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Multistep Growth “Polymerizations”

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Abstract.

Chain-growth and step-growth polymerizations are the two main mechanisms that are classically used to synthesize polymers. In this article, we describe a third approach that is usually not listed in polymer textbooks, namely multistep growth “polymerization”. This synthetic strategy does not proceed in one pot as the aforementioned ones but relies on a series of distinct chemical reactions. It includes different types of stepwise syntheses such as solid-phase iterative chemistry, exponential iterative growth and dendrimer synthesis. Although these methods are more time-consuming and experimentally-demanding than chain-growth and step-growth polymerizations, they allow a very high level of control over macromolecular structure. In particular, they enable a perfect control over molecular parameters such as chain-length, molecular weight, molecular weight distribution, tacticity and comonomer sequence. Here, the common “multistep growth” mechanism shared by all these approaches is described and critically analyzed. Furthermore, the structure, properties and applications of the formed polymers are discussed. This manuscript can serve as a reference guide to understand and rationalize the emerging domain of precision polymer synthesis.

Introduction.

Classical polymer textbooks describe two main mechanisms to synthesize polymers, namely chain-growth polymerizations and step-growth polymerizations.^[1-3] In the former approach, a growing polymer chain carrying a reactive center reacts with monomers and incorporates them one-by-one; while in the latter one, multifunctional monomers react initially with another and lead progressively to the formation of reactive oligomers of increasing length. In both mechanisms, all successive reaction steps proceed in one pot, which is easy and practical. Consequently, these methods are predominantly used in academia and industry to synthesize polymers. However, although widespread, these one pot processes are based on statistical factors, which result in the formation of non-uniform macromolecules. Even highly-controlled versions of these methods, such as living anionic polymerization,^[4] reversible activation-deactivation polymerization,^[5] chain-growth polycondensation^[6] and polymerizations regulated by external events^[7] lead to polydisperse samples. Consequently, polymer scientists are trained during their education to handle the concepts of average chain-length, average molecular weight and polydispersity; some notions which are less familiar to organic chemists who are accustomed to describe pure compounds.

However, over the last years, there is growing research about the synthesis of molecularly-defined macromolecules. This trend is in large parts inspired by biological polymers such as nucleic acids and proteins, which exhibit advanced structures, properties and functions.^[8] Thus, the search for molecular “precision”^[9] is today one of the main objectives of polymer synthesis because it opens up the possibility to control in an absolute manner important parameters such as chain-length, polydispersity and microstructure (*i.e.* monomer sequence^[10] and tacticity^[11]). Consequently, the number of publications dealing with the synthesis of uniform oligomers and polymers has drastically improved during the last decade.^[12] Uniform polymers are predominantly synthesized by stepwise chemistry using strategies that are at the

interface between classical polymer chemistry and organic synthesis,^[13] even though some of them can also be achieved with bio-engineering methods.^[14] Stepwise chemical approaches include divergent and convergent dendrimer synthesis,^[15] solid-phase iterative synthesis,^[16] liquid phase iterative synthesis^[17] and iterative exponential growth.^[18] In these approaches, the successive steps do not occur in one-pot as in chain-growth and step-growth polymerizations. They involve distinct reactions steps separated by purification procedures. As a consequence, these methods enable the attachment of discrete building-blocks (*e.g.* a single monomer unit or a molecularly-defined macromolecular synthon) and ultimately the synthesis of uniform macromolecules. In 2016, it was proposed to unify all these approaches under the generic term multistep growth polymerizations.^[19] Indeed, since these tools are increasingly used in synthetic polymer chemistry, they shall be from now on described and categorized in polymer textbooks, even though the use of the term “polymerization” to describe these processes may be debated and shall probably be placed between quotation marks. In this context, the aim of the present article is to give a rapid overview of these tools for polymer synthesis. Their advantages and limitations are critically discussed within the next pages.

