymer chain. For instance, if the copolymerization is started in the presence of both donor and acceptor comonomers, the MI is fully integrated at the beginning of the chain.[18] Interestingly, when the polymerization is started in the presence of the sole donor monomer and the MI is added later in the process as described in Figure 1, the MI-containing zone is formed inside the chain. Such a time-controlled addition is actually one of the main strengths of our approach because it allows placement of the MI at different chain-locations.[18] The chain-positioning can be extremely precise as described in the third section of this Account. However, it should be clearly explained that the MI placement is not uniform in all chains. The zones created in such a copolymerization process are still, to some degree, statistical. In fact, as depicted in Figure 1, two different types of chain-to-chain variations occur. First, differences in chain placement exist. The localization of a MI in a chain is estimated by comparing the kinetics of consumption of the donor and acceptor comonomers during a given time interval (i.e., the amount of time needed for reaching complete conversion of the acceptor comonomer). Generally, while a single molar equivalent of MI is polymerized, a comparatively higher amount of styrene is consumed. Thus, during the time interval required for full MI consumption, a short PS "patch" is formed, and it is therefore not possible to assess precisely the location of the MI is in this region. In fact, the placement slightly varies from chain to chain as depicted in Figure 1. The MI can be located at the beginning of the patch, at the end, or anywhere between these two extremes. In general, we use a short colored bar to symbolize this region of uncertainty.[8] This way to represent the formed copolymers can be easily misinterpreted and therefore our systems have been sometimes described in the literature as multiblock or gradient copolymers. These are erroneous descriptions. Strictly speaking, the regions formed using our strategy cannot be blocks or gradients because they usually only contain one single MI unit. Still, they can be somehow described as blocks with a degree of polymerization of 1 (DP_1). The second type of deviations that exists in our systems is the chain-to-chain variation in composition. When 1 molar equiv of MI is used as compared to initiator, the formed chains contain in average 1 MI. However, a chain-to-chain distribution of composition exists (i.e., some chains contain no MI, whereas other contains 1, 2, or more MIs as shown in Figure 1). Nevertheless, recent MALDI-TOF MS[18,19] and LACCC[25] studies indicate that this distribution is usually rather narrow.

Donor Comonomers: Main Constitutive Units of the Chains

In the concept described above, two types of monomers are mandatory, that is, a donor and an acceptor comonomer. The donor comonomer is used in large excess and is therefore the main constitutive unit of the polymer backbone, whereas the acceptor comonomer is used for local encryption (see the following section). The molecular structure of this main building-block is important since it determines the properties (e.g., chain rigidity, solubility, and reactivity) of the formed backbones. In our early studies, styrene was always used as a donor comonomer.[8,18] This monomer is indeed a convenient model because its reactivity in radical polymerization has been extensively studied and therefore many kinetic parameters (i.e., rate constants, reactivity ratios) have been reported. In addition, optimized CRP conditions have been identified for styrene homopolymerizations and copolymerizations.[26,27] This aspect is actually crucial. Indeed, the concept described in Figure 1 is only valid if the homopolymerization of the donor monomer is perfectly

