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The Future of Sequence-defined Polymers

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Abstract.

The objective of this perspective article is to critically analyze the emerging domain of sequence-defined polymers and to discuss future challenges and trends in the field. Sequence-defined polymers are macromolecules, in which the monomer arrangement is perfectly controlled from one chain-end to the other. They therefore have a defined chain-length and primary structure. This article focuses mainly on synthetic polymers and does not provide an in-depth discussion about the chemical synthesis of biopolymers (*i.e.* nucleic acids and proteins) and biopolymer mimics (*i.e.* peptidomimetics and xeno-nucleic acids). Although the synthesis of non-biological sequence-defined polymers was initially a challenge, it has grown over the last fifteen into a mature discipline. Indeed, major progress has been made for the synthesis, characterization and application of these manmade macromolecules. Thus, in the first section of this article, a brief summary of the most important achievements is provided. For instance, synthesis by multistep-growth “polymerization”, sequencing (*i.e.* complete sequence determination) and emerging applications (*e.g.* data storage, anti-counterfeiting technologies, catalysis, selective drug carriers) are discussed. The second section of this article provides an in-depth discussion about the future of the field. Despite enormous progress, there are still major limitations regarding the synthesis and applicability of sequence-defined polymers. Moreover, some important properties of sequence-defined polymers still have to be discovered. All these aspects are discussed in details herein and some priority topics are suggested for the future.

Keywords.

Sequence-controlled polymers; Informational Polymers; Precision Polymers; Sequencing; Polymer Materials.

1. Introduction

The idea of placing each monomer at a defined position in a man-made macromolecule has emerged in the early 21st century as an exciting new challenge in polymer chemistry.[1] Indeed, most of the synthetic copolymers prepared in the 20th century contained uncontrolled (*e.g.* random) or poorly-controlled (*e.g.* blocky) monomer sequences.[2] In fact, absolute sequence control was achieved by chemical means in the 20th century but mostly for recreating in the laboratory sequence-defined biopolymers such as nucleic acids and proteins.[3, 4] Some bio-inspired sequenced-defined oligomers such as peptidomimetics[5] and xeno-nucleic acids[6] were also developed but only few attempts were made to develop other families of abiotic sequence-defined polymers (SDPs), as described in early reviews on the topic.[7, 8]

Starting about 15 years ago, research on non-biological SDPs has become more prominent. A broad variety of oligomers and polymers have been reported, as described in a number of recent reviews.[9-12] Additionally, some innovative properties as well as some emerging applications were rapidly identified for SDPs.[12-16] One of the major advantages of SDPs as compared to ill-defined copolymers is the possibility to include a functional monomer at a specific position. This can be used as a powerful strategy to tailor the intramolecular conformation (*e.g.* folding) as well as the intermolecular interactions (*e.g.* self-assembly, host-guest interactions, catalytic activity) of a macromolecule. Furthermore, a defined set of monomers can be used as a molecular alphabet to write and store information in polymer chains.[17] Although such a concept is central in molecular biology, it was unexplored in synthetic polymer chemistry until 10 years ago.[2, 18] Its development has therefore rapidly enabled the discovery of new types of applied polymer materials.

Yet, the synthesis of SDPs remains overall very demanding. Indeed, it relies on multistep growth mechanisms,[19] which are time-consuming and limited in yields, scale and chain-length. In this context, the aim of this short article is to critically analyze the possible

future of this emerging area. Recent achievements will be described in a first section, followed by a discussion about future challenges and prospects in the field.