Fundamentals and mechanisms

As defined in the introduction, a multistep growth polymerization is a process involving successive reactions and purification procedures. Figure 1 shows the mechanisms of different classical multistep growth approaches. The oldest strategy is the synthesis of linear polymer chains by stepwise iterative synthesis (Figure 1a).^[10] The roots of this approach go back to the first half of the 20th century and early attempts to synthesize artificial peptides in solution.^[20-21] Stepwise peptide synthesis was afterwards simplified by the use of solid- or soluble-supports as introduced by Merrifield^[22] and Shemyakin,^[23] respectively. In all cases (solution-, liquid-phase^[24] or solid-phase^[22] synthesis), the mechanism is the same, as shown in Figure 1a. A

bifunctional monomer AB containing a protected, thus inactive, function A and a reactive function B is selectively reacted with an initiating molecule or support containing the reactive function A. In these conditions, the uncontrolled polymerization of the AB monomer is avoided and instead the controlled insertion of a single building-block is obtained. The formed adduct is the purified (*i.e.* column chromatography for solution phase synthesis, precipitation for liquid phase synthesis or filtration for solid-phase synthesis) and function A is deprotected to react with the next monomer. These steps are repeated a certain number of times until a polymer of desired chain-length is obtained. The process also enables synthesis of sequence-defined polymers since monomers with different substituents can be used at each step.^[10] However, such strategies are, of course, not limited to protected AB-type monomers that are only discussed here as a typical example. Many other strategies exist, including several protecting-group-free approaches. For additional information on those aspects, the reader is referred to prior reviews.^[25-26]

Another interesting strategy to achieve uniform linear polymer chains is iterative exponential growth (Figure 1b) that was initially referred to as molecular multiplication.^[27] This approach was pioneered by Whitig and coworkers^[28] and also involves bifunctional AB building blocks. The main difference between it and stepwise iterative growth described in the previous paragraph is that it involves two different derivatives of the AB building block instead of one. As shown in figure 1b, one building block has a protected A group and a reactive B group; whereas the other building block display the opposite configuration. Consequently, the coupling of these two molecules leads to a defined dimer terminated by protected functions A and B. The formed adduct is then divided in two batches. In one of them, function A is selectively deprotected, whereas function B is selectively deprotected in the other one. The coupling of these two dimers leads therefore to a defined tetramer. The process is then repeated a desired number of times to obtain uniform 8-mer, 16-mer, 32-mer and so on.

Another widespread multistep strategy is dendrimer synthesis. The first example of such a synthesis was reported by Vögtle and coworkers.^[29] Afterwards, the field has been extensively studied in the 1980s and 1990s.^[30] Dendrimers are branched macromolecules with a precisely controlled topology and molar mass. The strategies to prepare them are relatively comparable to those described in the two previous paragraphs but rely on multifunctional monomers (*i.e.* at least trifunctional) instead of bifunctional ones. Figure 1c shows, for example, a divergent strategy involving a trifunctional AAA reactive core and a building block ABA, in which B is reactive and both A groups are protected. Repeating coupling and deprotection steps n times leads to a uniform dendrimer of defined generation G_n . It shall be remarked that the example displayed in Figure 1c was selected to emphasize analogies with stepwise iterative synthesis (Figure 1a) and iterative exponential growth (Figure 1b) but is certainly not the most applied strategy to synthesize dendrimers. Indeed, many other methods exist, in particular protecting-group free approaches. Furthermore, both divergent and convergent strategies can be applied. Additional details and information about dendrimers and their preparation can be found in excellent classical reviews.^[15, 31-32]

Molecular structure of multistep growth polymers

A major advantage of multistep growth approaches over conventional one-pot polymerizations is the possibility to control accurately the molecular structure of the formed polymers. As described in the previous section, an important feature that is shared by all multistep growth processes is molecular-uniformity. Indeed, polymers prepared by these methods exhibit in most cases perfectly-controlled chain-length, molecular weight and molecular weight distribution. However, purifications are mandatory to isolate such uniform polymers. Indeed, these methods are not exempt of defects and the purity of the formed macromolecules depends on the yields of the successive steps. For instance, in stepwise iterative synthesis, near-quantitative coupling

