From Nucleobase to DNA Templates for Precision Supramolecular Assemblies and Synthetic Polymers

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Owing to the great advances in the automated synthesis and programmed self-assembly of nucleic acids, these are readily used for progresses in nanoscience, polymer science, supramolecular chemistry, and for elaborating complex chemical systems in link with the origin of life. In this minireview, we report on the recent advances of utilization of nucleobases, nucleotides, and nucleic acids as templates to achieve well-defined supramolecular polymers, synthetic polymers, and sequence-controlled polymers. We particularly emphasize the aspects of supramolecular organization, self-assembly, chirality effects, and information transfer, going from nucleobase templating to DNA-templated polymerizations. Some recent developments of supramolecular hybrids involving nucleic acids are underlined for prospective biological applications.

Introduction

DNA is the most informed molecule, a molecule of life stocking and transmitting the genetic information. DNA-templated polymerization, *i.e.* the 'writing' of a daughter polymer based on the mother DNA sequence, is an essential process of gene replication, transcription, and translation. Besides, Nature offers us a wealth of highly organized nanostructures involving supramolecular self-assembly of nucleic acids and proteins, a well-known example being the Tobacco Mosaic Virus (TMV). DNA-based structures and DNA-templating processes have therefore inspired many researchers, to evolve towards a control of synthetic architectures both in terms of dimension and sequence. This inspiration has been boosted by the great advances in biotechnological tools concerning nucleic acids automated synthesis, selection, amplification, and organization, which have spread DNA in many areas of (bio)materials science and nanoscience.[1-6] The design of DNA junctions, DNA origami, and DNA crystals, opened the door to scaffolding in 2D to 3D from the sub-nm scale to the few hundreds nm scale.[7] Notable recent examples include large origami up to the 300 nm-wide,[8] and DNA reconfigurable devices of desired shape.[9] Indeed, DNA is now readily used as a scaffold for elaborating tailored nanomaterials, and many examples show the controlled organisation of proteins, metal nanoparticles, or inorganic nanostructures onto DNA origami.[7,10]

Besides, the combination and/or self-assembly of molecules with DNA, a topic often referred to as *Supramolecular DNA assembly*,[11,12] can yield highly organised, functional nanostructures of high interest for catalysis, (bio)sensing, transport, delivery, and optical/electronic nanomaterials.[10, 12, 13]

DNA is also a robust template to organise organic structures into desired, programmable architectures, with a sub-nm precision.

In this context, the utilization of nucleic acids as templates to direct the self-assembly, supramolecular polymerization, or covalent polymerization of synthetic molecules is a sound bioinspired chemistry approach, as the current control over DNA length and sequence permits to achieve -ideally-monodisperse and sequence-controlled polymers.[14] This bioinspired polymerization is still in infancy but recently there were interesting developments in this area, by merging original polymerization procedures with DNA recognition approaches. Note that the aspects of organic synthesis, reactions, and template-directed ligation strategies involving nucleic acids analogues were covered elsewhere, see references[15-17].

In this minireview, we intend to give a glimpse into nucleobases and nucleic acids templating approaches for achieving precision supramolecular or synthetic polymers, and DNA/polymer hybrid architectures, with a particular emphasis to the aspects of supramolecular organization, self-assembly, chirality, and information transfer. We first introduce the templating mechanisms in relationship with the nucleic acids structure and the supramolecular interactions at play. Note that hereafter we refer to nucleic acids templating in the broad sense, *i.e.* involving nucleobases, nucleosides, and (oligo)nucleotides, up to the use of long DNA templates (*i.e.*

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several thousands of base pairs). First, templated structures involving a single nucleobase approach are reviewed, with examples from nucleobase-functionalized molecules up to nucleobase-substituted polymers. Going towards more complex architectures, we then cover the recent research efforts on DNA-templated polymerizations, from supramolecular polymerization to covalent polymerization of synthetic monomers, including enzyme-mediated polymerization. The emerging topic of artificial translation of nucleic acids into sequence-controlled synthetic polymers is appraised. Finally, we describe some interesting developments of nucleic acids/templated polymer hybrids in the context of biological applications, such as biosensing and gene-delivery.

Nucleic acids templating: a game of interactions

Templates can be described as molecular matrices that direct the self-assembly of molecular guests.[18] The template recognizes and organizes the molecular guests, and transfers the information (the nucleic acid sequence) to the reaction product, from the monomer to the polymer. For nucleotide and nucleic acids templating, this involves:

1) *Recognition*: the molecular guests recognize the DNA binding sites through supramolecular interactions, which impart selectivity. Obviously, one first thinks to base pairing (A=T and G≡C) for complementary H-bonding patterns imparting selectivity with a ssDNA. Indeed, most DNA templating approaches involve the base pairing of nucleobases-modified synthetic molecules with single-stranded DNA (ssDNA) scaffolds. Besides, electrostatic interactions or salt-bridge interactions between a cationic molecular guest and the anionic phosphodiester backbone can also be exploited, offering one charge $-|e|$ per phosphate binding site. When considering a double-stranded DNA (dsDNA) template, other recognition sites can be envisioned, even if these are less specific than base recognition, such as groove-binding (alignment of the guests along the DNA minor-groove or major-groove), through-base intercalation, shape complementarity, or phosphate binding, which all combine several types intermolecular interactions (such as electrostatic, π-type interactions, H-bonds, van der Waals close packing).[19] Indeed, the size of the minor-groove locally depends on the sequence: dsDNA with a few consecutive A:T base pairs in the sequence possess to narrower minor grooves at this site, which could lead to sequence-specific recognition. Overall, the balance of these intermolecular interactions and their cooperativity are crucial for the recognition. Indeed, DNA is inherently a multivalent template, allowing to play with various types of interactions and possibly template distinct types of monomers on several recognition sites.

2) *Organization*: the nucleic acid template spatially organizes the molecular guests, which modifies their reactivity by increasing the effective molarity of the reactive groups. Indeed, to organize the molecular guests the structure of the nucleic acid is important: for example, a homothymidine ssDNA is a coiled polymer, whereas homoadenine ssDNA is helically pre-organized, and guanine-rich ssDNA sequences may fold in intramolecular G-quadruplexes (G4) structures.[20] Beyond organizing the building blocks along the template, DNA is also a chiral template, which can therefore induce a chiral (helical) organization of the molecular guests. Chiral induction is an important mechanism in nucleic acids templating, and is used both at the nucleotide level and at the DNA level. The organization of the synthetic building blocks along the template is critically dependent on the mode of self-assembly, *i.e.* if cooperativity effects take place upon the propagation of the monomers along the template.[21] Besides interactions and size effects, one should also pay attention to the entropic cost to organize the molecules along the template.

3) *Information transfer*: the information stored in the DNA template in terms of recognition pattern and spatial arrangement is transferred at the level of the reaction product, here the templated polymer. In the context of templated polymerization, this can lead to sequence-controlled synthetic polymers based on the mother DNA template sequence. In the ideal case, the template must then be removable from the reaction product. Note that the term template is also accepted for reactions in which the template becomes part of the reaction product, in this case for achieving DNA/templated polymer complexes.

