Nucleic Acid Nanotechnology: Modified Backbones and Topological Polymer Templates

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Abstract DNA-based nanotechnology has revolutionized the construction of nanoscale objects and devices—primarily by using Watson–Crick base-pairing to program the self-assembly (and reaction pathways) of DNA oligomers into branched structures. However, Watson–Crick-controlled self-assembly is not limited to the use of the "natural" D-(deoxy)ribose phosphodiester backbone.

This chapter describes nanoscale objects synthesized from oligomers containing sugars other than D-deoxyribose or linkages other than phosphodiester linkages. This chapter also focuses on using the backbone of DNA as a topological guide for polymer synthesis.

As these chemical modifications profoundly affect the bioavailability, nuclease resistance, protein binding, optoelectronic, and materials properties of nano-objects compared to their "natural" DNA counterparts, they may find great utility in biomedicine.

Keywords DNA • Polynucleotides • Templated syntheses • Backbones • Nylon • Conducting polymers • Nanotechnology • DNA nanotechnology • DNA-based nanotechnology • Junctions • L-DNA • PNA • LNA • GNA • Methylphosphonate

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1 Introduction

This chapter is aimed at summarizing recent research diversifying the backbone of polynucleotides used in DNA-based nanoconstructions and using the backbone of DNA to control polymer synthesis (Fig. 1).

DNA-based nanotechnology has been influenced by many approaches, branched into many disciplines, and spawned many applications. By necessity, the vast majority of these streams, while *related* to the title of this chapter, are not described. Below are a series of leading references for the interested reader.

While there is a vast literature on construction using nonlinear DNA, this chapter is not a general review (Seeman 2010; Pinheiro et al. 2011) of DNA-based nanotechnology (Seeman 1982), nor a general review (Sacca and Niemeyer 2012) of DNA origami (Rothemund 2006); the chapter is not a review of triplex-based nanostructures (Fox and Brown 2005; Mukherjee and Vasquez 2011) nor of dendrimer-based DNA nanostructures (Caminade et al. 2008), nor of knotted or otherwise topologically intertwined DNA structures (Dobrowolski 2003).

There are many modified oligonucleotides that have been synthesized for a variety of purposes. This chapter does not cover modified oligonucleotides for antisense applications (Yamamoto et al. 2011; Keum et al. 2011), nor alternative base-pairing in DNA (Wojciechowski and Leumann 2011) including metal base pairs (Clever and Shionoya 2010), nor click chemistry as applied to oligonucleotides (El-Sagheer and Brown 2010), nor azobenzene-based switching of DNA (Beharry and Woolley 2011). Defined, branched nanostructures have been constructed using metal–ligand interactions (Yang et al. 2010) and using DNA as "smart-glue" to hold together various nanoparticles (Geerts and Eiser 2010)—this chapter does not cover these either.

The covalent chemistry touched upon in this chapter has also been used for functionalizing DNA nanostructures with proteins (Sacca and Niemeyer 2011) and to template small-molecule synthesis for reaction discovery (Kleiner et al. 2011) and macrocycle production (Milnes et al. 2012). Generally, if the modification is merely at the 3′ or 5′ end of an oligonucleotide or duplex, this chapter will not cover it.

The backbone of DNA has been used as a template for semiconducting materials (Houlton et al. 2009) and dye/pi systems (Ruiz-Carretero et al. 2011). Duplexes of every flavor using many phosphodiester-backbone (Eschenmoser 2011) and peptide-backbone (Nielsen 2010)-based structures have been synthesized; base-pairing has been used to template the synthesis of unnatural polymers (Brudno and Liu 2009); again, these topics are not the subject of this chapter.