controlled (i.e., all living polymerization criteria should be verified). Still, styrene is not the only donor monomer, which can be used in our concept. For instance, para-substituted styrene derivatives can also be utilized (Figure 2). The chemical nature of the para-substituent may lead to interesting backbone properties such as water-solubility, side-chain crystallinity or reactivity. However, not all types of substituents lead to sequence-controlled copolymerization with MIs. Another mandatory criterion in our approach is that the donor/acceptor copolymerization is kinetically highly favored as compared to homopolymerization. Roughly speaking, the concept works well for donor/acceptor comonomer pairs with reactivity ratios below 0.05. Above this value, copolymerization starts to be too slow as compared to homopolymerization and therefore MIs are imprecisely incorporated in the chains. For example, although interesting for postpolymerization modifications strategies,[28] monomers, such as vinyl benzyl chloride (**g**) or PFP-activated vinyl benzoic acid (**h**), are not suitable for our concept.[29] These results are most probably due to the electron-withdrawing nature of the para-subsitutents, which decrease the electron donor properties of **g** and **h**. Yet, the factors preventing the utilization of a donor monomer in our concept are not always related to copolymerization kinetics. For instance, phthalimide-protected 4-vinyl benzyl amine (**i**) is an interesting monomer for preparing amine-containing polymers. However, the preparation of such polymers requires a deprotection step, which is not compatible with our approach.[29] Indeed, the basic conditions required for phthalimide deprotection are also leading to the hydrolysis of chain-incorporated N-substituted succinimide units. The *tert*-butyl ester of vinyl benzoic acid (**f**) is an example of para-substituted monomer that can be used in our approach.[30] This monomer can be copolymerized with MIs and afterward deprotected to afford sequence-controlled polyelectrolytes. In this strategy, the *tert*-butyl esters are cleaved in acidic conditions that do not affect succinimide units. However, because of the electron-withdrawing character of the *tert*-butyl ester substituent, the reactivity ratios measured for **f** in the presence of various MIs were found to be slightly too high for a perfect sequence regulation. Sequence-controlled water-soluble polymers with more precise microstructures can be synthesized using donor monomers, such as 4-acetoxystyrene (**b**) or 4-*tert*-butoxystyrene (**c**).[31] Indeed, both monomers have donor substituents in para-aromatic position and lead therefore to extremely favored copolymerization behaviors with MIs. After copolymerization, the ether functions can be selectively cleaved in acidic conditions to afford hydrophilic polymers. Very precise

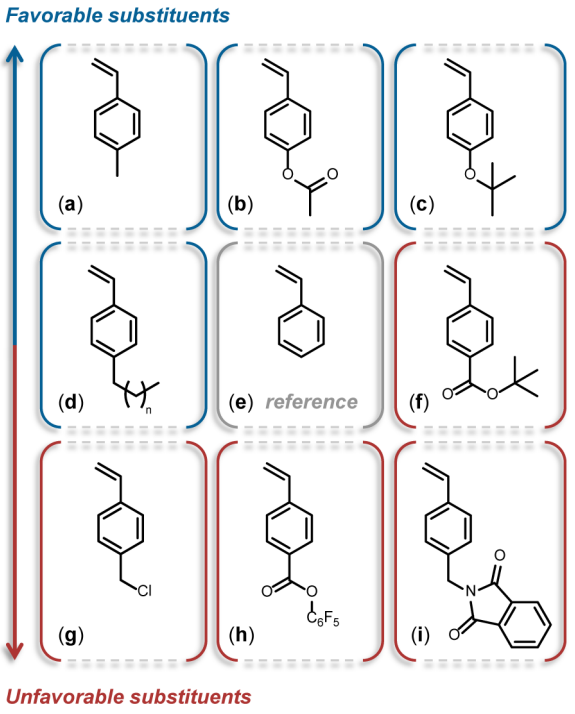

FIGURE 2. Styrenic derivatives studied in our laboratory as donor comonomers in sequence-controlled copolymerizations. The monomers highlighted in blue exhibit donor substituents in para-aromatic position and are therefore highly suitable for sequence-controlled synthesis. The monomers highlighted in red are more problematic.

copolymerization trends with MIs were also observed for donor monomers, such as 4-methylstyrene (**a**) or styrene derivatives with longer alkyl para-substituents (**d**).[29,31]

