Sequence-Controlled Polymers

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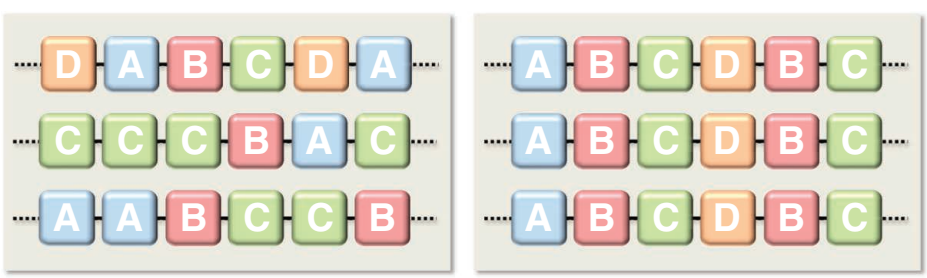
Background: During the last few decades, progress has been made in manipulating the architecture of synthetic polymer materials. However, the primary structure—that is, the sequential arrangement of monomer units in a polymer chain—is generally poorly controlled in synthetic macromolecules. Common synthetic polymers are usually homopolymers, made of the same monomer unit, or copolymers with simple chain microstructures, such as random or block copolymers. These polymers are used in many areas but do not have the structural and functional complexity of sequence-defined biopolymers, such as nucleic acids or proteins. Indeed, monomer sequence regulation plays a key role in biology and is a prerequisite for crucial features of life, such as heredity, self-replication, complex self-assembly, and molecular recognition. In this context, developing synthetic polymers containing controlled monomer sequences is an important area for research.

Advances: Various synthetic methods for controlling monomer sequences in polymers have been identified, and two major trends in the field of sequence-controlled polymers have emerged. Some approaches use biological concepts that have been optimized by nature for sequence regulation. For instance, DNA templates, enzymes, or even living organisms can be used to prepare sequence-defined polymers. These natural mechanisms can be adapted to tolerate nonnatural monomers. The other trend is the preparation of sequence-controlled polymers by synthetic chemistry. In the most popular approach, monomer units are attached one by one to a support, which is an efficient method but demanding in practice. Recently, some strategies have been proposed for controlling sequences in chain-growth and step-growth polymerizations. These mechanisms usually allow fast and large-scale synthesis of polymers. Specific kinetics and particular catalytic or template conditions allow sequence regulation in these processes.

Outlook: The possibility of controlling monomer sequences in synthetic macromolecules has many scientific and technological implications. Information can be controlled at the molecular level in synthetic polymer chains. This opens up interesting perspectives for the field of data storage. In addition, having power over monomer sequences could mean structural control of the resulting polymer, as it strongly influences macromolecular folding and self-assembly. For instance, functional synthetic assemblies that mimic the properties of globular proteins, such as enzymes and transporters, can be foreseen. Moreover, monomer sequence control influences some macroscopic properties. For example, bulk properties such as conductivity, rigidity, elasticity, or biodegradability can be finely tuned in sequence-controlled polymers. The behavior of polymers in solution, particularly in water, is also strongly dependent on monomer sequences. Thus, sequence regulation may enable a more effective control of structure-property relations in tomorrow's polymer materials.



Precise molecular encoding of synthetic polymer chains. In most synthetic copolymers, monomer units (represented here as colored square boxes A, B, C, and D) are distributed randomly along the polymer chains (**left**). In sequence-controlled polymers, they are arranged in a specific order in all of the chains (**right**). Monomer sequence regularity strongly influences the molecular, supramolecular, and macroscopic properties of polymer materials.

ARTICLE OUTLINE

Sequence-Controlled Biological Polymerization Processes

Sequence-Controlled Polymerizations Based on Chemical Approaches

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Outlook

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Sequence-Controlled Polymers

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Sequence-controlled polymers are macromolecules in which monomer units of different chemical nature are arranged in an ordered fashion. The most prominent examples are biological and have been studied and used primarily by molecular biologists and biochemists. However, recent progress in protein- and DNA-based nanotechnologies has shown the relevance of sequence-controlled polymers to nonbiological applications, including data storage, nanoelectronics, and catalysis. In addition, synthetic polymer chemistry has provided interesting routes for preparing nonnatural sequence-controlled polymers. Although these synthetic macromolecules do not yet compare in functional scope with their natural counterparts, they open up opportunities for controlling the structure, self-assembly, and macroscopic properties of polymer materials.

Copolymers are long macromolecular chains composed of at least two monomers of different chemical natures (*1*). In many copolymers, the distribution of the monomers along the chains is uncontrolled and, therefore, varies from chain to chain. In sequence-controlled polymers, however, the monomer units are arranged in the same precise order in all chains rather than randomly distributed. Alternating, periodic, or block copolymers composed of two monomers, A and B, for example, represent the simplest level of sequence-controlled polymers (*2*). Beyond that, there are more complex monomer sequence patterns. For instance, two or more monomer units can constitute a precise molecular "code" in a polymer chain. Prime examples are found in biology. Nucleic acids, such as DNA and RNA, exhibit ordered sequences based on four-nucleotide monomer units. In proteins, 20 amino acids are used to form precisely regulated monomer sequences. Such precise positioning of monomer units (or functionalities) has an important influence on polymer structure and creates unique properties, such as molecular recognition, biocatalysis, and molecular encoding of information.

Similar to the role DNA plays in genes, well-defined sequences in synthetic polymers may serve as molecular-level information storage devices in which each functional side-group may be regarded as an information "bit." Therefore, sequence-defined oligomers and polymers have gained importance in both fundamental polymer science and numerous technological applications. For instance, the application of DNA goes well beyond biotechnology to areas of nanotechnology and materials science (*3*). However, DNA is not unique in its suitability as a manipulable sequence-controlled polymer. Chemistry and biology offer many interesting alternatives for the preparation of sequence-defined macromolecules. The most serious challenge may be that no general and versatile strategy has been found for synthesizing sequence-controlled polymers. In principle, polymers with regulated sequences of monomers can be prepared using either chemical or biological methods. The latter strategy is especially efficient, as it relies on highly evolved biological mechanisms. For example, the enzymes—or even the complete systems for replication, transcription, and translation—of living organisms can be reprogrammed for the synthesis of sequence-defined macromolecules. The polymerase chain reaction (PCR) (*4*) and protein engineering (*5*) are two successful examples of such strategies. Although these methods remain limited to natural biopolymer backbones, they can be extended to the synthesis of nonnatural biopolymers using noncanonical monomers. The pros and cons of these approaches are discussed in the first section of this review.