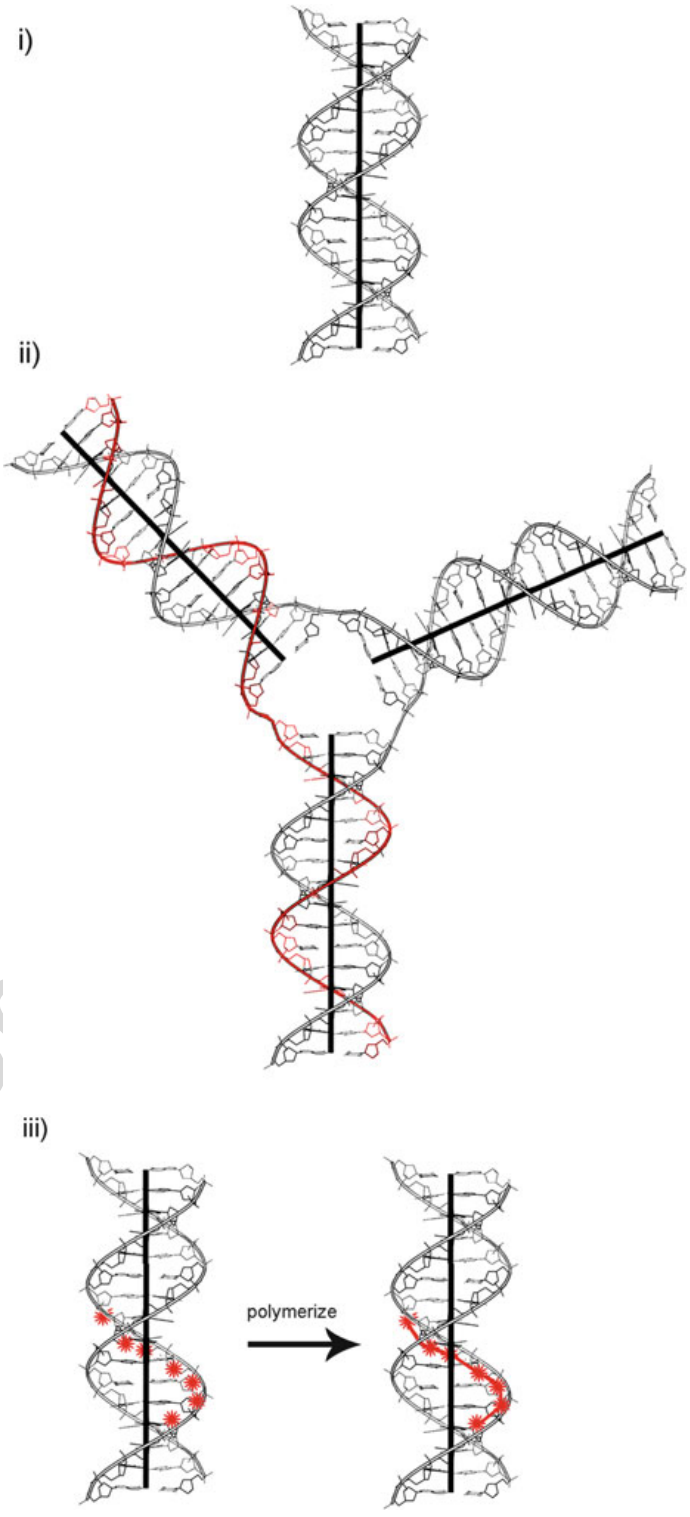

Fig. 1 (**i**) A diagram showing a B-DNA double helix. Note the "helix axis"—a *central line* proceeding down the double helix. The duplex structures described in the chapter are predominantly B-like. (**ii**) The first part of this chapter describes modifications to the backbone of DNA (the internucleotide linkage and sugar-modified parts are highlighted in *red*) *and* these modified polynucleotides incorporation into branched structures (the example shown is a three-way "junction" where multiple helix axes converge). (**iii**) The second part of this chapter describes polynucleotides functionalized with reactive groups (schematically illustrated with *red stars*) that can react to form a polymer that follows the backbone of duplex DNA