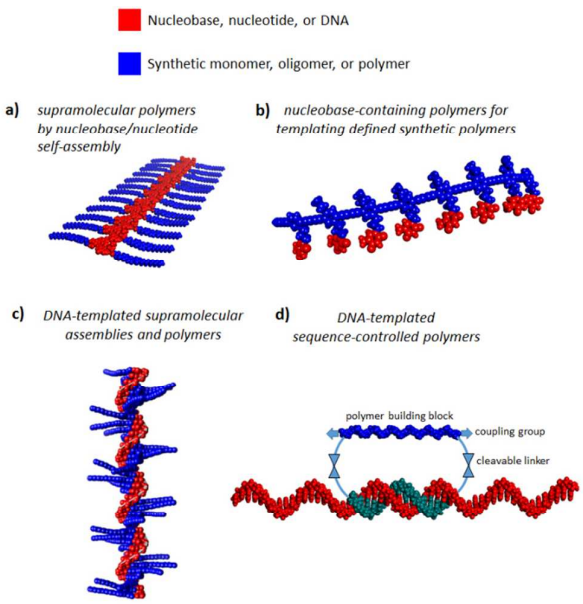

Figure 1. Sketch of the different templating approaches considered in this minireview, from the nucleobase/nucleotide level (a,b) to the DNA level (c,d) for achieving precision supramolecular polymers or synthetic polymers.

The success of DNA templating approaches stems from the high level of programmability of DNA-directed self-assembly, the huge information density attainable, and the robustness of DNA scaffolds offering long-term information storage.[22] Nucleic acids templating is also quite versatile, see a few

different possible approaches in Figure 1. To achieve precision polymers, one can use either nucleobases covalently bound to synthetic molecules or incorporated at the monomer level of a synthetic polymer chain (Fig. 1a-b, and next section). At the DNA template level, one can scaffold these nucleobase-molecule conjugates to self-assemble along a DNA template, acting as a tape-measure for achieving monodisperse supramolecular polymers, which could be subsequently covalently polymerized (Fig. 1c). One alternative is the DNA-templated organization of macrocycles,[23] which makes use of cleavable linkers between the recognition units and the polymer building block (Fig. 1d). In terms of polymerization, one may envision classical step-growth procedures of monomers adsorbed along the DNA minor-grooves, enzyme-assisted polymerization, or dynamic covalent polymerization, as covered in the following sections.

Nucleobase-templating

The nucleobase approach consists in the functionalization of synthetic molecules by nucleobase(s). This is a straightforward approach to self-assemble molecules by exploiting base recognition mechanisms, either by Watson-Crick base pairing or by Hoogsteen H-bonding networks. Two approaches are distinguished here: appending nucleobase(s) (or nucleoside/nucleotide) to an organic molecule, or the incorporation of nucleobases in synthetic polymer chains. In both cases, nucleobase self-assembly or the addition of a complementary nucleobase (or oligonucleotide) provide means to modulate the supramolecular organization.

Nucleobase-directed self-assembly of small molecules

Much effort has been devoted to append organic molecules possessing interesting optical/electronic properties to nucleobases or nucleotides, in order to scaffold 1D to 2D self-assembled nanostructures. This concerns square-planar molecules such as porphyrin derivatives, up to small oligomers (*e.g.* of thiophene or phenylene vinylene) in the range of a few monomer units. For instance, Champness and colleagues have designed porphyrins functionalized with thymine bases at each *meso* position, a molecule that self-assemble forming squared 2D networks (on a planar graphite surface), due to inter-thymine H-bonds, as observed with Scanning Tunneling Microscopy (STM), see Figure 2.[24] By adding of an adenine derivative (9-propyladenine), it was observed 2D heteromolecular complexes by H-bonding between A and T, and they noticed that the degree of order in these 2D cocrystals is highly dependent on the concentration and the molar ratio between the two compounds. Small oligomers linked to nucleobases were also shown to self-assemble in a variety of morphologies depending on the nucleobase with which these are functionalized and on the solution conditions. For instance, this sensitivity of self-assembly of nucleobases was observed in oligomers functionalized with guanosine, as reported by Spada and colleagues.[25] Indeed, lipophilic guanosine derivatives are known to self-assemble in a variety of H-bonding motifs depending on the solution conditions.[26] A particular structure is the guanine-quartet, a square-planar network of four guanines, which can stack on top of each other, ultimately forming G-quartet supramolecular polymers in the presence of alkali ions (such as K^+ or Na^+). These G-quartet stacks may yield liquid crystals or hydrogels depending on the guanosine side groups.[26-28] It was shown that the self-assembly of a guanosine-terthiophene derivative can be modulated through the solution conditions, from one-dimensional ribbon-like Hoogsteen H-bonding networks (in chloroform) to G-quadruplexes structures in octamer form (*i.e.* two parallel guanine-quartets complexing one K^+) in solutions containing potassium ions.[25] When adding a K^+-complexing agent, a [2.2.2] cryptand, to the solution of octamers, a conversion from G-quadruplexes to G-ribbons was achieved. Regarding the self-assembly of these molecules on surfaces, it was observed highly-directional supramolecular nanowires, as observed by STM, see Figure 2. These were formed by H-bonding of the guanine bases in parallel zig-zag ribbon-like networks (so-called *B*-type networks), with the lateral groups containing thiophene oligomers assembled almost perpendicularly to the ribbon axis, see Figure 2.[25]

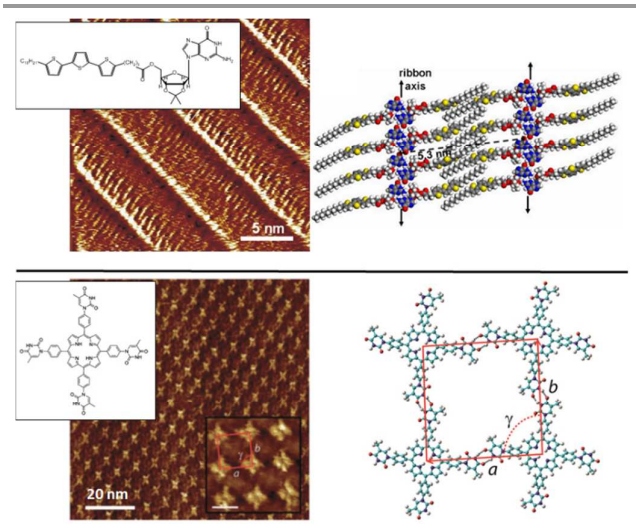

Figure 2. Self-assembly by nucleobase/nucleoside recognition in 1D (top, guanosine ribbons) and in 2D (bottom, thymine square networks) on a graphite surface. Left: structures of the molecules and corresponding STM image of a monolayer (scale bar for the bottom inset: 2 nm) Right: models of supramolecular assembly, as obtained via molecular mechanics simulations. Adapted from refs. 24 and 25 with permissions from Wiley-VCH and The Royal Society of Chemistry.

The supramolecular arrays of several types of monolayers formed by guan(os)ine derivatives bearing alkyl or alkoxy groups were further studied by STM, and interestingly the dynamics of interconversion between ribbon-like networks to G4 networks was monitored upon subsequent additions of solutions containing K^+ (from ribbons to G4) or [2.2.2] cryptand (from G4 to ribbons).[29] The dynamics of these systems renders them suitable as 2D 'dynamers', for which the supramolecular

assembly dynamically responds to external chemical stimuli. Meijer and colleagues also reported the self-assembly of a guanine-oligo(*para*-phenylene vinylene) conjugate, which self-assemble into G-octamers. Upon careful control of the solution conditions, the hierarchical assembly of G-octamers leads to organic nanoparticles with a chiral arrangement of the oligo(*para*-phenylene vinylene), and for which the size greatly influences the fluorescence intensity.[30] Besides, the same group reported on the self-assembly of the same type of oligomers bound to a non-natural base, a diaminotriazine (DAT). The oligo(*para*-phenylene vinylene)-diaminotriazine conjugate self-assembles in monolayers by forming rosette-like assemblies on graphite. Note that this diaminotriazine derivative can bind through three complementary H-bonds to the thymine base (see below). Hence, the addition of thymidine to the rosette-like assemblies of OPV-DAT led to the transition from rosettes to dimers. Interestingly, depending on the D or L enantiomer form of thymidine used, the chirality of the 2D assembly was reversed, forming counter-clockwise dimers or clockwise dimers, respectively.[31] Very recently, González-Rodríguez *et al.* designed a rigid linear building block (*para*-diethynylbenzene) end-capped with a guanosine base at one extremity and a cytosine base at the other extremity. The molecule has been designed to have G≡C Watson-Crick pairing that direct self-assembly of molecules at 90°. The self-assembly of these molecules yielded well-defined macrocyclic squared structures in organic solvents,[32] and 2D nanoporous networks on a surface, which can host small molecules such as coronene.[33]