Acceptor Comonomers: The Alphabet for Molecular Encryption

As shown in Figure 1, MIs are the molecular units used for chain encryption in our approach. MIs are not the only type of acceptor comonomers that can be used in our concept, but they present the great advantage of being easily functionalized at their N-site. Indeed, the synthesis of these monomers is, in general, relatively easy.[18] Moreover, a large number of functional MIs are commercially available since this class of compounds is also widely used for protein modification via Michael addition. It is therefore possible to create a full "alphabet" of MIs. Figure 3 shows the molecular structure of some MIs that have been tested in our laboratory in donor/acceptor sequence-controlled polymerizations. Not all these monomers are suitable for our technique. First, it is necessary to check, for each MI, whether the reactivity ratios are sufficiently low for an accurate sequence-control. In general, the chemical nature of a N-substituent does not influence considerably MI double

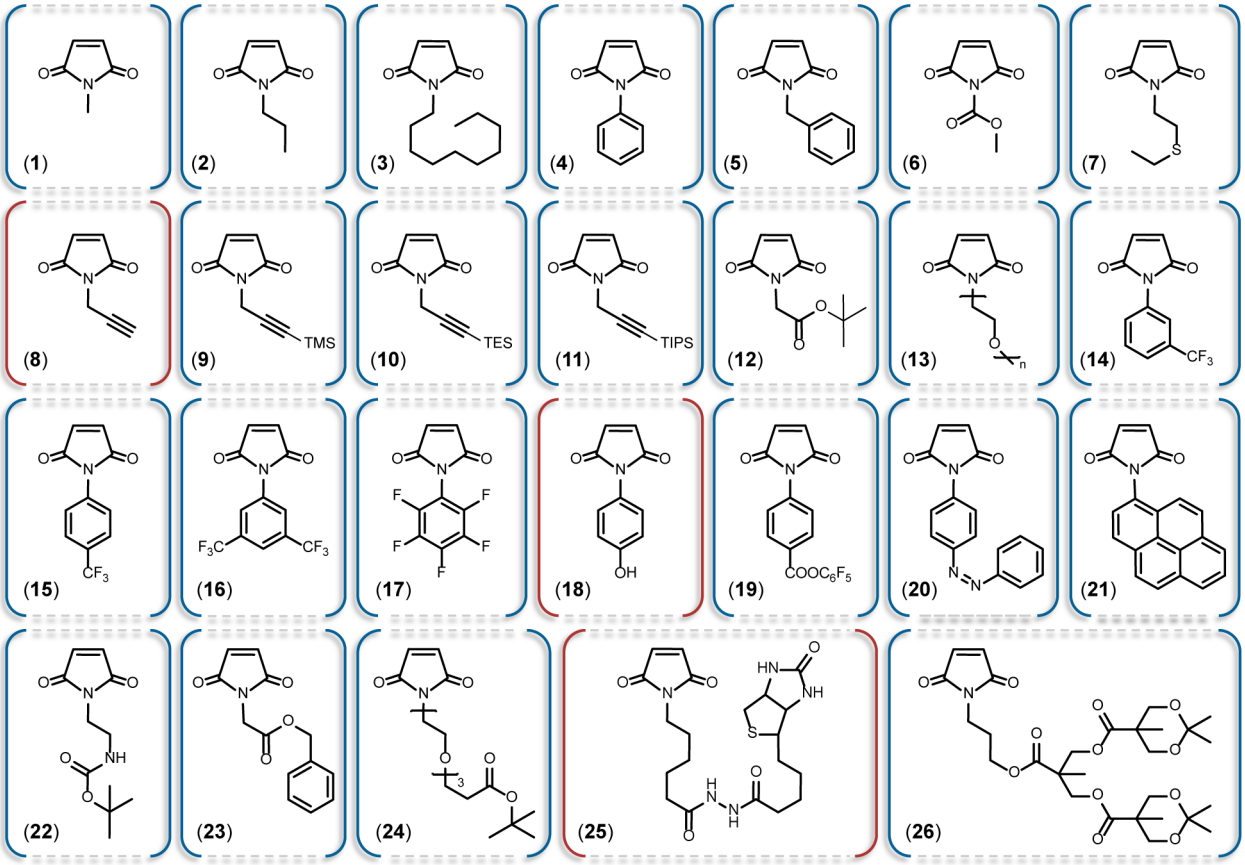

FIGURE 3. N-Substituted maleimides studied in our laboratory as acceptors comonomers in sequence-controlled copolymerizations. The monomers highlighted in red are problematic structures.