Synthetic chemistry can be used to prepare sequence-controlled macromolecules with diverse chemical structures. Moreover, in comparison with DNA technologies, chemical procedures may enable larger-scale production of simpler and cheaper sequence-defined materials. However, fully synthetic sequence-controlled protocols are more challenging than biotechnological pathways and are often limited to short oligomer synthesis. The most obvious method for preparing sequence-defined segments is to connect monomer units one by one by using iterative chemical steps (see Box 1). This strategy was studied as early as the late 1940s for the synthesis of oligopeptides. The introduction of solid-phase chemistry (*6*) and automated synthesizers has greatly simplified this approach; however, it remains a tedious process requiring very high reaction yields and repeated purification steps. Therefore, other mechanisms for monomer sequence control in polymerizations have been investigated. For instance, the development of living polymerization methods—such as ionic polymerizations (*7*), controlled radical polymerizations (*8*, *9*), and ring-opening metathesis polymerization (*10*)—has aided progress in the field of polymer science, and it is now possible to form multiblock copolymers with complex microstructures in ways that were unimaginable a few decades ago (*11*). Synthetic sequence regulation constitutes the obvious next step in the field. Current progress in macromolecular chemistry points to a new era for polymers (*12*), in which the development of molecularly encoded synthetic polymer chains may open up opportunities in materials science and nanotechnology.

Sequence-Controlled Biological Polymerization Processes

Three sequence-controlled polymerization processes are dominant in living organisms: DNA replication, DNA→RNA transcription, and RNA→protein translation, in which the molecular information carried by nucleic acids is converted into sequence-defined protein chains. During DNA replication and transcription, nucleic acid–templated polymerization takes place by the action of DNA and RNA polymerases. The mechanism of translation is even more complex and relies on ribosomes, large catalytic particles composed of both RNA and proteins. All three of these polymerizations are more tightly controlled than any known synthetic polymerization processes. Thus, there are obvious advantages in using biological methods for polymer synthesis and materials science.

The principles that mediate biological polymerization can be adopted at different levels of complexity (Fig. 1). The most basic adaptation of a biological mechanism uses DNA templates to direct the coupling of nucleic acids and their analogs (Fig. 1A). In such approaches, activated nucleotides are associated to an oligonucleotide template via Watson-Crick base pairing and polymerized by chemical means (i.e., in the absence of enzyme). This field of research has been pioneered and chiefly developed by Orgel and co-workers, who optimized the nonenzymatic replication of nucleic acids (*13*). Such protein-free replicating systems often suffer from lack of efficiency and replication fidelity. Another drawback is the strong binding of the newly formed oligomers to the template, which hinders repetition of the process. Nevertheless, convincing proof of the concept has been reported (*14*–*16*). It has also been shown that nonenzymatic replication can be extended to nonnatural nucleic acids. For instance, artificial backbones based on nonribose sugars were efficiently used as templates for RNA synthesis (*16*). Perhaps even more remarkably, complementarity between RNA and peptide nucleic acids (PNA) was described (*17*). Although constructed from polyamide backbones, PNA oligomers can act as templates for sequence-defined RNA synthesis and vice versa. This behavior was further developed by Liu and colleagues, who reported the synthesis of long sequence-defined PNA oligomers on DNA templates (*18*, *19*). Recently, the Liu group used DNA-templated polymerization to synthesize sequence-defined

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polymers with no necessary structural similarity to nucleic acids by using macrocyclic PNA adapters, analogous to transfer RNAs (tRNAs), that serve as an intermediate layer between DNA templates and corresponding synthetic monomers (*20*). With this approach, a variety of synthetic polymers have been translated from DNA templates, including β-peptides of up to 26 kD containing 16 consecutively coupled building blocks comprising 90 densely functionalized β-amino acid residues. Without relying on a polymerase enzyme or on direct polymer-template hybridization, this approach enables a wide variety of potential polymer structures. Limitations include lower polymerization yields than with enzyme-catalyzed polymerizations, correspondingly lower numbers of consecutive coupled building blocks, and the need to synthesize complex substrates.

The next level of complexity in biologically based polymerization strategies is using enzymes for performing in vitro replication (Fig. 1B). The most important example of such processes is PCR, which allows copying and amplification of sequence-encoded DNA strands. Such approaches were initially performed using the Klenow fragment of DNA polymerase I. However, the high temperatures required for strand dissociation in PCR strongly limited the use of this enzyme. The utilization of the thermostable *Taq* polymerase allowed the successful development and commercialization of PCR (*4*). Today, this approach is certainly the most widespread in vitro sequence-regulated polymerization technique. However, PCR is routinely used only for natural nucleic acids. Polymerase-based approaches can be applied to nonnatural monomers, which expands the natural alphabet. For instance, the groups of Benner (*21*) and Kool (*22*) reported the use of nonnatural base pairs in enzyme-catalyzed polymerizations. Still, PCR amplification of enzymatic processes involving noncanonical monomers remains very challenging. Indeed, the fidelity of certain combinations of nonnatural (versus natural) nucleotide incorporation during PCR can be modest. Nevertheless, progress has been reported (*23*), opening new opportunities for the enzymatic synthesis of nonnatural sequence-defined polymers.