2. Emerging trends

Important achievements have been made for the preparation of SDPs during the last 15 years. It shall be first reminded to the readers that the terms “sequence-defined” imply an absolute sequence control; meaning that the positioning of every monomer unit in a linear chain is perfectly controlled from one chain-end to the other.[20] It implies molecular uniformity and shall therefore be distinguished from the broader category of sequence-controlled polymers,[2] which may exhibit some dispersity. Consequently, SDPs are generally synthesized using multistep growth “polymerizations”, for example using stepwise approaches such as linear iterative growth (performed in solution or using soluble- or solid- supports), iterative exponential growth or dendrimer synthesis. These mechanisms have been described in details in a recent review and will not be re-explained in details herein.[19] In brief, these syntheses are not performed in one-pot like classical chain-growth or step-growth polymerizations but using a series of discrete reactions steps.[21] Thus, their syntheses are limited by several aspects. Since they rely on successive reactions and purifications, they usually require more time (*e.g.* from a few hours to several weeks depending on the chosen chemistry) than classical polymerizations. Furthermore, the global yield for polymer synthesis depends on the number of performed steps and therefore drops down with chain-length. It is therefore challenging to synthesize very large macromolecules in these approaches. In addition, the typical laboratory scale for the synthesis of these polymers is generally quite low (*i.e.* from mg to g). All these aspects also reflect on the cost of the formed polymers, which are much more expensive than classical commodity polymers. Despite all these limitations, significant progress has recently been made in the field as described in the following sections.

2.1. Chemodiversity

Multistep growth mechanisms allowing the synthesis of SDPs have been identified long time ago.[19] However, as mentioned in the introduction, there were initially principally used for the synthesis of biopolymers or bio-related polymer mimics. This implies that most SDPs had phosphate-sugar or amide-based backbones.[8] One important step-forward of the last fifteen years has been the identification of a wide variety of chemistries that were previously not considered for the synthesis of sequence-defined polymer backbone. It is not the purpose of the present article to describe all these main-chain chemistries in details and the reader is guided towards recent reviews for an exhaustive description.[9-11] As selected examples, one may mention the use of: azide-alkyne cycloadditions,[22] thiolactone chemistry,[23] Michael additions,[24, 25] multicomponent reactions,[26] nitroxide radical coupling,[27] activated carbonate chemistry,[28] Sonogashira coupling,[29] silane chemistry,[30] Menshutkin reaction[31], single unit radical addition,[32] and carbene disulfide chemistry.[33] This backbone chemodiversity has opened up new horizons in the field. Most of these chemistries were selected because they lead to high yields coupling steps, which is a prerequisite for multistep growth “polymerizations”. [19] However, some of them are also orthogonal to other functional groups and can therefore be combined to achieve protecting-group-free iterative synthesis.[9] The tolerance to other functional groups is also an advantage for side-chain functionalization. For example, as reported in this journal,[34] multicomponent reactions allow combination of a broad variety of functional building blocks. Yet, one drawback of this increased chemodiversity is that it gives access to an extremely large pool of possible sequences. Consequently, the assessment of structure-properties relationships is an enormous task, which is by far much more complex than for simple copolymers such as block copolymers.[35] In an excellent recent review, Perry and Sing have discussed the emerging

physics of SDPs and pointed out the challenge that constitutes such a vast parameter space.[36] It is obvious that, in addition to current synthetic efforts, theoretical studies and chemoinformatics will be mandatory in the future to address this broadening chemodiversity.

2.2. Characterization

During the last ten years, important progress has been made regarding the characterization of SDPs. As discussed above, there are two main features that SDPs do not share with classical copolymers: (i) an exact chain-length and (ii) a perfectly-controlled monomer sequence.[37] All other molecular features such as chain-ends, tacticity and comonomer composition can be characterized using standard polymer analytics, for example using NMR.[38] For the characterization of chain-length and molecular uniformity, two main techniques are typically used namely size exclusion chromatography and mass spectrometry (electrospray or MALDI). In addition, ion-exchange chromatography and gel electrophoresis can be used for the characterization of charged SDPs.[39, 40] It shall be specified that polymers prepared by multistep growth “polymerizations” do not exhibit a molecular weight distribution like polymers prepared by chain-growth and step-growth polymerizations. When not perfectly uniform, these polymers exhibit a low molecular weight tailing that corresponds to incomplete reactions steps. Still, the most significant progress has been made for the sequencing of synthetic polymers. As underlined previously,[41] sequencing, which is the complete determination of a comonomer sequence from one chain-end to the other, shall be distinguished from classical sequence analysis that only gives a rough estimation of sequence motifs (*e.g.* dyads or triads). Initially, sequencing methods were only developed for the characterization of nucleic acids and proteins. Thus, one major achievement of the last decade has been the development of sequencing techniques allowing decryption of abiotic polymers. Comparing the content of the review recently published by Du Prez and co-workers[42] to the one published