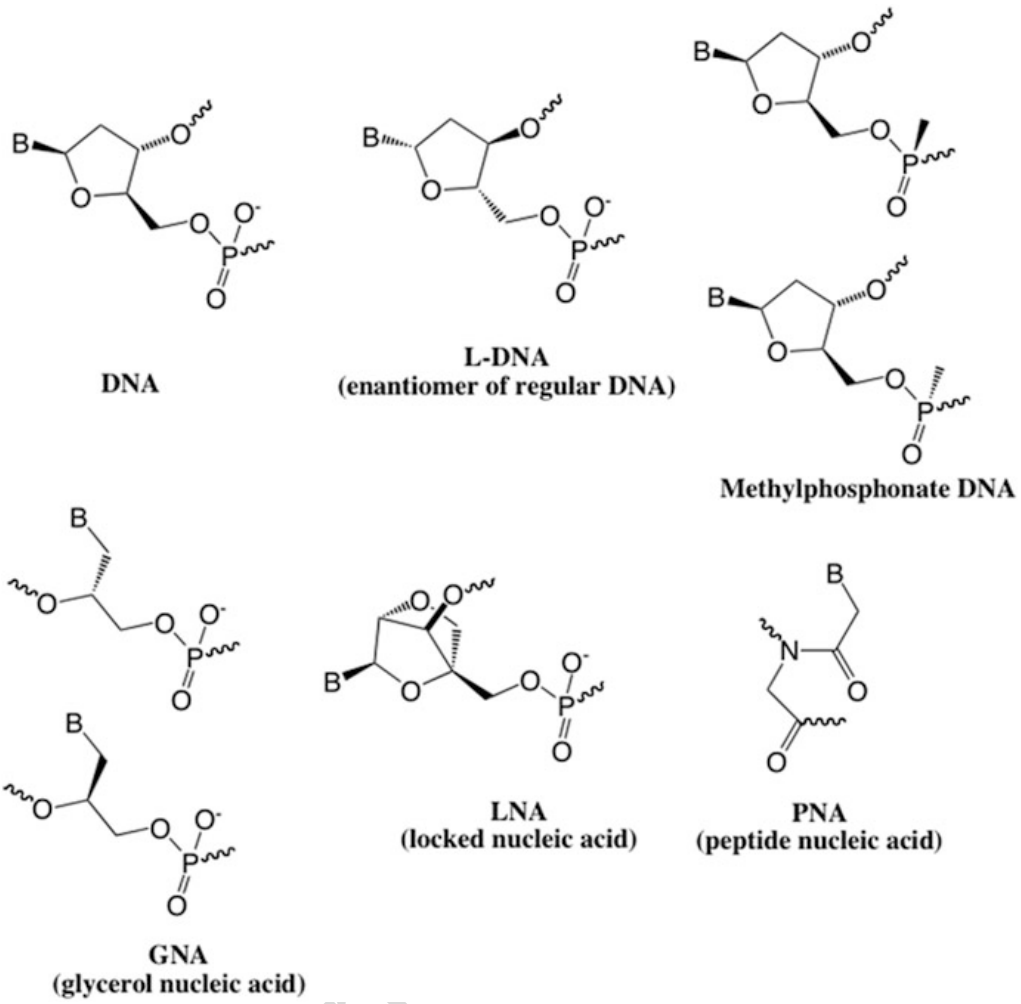

Fig. 2 The modified nucleotides referred to in this chapter

It is worth beginning this chapter by highlighting the chemical structure of the oligonucleotides used and thinking about the use of nonlinear DNA in nanoconstructions.

2 Unusual Oligonucleotide Backbones in Junction-Based Nanosystems

Figure 2 shows the modified nucleotide backbones described in this chapter. As well as the commonalities of using the nucleobases A, T, G, and C to form Watson–Crick-paired structures, there are differences: there are 4-, 5-, and 6-atom repeats for the backbone, and both charged and uncharged structures. The ability of these diverse backbones to support duplex formation is utilized in the work that follows.

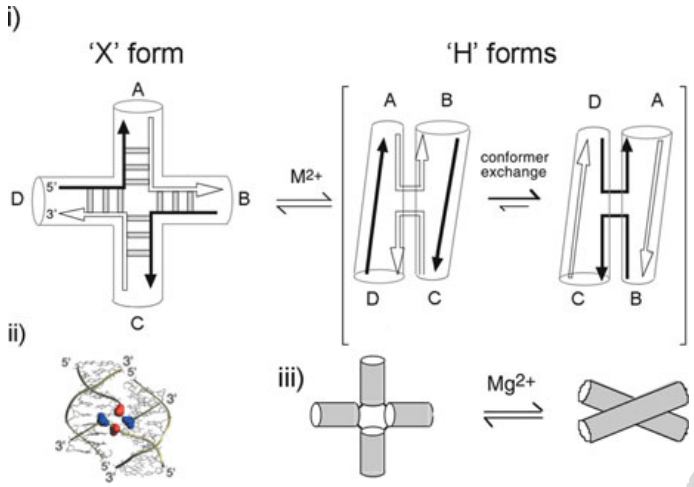

Fig. 3 (**i**) Schematic to illustrate the ion-induced folding of the four-way DNA junction into two possible stacked conformers. The junction comprises four DNA strands that associate to form the four helical arms A, B, C, and D. In the absence of added metal ions, the unmodified junction is extended into an "X" conformation, with the four arms directed toward the corners of a *square* shown on the *left*. On addition of metal ions, the junction may undergo a transition to form the stacked "H"-structure by pairwise coaxial stacking of helical arms. This can exist in either of two conformers—with the ratio of conformers being predominantly controlled by sequence of nucleotides at the junction. The junctions used in this chapter have sequences whose equilibria are biased toward the rightmost conformation, or are otherwise constrained. (**ii**) An illustration showing the proximity of phosphate groups in the stacked junction conformation. (**iii**) A simplified version of the Mg^{2+}-dependent equilibrium. Image used with permission (Liu et al. 2004)