bond reactivity. For instance, the electronic nature (i.e., electron donating/withdrawing character) of a N-substituent in a MI is less critical in our approach than the one of a para-substituent in a donor monomer (see discussion in the previous section). Nevertheless, different MIs exhibit different reactivities. For example, monomers with strong electron-withdrawing substituents, such as PFP 4-maleimidobenzoate (**19**), work very well in our concept and can be positioned extremely precisely in polystyrene chains.[32] In comparison, MIs with alkyl chain substituents (e.g., **2**) are usually incorporated in broader regions.[33] However, despite these small differences, most MIs have suitable reactivities for being used in our concept. Yet, the chemical reactivity of the N-substituent is another limitation. Indeed, some substituents may disturb the polymerization reaction. For instance, phenols (**18**) inhibit radical polymerization.[18] Similarly, terminal alkynes (**8**) interfere with polymerization radicals and shall be protected in our technique (**9**, **10**, **11**).[18,34,35] Some substituents may also interact with polymerization catalysts. For instance, carboxylic acids and primary amines (**12**, **22**, **23**, **24**) shall be protected in sequence-controlled ATRP.[18] It was also observed than pyrene maleimide (**21**) is problematic in ATRP reactions employing dNBipy as a ligand.[36] Although not yet fully explained, this behavior might be due to pyrene/ligand $\pi-\pi$ stacking.

Another important aspect is the solubility of MIs in the polymerization medium. Indeed, our concept requires that MIs are homogenously solubilized in the reaction medium (i.e., bulk donor monomer) at the temperature at which the copolymerization is conducted (i.e., typically above 90 °C). Some MIs are not well-soluble in styrene or other donor monomers at room temperature but can be dissolved at higher temperature and therefore used in our approach. This aspect is unproblematic when MIs are added at the beginning of the reaction but more critical when time-controlled additions are performed as shown in Figure 1. In such cases, a solution of MI in a minimal amount of solvent is added via a syringe. For some particular MIs (e.g., **19**), hot solutions or solvent dispersions are also sometimes used. Another important point is that, after each syringe addition, the MIs should be rapidly dispersed in the reaction medium to avoid local copolymerization effect. This aspect is in fact not really

critical when CRP conditions are used. Indeed, in styrene CRP, the polymer chains are predominantly in a dormant state and are therefore not consuming MIs directly after addition. The chain incorporation of a single molar equivalent of MI requires, in general, more than 20 min to be completed. Thus, under vigorous stirring conditions, the influence of diffusion can be neglected.

In some rare cases, MIs are not soluble in the polymerization medium even at high temperature. For example, biotin-functionalized MIs (**25**) cannot be dissolved in styrene.[18] In such cases, the copolymerization can be performed using a cosolvent. However, the kinetics of copolymerization are slower in solution than in the bulk. To bypass such limitations, problematic functions can be attached to positioned MI sites using postpolymerization modification strategies.[28] For instance, we have recently reported the biotin functionalization of a PFP-modified sequence controlled polymer (i.e., using **19** during the copolymerization).[32] Such a strategy is of course not restricted to biotin. Indeed, a wide variety of functional groups can be reacted with PFP activated esters.[28] In addition to **19**, other types of reactive MIs can also be used in postpolymerization modification strategies. For instance, MIs containing protected alkyne functions (**9**, **10**, **11**) can be modified after polymerization by copper-catalyzed azide−alkyne cycloaddition, Glaser coupling, or Sonogashira coupling.[34,35,37,38]