by our group in 2014[41] gives a good measure of what has been achieved. Currently, the most widespread analytical technique for the sequencing of non-biological polymers is tandem mass spectrometry (MS/MS).[43] In this approach, sequence-defined macromolecules are subjected to collision-induced fragmentations and the resulting MS/MS spectra allow primary structure determination.[44] One important feature that was highlighted during the last decade is that the broad diversity of reactions and building blocks that can be used for the synthesis of SDPs (see previous section about chemodiversity) allows the intentional design of polymers that can be easily sequenced by MS/MS.[45] It is even possible to induce stepwise controlled fragmentations (e.g. MS³) that allow deciphering of long polymer chains.[46] Furthermore, MS/MS and MS³ spectra may be rapidly interpreted with the help of decoding softwares.[47, 48] As an interesting alternative to MS/MS fragmentations, SDPs may also be pre-fragmented by chemical degradation and the formed fragments may be analyzed using by simple MS[49] or LC-MS.[50] Another powerful method for the sequencing of non-biological polymers is nanopore sequencing.[51] It has been recently shown for the first time that non-biological oligomers can be decoded by this technique (Figure 1).[52] Yet, this promising approach is still underexplored.

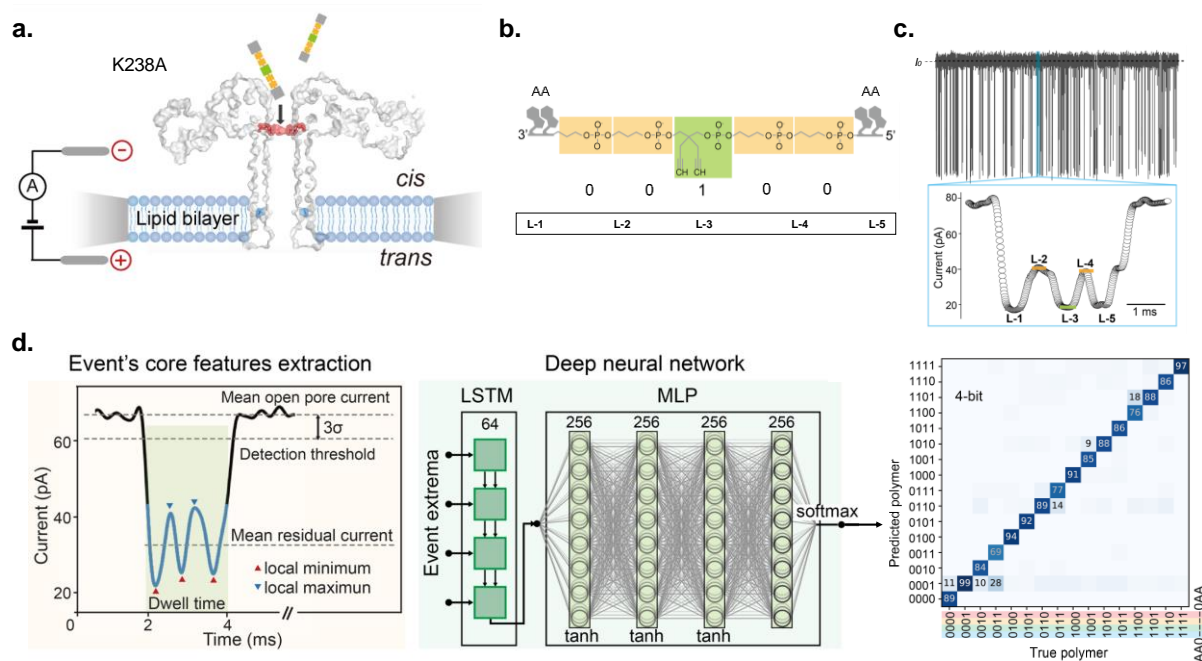


Figure 1. Nanopore sequencing of digitally-encoded SDPs. **(a)** Schematic representation of the single-channel recording experiment using a K238A aerolysin pore. **(b)** Molecular structure of the digital polymers. The color code correlates with the levels of current blockade shown in **(c)**. The letter A denotes adenine nucleotides. **(c)** Typical current recorded for the oligomer shown in **(b)**. **(d)** Raw current traces are first filtered (left) and then classified using a deep neural network (middle). The resulting confusion matrix for polymers encoding 4 bits is reported on the right. Adapted from ref [52].

2.3. Properties and applications

Perhaps one of the most important achievements of the last decades has been the identification of reliable applications for SDPs. These emerging applications have been reviewed and only a brief summary will be provided herein.[13, 14, 16, 53] First, very interesting discoveries have been made regarding the catalytic activity,[54] molecular-recognition properties[55] and guest-inclusion properties[56] of SDPs. In such applications, not only the monomer sequence matters (*i.e.* the primary structure) but sometimes also the folding of the chain into a defined three-dimensional shape (*i.e.* secondary or tertiary structure). Although the field of synthetic foldamers has been widely explored,[57] there are few studies describing the folding of

sequence-defined oligomers. Here, the pioneer research of Huc and coworkers shall be highlighted, in particular recent work describing the selective encapsulation of fructose in sequence-defined oligoamide foldamers (Figure 2).[56] Significant progress has also been made regarding biotechnological applications of SDPs, for example with the development of selective drug carriers[55] and antimicrobial agents.[58]