Ultimately, the whole ribosomal machinery of a living organism can be used to produce sequence-controlled polymers (Fig. 1C). Genetic engineering has been used for several decades for the synthesis of therapeutic proteins, structural proteins, and enzymes. In this approach, an artificial gene, encoding the protein of interest, is incorporated into plasmid DNA, which is introduced into a bacterial host (usually *Escherichia coli*) (*24*). Bacterial expression of the artificial gene produces the desired protein, which is ultimately extracted from the host and purified. This strategy is not restricted to natural amino acids but also tolerates noncanonical monomers (*25*). For incorporating nonnatural amino acids into proteins, the simplest approach is replacing natural amino acids with noncanonical residues in a competitive process (*26*). Alternatively, Schultz and others have described a set of related approaches for adding nonnatural monomers to the common 20–amino acid alphabet (*27*). This strategy creates an "expanded" genetic code, in which nonsense or four-base codons encode nonnatural amino acids. All these features make protein engineering a robust technique for materials science (*5*, *24*). In comparison with the other biological concepts described earlier, protein engineering is the most accepted approach in the field of polymer science. Limitations to this approach of coopting the ribosomal machinery to generate nonnatural polymers include modest yields of polymers, in which multiple nonnatural monomers are successively incorporated, and the considerable structural constraints imposed by the ribosome that limit the functional diversity of the resulting polymeric products.

Sequence-Controlled Polymerizations Based on Chemical Approaches

Biological polymerization approaches can offer outstanding sequence control but are limited in terms of structural diversity. In comparison, synthetic chemical processes give access to a much broader range of chemical structures. As described in Box 1, iterative synthesis onto insoluble supports (e.g., cross-linked resins) is one of the best pathways for monomer sequence regulation. Monomers can be sequentially connected one by one, stepwise, with washing of unreacted reagents and/or catalyst and deprotection of the reactive site, followed by cleavage of product from the support. The solid-phase methodology has been primarily developed for peptide synthesis using amino acids as monomers, but many other types of building blocks can be used (see Box 1). One drawback of solid-phase synthesis is the restricted accessibility of the reaction sites in the resin, which influences coupling efficiency. An interesting alternative to this problem is the use of individual soluble polymer chains as supports. For example, polystyrene, which is soluble in common organic solvents but insoluble in methanol, is an efficient liquid-phase support. Linear polystyrene soluble supports can be prepared by living polymerization techniques and carry optimized end-groups for iterative synthesis (Fig. 2A) (*28*). This efficient approach can be used to prepare new types of nonnatural sequence-controlled oligomers. However, conceptually, the use of soluble supports is only an optimization of the solid-phase methodology.

A more important challenge in the field is the control of monomer sequences in "traditional" polymerization processes, such as chain growth or step growth. For instance, if single-monomer addition could be controlled in living chain-growth polymerization, a stepwise addition of equimolar amounts of monomer and initiator would allow sequence regulation. However, even when living polymerization mechanisms that are highly

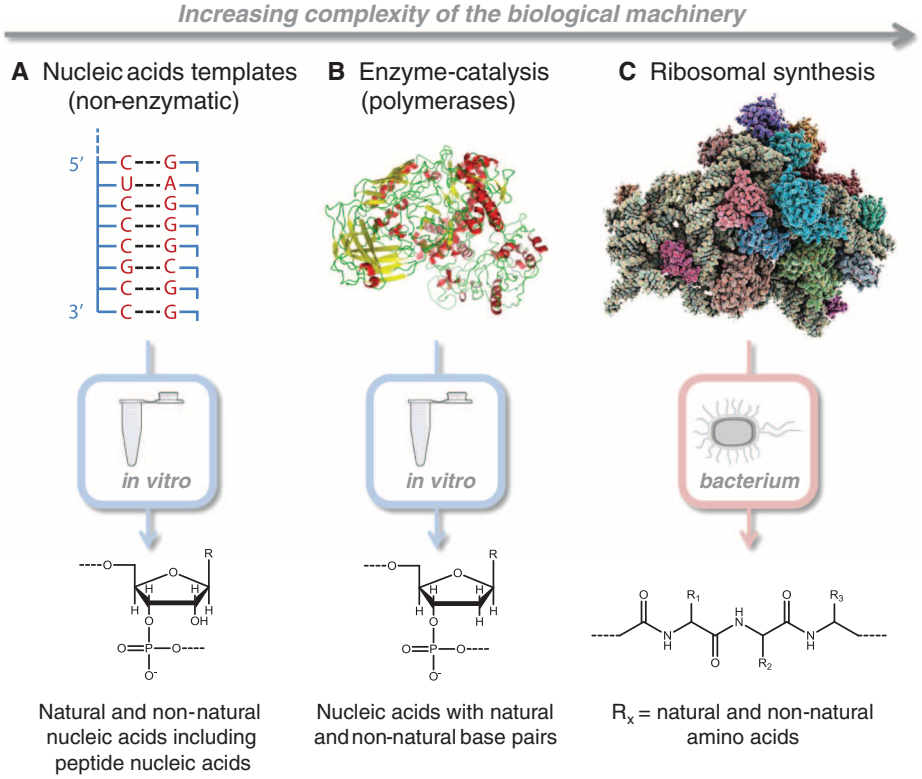
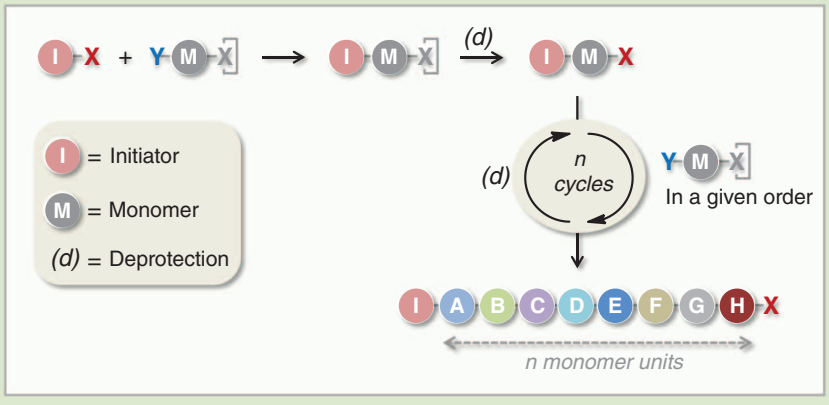