Instead of nucleobases or nucleosides, one can exploit nucleotides templates, which allows to use the phosphate anionic groups to bind cationic monomers able to polymerize. This approach was notably used by George *et al*., who used adenosine-phosphates (AMP, ADP, or ATP) for supramolecular polymerization of naphthalenediimide (NDI) decorated with dipicolylethylenediamine-Zn^{2+} complexes at each NDI extremity. These Zn^{2+} complexes bind to the anionic phosphate groups of nucleotides with high affinity, which in synergy with π-stacking interactions between NDI derivatives yield helical supramolecular polymers. Interestingly, by mixing this molecule with either AMP, ADP, or ATP, they obtained chiral stacks of opposite handedness : ADP (or AMP) gives rise to left-handed helices, whereas ATP induces right-handed helices.[34] In competition experiments, ATP replaces ADP, as observed with instantaneous reversal of its helix handedness as monitored by Circular Dichroism (CD). This provides an allosteric control of the helicity of the supramolecular polymer, a characteristic that has been used to probe the enzymatic activity of phosphatase towards ATP (see below).[35]

Overall, this nucleobase/nucleotide self-assembly approach, although not giving rise to monodisperse polymers, allows for achieving size-controllable, shape-defined self-assemblies and possibly supramolecular polymers. In a few instances, it led to helically-organized, or long unidirectional supramolecular polymers, which are interesting for the development of chiral nanomaterials or supramolecular wires for photonics and electronics. Indeed, π-conjugated oligomer-nucleobase dyads constitute model assemblies to probe charge transfer processes between electron donors and electron acceptors, as recently studied for oligothiophene-nucleotide conjugates, for which the oligothiophene is the electron donor and the nucleobase the electron acceptor.[36] This type of design could be further extended to multiple types of conjugated oligomers appended with complementary nucleobases, ultimately forming well-defined multichromophore arrays.

Nucleobase-substituted polymers as templates

The incorporation of nucleobases in synthetic polymers chains is a promising approach to control the polymer folding (*e.g.* by using hairpin-forming sequences) and modulate the supramolecular organization of the polymer (*e.g.* by the addition of selected complementary nucleobases). Whereas the early works date back to around 50 years ago, this field has recently progressed due to the improved control over polymer architecture and the will to mimic templated polymerization.[37] A major advance was achieved with the design of Peptide Nucleic Acids (PNA),[38] for which the synthesis is nowadays automated and which is used in many areas of molecular biology, materials science, and as molecular templates.[39,40, 41] Apart for PNA and other nucleic acid analogues, the synthesis of nucleobase-containing conventional polymers (*e.g.* using vinyl, styrene, or norbornene monomers) was brought by several groups, for instance to obtain polymers with interesting self-assembly or DNA-mimetic properties.[42,43,44]

The incorporation of nucleobases as side groups along functional polymers such as π-conjugated polymers is particularly appealing to control the interchain interactions, which strongly influence the optical and electronic properties. For instance, a π-conjugated poly(*para*-phenylene butadiynylene) with pendant thymine nucleobases on each monomer unit was synthesized by Lo and Sleiman.[45] By adding either complementary nucleobases (adenosine or oligodeoxyadenine) to the polymer in water, they observed an enhanced fluorescence of the polymer, likely due a decrease in the degree of π-stacking between the polymer chains upon adenosine binding to thymine units. The design of those nucleobase-containing polymers opens the doors to templated-polymerization. A major step was the templated polymerization of adenine-substituted monomers by a thymidine-substituted diblock copolymer. The Sonogashira polymerization of the monomers in presence of the template (*i.e.* when monomers are assembled along the template through base pairing) yield poly(*para*-phenylene ethynylene) daughter polymer, possessing a degree of polymerization (*DP*) around 25 monomer units and a narrow molecular weight (polydispersity index around 1.2) comparable to the template polymer. In contrast, non-templated polymerization yield polymers with a much lower *DP* (around 10 units) and a broad molecular weight distribution (polydispersity index around 2.8).[42]

Since this pioneering work, other templated-polymerization using nucleobase-containing polymers were carried out, as covered in a recent review article.[37] An important step further

has been reached by O'Reilly and colleagues, who have combined nucleobase templated-polymerization with a segregation strategy using block copolymer self-assembly, see Figure 3. The polymerization of an adenine-substituted styrene monomer in the presence of a block copolymer containing a poly(vinylbenzyl thymine) template allowed for unprecedented control over daughter polymer molecular weight and polydispersity, up to 400,000 g.mol^{-1} and 1.08, respectively. The segregation strategy allows for this fine control, by localizing propagating radicals in micelles cores in which takes places the templated-polymerization.[46]

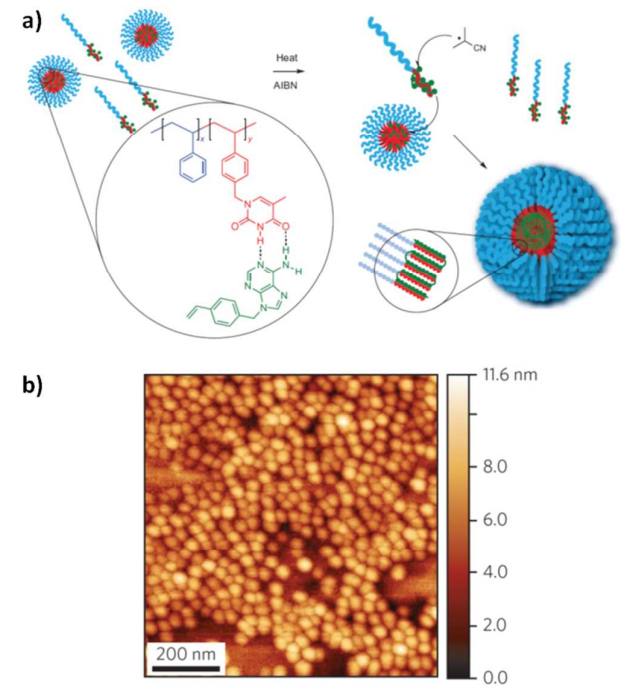

Figure 3. Polymerization of vinylbenzyl adenine monomers on a poly(vinylbenzyl thymine) template via A:T recognition and subsequent radical polymerization within the core of block copolymer micelles. a) Proposed mechanism of templated radical polymerization (AIBN being 2,2'-azobisisobutyronitrile, the initiator); b) AFM height image after polymerization of vinylbenzyl adenine monomer in the micelles. Adapted from ref. 46 with permission from Nature Publishing Group.

Besides templated polymerization, nucleobase-substituted copolymers are also interesting as such for their unusual self-assembly properties, which could lead to peculiar phase behavior compared to classical copolymers, as studied recently with copolymers made of adenine- or thymine- substituted methacrylates.[47] Yet, templated-polymerization using nucleobase-containing polymers remains a scarce topic in the realm of polymer chemistries, but this biomimetic materials strategy is promising for reaching the properties of biomolecules, and control intramolecular folding, supramolecular organization with complementary bases, and self-assembly.