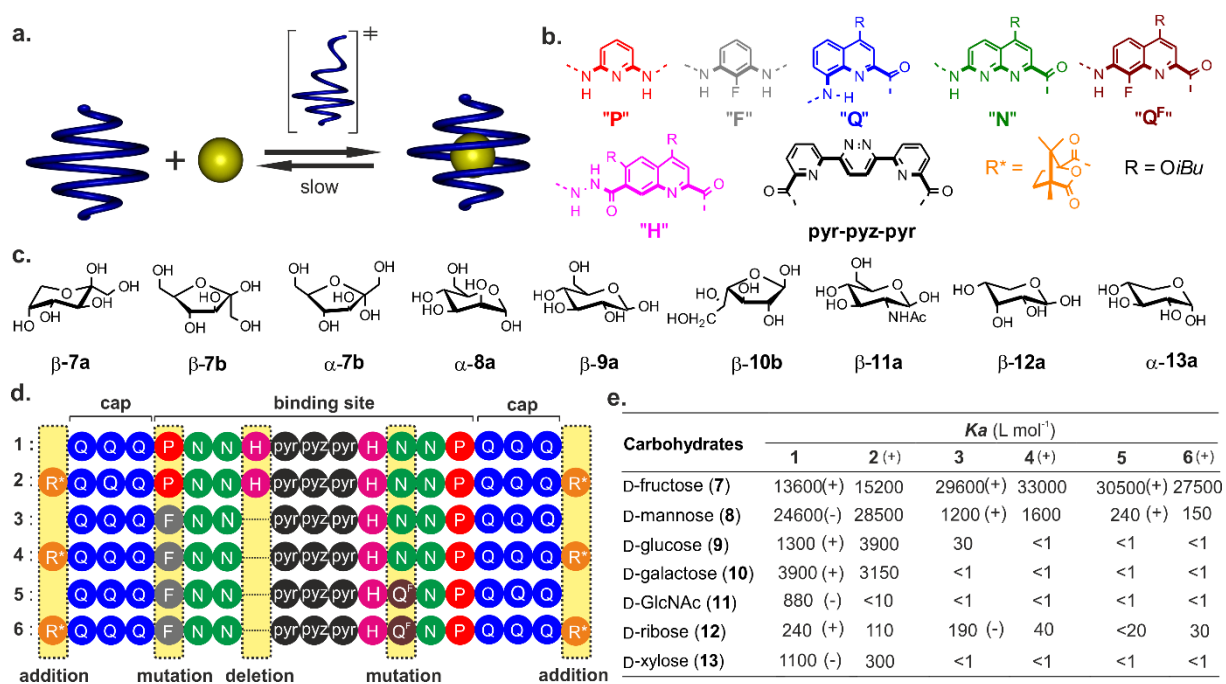


Figure 2. (a) Selective encapsulation of guest molecules (schematized in yellow) in a folded helical SDP (drawn in dark blue). (b) Molecular structure of the monomer units. (c) Molecular structures of monosaccharide guests. (d) Different monomer sequences that were studied. (e) Association constants measured for different host-guest combinations. Redrawn with permission of the authors.[56]

Another major development in the field has been the discovery of so-called informational polymers, in which the monomer sequence stores a readable message.[18] The type of information stored in the polymer can be computer data (*e.g.* text, image, video, audio files, program) or security data (*e.g.* identification number, security key, pin code, encrypted sequence). Thus, this new family of functional polymers has opened up applications in the field

of data storage but also in the areas of anti-counterfeiting technologies, product identification, plastics recycling and steganography. For data storage applications (mostly cold storage and long-term archiving), the stored information is a binary sequence and the formed macromolecules are therefore named digital polymers. It can be written with an alphabet of two monomers but also using expanded alphabets containing more symbols.[17] Since the first description of a binary-encoded abiotic oligomer in 2014,[59] various types of digital polymers have been reported as described in a recent review.[60] The decryption of digital polymers has also been significantly explored and improved during the last ten years (see section 2.2).[42] Approaches for erasing,[27] editing[61, 62] digital polymers have also been reported. Here again, the chemodiversity of SDPs (see section 2.1) brings many opportunities for adjusting storage properties. Last but not least, since digital polymer cannot be of infinite chain-length (the current highest reported single chain capacity is 440 bits/chain[63]), the spatial organization of library of digital polymers has also been investigated, as summarized in a recent overview published in this journal.[64] For example, Zhang and coworkers have recently reported the preparation of a 2D microarray of digital polymers (Figure 3).[65] Besides data storage, various concepts have recently been reported for cryptography,[66] product identification[67] and anti-counterfeiting applications.[28, 68, 69] In the latter case, sequence-defined oligomers are used as taggants that can be dispersed as traces in solid, gel or liquid materials. They can be extracted from the host material and decoded using MS/MS or other analytical techniques. A sequence-defined polymer taggant was recently commercialized under the name Poltag[®].