Fig. 1. (A to C) Synthesis of sequence-defined artificial macromolecules with evolutionarily optimized biological mechanisms. Note that the diagram is not to scale; a bacterial ribosome is about 50 times the size of a polymerase. [Sources of polymerase image (B) Wikimedia Commons and bacterial ribosome image (C) Laguna Design/Science Photo Library]

controlled and involve dormant species are used, such "single-monomer addition" strategies are difficult because of the inherent tendency of the monomers to react with themselves (i.e., in the propagation step). One way to overcome this problem is to decrease gradually the reactivity of the added monomers. This idea was verified in living cationic polymerization of vinyl ether monomers using ZnI_2 as a catalyst, although absolute control was not reached and, therefore, chromatographic purification was required at each step (*29*). Moad and co-workers have investigated single-monomer addition in the RAFT process, which is a controlled radical polymerization method (*30*). However, the measured yields of monomer insertion were low and, therefore, unsuitable for a reliable stepwise process.

Tong and colleagues have described single-monomer addition by atom-transfer radical polymerization (ATRP), which is another type of controlled radical polymerization (Fig. 2B) (*31*). Allyl alcohol, a nonconjugated vinyl monomer that cannot radically propagate into polymers can, nevertheless, undergo atom-transfer radical addition (i.e., single-monomer addition) because the resulting halogen terminal is inactive for radical generation or further propagation, even in the presence of a metal catalyst. However, once the hydroxyl methyl side chain is subsequently oxidized into a carboxylic acid, the terminal bond becomes active for another allyl alcohol single addition. The acid side chain can become functional by means of esterification, and thus, an iterative cycle of single-monomer addition, pendent-transformation, and functionalization allows monomer sequence control regulation as shown in Fig. 2. Similarly, in olefin cross-metathesis (CM), 4-vinylbenzaldehyde becomes a monomer potentiating single-monomer addition and further coupling via transformation into active form thereafter: The aldehyde unit can be converted into a vinyl group via Wittig olefination after CM reaction (*32*). Thus, an iterative cycle of CM and olefination gives a sequence of well-defined conjugated oligomers [i.e., oligo(phenylene-vinylene)s]. Recently, a series of sequence-defined oligomers (from dimer to hexamer) were synthesized with "electron-poor" unsubstituted monomers and "electron-rich" dialkoxy-substituted counterparts. Such an approach could facilitate sequence-oriented functions for conjugated materials (*33*).

Sequence regulation can also be attained in chain-growth polymerizations by using specific comonomer pairs. For example, some combinations of an electron-donor monomer (e.g., styrene or vinyl ether) and an acceptor one (e.g., maleic anhydride or maleimide) can be copolymerized in an alternating manner to give an AB repeat sequence (*34*), because, in these specific combinations of monomers, cross-propagation is favored over homopropagation. Note that such an alternating behavior can be tuned through specific interactions. For instance, when a bulky fluoroalcohol is used as solvent for copolymerization of limonene (donor) with a maleimide derivative (acceptor), AAB repetitive sequences (A: maleimide, B: limonene) are obtained instead of the conventional AB pattern (*35*). This particular sequence is most probably due to the interaction of the fluoroalcohol with the carbonyl of the maleimide and to the bulkiness of the limonene monomer. Conventional alternating behaviors can also be tuned using time-controlled additions of monomers in conjunction with living polymerization mechanisms. Lutz and co-workers have used such a concept to achieve the local functionalization of polymer chains (Fig. 2C) (*36*, *37*). In this strategy, a donor monomer, such as styrene, is polymerized in excess by controlled radical polymerization (e.g., ATRP), and small amounts of functional acceptor comonomers are added during the course of the reaction. Because of the favored donor-acceptor cross-propagation, the acceptor monomers are incorporated into narrow regions of the growing polymer chains. Thus, by controlling addition time, the positions of the acceptor monomer units can be precisely controlled in the polymer backbone. However, this approach to chain growth leads to chain-to-chain deviations in length, composition, and sequence. These defects can be considerably minimized by using optimized polymerization protocols (*38*) but cannot be fully suppressed. However, this strategy is applicable to a wide variety of functional N-substituted maleimides (*39*) and was shown to be efficient for the preparation of periodic polymers (*40*), encoded chain microstructures (*41*), and complex macromolecular topologies (*42*). Such appealing concepts are not restricted to radical polymerization. In anionic polymerization, 1,1-diphenylethylene derivatives are suited for such local modification in growing polymer chain, because they are not polymerizable but are reactive for growing anion species (*43*).



Box 1. Going the long way: Attaching monomers one by one.
An evident chemical strategy to attain sequence-defined polymers consists in covalently attaching monomers one by one in a given order. Such a concept implies that polymer chain growth has to be regulated in order to avoid repeated incorporation of the same monomer in a given chain. Although different mechanisms of regulation may be considered, the most common approach is using a self-reacting bifunctional monomer XY, in which one of the reactive functions is temporarily protected (i.e., deactivated) as depicted above.

The self-reacting bifunctional monomer XY strategy was developed and optimized for the solution synthesis of oligopeptides (*91*). However, solution approaches are limited and time-consuming because they require purification after each monomer coupling. The field was revolutionized by the development of solid-phase supports by Merrifield (*6*). In this simple approach, the growing oligomers are covalently bound to filterable polymer beads, which greatly improve and facilitate purification protocols. Moreover, the automation of this chemical process has substantially reduced reaction times. The concept was applied for the synthesis of many natural and nonnatural sequence-defined oligomers, including oligopeptides and oligonucleotides (*92*). Such iterative approaches still exhibit some drawbacks. First, in order to avoid substantial sequence defects, the yields of monomer coupling should be very high, particularly if a long polymer chain is targeted. Another limitation is the use of main-chain protecting groups, which imply time-consuming deprotection steps. Protecting groups are currently mandatory in bio-oligomer synthesis, e.g., peptide solid-phase chemistry. However, some nonnatural sequence-defined oligomers can be synthesized in the absence of main-chain protecting groups, for example, if two successive building blocks are used instead of a single XY monomer (*28*, *93*, *94*). An elegant example of that type is the synthesis of peptoids (i.e., oligomers of N-substituted glycines) described by Zuckermann and co-workers (*95*). This approach relies on a "submonomer" strategy. Each N-substituted glycine unit is formed by successive coupling of two submonomer synthons. The backbone chemistry is chemoselective and, therefore, does not require main-chain protecting groups.