As with other macromolecules, in order to use DNA for construction on the nanoscale the researcher requires an understanding of primary through quaternary structure. DNA Junctions, which can be thought of as points at which three or more helical axes converge, are the key secondary structure element required to make nonlinear objects, lattices, and devices from polynucleotides (Seeman 2010).

The archetypal (Kallenbach et al. 1983) four-way junction used in DNA nanotechnology has two gross conformational populations (Duckett et al. 1988); an extended "X" like conformation in which the four helical domains are unstacked, and stacked "H" like structures in which pairs of helical domains stack on top of each other (Fig. 3). The equilibrium between these conformations is sensitive to metal ion concentration; maximizing the energetically favorable base stacking in the H form involves the juxtaposition of phosphates that repel each other.

A four-way junction was investigated using methylphosphonate substitution (Liu et al. 2004) to address charge-related issues. This study demonstrated that the nature of the central phosphate groups of the "exchanging" strands were crucial to the metal ion determined stability of the junction. If both phosphates were substituted with methylphosphonate groups, the junction folded into the "H" conformation without addition of metal ions. Replacement of a single phosphate group reduced the requirement for metal ions in folding; the phosphate groups in proximity to the junction also exerted a significant influence on the folding process. The effect is subtle; further study (Liu et al. 2005) using diastereopure

methylphosphonate substitution showed that metal ion coordination at the junction is geometrically demanding (i.e., dependant on the orientation of the phosphate) and not merely a regional charge screening effect.

What does this study have to do with DNA-based nanotechnology? The conformation of a junction can be fixed in place by torsionally linking at least two duplexes with at least one other junction. This is the technique used for multijunction structures such as DX and nX tiles, triangles, and most origami approaches. Interphosphate repulsion at these junctions still likely destabilizes these structures in the absence of divalent mental ions. Repulsion-based destabilization allows the formation of multimers and other undesirable nondesigned structures at equilibrium in junction-based systems (Li et al. 1996); also, in dynamic nucleic acid systems with strand displacement events (Zhang and Seelig 2011), new equilibrium distributions can be established even from homogenous samples of well-folded structures. The incorporation of uncharged nucleic acid analogues into junction-based structures should allow the synthesis of robust structures with less dependence on metal ion concentration, and less tendency to want to "relax" into alternate, unwanted configurations.

A stereochemical study of four-way junctions was conducted with enantiomeric L-DNA and DNA (Lin et al. 2009). Unsurprisingly, the junctions had identical physical properties such as stability and gel mobility, and the expected mirror-image CD spectra. However, their interaction with chiral reagents provides potential biological utility—the L-DNA junction was completely resistant to degradation by exonuclease. As L-DNA has the same physical properties as DNA, the hard-won design lessons of nucleic acid objects (providing they do not rely on enantioselective interactions with the nanostructure) should be *directly* portable to this polynucleotide.

Junctions were also synthesized from enantiomeric (R) and (S) GNA oligonucleotides (Zhang et al. 2008). These materials again displayed identical physical properties and mirror image CD spectra. However, the GNA junctions had unusually high thermal stabilities—35 °C greater than the cognate DNA system; this is a remarkable stability for a system formed bringing together polyanionic species. As GNA does not pair with DNA, and the geometric parameters of the helix are unknown, if this oligonucleotide is to be used in nanoconstructions significant further study will be required. It is particularly tantalizing that such stable structures are accessible via routine, commercial phosphoramidite chemistry that allows facile synthesis of GNA–DNA chimeras; this is much simpler (and potentially multiplexable) chemistry than, for example, synthesizing PNA–DNA hybrids.

Other structural considerations are necessary for the incorporation of nonnatural polynucleotides into nanostructures. The DX tile (Li et al. 1996) was the first rigid, well-defined, B-DNA nucleic acid motif that was capable of tiling the plane with two-dimensional, sticky-end associated crystals (Winfree et al. 1998). It thus served as an attractive target for the incorporation of modified polynucleotides.