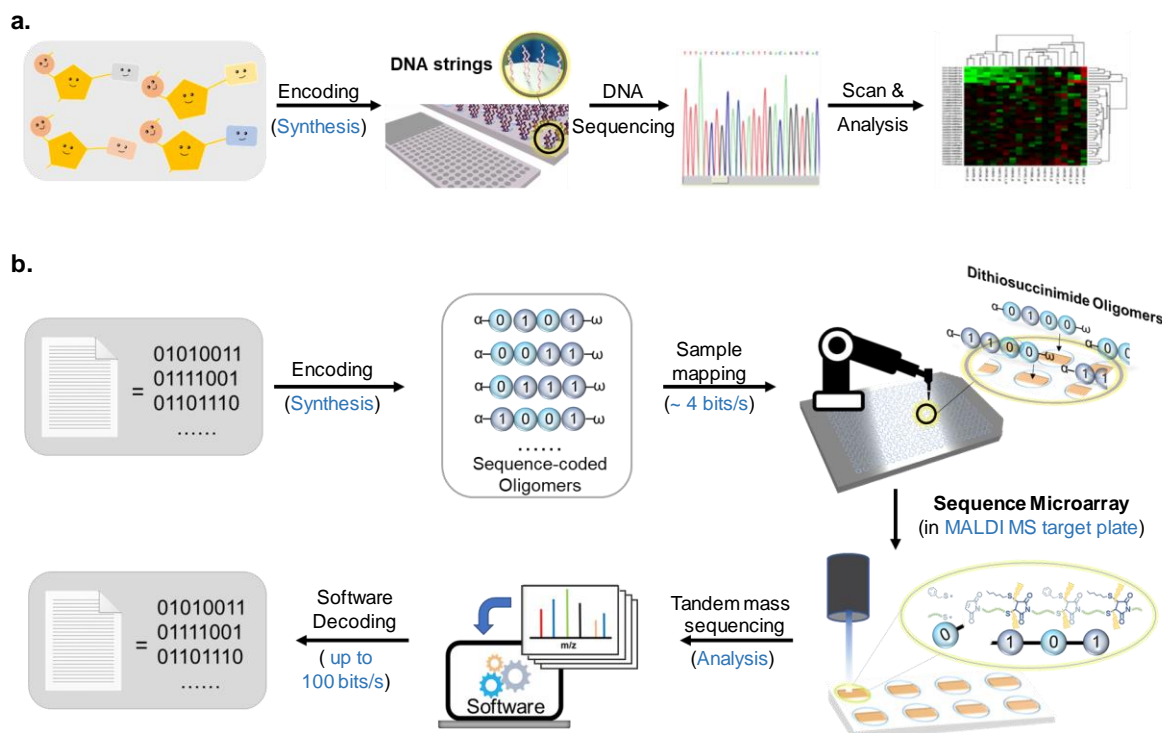


Figure 3. Fabrication of microarrays of digital SDPs. **(a)** Schematic representation of DNA microarrays used in genomics. **(b)** Concept for the elaboration of microarrays of 4-bits digitally-encoded dithiosuccinimide oligomers. The oligomers are loaded on the substrate using a robotic arm and decoded on the surface by MALDI MS/MS. Reprinted with permission from reference [65]. Copyright Wiley VCH 2022.

3. Future vision

3.1. Challenges in synthesis

Despite the significant progress described in section 2, many challenges lie ahead for the design and synthesis of SDPs. First of all, there was no real mechanistic breakthrough during the last 15 years. Step-by-step (or piece-by-piece) iterative synthesis is known for decades[19] and is still the hard way to achieve absolute sequence-control. Interesting alternatives have been proposed such as template polymerizations,[70] DNA-guided synthesis[71] and processing molecular machines.[72] However, these approaches remain currently even more complicated than stepwise synthesis and limited to the synthesis of oligomers. Using natural biocatalysts (*e.g.* enzymes, ribosome) and cell machinery is also an interesting strategy to synthesize SDPs.

Protein engineering allows the use of non-canonical monomers but remains restricted to the synthesis of natural protein backbones.[73] To bypass such limitations, there was recently some interesting efforts for achieving ribosomal synthesis of other polymers than α -amino acids-based proteins.[74] Still, these approaches remain for the moment limited to the synthesis of oligoamides.