Step-growth polymerizations also allow synthesis of sequence-regulated macromolecules and are highly suited to the preparation of periodic microstructures. Indeed, sequence-defined oligomers containing reactive chain ends can be polymerized by step growth. A variety of efficient reactions can be used, for example, the azide-alkyne click reaction (*44*). Satoh, Kamigaito, and co-workers have described the preparation of sequence-controlled vinyl polymers by a step-growth process. (Fig. 2D) (*45*, *46*). Their approach involves a metal-catalyzed radical addition reaction between nonconjugated olefin and a carbon-chlorine bond (active under a one-electron redox catalyst) to give a unit of vinyl chloride as the junction linkage. They thus used a sequence of well-defined vinyl oligomer blocks carrying olefin and chlorine at the terminals to construct vinyl polymers of periodic sequence. As pioneered by Wagener (*47*), an acyclic diene metathesis polymerization of symmetric α,ω-dienes can form sequence-regulated vinyl polymers, in conjunction with subsequent hydrogenation. Various alkyl chains can be substituted at the center in the symmetric α,ω-diene [R· in CH_2=CH–$(CH_2)_n$–CH(R)–$(CH_2)_n$–CH=CH_2], which leads to unique polyethylene of precisely branched structures (*48*). This versatile design also allows the introduction of amino acids and drugs at well-defined positions in polyethylene for biological applications (*49*). Hillmyer proposed making sequence-specific vinyl copolymers by regioselective ring-opening metathesis polymerizations (ROMP) of asymmetric substituted cyclooctenes and subsequent hydrogenation (Fig. 2E) (*50*). Both metathesis systems are expected to generate polyolefins displaying sequence-oriented functions.

In nature, template systems are crucial to regulating monomer sequences in biopolymers, such as RNA and proteins. Thus, template effects have also been extensively studied in synthetic polymerizations. In the late 1970s, sequence control by free radical polymerization was attempted with vinyl monomers carrying a set of nucleobases on the side chains (*51*). A few interesting results demonstrating template effects with the complementary interactions in polymerizations have been reported (*52*–*54*). However, these approaches did not reach sequence regulation, and the template effects were restricted to rate enhancement or molecular weight transcription. The limitations of enzyme-free templating approaches are also relevant to these synthetic approaches. O'Reilly and Turberfield have demonstrated another type of DNA-templated synthesis to prepare sequence-regulated oligomers (*55*). They used the end groups of stranded DNA molecules as adjacent and dissociative reaction scaffolds for the Wittig reaction between triphenylphosphonium (ylide) and aldehyde that gives a C=C bond and phosphine oxide. The molecules are sophisticatedly designed for sequential transfer reaction of the embedded building block from one DNA terminal to another, which allows construction of sequence-regulated molecules. Eventually, they achieved sequence control for a decamer with this methodology (*56*). Lynn and co-workers have described the DNA-catalyzed step-growth polymerization of monomers containing primary amine and aldehyde reactive functions (*57*). Although limited to short oligomers, this approach allows the synthetic translation of information encoded in DNA chains. Schuster and colleagues have also taken advantage of the complementarity of DNA strands to synthesize sequence-defined linear and cyclic oligomers based on bis(2-thienyl)pyrrole and aniline (*58*). To achieve sequence control with synthetic templates, a positional regulation of an initiator or active species generator is first important, and thus, a combination with living polymerization should be promising. Ouchi and Sawamoto designed template molecules to embed an initiator site (i.e., radical generator) close to a recognition site for vinyl monomer and, thus, demonstrated a way to control selectivity of radical species for "recognized" monomer