A two-tile system was synthesized using uncharged PNA strands as one crossover strand per junction (Lukeman et al. 2004) in the DX tiles (Fig. 4). This system showed reduced dependence on divalent ions; 50-mM sodium with no divalent

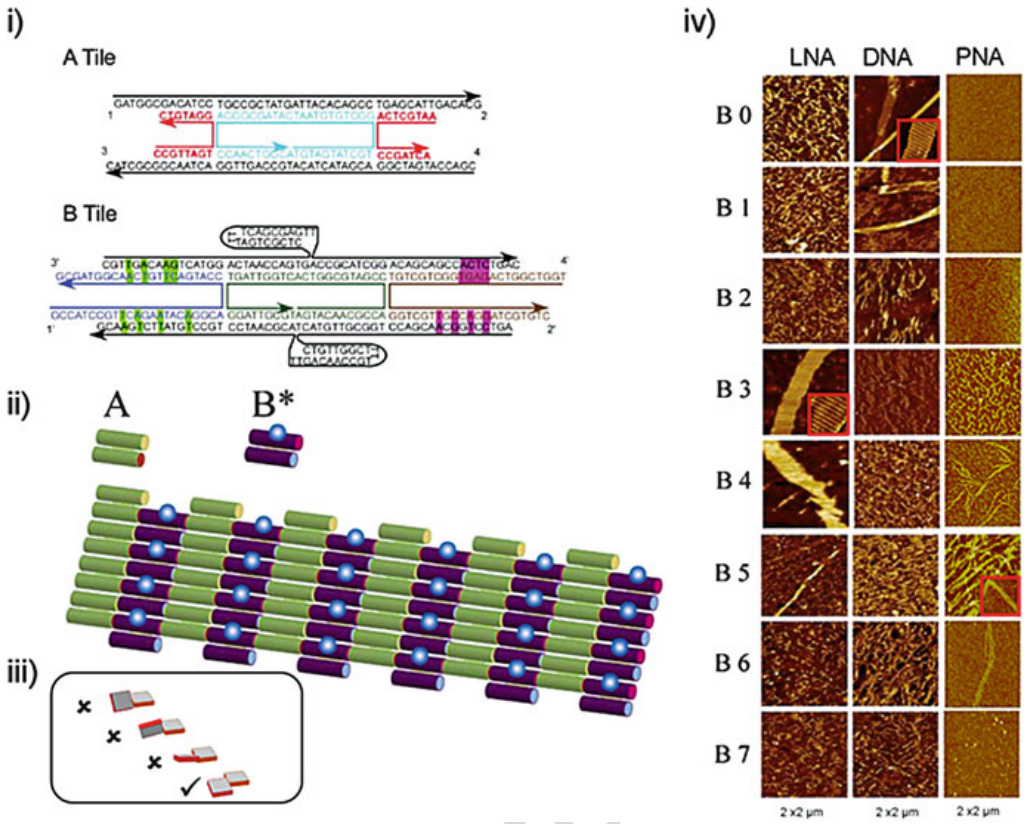

Fig. 4 (**i**) DX tiles used in this study. The *upper tile* is the A tile: the *red* strands are either LNA, PNA, or DNA. The *lower tile* is a version of the B tile. Base pairs are added alternately to the *left* and *right* pairs of outer arms to form tiles B1–B7 as shown by the *pink* and *green highlights*, e.g., to form B1 from B0, a base pair is added to both *pink regions*; to form B2 from B1, a base pair is added to both *green regions*. Complementary sticky ends are shown as numbers. All B tiles have hairpins, which will act as topographic markers when incorporated into an *array*. (**ii**) A and B* tiles forming a two-dimensional array. Helical regions are abstracted as *cylinders*, hairpins protruding from surface of array are abstracted as *dots*. (**iii**) PNA/LNA–DNA duplexes have a different helical repeat than DNA–DNA duplexes. Using the original "B0" design, the array will not form because the tiles are not held flat. In order to form flat arrays, we must alter geometry of other tile to compensate for this difference: adding bases to the "B" tile returns the system to planarity. The effect of adding extra bases to the B tile that bring the A tile back into the plane is shown here. (**iv**) AFM images of arrays formed from the tiles B0–B7. The images in the two columns are of a 2,000-nm field and the height scale is 6.0 nm. *Insets* for B3 (LNA), B0 (DNA), and B5 (PNA) show periodic features in well-formed arrays that correspond to different helical repeats of the duplex regions formed by the different polynucleotides. Images derived with permission (Rinker et al. 2006; Lukeman et al. 2004)