Another major aspect that shall be improved in the future is the chain-length of SDPs. As aforementioned, multistep growth approaches are limited by the yields of repeating steps. Thus, current iterative methods mainly allow the synthesis of oligomers or short polymer chains (*i.e.* between 2 and 20 monomer units). Although such sizes are sufficient for some applications (see section 2.3.), it would be important for the future of polymer chemistry to go beyond current boundaries. With the help of automated synthesis, capping chemistries and column purification, chain-length above hundred monomer units can be achieved[39] but it seems conceptually difficult to go above using a pure step-by-step approach. Thus, alternative concepts shall also be explored. One of them is the controlled ligation of preformed sequence-defined macromolecular segments. This is rather difficult to achieve by covalent chemistry because of the accessibility of reactive chain-ends in macromolecular reagents. However, some non-covalent strategies can also be considered. For instance, our group has recently reported the synthesis of large sequence-defined supramolecules by DNA-guided assembly of preformed bio-hybrid segments.[40] Another important aspect that has not been sufficiently explored is the tacticity of SDPs.[75, 76] The majority of non-biological SDPs that have been recently reported are either achiral or synthesized using racemic building-blocks, thus atactic. Although stereocontrol is not mandatory for some applications described above (*e.g.* information storage), it could be of major importance in other areas, in which precise chain folding is needed (*e.g. enzyme mimics*). Progress for preparing abiotic polymers that are both sequence-defined and stereocontrolled were described in a very recent review.[77] Another important progress

would be to achieve absolute sequence-definition in supramolecular copolymers.[78] There were recently some interesting studies for rationalizing and controlling non-covalent copolymerizations.[79] However, the dynamic rearrangement of supramolecular backbones renders sequence control particularly challenging.