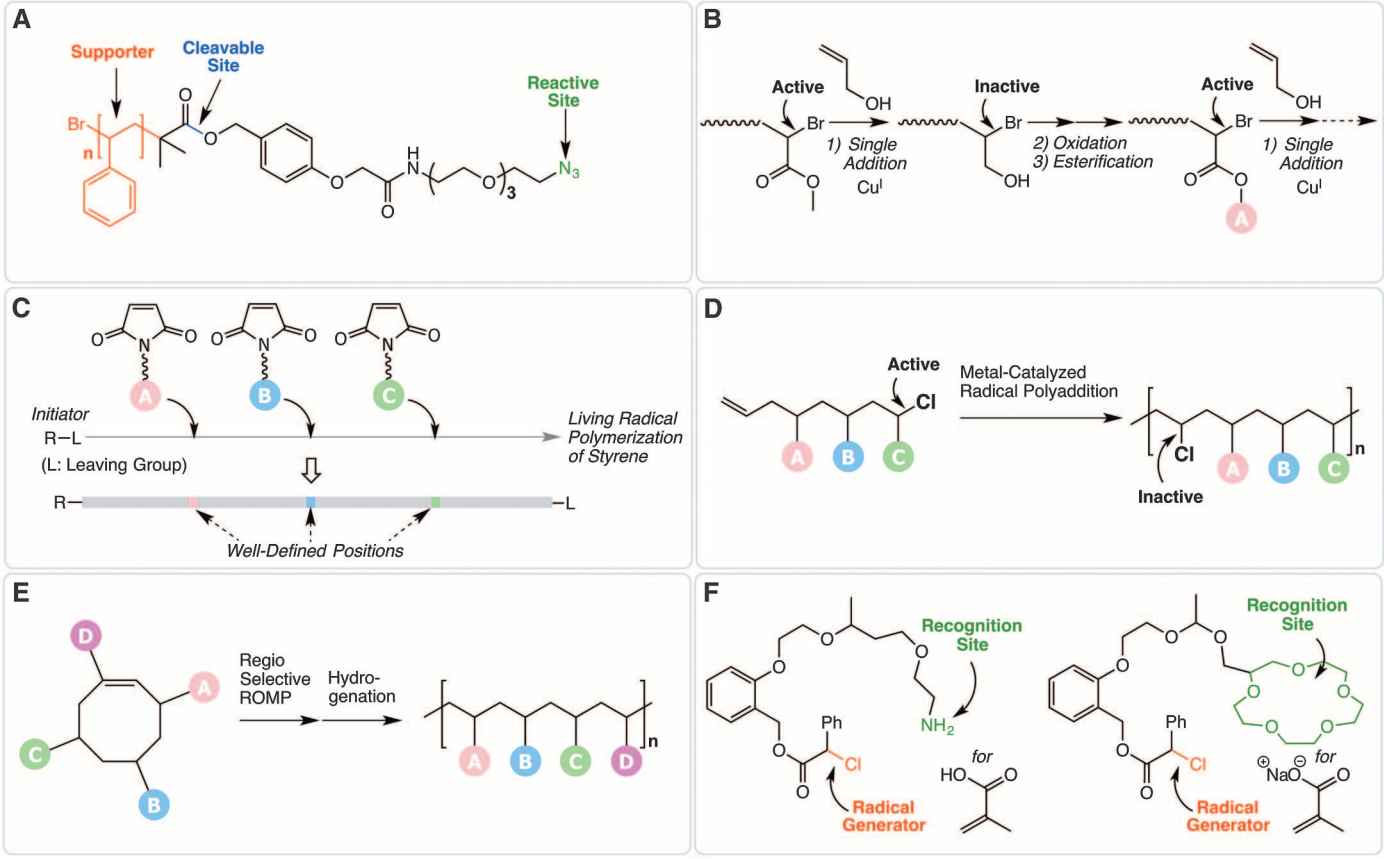


Fig. 2. Representative chemical approaches to sequence control. (**A**) Soluble polymer supporter for azide-alkyne click reaction, (**B**) iterative single-monomer addition with allyl alcohol in living radical polymerization, (**C**) positioning control in living radical polymerization of styrene, (**D**) metal-catalyzed radical poly-addition, (**E**) region-selective ROMP of asymmetric substituted cyclooctene, and (**F**) template initiators for living radical polymerization.

over "not recognized," but similar, reactive counterpart (Fig. 2F) (*59*, *60*). Such selectivity was just achieved in a single monomer–addition process, but the control was noteworthy. However, this strategy presumably falls into difficulty, as the chain is longer, because multiple recognition sites need to be arranged on template. A more feasible way to use a template is chain-growth polymerization of multivinyl monomers on a cleavable template, although the sequence pattern is limited to being periodic. In this strategy, immobilization of the vinyl groups on a template during polymerization is important to avoid both cross-lining reaction and unfavorable jumping propagation. AB and ABA patterns were achieved via radical polymerizations (*61*, *62*).

Another strategy for sequence-regulation in synthetic processes is catalysis. This approach is currently underexplored. Thomas, Coates, and coworkers demonstrated catalyst-driven sequence control (*63*), and they achieved alternating sequence control in a polyester from a set of enantiomerically pure, but different, substituted monomers (i.e., β-lactones) by using yttrium catalysts for stereospecific polymerization. Ultimately, the development of artificial catalytic nano-machines resembling ribosomes would be a key to controlling sequences in chemical processes. Although this dream is far off, promising concepts have been described. For instance, Leigh's group has reported a rotaxane-based molecular machine that allows synthesis of sequence-specific peptides (*64*). In this approach, a molecular ring bearing a thiolate initiator moves on a molecular axle on which are attached amino acids. The directional progression of the ring on the axle allows sequence-controlled polymerization to occur (Fig. 3). Such an advanced chemical design, combining macromolecular and supramolecular concepts, is at the forefront of the field and opens up interesting avenues for the future.