yields are typically required.^[13, 25] With average yields of 99%, after 20 successive coupling steps, the fraction of chains having the correct chain-length is still 81% but after 100 steps, it goes down to only 35%. Therefore, these methods cannot be repeated indefinitely. For stepwise iterative synthesis, the maximum attainable chain-length is generally assumed to be about 200 residues, even though the longest synthetic polymer reported so far had 107 monomer units.^[33] For iterative exponential growth, the synthesis of 128-mer is to our knowledge the highest chain-length ever reached (*i.e.* 7 amplification steps).^[34] For dendrimers, giant macromolecules with molar mass in the megadalton range have been reported (*i.e.* G9).^[35] Although not completely impossible, it seems currently very difficult to go beyond these limits. The synthesis of large molecularly-defined macromolecules is therefore an open challenge in current polymer chemistry. One strategy to achieve such a goal is the controlled ligation (either covalent or non-covalent) of molecularly-defined macromolecular synthons prepared by multi-step growth approaches.^[36] For example, our group has recently reported the synthesis of giant sequence-defined macromolecules by DNA-guided self-assembly of bio-hybrid precursors containing synthetic polymer segments connected to single-stranded DNA extremities (Figure 2).^[37] Using this strategy, it was possible to prepare linear supra-macromolecules containing a precise sequence of 352 non-natural monomers. Yet, the self-assembly process is not perfect and only a fraction of the self-assembled macromolecules exhibits the expected primary structure. Nonetheless, this first example emphasizes that there are valid strategies to go beyond the current limitations of multi-step growth polymerizations.

Another important advantage of multistep growth approaches is the possibility to perfectly control the microstructure (*i.e.* monomer sequence and tacticity) of the formed polymers.^[11] This is a major difference with chain-growth and step-growth approaches, in which this aspect is, in most cases, uncontrolled. For instance, in stepwise iterative strategies, the possibility to incorporate building blocks at given stages of the synthesis enables a perfect

degree of control over monomer sequence.^[10] Hence, the precision of sequence regulation in these syntheses is comparable to what is found in biological systems. Sequence control is, of course, less precise in iterative exponential strategies. Because of the multiplication mechanism of these syntheses, the formed sequences are in general periodical.^[13] However, some related strategies, such as the cross-convergent method,^[38] allows synthesis of aperiodic sequences.^[39] Tacticity can also be controlled in multistep growth strategies if enantiomerically pure building blocks are used (*e.g.* as in peptide or in DNA synthesis). This aspect can also be controlled in some chain-growth polymerizations such as living anionic polymerizations.^[4] Yet, stepwise iterative growth allows synthesis of precisely-controlled stereo-sequences (*i.e.* eutactic sequences^[40]), which are beyond the classical situations (*i.e.* isotactic, syndiotactic, heterotactic) that can be achieved in chain-growth copolymerizations. However, these possibilities are currently barely explored, even though some interesting examples of precision polymers with controlled stereosequences have already been reported.^[41-42]

Multistep-growth approaches also allow precise control over macromolecular topology, even though this aspect has not been as widely investigated as in chain-growth polymerizations.^[43] Besides linear and dendritic topologies, branched^[44] and cyclic architectures^[45-46] can also be attained in stepwise synthesis. One last important aspect that shall also be discussed is the chemo-diversity of the macromolecules that can be produced by multistep growth approaches. Although iterative strategies were first developed for the synthesis of biological macromolecules such as oligopeptides and oligonucleotides, they have now been extended to a very broad variety of synthetic polymers.^[13] For example, polyesters can be synthesized by stepwise iterative chemistry,^[47] iterative exponential growth^[18] and dendrimer strategies.^[48-49] In fact, as in chain-growth and step-growth polymerizations, the spectrum of chemical reactions and building blocks that can be used in multi-step growth syntheses is extremely diversified, not to say almost infinite.

Properties and applicability

As described in the previous section, the main advantage of multistep growth “polymerizations” is the control over macromolecular structure that they provide. In that regard, these approaches are undoubtedly superior to conventional polymerization methods. Consequently, they open up a brand new range of properties and applications, which are closer to those of functional biopolymers rather than commodity plastics. These applications are discussed in details in comprehensive reviews^[15, 50-51] and therefore only a few of them will be briefly listed herein. For example, both linear sequence-defined polymers and dendrimers have been proven to be interesting and efficient platforms for catalysis.^[52-53] Sequenced-defined polymers also exhibit interesting biomedical properties such as antibacterial activity^[46] or the capacity to selectively bind poorly-soluble drugs.^[54] For all these applications, it has been proposed that controlled monomer sequences allow highly-specific molecular recognition and binding.^[55] It has also been evidenced that the information-storage properties of DNA can be mimicked in synthetic polymers.^[56] For example, digital sequences can be efficiently stored in synthetic polymers prepared by solid-phase chemistry,^[57-59] iterative solution synthesis,^[60] dendrimer synthesis^[61] or the cross-convergent method.^[38] This topic has progressed very rapidly in recent years and it is now possible to store complete data files such as short text or pixelated images in a single macromolecule.^[62] As shown in Figure 3, the current record in the area is a storage capacity of 440 bits/chain.^[63] Furthermore, sequence-coded polymers can be used in anti-counterfeiting and traceability applications.^[64] Commercial products such as the polymer taggant Poltag[®] are already on the market.