DNA-templated self-assemblies and supramolecular polymers

The "base-by-base" DNA automated synthesis using solid-phase phosphoramidite chemistry allows one to control the sequence and length of oligodeoxynucleotides (ODN), *i.e.* DNA oligomers, which can be purified to achieve a high degree of purity in sequence (~95 %). Nowadays, the length achievable can go over 200 bases per ODN, and therefore the attainable control over oligonucleotide hybridization could be attained at least up to the 70 nm scale. Therefore, DNA oligonucleotides can act as a "tape-measure" templates for supramolecular polymerization using base recognition. This approach was introduced by Iwaura, Shimizu and colleagues, who designed bolaamphiphiles made of an aliphatic chain of $(CH_2)_{20}$ appended by two thymidine nucleotides at each extremity. They mixed this molecule in aqueous buffered solution with oligodeoxyadenine ssDNA of different lengths. In specific cases, long, helical nanofibers were formed by double-zipper self-assembly.[48-50] This approach was also exploited with an oligo(*para*-phenylene vinylene) appended with thymidine bases at each extremity of the oligomer. By mixing this oligomer with a single-stranded oligodeoxyadenine of 20 bases (dA_{20}), very long (up to a few µm) nanofibers were observed.[51] The proposed organization in these nanofibers consists of a right-handed helix of π-stacked oligomers, tighten by T:A base pairing with the template at each extremity of the oligomer, see Figure 4. The fact that the length of these wires is way longer than the maximum length of the dA_{20} template (around 7 nm-long) is because the growth of a supramolecular polymer with overlapping templates on each side of the stack of molecules (see gray tubes in Figure 4 left), allowing an elongation mechanism. An identical approach was recently exploited for organizing perylene bisimide chromophores in the form of double-zipper helical assembly.[52]

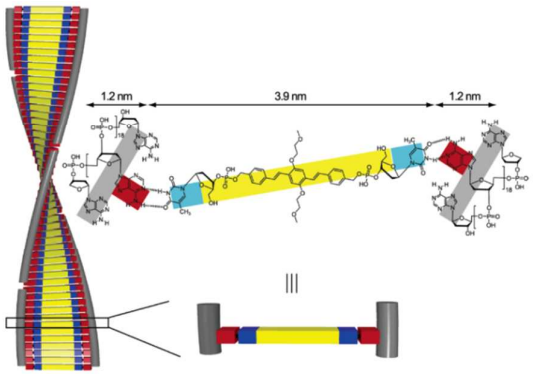

Figure 4. Sketch of the ssDNA-templated supramolecular polymerization of an oligo(*para*-phenylene vinylene) end-capped with thymidine bases at each extremity. The left model shows the proposed formation of long, helical nanowires via double-zipper assembly with overlapping templates at each side of the helix. The structure of the oligomer is shown in right with the color code for the model. Reproduced from ref. 51 with permission from the American Chemical Society. Copyright 2006 American Chemical Society.

The single-zipper approach was studied too, as reported by Schenning and colleagues who appended a single diaminotriazine (DAT) non-natural base attached to a naphthalene-ethylene glycol derivative. This molecule self-assembled with oligodeoxythymidine template, with three possible H-bonds for a diaminotriazine:thymine pair. A right-handed chiral assembly was observed in the chromophore stacking (*P* helix) as directed by the ssDNA template,[53, 54] which switches in a left-handed helical assembly (*M* helix) at low pH, likely as a consequence of protonation of the molecular guest that induce reorganization of the templated assembly.[55] These DNA-templated supramolecular polymers were used to direct energy transfer process between a one-dimensional helical stack of molecular guests as donors and a fluorophore acceptor appended at the terminal position of the single-stranded DNA template.[56, 57] A similar approach was exploited by Balaz *et al.* to helically organize and form monodisperse supramolecular polymers of porphyrins along a ssDNA template, using 8-acetyl-2,6-diaminopurine (DAP) as non-natural base for recognition with oligodeoxythymine (see Figure 5).[58] It was also observed that the handedness of the helical porphyrin supramolecular stack along the DNA template was dependent on the solution conditions: *M* (left-handed) or *P* (right-handed) helices were obtained depending on the rate of annealing and the presence of NaCl salt in the aqueous solution, as sketched in Figure 4c.

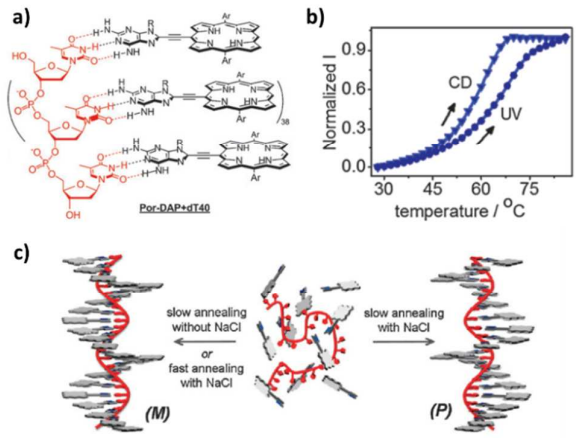

Figure 5. a) Structure of a ssDNA-templated supramolecular polymer of porphyrin derivatives bearing a non-natural base (Por-DAP). b) Normalized plot of the UV-Vis and CD intensities in the absorption range of the porphyrin upon heating the aqueous solution. c) Sketch of the supramolecular helical organization depending on the heating/cooling conditions and presence of NaCl salt in the aqueous solution. Adapted from ref. 58 with permission of the Royal Society of Chemistry.

In this "single-zipper" approach, we showed that the length of the ssDNA template and the size of the chromophore have a strong influence on the template effect: molecules having large conjugated planes yield stronger π-stacking interactions, which is at the expense of the H-bonding interactions with the DNA template.[59] Therefore, ssDNA-templated self-assemblies with small molecules (such as naphthalene derivatives) show a higher stability than with longer oligomers (such as oligo(*para*-phenylene vinylene)). An important result is that the maximum length of the π-conjugated oligomer corresponds to around 3-4 units, above which π-type interactions between the π-conjugated oligomers overcome the H-bonding interactions between the bases. Let us notice that the length of the oligonucleotide template also affects the self-assembly, with the elongation temperature (*i.e.* the temperature at which start the supramolecular polymerization of guests upon cooling the solution) being lower for shorter templates. This has been rationalized by a coarse-grained model of templated self-assembly developed by van der Schoot.[21] This model deciphers the roles of monomer-monomer interactions and template-monomer interactions. From this model, it was concluded that for short templates (shorter than the correlation length, see note [60]), monomers are distributed according to an "all-or-nothing" distribution, *i.e.* a fraction of templates are totally filled and the rest are empty templates. However, for long templates, the guests are evenly distributed over all the templates according to a Gaussian distribution centred on the average bound fraction.