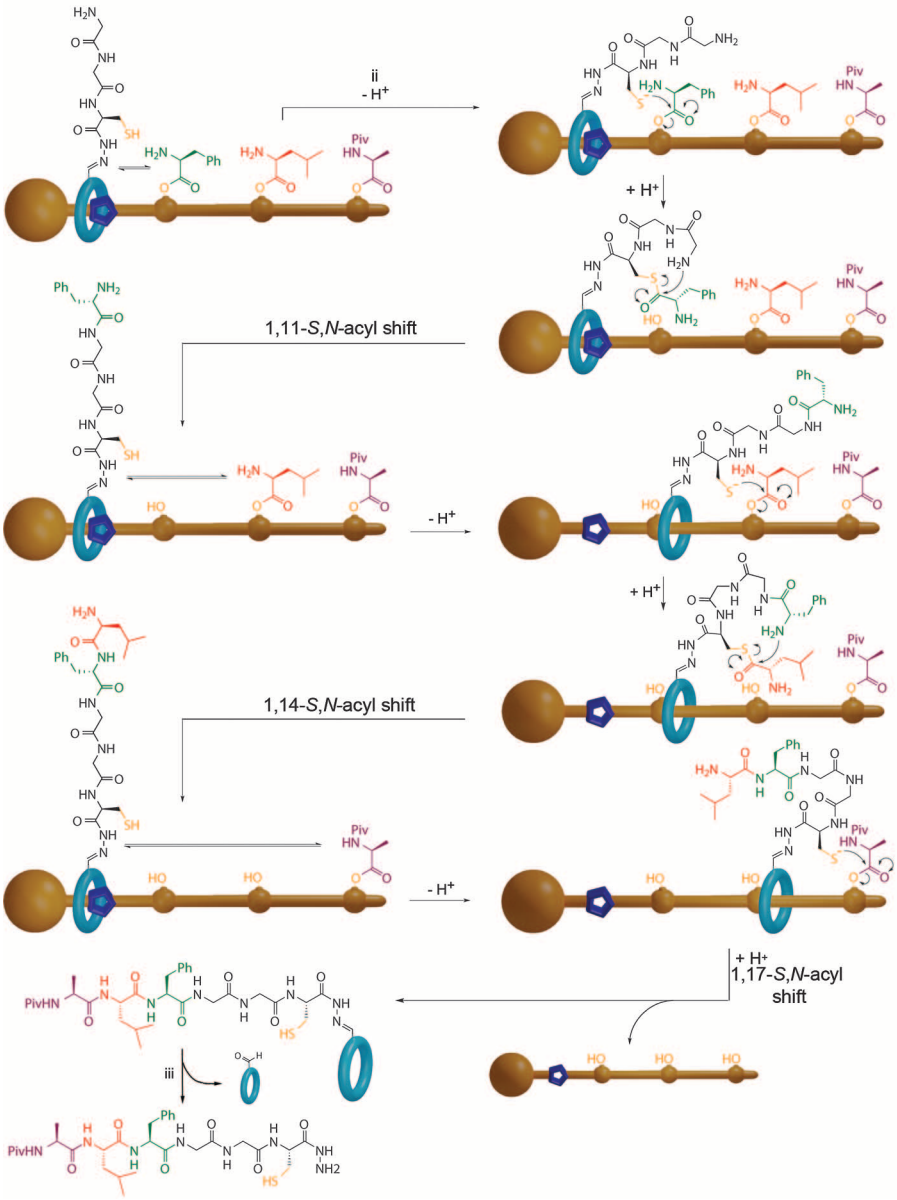


Fig. 3. Proposed mechanism for the synthesis of sequence-defined oligopeptides on a molecular machine. The molecular structure of the rotaxane machine and the detailed experimental conditions can be found in (*64*). [Adapted with permission from (*64*), copyright AAAS 2013]

Properties and Promises of Sequence-Controlled Polymers

In comparison with conventional synthetic macromolecules, such as homopolymers and block copolymers, sequence-controlled polymers allow a higher level of control over structural and physicochemical properties. The most remarkable features of sequence-controlled biological polymers and their degree of utilization and mimicry in synthetic materials are listed in Table 1. The first and last entries of this table are not directly discussed in this section. Using encoded primary structures for data storage is presented in more detail in Box 2, whereas self-replication is described partly in the first section of this review, but can be explored in (*65*, *66*).

The self-assembly of sequence-controlled oligomers, such as oligopeptides and oligonucleotides, has been investigated (*3*, *67*). Many of these studies have shown the relevance of such oligomers in materials science. For instance, sequence-defined oligopeptides self-organize into a variety of nanostructures, including fibers, tapes, ribbons, vesicles, and tubes. This broad range of self-assembly behaviors has been used to guide the organization of other types of materials, such as biocompatible polymers (*68*), conducting polymers (*69*), and inorganic matter (*70*). Beyond oligopeptide self-assembly, protein engineering allows the design of artificial materials with highly optimized properties. For example, Tirrell and coworkers have described the preparation of stimuli-responsive hydrogels based on triblock proteins (*71*). The monomer sequences of these macromolecules were engineered in order to obtain charged water-soluble middle blocks flanked by two self-associating leucine zippers. Such optimized primary structures exhibited pH and thermo-reversible gelling in aqueous medium. Sequence-defined nucleic acids have also opened up avenues for materials design. As demonstrated by Seeman (*72*) and many others, the self-recognition of complementary DNA strands is currently an unrivaled feature for organizing and sorting building-blocks such as polymers, nanoparticles, or nanocrystals (*3*, *73*).

Aside from biopolymers, the nonnatural sequence-controlled polymers discussed in the previous sections and Box 1 also open up technological opportunities. In terms of folding and self-assembly, some basic features of proteins can be mimicked using synthetic sequence-defined foldamers (*74*). However, many of these approaches rely on synthetic chemical concepts, which are very close to natural design (e.g., peptidomimetics). Yet, proteinlike materials can also be prepared

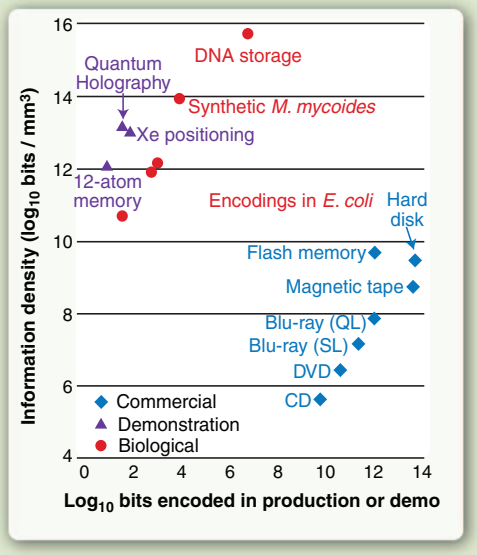
Table 1. Known properties of sequence-controlled polymers and their utilization in materials science.

Sequence-dependent property	Some important implications in biology	Degree of realization in synthetic materials
Molecular storage of information	Heredity	Proof of principle
Spatial organization of functional elements	Cell signaling	Proof of principle
	Photosynthesis	
Folding and self-assembly	Complex globular objects	Multiple examples
	Mechanical properties of tissues	
	Molecular motors	
Molecular recognition	Biocatalysis	Multiple examples
	Molecular transport	
	Signal transduction	
	Cell signaling	
Self-replication	Reproduction	Limited success
	Evolution	
	Living matter	

using very different chemistries (*75*). For example, Meijer and co-workers described the preparation and catalytic properties of enzyme like globular particles (*76*). These objects were obtained by the folding of individual polymer chains in aqueous medium. The monomer sequence distribution of these polymers was regulated with a controlled radical polymerization process, and their folding in water was driven by the helical assembly of nonnatural side-chain supramolecular motifs. Despite being based on fully nonnatural chemical design, these single-chain particles exhibited promising enzymelike behaviors. As listed in Table 1, another advantage of sequence-controlled polymers is the possibility of controlling the chain positioning of functional elements. For instance, it was demonstrated that the sequence-controlled copolymerization of styrene and N-substituted maleimides allows preparation of single-chain sugar arrays (*77*). Such sequence-controlled glycopolymers interact with complementary lectins and are, therefore, interesting glycoprotein mimics.