Yet, multistep syntheses are much more technically-demanding, time-consuming and expensive than classical one-pot methods. Thus, there are some legitimate concerns about the scalability and industrial applicability of this new generation of precision polymers.^[65] It shall be clarified that the applications listed above are not classical commodity or specialty

applications of polymers. For example, anti-counterfeiting applications require typically ppm or ppb of informational polymers to label commercial products. Thus, small scale (typically gram-scale or multi-gram scale) synthesis is sufficient for many potential applications. Yet, if needed, higher scales (*i.e.* multi-kilos) can be implemented in large reactors. For instance, the solid-phase synthesis of peptides is applied industrially up to the 100-kilo scale.^[66] Methods for the kilogram production of dendrimers have also been reported.^[67-68] Thus, the industrial scalability of multistep growth polymers is not an issue by itself. In fact, the cost of synthesis is probably more the limiting factor. Hence, precision polymers, synthesized by multi-step growth strategies, are probably best suitable for high-end applications, which combine a low/medium-scale production with a high-profit margin.

Outlook

It is now obvious that conventional chain-growth and step-growth polymerization methods, which have been discovered during the early days of polymer science^[69] and have been extensively investigated, have probably reached their limits in terms of structural control.^[9] Consequently, to attain further perfection in polymer design, new polymerization concepts have to be identified and studied. The multistep growth strategies described in this short article already go in this direction. Indeed, the last three decades of polymer research have evidenced that linear and dendritic macromolecules with perfectly defined molecular structures can be prepared. Still, one may question if all these methods are really “polymerizations” and if they really belong to the field of polymer chemistry? As emphasized in the previous pages, the answer to all these questions is probably yes. Even though multi-step growth methods employ time-consuming repeating steps that are inspired by organic chemistry and total synthesis, the construction and characterization of molecularly-defined macromolecules requires undoubtedly the expertise of polymer scientists. Nevertheless, these methods still have very important drawbacks, for example regarding attainable chain-length, cost and applicability, as emphasized

in this manuscript. However, these hurdles can be overcome with the development of engineering and robotic solutions.^[33, 70-71] Hence, the search for macromolecular structural “perfection” will most probably remain a dominating theme in polymer synthesis in the coming decades.

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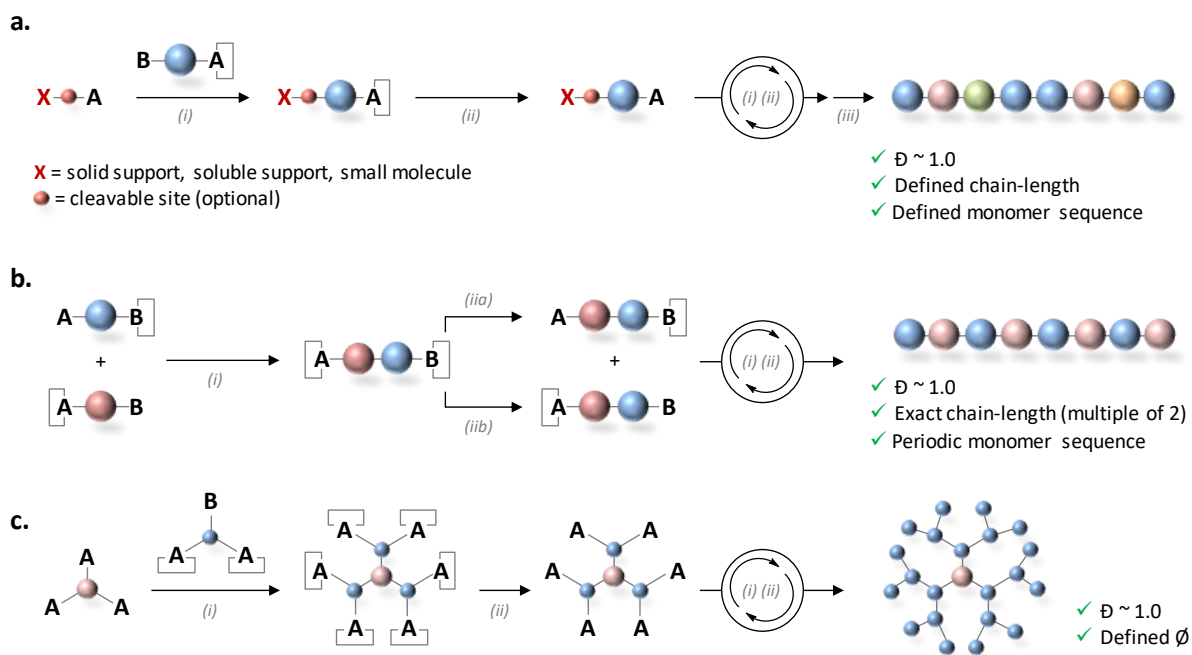