Precision and Density of Molecular Information

The concept for MI positioning shown in Figure 1 is, of course, not limited to one addition. Successive time-controlled additions can be performed in order to install several MI zones in the chains. In our first publication, it was demonstrated that four functional MIs can be added sequentially during the bulk ATRP of styrene. It should be noted that, when multiple additions are performed, it is recommended to use more than 1 molar equiv of MI per addition (e.g., 2−3 molar equiv as compared to initiator). Because of chain-to-chain discrepancies in composition, the repeated utilization of a single equivalent of MI leads to a high level of chain defects.[19] It should be also specified that copolymerizations employing successive time-controlled additions are experimentally demanding and require a detailed kinetic monitoring. For instance, when such experiments are conducted manually, it is challenging to install more than 4 MIs zones in a chain. This situation can be improved by using synthetic robotic platforms that allows rapid screening and optimization of experimental conditions. For instance, we have recently reported that a large density of information can be incorporated in polystyrene chains using automated protocols.[33] Using *N*-benzyl maleimide (**5**) as a model MI, we have explored the boundaries of our concept (Figure 4b). It was shown that 4, 7, and 8 nonoverlapping MI zones can be positioned in polystyrene chains with an average chain length of 20, 50, and 100, respectively. These results open interesting avenues in terms of information storage. Indeed, more than 65000 microstructural arrangements can be potentially created on a chain of *DP*100 using a 4-letter alphabet of MIs (Figure 4c). This number rises up to 100 million if 10 different MIs would be used. This is undoubtedly the highest level of chain-encoding reported to date for chain-growth polymers.

It should be however clearly reminded that our concept is not leading to perfectly controlled monomer sequences. Thus, in our polymers, a "bit" of information is not a single monomer unit like in proteins or nucleic acids but a larger functional zone containing 2 or 3 MIs in average. However, as depicted in Figures 4b and 4c, the precision of MI incorporation increase with styrene conversion. MIs added at the end of the polymerization (i.e., at high styrene conversion) are much more precisely installed in the chains than MIs added at the beginning. A simple explanation of this behavior was reported in a recent communication.[38] In fact, the precision of incorporation depends on the donor/acceptor comonomer ratio present in the reaction medium at the time the MI is added. If this ratio is high, donor−donor propagation competes with donor−acceptor cross-propagation, thus leading to broad uncertainty regions. On the other hand, when this ratio is low a very precise incorporation is observed. In fact, at high styrene conversions (e.g., above 70%), an almost perfect MI monoinsertion is observed (i.e., only 1 or 2 styrene units are incorporated in the chains during the interval of time needed for full MI consumption). We have shown that this interesting situation can be restored at different moments of a polymerization if the donor monomer is used in starved conditions (Figure 4a).[38] In this "ultraprecise" strategy, a partial amount of the donor monomer is added at the beginning of the reaction (feed 1 in Figure 4a) instead of the full amount that is usually introduced in the conventional procedure. When this partial amount reaches high conversion, a MI is added in the copolymerization medium (feed 2 in Figure 4a). In these conditions, the donor/acceptor comonomer ratio is low and therefore the MI is precisely incorporated in the chains. Afterward, a new batch of donor monomer is added in the copolymerization medium (feed 3 in Figure 4a). This should