Besides base recognition, other intermolecular interactions can be utilized in DNA-templated self-assembly. For instance, one can combine electrostatic/H-bonding interactions (referred to as salt-bridge interactions) between guanidinium derivatives and the phosphodiester backbone of DNA. Indeed, guanidinium groups act as "phosphate clamps", and can bind to DNA in 1:1 ratio guanidinium/phosphate. By studying a series of guanidinium derivatives bisfunctionalized with aromatic moieties, Ulrich and us observed that the size of the aromatic moiety strongly influences the self-assembly, and notably that stronger π-type interactions favour the stabilization of the templated self-assembly.[61] The guanidinium-phosphodiester interactions were also utilized by Barboiu and colleagues for directing the supramolecular polymerization of a triphenylamine derivative along a ssDNA template.[62] Templating triphenylamine into supramolecular polymers is appealing because of their stacking into nanowires may yield conducting fibers in the doped form.[63] Others have studied the oligonucleotide templating of naphthalenediimide (NDI) attached to Zn^{II}-crown-ether at extremity of NDI.[64] These molecules can bind to thymine bases by combined coordination/H-bonding interactions: the metal center coordinates to the thymine imide nitrogen atom and two H-bonds can occur between NH groups of the complex and the C=O of thymine. The ssDNA templating with oligodeoxy-thymidine (dT) gives rise to helical stacks of NDI, which can be modulated by the DNA length and the temperature. Interestingly, upon illumination these templated NDI arrays generate photocurrents for which the efficiency is linked to the length of the array, as controlled by the template.

The intercalation binding mode, *i.e.* π-stacking of a molecule in between DNA base pairs, is also attractive to anchor a molecule to a duplex dsDNA. Therefore, one can end-terminate a polymer with a small molecule intercalator, which may direct the adsorption of the polymer along the DNA

grooves. In this context, the group of O'Reilly synthesized a series of polymers by reversible addition-fragmentation chain transfer (RAFT), such as poly(N-isopropylacrylamide) (PNIPAM) or poly(N,N-dimethylacrylamide) (PDMA), which were end-terminated by an acridine group. Indeed, acridine is well-known to intercalate in between base pairs of a DNA duplex. By mixing the acridine-terminated polymers with calf thymus DNA, the association constant (K_a) of the complex polymer/DNA was estimated, and ranges from 1.10^3 M^{-1} to almost 8.10^3 M^{-1}, depending on the structure of the polymer, and notably the possibility of hydrogen-bonds among the polymer particles bound to DNA. Using a defined dsDNA of 63 bp, discrete and well-defined DNA–polymer hybrid nanoparticles were formed on the 10 nm scale.

Instead of molecules that bind to a single site (nucleobase), one can exploit multinucleotide recognition and/or electrostatic interactions. This is observable in virus structures such as the Tobacco Mosaic Virus (TMV), an almost monodisperse structure composed of around 2130 proteins bound on a single-stranded RNA, each protein interacting with three nucleotides. Taking inspiration from this virus structure, Stupp and colleagues developed a DNA-templating approach by scaffolding peptide-based nanostructures onto double-stranded DNA templates,[65] see Figure 6.

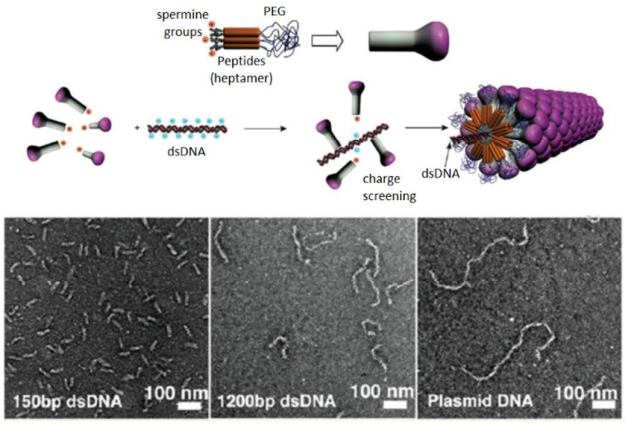

Figure 6. Top: sketch of the shape of peptide-based cationic supramolecules considered in ref [65] and model of dsDNA-templated self-assembly. Bottom: TEM images of templated self-assemblies for different DNA lengths. Adapted from ref. 65 with permission from the American Chemical Society. Copyright 2013 American Chemical Society.

The peptides structures were triblock molecules that contained: i) spermine at one extremity, a molecule which is known to bind and condense dsDNA; ii) a coiled-coil peptide (34 amino acids) structures, and iii) a poly(ethylene glycol) (PEG) chain that provides solubility in water. These triblock molecules self-assemble into heptameric structures in water, forming "mushroom-like" supramolecular assemblies. Upon addition of long dsDNA, electrostatic self-assembly drives the formation of filamentous DNA/molecules superstructures. Among other factors, the effect of the length and topology of DNA template on the nanoscale morphology was studied, from linear dsDNA of 150 bp to 1200 bp and with circular, plasmid dsDNA of around 2700 bp (Figure 6 bottom). By a careful tuning of the steric forces between the "mushroom-like" structures (by modifying the size of the PEG chain) binding to dsDNA templates, they obtained homogeneous supramolecular rod-like objects with lengths of up to 1.6 µm with extended supercoiled plasmids, see Figure 6 right. These virus-mimetic structures can be viewed as ultimate templated supramolecular polymers, for which the polymer consists in a well-organized array of nanoscale macromolecules along a template of defined length.

DNA-templated synthetic polymers

Beside templated reactions involving chemical ligation between DNA phosphodiester backbones, the search for DNA-templated synthetic homopolymers (here, not involving nucleotide analogues) has rapidly progressed recently, notably using oxidative polymerization of monomers directed by DNA scaffolds, or by exploiting dynamic covalent polymerization, see some relevant examples highlighted below. In all cases, DNA templated polymerization forces chemists to consider the self-assembly and reactions in water, which is desirable for sustainability reasons. Nevertheless, alternatives towards DNA-templated reactions in organic solvent exist.[66]

DNA-directed oxidative polymerization

DNA-templated polymerization approaches rely on the increase the effective molarity of the monomers upon their organization along the template. A possibility is to attach a monomer to a ssDNA, and utilize the hybridization of a complementary ssDNA to approach an identical or different monomer. A recent study by Gothelf and colleagues took advantage of this approach, using complementary oligonucleotides (ssDNA) end-capped with alkynes to direct Glaser-Elington reactions into 1,3 diynes between conjugated subunits, eventually forming an oligo(*para*-phenylene-ethynylene) backbone with pendant DNA.[67] This templating approach allows for selective heterocouplings of terminal alkynes, and therefore the formation of non-symmetric products, which cannot be achieved in the intermolecular reaction without the template.

Apart from base pairing of modified ssDNA templates, dsDNA templates were used to direct monomers along the DNA strands, and form dsDNA/polymer nanowires by oxidative polymerization of the monomer.[68,69] For instance, Houlton and colleagues mixed pyrrole or 2,5-bis(2-thienylpyrrole) monomers with bacteriophage lambda dsDNA (around 48,000 bp) in aqueous solution containing $FeCl_3$ as oxidant, possibly with a co-solvent.[70]

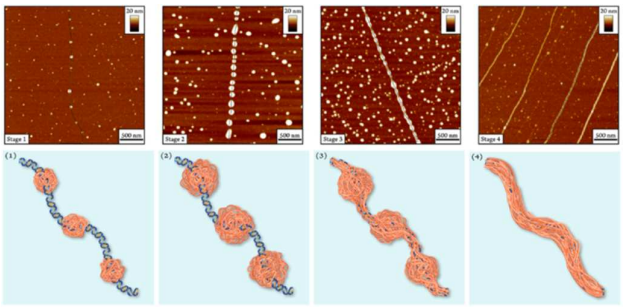

Figure 7. Top: Tapping-mode AFM images of thin deposits of dsDNA / 2,5-bis(2-thienyl)pyrrole) mixtures isolated at various stages of the polymerization reaction (from left to right: 10 min., 1h; 4h; 24h). The deposits are done on TMS-modified Si/SiO_x surface. Bottom: sketch of the various stages of the polymer growth mechanism (in pink) along the double-stranded DNA template. Adapted from ref. 70 with permission from the American Chemical Society. Copyright 2014 American Chemical Society.