Figure 1. Classical Multistep growth mechanisms: **(a)** stepwise iterative synthesis, **(b)** iterative exponential growth, **(c)** divergent dendrimer synthesis. In all displayed examples, function A reacts with function B. Step (i) is therefore a coupling step. The grey box symbolizes a protecting group for function A. Step (ii) is therefore a deprotection step. In all cases, the repetition of steps (i) and (ii) leads to the synthesis of uniform macromolecules. In strategy **a**, a final cleavage step (iii) is required in some cases (*e.g.* when using solid or soluble supports) to liberate the final macromolecule. The strategies displayed in this figure are only examples. Numerous variations of these mechanisms exist.

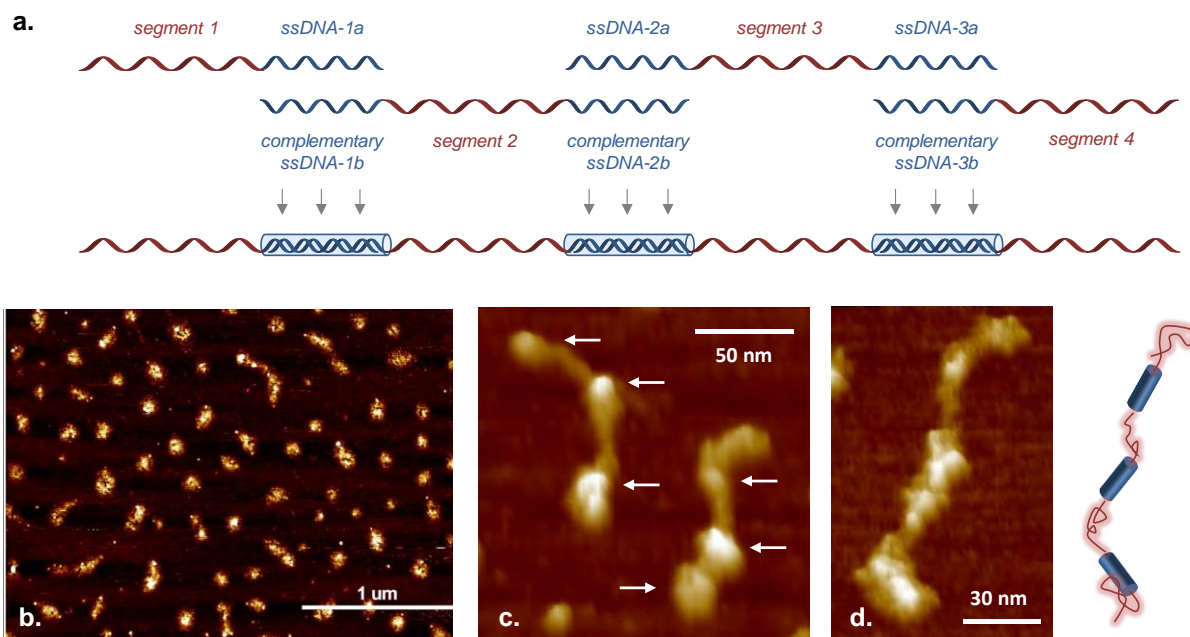


Figure 2. (a) DNA-guided assembly of four uniform poly(phosphodiester)s prepared by stepwise iterative phosphoramidite synthesis into large molecularly-defined supra-macromolecules. The uniform precursors contain synthetic segments (red) connected to DNA single-strands (blue). The sequence-specific hybridization of the DNA strands leads to a programmed superstructure with a precisely-controlled chain-length. (b) Height AFM characterization of the formed superstructure on a dried substrate. (c, d) Height AFM characterization of the formed superstructure in aqueous solution. The arrows indicate thicker regions that probably correspond to double-stranded DNA.^[37]

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