cation was sufficient to allow the tile to form at room temperature. Array synthesis failed using the system that worked for an all-DNA array; this was attributed to the difference in helical repeat of the PNA/DNA duplex that formed part of the tile. By systematically compensating for the changed helical repeat, arrays were formed successfully. This process also allowed the investigators to *measure* the helical repeat of the PNA/DNA duplex (15.6 bp/t with a maximum error of ±1.4 bp/t measured over the 30 DNA–PNA base pairs present per tile) using picomole

quantities of sample. This helical repeat measuring technique appears to be general for any polynucleotide that can form the outer arms of a DX. DX tiles capable of forming two-dimensional arrays with LNA/DNA duplex arms were assembled (Rinker et al. 2006), and the helical repeat was successfully measured (13.2 bp/t with a maximum error of $\pm$0.9 bp/t).

Two-dimensional arrays and tubes were successfully constructed from single strands of L-DNA (Lin et al. 2009); no compensation was needed for helical repeat changes, as helical repeat is an achiral molecular property of the molecules. However, AFM observation of this system nicely illustrated a microscopic to macroscopic helical chirality transfer with enantiomeric strands forming "visibly" enantiomeric micron-length tubes.

The assembly of hundreds of designed two-dimensional shapes from "Single Stranded tiles" (Wei et al. 2012)—a kind of "scaffoldless" DNA origami—was recently demonstrated. L-DNA was used to assemble ~15 nm $\times$ 8 nm rectangular system that was resistant to degradation by DNAse I and T5 exonuclease.

2.1 Future Directions for Unusual Oligonucleotide Backbones

The menagerie (Eschenmoser 2011) of charged natural-nucleobase polynucleotides used for investigation of origin-of-life studies and antisense purposes has not been explored systematically for nanoconstruction: the two clear advantages of these systems over regular DNA are thermal stability and nuclease resistance. Serum survival times of nanoconstructions based on DNA appear to be significantly longer (Mei et al. 2011; Walsh et al. 2011) than predicted (based on duplex stability), and simple DNA-based nanomachines have been used in vivo to monitor (Bhatia et al. 2011; Surana et al. 2011) endocytotic processes; this implies, that at least for some applications, modified nucleotide usage may not be necessary for in vivo work.

One selling point for these materials is the resultant assemblies' thermal stability; although covalent cross-linking (Rajendran et al. 2011; Tagawa et al. 2011) can make assemblies far more stable to disassociation than any noncovalent approach. These cross-linked assemblies are, however, covalently fixed, and, once so fixed, are unable to undergo the branch-migration and strand-invasion driven processes that complex folding pathways require.

Modified backbones can help with the above problem. Currently, complex DNA systems with multiple helical regions have assembly kinetics that is programmed by duplex length and GC content. Systems that have complex folding pathways are designed to avoid kinetic-folding traps by having longer/GC heavier regions fold first (Ke et al. 2012). There may be system designs where this process of optimizing length and GC content are unfavorable for the structure's formation. Using DNA *in combination* with GNA or other polynucleotides capable of superstable base-pairing as *structural elements* will allow the avoidance of assembly kinetic traps while allowing the structure to be freed from length/GC content as a concern.

Uncharged polynucleotides have a broader range of uses; cell permeability and trafficking, thermal stability, all forms of biomolecular interaction are all

profoundly affected by neutral or near-neutral species (in comparison to a polyanion like DNA). Unfortunately, even well-studied species like PNA exhibit serious conformational heterogeneity in a double-helical context (Totsingan et al. 2010), although this is being addressed by new derivatives (Corradini et al. 2011). The ability to play with charge to reliably modify biotransport properties of proteins is just now coming of age (Cronican et al. 2010); perhaps similar approaches can be used for nucleic acid assemblies.

3 Topological Polymer Synthesis Using the DNA Backbone

On one structural level, most of the structures described previously can be viewed as a series of "stick figures" (where each stick is the helix axis of DNA); these "sticks" are joined by junctions. At a finer level, the helical nature of DNA also allows one to control strand *topology*; the helical structure of the DNA backbone generates "nodes" (regions of lines crossing in space—the fundamental topological operator) (Seeman 2000); node control is the essence of synthesis of catenanes, catenates, and knots (Dobrowolski 2003). Due to sequence-level programmability and the large number of nodes that can be inserted into a DNA-based structure, there is no other molecular system that allows the construction of topological nanoscale objects with such fine control. For example, objects with braided topologies were generated using DNA and L-DNA as the source of positive and negative nodes (Ciengshin et al. 2011).