The samples were isolated from the reaction mixture at various times and deposited on flat substrates for Atomic Force Microscopy (AFM) analysis, see Figure 7 top. The different stages of the oxidative polymerization were clearly identified, as shown from left to right in Figure 7, in the case of DNA/poly(2,5-bis(2-thienyl)pyrrole). In the early stages of the reaction, small spherical polymer particles form on the template, like a bead-on-a-string assembly (Fig. 7 left). Then, the density of these particles increases, up to a point where the particles merge by elongation forming an ellipsoid, and eventually the polymer covers the entire surface of the dsDNA template (Fig. 7 right). Ultimately, a smooth wire is formed, the polymer likely spreading to form a sheath around DNA. The various stages were explained by a coarse-grained thermodynamic model assuming morphological wetting transitions, similarly to the wetting of fibres. These results provide clues for building DNA/polymer nanowires of interest for supramolecular electronics and organic bioelectronics.

Another approach consists in the chemical modification of nucleobases by substituting a monomer along a ssDNA, the alignment of these monomers using double-stranded duplex DNA formation, and subsequently polymerize, as proposed by Schuster and colleagues using monomers such as aniline or 2,5-bis(2-thienyl)pyrrole substituted on a modified cytosine.[71-73] The addition of a pseudo-complementary sequence ssDNA to the modified oligonucleotide allows for the formation of a duplex in which the monomers were aligned along the major groove. The polymerization of the monomers was achieved using Horseradish Peroxidase and H_2O_2 (as oxidant), resulting in oligomers with interesting optical properties, similar to that of conjugated polymers. This approach was then extended to form linear or cyclic co-oligomers of 2,5-bis(2-thienyl)pyrrole and aniline co-joined with the dsDNA, a study that paves the way to create DNA-copolymers hybrids of well-defined topology.[72]

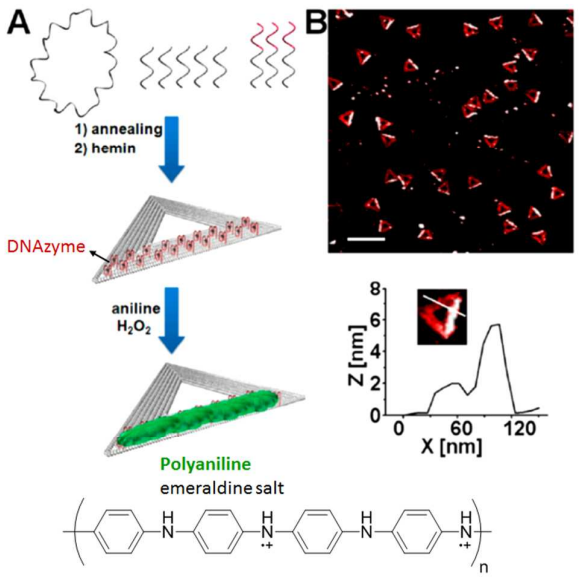

Figure 8. (A) Sketch of the site-selective polymerization of aniline on a triangular DNA origami template (using M13 phage as scaffold DNA). Guanine-rich sequences are complexed with hemin, forming a so-called DNAzyme, at programmed locations on the origami, and the addition of aniline and hydrogen peroxide activates the DNAzyme. (B) AFM height image (top) and cross-section (bottom) after templated polymerization on one side of the origami triangle. The scale bar is 200 nm-long. Adapted from ref. 74 with permission from the American Chemical Society. Copyright 2014 American Chemical Society.

Other lines were followed, as for instance site-specific polymerization on 2D DNA scaffolds, by taking advantage of the DNA origami structures. Ding *et al.* cleverly used the formation of a DNAzyme, formed by complexing hemin onto specific guanine-rich regions of the DNA origami, to initiate the polymerization of aniline.[74] This is illustrated in Figure 8, showing the principle (left) and AFM image of a sample (right). Basically, a triangular DNA origami is built on conventional M13 phage scaffold with modified G-rich staple strands, which are programmed to be positioned on one side of the triangle. By addition of hemin (*i.e.* an iron proto-porphyrin) and potassium ions, the G-rich part behaves as a Horseradish Peroxidase-mimicking DNAzyme. This well-positioned DNAzyme was then used catalyse the oxidation of aniline by H_2O_2 (in certain conditions of pH) into aniline radicals, which then underwent coupling into dimers, eventually yielding the formation of poly(aniline), PANI. The example shown in Figure 8 effectively shows that PANI is formed 12 hours after initiating the reaction, covering only one side of the triangular DNA origami, as observed with AFM (Figure 8b). The formation of PANI was evidenced by doping-dedoping cycles on UV-Vis absorption spectra, which indicated that PANI is in emeraldine salt form after polymerization (Figure 8 bottom).

DNA-templated dynamic covalent polymerization

Dynamic covalent chemistry provides a wealth of chemical strategies for achieving dynamic polymers and self-replicating oligomeric systems.[75,76] DNA-templating is of great significance for directing dynamic polymerization, in view of attaining

dynamic polymers (dynamers) of complex sequence that dynamically exchange depending on the environment and chemical stimuli. DNA-templated dynamic covalent polymerization has been pioneered by Lynn and co-workers, who have developed DNA-templated oligomerization of nucleoside derivatives using dynamic imine bonds.[77] They designed a monomer, containing two thymine bases, that is end-terminated with an aldehyde and an amine group (5'-amino-3'-acetaldehyde). After self-assembly of the thymidine-modified monomers along an oligodeoxyadenine ssDNA template via base pairing, followed by reductive amination, an imine oligomer was formed for which the length matched the template sequence, up to octamers. The approach was then extended to longer templated structures, up to a copolymer of 32 nucleobases for which the order of the monomers is dictated by the ssDNA template sequence.[78] More recently, Schenning and us introduced a dynamic polymerization of non-natural bases using a ssDNA template,[79] by using the supramolecular approach described in the previous section.[53,59] Naphtalene chromophores (bearing ethylene oxide for solubility) were end-capped with a dihydrazinetriazine (Figure 9 top), which possibly form three H-bonds per thymine nucleobase along the ssDNA template. A first cooling of the solution allows for the templated self-assembly of monomers to occur, likely by an Ising chain supramolecular polymerization process. The two amino groups on the dihydrazinetriazine unit can react with glyoxal, possibly yielding an imine (hydrazone) dynamic polymer. In absence of DNA template a [2 + 2] cyclic hydrazone is formed exclusively. In presence of the template, when the monomers are preassembled along the ssDNA, the formation of the hydrazone polymer is confirmed by Gel Permeation Chromatography (GPC), CD spectroscopy and MALDI-ToF. The degree of polymerization of the polymer did not match the number of nucleobases in the ssDNA template. This is because the mismatch between the interbase distance (0.34 nm) and the length of a hydrazone monomer (0.9 nm) in the polymer, which renders the average degree of polymerization much lower than the number of bases in the template. Very interestingly, by using heating/cooling cycles the ssDNA template could be recycled, and then used again for another cycle of templated dynamic polymerization. This is represented in Figure 9, showing a sketch of the recycled DNA template polymerization and the change in the CD intensity (monitored at 330 nm) as a function of heating/cooling cycle.