Sequence-regulation also strongly influences the macroscopic properties of synthetic polymer materials. For instance, the solution and solid-state behaviors of polymers closely depend on their primary structure. Solubility and phase transitions in water and organic solvents can be tuned by using subtle monomer sequence modifications (*78*–*80*). Some properties of polyelectrolytes, such as charge density (*81*) and persistence length (*82*), can also be precisely adjusted by sequence regulation. It was also reported that the solution self-assembly behavior of triblock copolymers containing nucleobases is strongly influenced by the block sequences (*83*, *84*). In the solid state, it was reported that both block copolymer mesophases and semicrystalline phases are strongly dependent on monomer sequences (*85*, *86*). For example, Zuckermann and co-workers have studied the influence of sequence-controlled segments on the phase behavior of polystyrene-based block copolymers (*86*). Their results indicate that order-disorder transition can be finely controlled using composition and sequence variations. Other important macromolecular properties have been found to be strongly sequence-dependent. For instance, Meyer and colleagues have shown that the degradation kinetics of biodegradable aliphatic polyesters is influenced by comonomer sequences (*87*, *88*). Nearly linear release profiles were found for poly(lactide-*co*-glycolide) (common name PLGA), which is one the most used polymers for biomedical applications. Sequence-controlled nonnatural polymers can also be tailored to create optimal interactions with specific materials. Börner and co-workers have highlighted the relevance of sequence-defined poly(amidoamine)s in nonviral gene-delivery (*89*). Indeed, the primary structure of these synthetic gene carriers can be tailored for optimal DNA complexation. Similarly, nonnatural macromolecules with optimized monomer sequences can

Box 2. Data-storage on sequence-controlled polymers.
In living organisms, all heredity information is encoded by the four-monomer units of DNA chains. Such monomer encoding offers a huge storage capacity. Moreover, as genetic archeology has shown, the message of DNA chains can be preserved for thousands of years if nucleic acid degradation is prevented. Thus, DNA and, perhaps, other sequence-controlled polymers appear to be valid options for storing data in man-made technologies. For instance, the storage mechanism of DNA can be used in a nonbiological context, as for artificial DNA encryption (*96*). Short messages, sentences, and poems have been written in DNA chains (*97*). However, in most of the reported examples, the number of encoded bits of information remained relatively limited.



A breakthrough was described by Church and co-workers (*96*). These authors have demonstrated that a full textbook containing about 50,000 words could be written on DNA and read. In particular, two interesting innovations were reported in that work. First of all, a single bit of information was encoded on each base, i.e., both adenine and cytosine encoded a 0, whereas guanine and thymine encoded a 1. This simplification allows more flexibility in terms of synthetic chemistry. The authors did not attempt to synthesize very long macromolecules but developed instead a library of oligonucleotides, in which each element can be tracked by a short molecular barcode. Each oligomer contained 159 monomer units: 96 for information storage, 19 for the barcode, and 44 for PCR amplification. These fragments were synthesized on DNA microchips and, after amplification, were read using next-generation sequencing technology. Although technological applications are not yet in sight, this scientific breakthrough reduces the limits of artificial DNA storage. As shown in the displayed graphic, this system combines a huge information density with a relatively large storage capacity. Moreover, recent innovations in rewritable nucleic acid storage indicate that this technological field is rapidly progressing (*98*). [Image adapted with permission from (*96*), copyright AAAS 2012.]

be used to control the mineralization of inorganic materials (*90*).

Outlook

Sequence-controlled polymers should provide major improvements for atom economy, molecular precision, adjustment of physicochemical properties, and device miniaturization. However, as described above, this emerging field consists of two converging trends: (i) exploitation and engineering of readily available sequence-defined biopolymers (*26*); and (ii) development of synthetic sequence-regulated polymerization processes. The former option is more promising on a short-term basis because it uses already existing structures. Nucleic acids and proteins are in a sense "perfect" sequence-defined macromolecules, and their properties and functions are now well-understood. However, these macromolecules were optimized by nature for use in a given environment (i.e., biological conditions) and are, therefore, not always suitable or practical in other contexts. The recent progress in the synthesis of nonnatural nucleic acids and proteins has broadened the scope of use of these polymers. However, their widespread utilization in nonbiological applications remains limited by economical, technical, and scalability issues.

In that regard, synthetic sequence-controlled polymers, prepared using traditional high-scale polymerization processes, such as chain-growth and step-growth polymerizations, represent an interesting alternative to natural polymers. Primary progress has come from controlled radical chain-growth polymerizations. The degree of sequence regulation in such approaches still remains low in comparison with DNA. Nevertheless, synthetic sequence-controlled polymers bring additional benefits in terms of chemical diversity and scalability. As the fields of natural and synthetic sequence-regulated polymers start to converge, we can expect the selection of practical, scalable, and versatile systems. It is tempting to speculate that protein engineering is simply the first example of a discipline bridging the gap between biological sciences and polymer science and that many new analogous fields will emerge as our ability to create and manipulate sequence-controlled polymers comes of age.

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Sequence-Controlled Polymers

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Controlled Polymers
Nature has achieved exquisite sequence control in the synthesis of polymers like DNA. In contrast, synthetic polymers rarely have the same fidelity in their chemistry or uniformity in chain-length distribution, especially when more than one monomer is involved. Lutz *et al.* (1238149) review the progress that has been made in making sequence-controlled polymers of increasing length and complexity. These developments have come from both advances in synthetic chemistry methods and the exploitation of biological machinery.