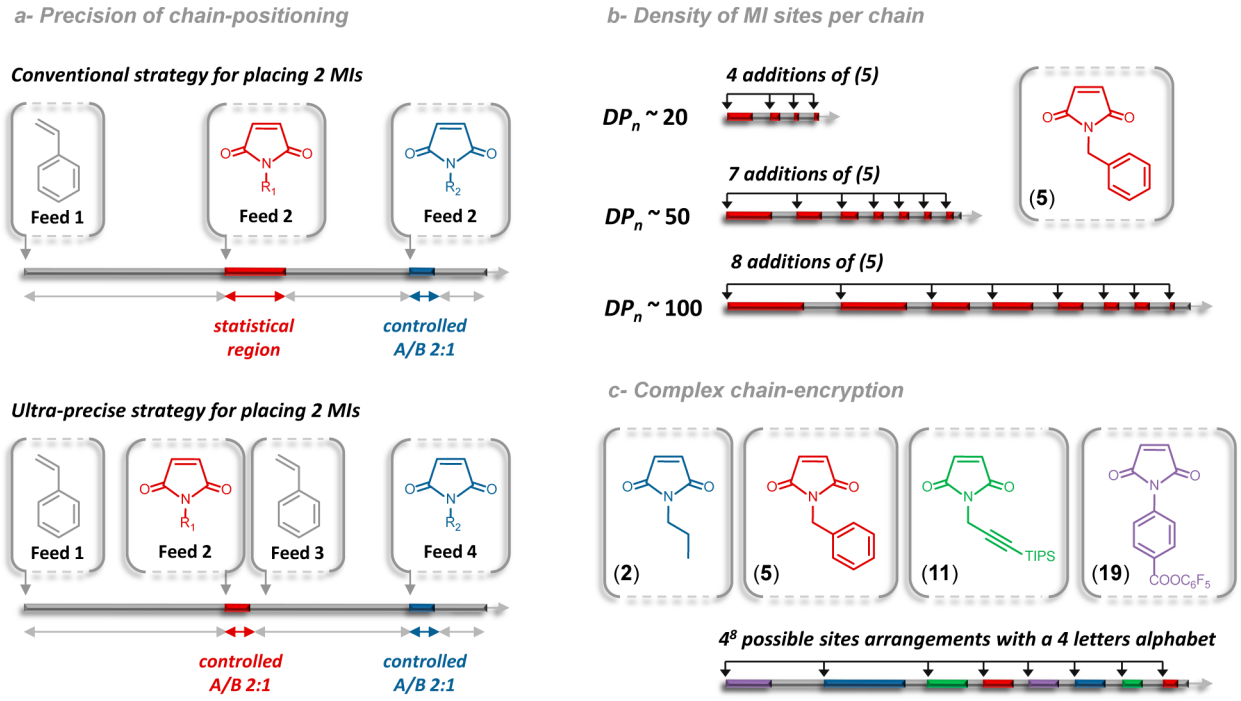

FIGURE 4. Possibilities of microstructural control: (a) chain-positioning of functional N-substituted maleimides using a conventional strategy and an ultraprecise strategy, (b) maximum incorporation of discrete N-substituted maleimides zones in polystyrene chains of different chain-length, and (c) microstructural encoding using a set of 4 different N-substituted maleimides.

be rapidly done before the experiment loses its living character. Indeed, if the polymerization reaches too high donor monomer conversions, side reactions such as elimination or termination become kinetically dominant. However, if the addition of the second donor monomer feed is done in optimal conditions, the polymerization restarts. When this new batch reaches high conversion in its turn, a second MI can be then installed in the chains (feed 4 in Figure 4a). This simple strategy can be repeated 2 or 3 times and leads in all cases to ultraprecise MI insertions. However, it was found that the concept works better with advanced CRP methods such as ARGET-ATRP or SET-LRP, which minimize side reactions and prevent the loss of active centers.

Relevance in Single-Chain Technologies

The sequence-controlled polymers described in the previous sections of this Account are not only interesting in terms of polymer synthesis but also open up interesting opportunities in the field of materials science. Indeed, the possibility to write local functional patches on synthetic polymer chains is an important step-forward. However, it is important at this stage to discuss the molecular structures of our polymers. These macromolecules possess an atactic flexible backbone and are, in most cases, amorphous. Thus, it is not possible to form secondary structures using the same principles as those that govern protein folding (i.e., Anfinsen's dogma that links primary, secondary, and tertiary structures). However, other principles may be applicable. For instance, it was recently proposed that a certain degree of order (i.e., pseudocrystalline state) can be attained with atactic polymers in confined conditions.[39] Non-natural secondary structures can also be created in atactic polymers using synthetic supramolecular motifs. For instance, Meijer, Palmans, and co-workers have recently shown that side-chain supramolecular moieties induce order in atactic polymer chains.[40] Moreover, controlled covalent interactions can be used to organize atactic chains. Our group has reported that the donor/acceptor sequence-controlled copolymerization approach can be used to create precisely positioned covalent bridges.[34,41] In a first study, alkyne-containing MIs, such as **9** or **11**, were positioned in polystyrene chains and were involved, after deprotection, in intramolecular reactions in dilute conditions.[34] Different macromolecular topologies, such as α-, P-, Q-, or 8-shapes, were prepared using either azide–alkyne cycloaddition with azide chain-ends or alkyne–alkyne Glaser coupling. In a following work, more complex bridges were synthesized using two distinct reactive sites as shown in Figure 5.[41] In this approach, the reactive MIs **11** and **19** were positioned at different locations in the chains and were afterward reacted with a short heterofunctional