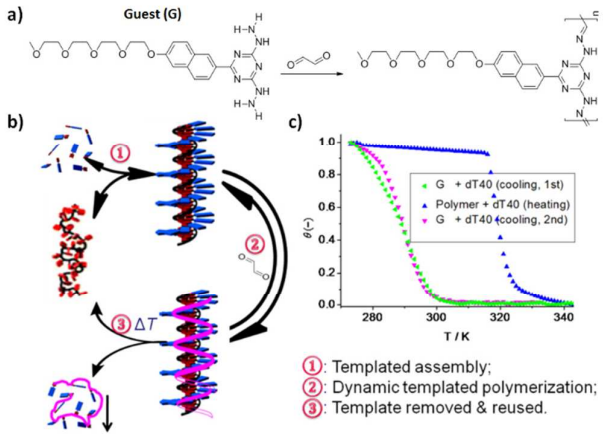

Figure 9. a) Chemical structures of the molecular guest (G) and dynamic covalent reaction to yield hydrazone polymer. b) Sketch of the templated dynamic polymerization using an oligodeoxythymidine (dT_{40}) as ssDNA template. The molecular guests are depicted in blue, the ssDNA in red, and the hydrazine polymer in pink. c) Normalized ellipticity at 330 nm as a function of the temperature during the heating/cooling cycles. Adapted from ref. 79 with permission from the Royal Society of Chemistry.

After one cycle of DNA-templated dynamic polymerization, a solution of the monomer was added to a mixture of the precipitated polymer and the ssDNA template. When the solution was cooled, a CD signal appeared at 330 nm, which is a signature of the templated supramolecular polymerization since the shape of the cooling curve is similar to the cooling curves measured during the first cycle (see normalized intensity of CD signals in Figure 9). This indicated that the DNA template could be used again. After this templated self-assembly, glyoxal was added for initiating a new polymerization process (Figure 9, process 2). The CD signal changed from positive to negative, as found earlier for the first polymerization cycle. This showed that heating/cooling cycles can therefore be exploited to recycle the DNA template for other templated polymerization reactions.

Dynamic covalent chemistry in presence of DNA also represents a combinatorial tool for finding molecules constituting oligomers/polymers for DNA recognition. In a recent paper, Ulrich *et al.* used dynamic covalent polymerization of functional groups able to promote the complexation of dsDNA. To this end, diethylenetriamine and guanidinium cationic moieties were copolymerized with ethylene glycol-based monomers using dynamic imine bond formation, ultimately forming dynamic acylhydrazone polymers which can be easily degraded with pH.[80] DNA-binding studies revealed that these polymers do complex well dsDNA, and that when polymerized the guanidinium groups are more effective than amines in terms of interactions between polymers and DNA. Furthermore, the same group undertook a dynamic combinatorial approach to identify side groups that stabilize DNA in an imine-based dynamic library involving multivalent peptides clusters.[81]

Translation of DNA templates into sequence-controlled synthetic polymers

Sequence-controlled polymers, it is to say polymers of controlled architecture at the monomer level, currently represent a challenge in polymer synthesis.[22] Nucleic acids-templated translation would permit to achieve ideally sequence-controlled polymers with high efficiency and fidelity, as one can be inspired by DNA transcription, DNA replication, and RNA translation processes. Indeed, templated ligations and polymerizations of sequence-controlled non-natural DNA analogues (such as PNA, TNA, HNA, etc.) were largely studied, as covered in refs.[16,17,82,83-85] However, the synthesis of DNA-templated sequence-controlled synthetic polymers in an enzyme-free manner remained elusive until quite recently.

Early reports focused of DNA templating of small oligomers with controlled sequence of the subunits. Gothelf and colleagues designed linear and triangular modules conjugated to oligonucleotides that form DNA-oligomer conjugates structures that are geometrically-defined and sequence-defined owing to DNA-directed manganese-salen formation. The coupling is of high yield up to tetramer structures, but longer structures were obtained in low yields, probably because of steric effects.[86, 87] Later, O'Reilly and colleagues introduced a strand-displacement method for DNA-templated synthesis of oligomers with controlled sequence. By using a strand-exchange mechanism and templated Wittig chemistry for group transfer, they were able to obtain an olefin tetramer bearing functional subunits (*e.g.* fluorescent dye and peptide) in a controlled sequence, ultimately yielding dsDNA-controlled oligomer conjugates.[88] Lately, Sleiman and coworkers introduced a new route to sequence-defined polymers attached to DNA.[89] In this case, the DNA does not act as the template, but the phosphoramidite chemistry employed for DNA synthesis was exploited to couple a sequence oligo(ethylene) and oligo(ethylene oxide) subunits to dsDNA, leading to DNA amphiphiles of interest for their self-assembly properties in micellar structures. Remarkably, the coupling efficiency was found to be excellent (> 97 %), which is promising for generating longer sequence-controlled polymers attached to DNA.

A major advance in DNA-translation into synthetic polymers was achieved by Liu and coworkers,[23] who cleverly designed a macrocyclic scaffold containing a recognition site (a PNA pentamer) and a synthetic polymer building block (*e.g.* oligo(ethylene glycol)) attached by two cleavable linkers (see sketch in Figure 10 top). This architecture allows not only for efficient and sequence-specific hybridization (to a codon of 5 nucleobases of a hairpin DNA, Figure 10), but also to decrease the entropic cost and increase the regioselectivity of the coupling reactions. The sequence-controlled polymer could be easily cleaved from the DNA hairpin template using P1 nuclease. Remarkably, this approach potentially permits to synthesize sequence-controlled polymers that have no structural relationship with nucleic acids.

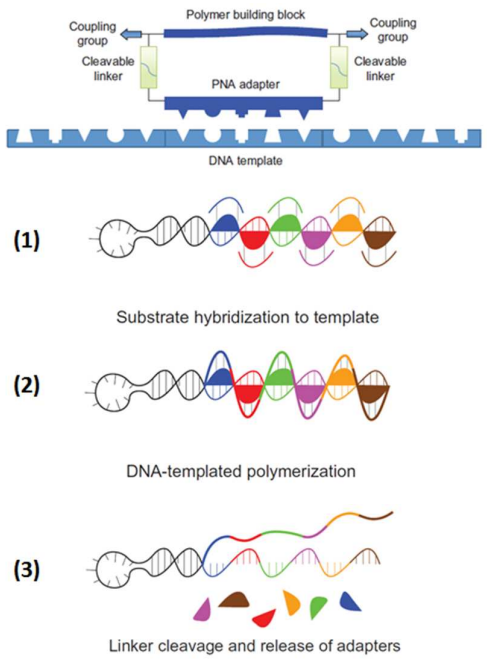

Figure 10. Top: Sketch of DNA-templated polymerization using a cleavable macrocyle carrying a PNA adapter as recognition unit. Bottom (1-3) Representation of the strategy of templated polymerization using a hairpin DNA template. Adapted from ref. 23 with permission from Nature Publishing Group.

The authors explored several chemical reactions compatible with DNA and solid-phase peptide synthesis, as for instance oxime formation, hydrazone formation, and copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction. For a PEG-based building block, the latter reaction gives the best results in terms of translation efficiency. Other types of building blocks were studied such as β-peptide and α-D-peptide, which demonstrates the generality of this approach. Remarkably, they attained sequence-specific polymers with up to 16 consecutive blocks (each made of 6 different monomers), with a molecular weight of around 26 kDa, *i.e.* 90 β-amino acid residues, which is in the range of functional biopolymers. This study expands the scope of DNA-translated sequence-controlled polymers to synthetic polymers with no ability to hybridize nucleic acids.

Enzyme-assisted nucleic-acid polymerizations are representing a next level of complexity. Very recently, Hili *et al.* reported an enzyme (T4 ligase)-assisted DNA-templated polymerization of peptides-modified pentanucleotides on a ssDNA scaffold, ultimately forming copolymer with a precise arrangement of specific peptides along the DNA backbone.[90] These DNA-peptide conjugates of precise architecture are of high interest as multivalent platforms for molecular recognition.