The backbones of these objects could act as *templates* for other polymer (Fig. 5) synthesis; other polymers have material properties that polynucleotides do not such as optical, electronic, or material strength.

Note that this approach is *not* the same as nucleating metal precipitation (Gu et al. 2006; Jones et al. 2011) or condensation of a polycation (Ma et al. 2004) on assembled DNA structures—this refers to a much finer angstrom-level control of individual covalent bonds "tracking" the helical path of a DNA strand.

The first controlled synthesis of a polymer following a DNA backbone was of the archetypal synthetic polymer—Nylon (Zhu et al. 2003). Modified deoxyuridine phosphoramidite monomers were synthesized with protected carboxylic acid and amine functionality appended to the 2′ position of the ribose ring. These monomers are divided into two types: "polymer forming" and "cap forming." The polymer-forming monomers were designed to display either a 5-carbon diamine (Unn) or a 5-carbon carboxylic acid (Ucc) upon deprotection; in the presence of condensing reagents, alternating Unn and Ucc monomers should form a "ladder polymer" along the backbone of the nucleic acid. The "cap forming" monomers displayed one amine (Un) or one carboxylic acid (Uc)—enabling the termination of polymer synthesis when positioned appropriately at the end of a polynucleotide sequence.

Poly-U segments displaying increasing numbers of amine/carboxylic acid functional groups were inserted into of a poly-T oligonucleotide; upon addition of a condensation reagent, up to four stereo-controlled amide bonds were formed up the