3.2. Applicability

In addition to the synthesis issues described in the previous section, the applicability and industrialization of SDPs remains an open challenge. Although some SDPs have already been commercialized, their production is still time-consuming and costly. It is probably clear to all readers that SDPs are not meant to become commodity polymers, and probably also not large-scale specialty polymers. The commercial applications that can absorb the high cost of SDPs are more dealing with specialty additives, pharmaceutical industry (*e.g.* drug carriers) and information technologies. In such applications, the scale of synthesis is not a limiting factor. As discussed in a prior text,[19] some iterative syntheses can be performed at the multi-kilo scale, which is sufficient for some specialty additives production. Yet, any development that shall simplify the production and characterization of SDPs will, of course, be beneficial for the field. Such improvements may come from chemistry as discussed above but also from engineering (*e.g.* automation, parallelization, nanofabrication, microfluidics), which is currently an aspect that has been scarcely investigated. For instance, interesting strategies such as monomer recycling[80] and fueled one-pot processes[81] (Figure 4) have already been reported for reducing the amount of reagents and solvents in iterative syntheses. In addition, automation is a crucial aspect to simplify the synthesis of SDPs. As long as SDPs will be prepared by stepwise chemical synthesis, it is hard to imagine industrial applications based on manual production. Although sequence-defined peptides and oligonucleotides are routinely synthesized by automated synthesis and sold by numerous companies, only a minority of polymers described

in section 2.1 were prepared using robotic instruments. Therefore, research on the automated synthesis of SDPs has to be significantly intensified. It may require the development of specific instruments allowing fast parallel synthesis. To this end, a synergy between synthetic chemists and chemical engineer seems mandatory. Similarly, the spatial organization of coded matter has to be further explored. This may include studies about the (co)crystallization and self-assembly of SDPs but also regarding micro-fabrication (*e.g.* development of 2D- or 3D-organized nanomaterials).[64]

3.3. Still to be discovered...

There are probably many more applications for SDPs than the ones described in Section 2.3. Based on a simple analogy with biopolymers such as nucleic acids and proteins, it seems obvious that all the properties of manmade SDPs have not been discovered yet. Indeed, in biology, nucleic acids and proteins have many other properties and functions besides molecular recognition, biocatalysis and information storage. For instance, DNA can self-replicate, self-repair, undergo Darwinian evolution and sustain life. RNA can act as a messenger and transfer its information to proteins. It cannot be excluded that man-made polymers may also exhibit comparable properties. This has been discussed in details in two recent essays.[82, 83] One important message of these prior texts is that a complex property such as artificial life can probably not be created by pure rational design and will require the development of directed out-of-equilibrium systems. However, the basic mechanisms of life-supporting polymers are pure fundamental polymer chemistry problems. For instance, mutations, which are the basic molecular events for Darwinian evolution, are simple monomer alterations in polymer chains. Similarly, replication, translation and transcription, which are the basis for life transmission and biomaterials synthesis, are simple questions of macromolecular information transfer.[70] All these events might be recreated in synthetic polymers and some rudimentary proofs-of-

principles of artificial mutations,[61] repair,[84] hybridization,[85] replication[86] and translation[87] have already been reported. Hence, research on all these aspects shall be strengthened in the future. Accessing such properties in synthetic polymers could open up interesting perspectives for xenobiology (*e.g.* for understanding if other polymers than nucleic acids could sustain life) but also for human applications such as data storage.

Data availability.

Not applicable.

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