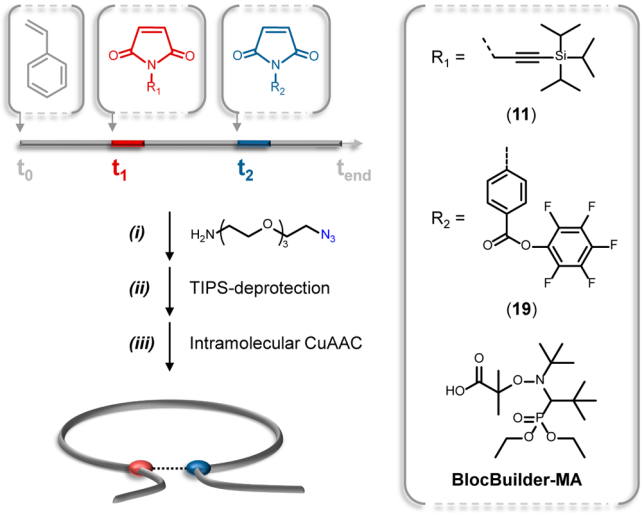

FIGURE 5. General strategy studied for folding polystyrene chains using asymmetric covalent bridges. The linear polystyrene precursors containing precisely incorporated reactive functions were first synthesized by sequence-controlled copolymerization of styrene (**e**) with functional N-substituted maleimides (structures **11** and **19** in Figure 3).[41]

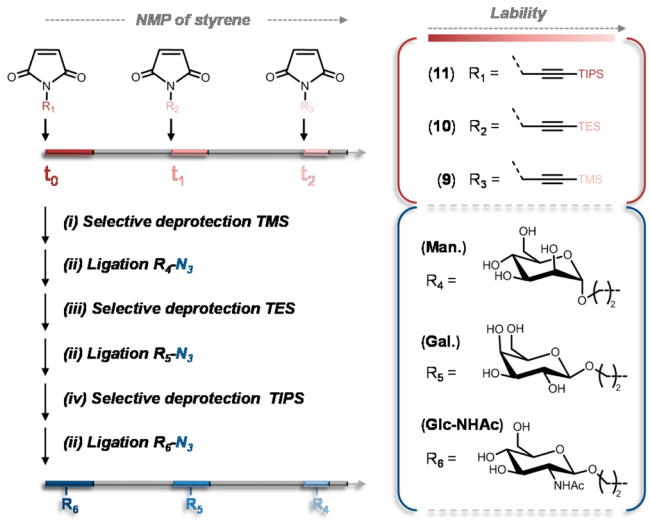

FIGURE 6. General strategy for the synthesis of single-chain sugar arrays. The polystyrene precursors containing precisely incorporated reactive functions were first synthesized by sequence-controlled nitroxide mediated polymerization (NMP) of styrene (**e**) with functional *N*-substituted maleimides (structures **11**, **10**, and **9** in Figure 3) and afterward postmodified using stepwise orthogonal deprotection steps.[35]

oligo(ethylene glycol) spacer. Interestingly, the resulting α-shaped macromolecules exhibited controllable loop and arm sizes. These results are just a beginning. In future, the combination of spatially controlled covalent and supramolecular interactions should lead to the development of single chain objects with controllable functions.[42] Such a vision opens up interesting options in the field of catalysis and molecular transport.[43]