Towards functional DNA-templated polymers hybrids for biological applications

Beside the utilization of nucleic acids-templated polymerization for a precise control over the length, shape, and possibly the sequence of the synthetic polymers, DNA-templated polymer supramolecular hybrids could be useful for tailoring nanosized biomaterials, as for instance to tune the permeability and circulation times in biological systems, as suggested by Stupp on DNA-templated peptides self-assemblies (Figure 6).[65] At a higher level of complexity, the encapsulation of DNA-templated self-assemblies of small molecules in virus protein tubes would allow for forming robust and monodisperse 1D nanotubes.[91]

Recently, some studies make use of supramolecular hybrid structures formed by nucleotide or nucleic acids templates and the polymer for interesting developments for biosensors, DNA-labelling, and delivery systems. Indeed, DNA-DNA hybridization sensing is a subject of capital importance for diagnostics, especially for detecting single-nucleotide polymorphisms. In this context a current challenge is to develop label-free single mismatch detection systems. Recently, Smietana and Vasseur developed a fluorescence-based detection system that make use of DNA-templated ligation of 5'-boronic acids oligonucleotides to detect a single mutation in a specific gene.[92]

The supramolecular chirality of these DNA-templated assemblies are advantageous for probing the enzymatic activity towards nucleotides, as shown in a recent report in which George and us exploited chiroptical spectroscopy for monitoring in situ the enzymatic (phosphatase) hydrolysis of adenosine-triphosphate (ATP), through the exploitation of dynamic supramolecular polymers formed by ATP and naphtalene diimide-Zn^{II} complex molecules (called NDI-Zn, see structure Figure 11 left).[35] Circular Dichroism signals were shown to be very sensitive to the progress of the ATP phosphate hydrolysis, as shown in Figure 11: starting from a right-handed (*P*) helical supramolecular polymer of NDI-Zn with ATP, the phosphate hydrolysis yield supramolecular assemblies with ADP and AMP, with left-handed (*M*) helices (see above), and finally pyrophosphate (CD silent). This type of dynamic self-assemblies could be exploited for developing chiroptical readout systems to follow enzymatic activity.

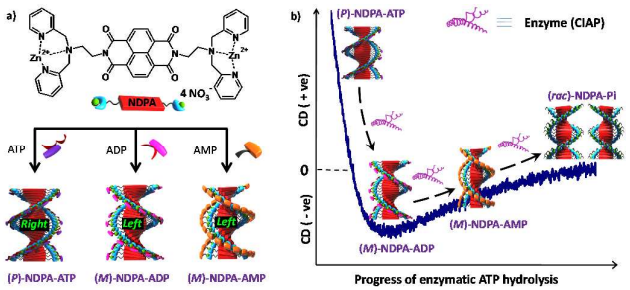

Figure 11. a) Chemical structure of NDI-Zn and sketch of helical supramolecular polymerization induced adenosine phosphates (AMP, ADP, or ATP). b) Schematic representation of the dynamic helix reversals upon enzyme (Calf Intestinal Alkaline Phosphatase) activity on the NDPA-ATP supramolecular polymer, and the real-time chiroptical readout. Reproduced from ref. 35 with permission from Nature Publishing Group.

Likewise, DNA-templated polymer hybrids could be utilized as fluorescent nanotags. Note that this was shown with bottlebrush-type copolymers with clickable DNA along the grafts, which can accommodate thousands of fluorescent dyes (either covalently or by intercalation). These polymer-DNA hybrids can then be linked with an antibody via DNA-DNA hybridization, resulting in a bright immunofluorescent label with around 10 times enhanced fluorescence intensity compared to conventionally tagged antibodies.[93]

Another topic of biomedical interest concerns intracellular delivery systems. In such context, templated structures allow for a precisely-controlled size and for tuning the interactions with cells. A recent report by Iwaura *et al.* showed that nucleoside-modified bolaamphiphile molecules (bearing a central fluorescent dye) can form self-assembled nanoparticles with a homogeneous diameter ≤ 100 nm, owing to the relatively weak stacking interactions of cytosine nucleosides at the extremities of the molecule. Remarkably, it was demonstrated that these fluorescent nanoparticles were taken up into cells and that their accumulation in the nuclei is dependent on the mammalian cell line studied.[94] Furthermore, DNA-templated dynamic polymerization of cationic molecules represent a promising approach to complex DNA for gene-delivery applications, as an alternative to the classical polyplexes, made by complexation between DNA and conventional cationic polymers (*e.g.* poly(ethylene imine)). This was shown with dynamic acylhydrazone polymers that efficiently complexed DNA.[80] These polymers could be degraded with pH, releasing the nucleic acid template for gene silencing applications. Especially, the exchange and hydrolysis of these polymers are much faster at pH 5.0 than at pH 7.0, which indicates that these polymer could be effective to promote endosome escape as delivery particles. Furthermore, the reversibility of DNA-templated dynamic polymerization can be triggered by tuning the pH, as demonstrated recently with DNA (or RNA)-templating of sequence-specific boronate oligomers.[95] These approaches are appealing as it permits to carry the genetic material that acted as the template, tailor the supramolecular self-assembly with different monomers units, and control the degradability of the dynamic polymers for DNA release upon external or environmental stimuli.

Perspectives

The control over the polymer sequence via the DNA template would allow for achieving *information-rich synthetic polymers* with fascinating properties of folding, self-assembly, and allosteric behaviour, comparable to what happens in biopolymers. Besides, DNA/polymer hybrids are interesting for constructing complex artificial 3D systems, as it was recently shown for self-assembled polymer-DNA conjugates into 3D arrays of nanosized boxes, and for chromatin-like superstructures upon complexation of polymer nanoparticles with long DNA.[96, 97]

Despite the recent developments described above, currently the structures formed by DNA-templated polymers remains

virtually unexplored. Deciphering the hybridization mechanisms and possible aggregation of these DNA-templated polymers supramolecular hybrids as a function of the aqueous solution conditions is essential, as it was done earlier for conventional DNA/polymer complexes (polyplexes) for gene therapy. Like for other supramolecular self-assemblies, revealing the kinetic pathways and mechanisms of templated polymerization is of prime importance to achieve optimal supramolecular organization and information transfer from the template to the monomer level.[98] The multivalence and chirality of nucleic acids, together with the dynamics and sequence of the templated polymers (with possibly reversible bonds), allow for the formation of complex chemical systems with a high density of information. Indeed, understanding the complexity of the nucleic acids-templated reactions and polymerizations is also enriching our view on the origin of life, a topic that now meets the fields of supramolecular chemistry and far-from-equilibrium assemblies.[99] Whether it is for a better understanding the origin of life, towards synthetic biology or functional nanomaterials, realising all the aspects of nucleic acids-templated supramolecular assembly and polymerization is crucial to achieve the complexity and functions of biological systems.

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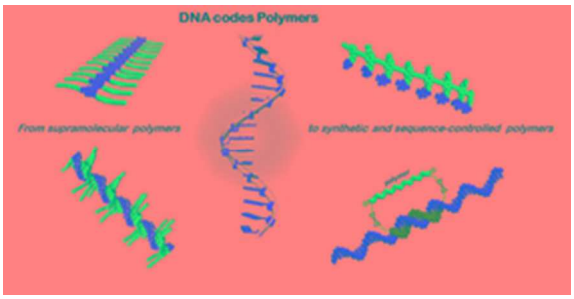
In this minireview, we report on the recent advances of utilization of nucleobases and DNA as templates to achieve well-defined supramolecular polymers, synthetic polymers, and sequence-controlled polymers.



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