The possibility to form local regions in polymeric microstructures is also an appealing strategy for preparing single-chain functional arrays (i.e., chain regions containing specific information). In theory, such a functional chain encoding is also achievable with multiblock copolymers.[44] However, in practice, the synthesis of precise multiblock copolymers is very difficult and requires weeks of experimental work. Our approach is indeed easier and faster since it allows synthesis of complex encoded microstructures in less than a day.[33] Another difference that should be noted is that multiblock copolymers are composed of long segments, in which each repeat unit contains the same functional group. Our design is different and involves short functional patches, containing 2/3 functional groups, that are separated by nonfunctional homopolymer spacers of controllable length. The simplest version of such a design is a periodic copolymer containing a functional group regularly spaced along the polymer backbone. We reported the preparation of periodic structures containing repeating primary amines, carboxylic acids or alkyne functions.[45] In this work, short reactive prepolymers were first synthesized by sequence-controlled copolymerization of styrene with MIs **22** or **23** and afterward polymerized by step-growth polymerization to afford periodic functional copolymers. The next step in terms of complexity is the preparation of microstructures containing different functional regions. It was shown in the previous section that our approach opens up interesting possibilities in terms of microstructural control (i.e., creation of 8 distinct zones in a single polystyrene chain). Thus, it is tempting to exploit this new synthetic tool to create functional materials.[35,46] For instance, we have reported very recently the synthesis of single-chain sugar-arrays (Figure 6).[35] In this work, different monosaccharides were installed on a well-defined polystyrene chain using a multistep postpolymerization modification approach. The reactive MIs **9**, **10**, and **11** were first positioned on the polystyrene backbone, deprotected selectively, one-by-one, and reacted with azido-functional hexoses. It was demonstrated that the formed sugar-arrays were recognized by complementary lectins. Such new types of sequence-controlled glycopolymers constitute interesting mimics of glycoproteins since the amount of sugar functions and their placement in the chain can be precisely controlled.

Outlook

The purpose of this Account was to summarize our recent achievements in the preparation of synthetic polymers with controlled primary structures by radical chain-growth polymerization. After a bit more than five years of research,

it is obvious that the controlled radical copolymerization of styrenic derivatives (donor monomers) and MIs (acceptor monomers) is a very versatile approach for preparing tailor-made microstructures. One of the main advantages of this approach is certainly its applicability to a large number of donor and acceptor comonomers. In particular, the library of MIs that we developed in recent years can be considered as a true molecular alphabet that allows chain-encryption. These different letters can be placed and spaced at desired locations in polymer chains. As described in the different sections of this Account, this versatile strategy opens up interesting opportunities for design of encoded microstructures, single-chain functional arrays and complex cyclic topologies. It should, however, always be kept in mind that our approach is a chain-growth copolymerization process and, therefore, that chain-to-chain sequence defects exist. Nevertheless, the "ultraprecise" concept, that we reported very recently, clearly shows that these imperfections can be minimized to a very low level. Thus, it seems obvious that the sequence-controlled chemistry described in this Account has not yet reached its limits.

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ABBREVIATIONS

ATRP, atom transfer radical polymerization; ARGET, activators regenerated by electron transfer; CRP, controlled radical polymerization; dNBipy, 4,4′-dinonyl-2,2′-bipyridine; LACCC, liquid adsorption chromatography in critical conditions; MI, N-substituted maleimide; NMP, nitroxide mediated polymerization; PFP, pentafluorophenyl; RAFT, reversible addition−fragmentation chain-transfer polymerization; SET-LRP, single-electron transfer living radical polymerization.

BIOGRAPHICAL INFORMATION

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FOOTNOTES

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The author declares no competing financial interest.

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