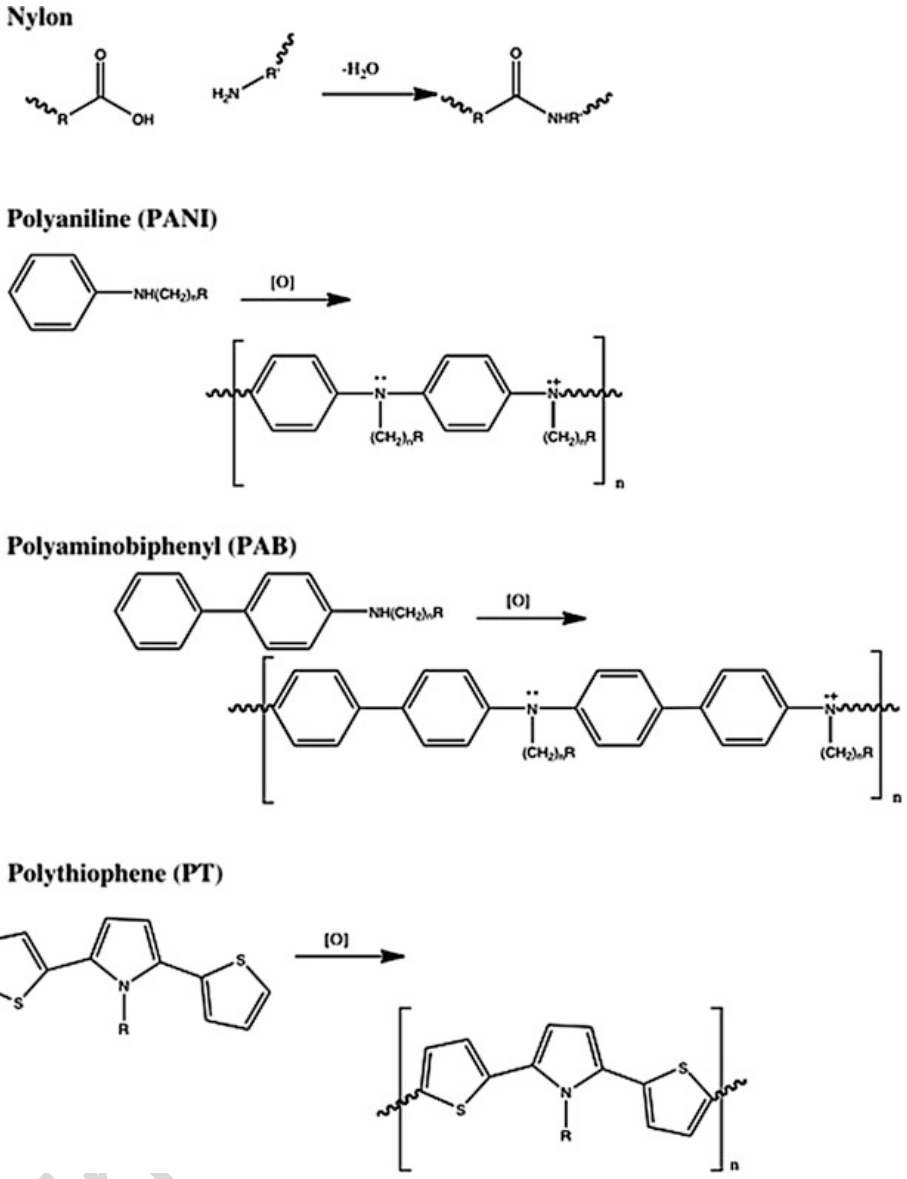

Fig. 5 The polymers referred to in this chapter

backbone of DNA. This synthesis was confirmed by gel electrophoresis and MALDI-MS with an estimated individual amide-bond forming yield of >95 %.

In follow-up work (Liu et al. 2008), the polymer synthesis was templated by hybridization to a complementary strand. This allowed for five amide bonds to be formed in higher yield and with greater ease of purification. Thermodynamic studies of these oligomers showed that both DNA and RNA duplexes formed from oligomers containing uncoupled side-groups were destabilized relative to their unmodified counterparts. The duplexes formed from coupled oligomer were, however, more stable than the uncoupled systems, and, with four or more amide bonds, coupled duplexes became more stable than the unmodified counterparts. As

estimated by Circular Dichroism, duplexes formed from coupled oligomer did not change gross conformation in comparison with their unmodified counterparts; thermodynamic study suggests that conformational preorganization of the ladder polymer plays a role in this increase in stability.

Further optimization (Liu et al. 2012) of the coupling and templation procedure (Fig. 6) allowed amide-bond formation yields to exceed 99 % and allowed the study of a molecule that contained seven amide bonds. Upon digestion with a nuclease, a neutral polynucleoside was formed where the oligomer was formed from the nylon backbone (via attachment to the 2′ position on the sugar ring). Duplexes formed from this polynucleoside and DNA exhibited an unusual inverse stability dependence on salt concentration.

The DNA backbone has been used as a template for conducting polymer syntheses (Fig. 7). The convertible nucleotide approach allowed the attachment, onto sequential nucleotides, of amines bearing aromatic rings capable of oxidative coupling. Upon hybridization to a complementary strand and oxidation, a templated polymer is formed. The first demonstration of this was with polyaniline (PANI) (Datta et al. 2006); up to six derviatized cytosines were placed in a duplex context and polymerized, with the polymer forming along the major groove according to modeling studies. The polymerization was duplex dependent; polymerization in the absence of partner formed branched product, which did not hybridize to its complement; UV spectra of untemplated reaction indicated less extended conjugation of the system.

In a follow-up study (Datta and Schuster 2008), longer stretches of PANI and 4′-aminobiphenyl (PAB) homopolymers (up to eight bases in sequence) were made, and the oxidation of these systems investigated; notable differences between the blue shift of increasingly conjugated PANI versus the geometry-restricted PAB were observed. Monomers that were blocked in the *para* position of the aromatic rings inhibited polymerization—along with UV spectra this confirms the presence of controlled PANI and PAB syntheses.

While the conjugation properties of these molecules was demonstrated with UV absorption spectra, the duplexes of both the unpolymerized and polymerized strands were destabilized relative to the unmodified system. The three-dimensional structure of PANI and PAB is incommensurate with that of DNA, limiting the length of polymer formation. In order to address the geometric incommensurability of PANI/PAB-based materials, polythiophene-like polymers (PT) using a duplex displaying alternating thymine and a thieno[3,2-b]pyrrole monomer were shown to oxidatively polymerize in a duplex context (Srinivasan and Schuster 2008), and still form B-DNA like products; however, stability of duplexes was still poor.

A more complete study was performed on 2,5-bis-(2-thienyl)pyrrole containing system (Chen et al. 2010), again showing complete polymerization, the expected UV properties of a conjugated system, CD properties of a B-like duplex. These duplexes were *stable* relative to duplex of the unmodified bases; indeed as the oligomers get longer, their stability in a duplex context increases relative to unmodified DNA. This monomer was used to make cyclic assemblies of up to 90 polymerized thiophene rings (Chen and Schuster 2012), the largest such stereo-controlled synthesis to date.

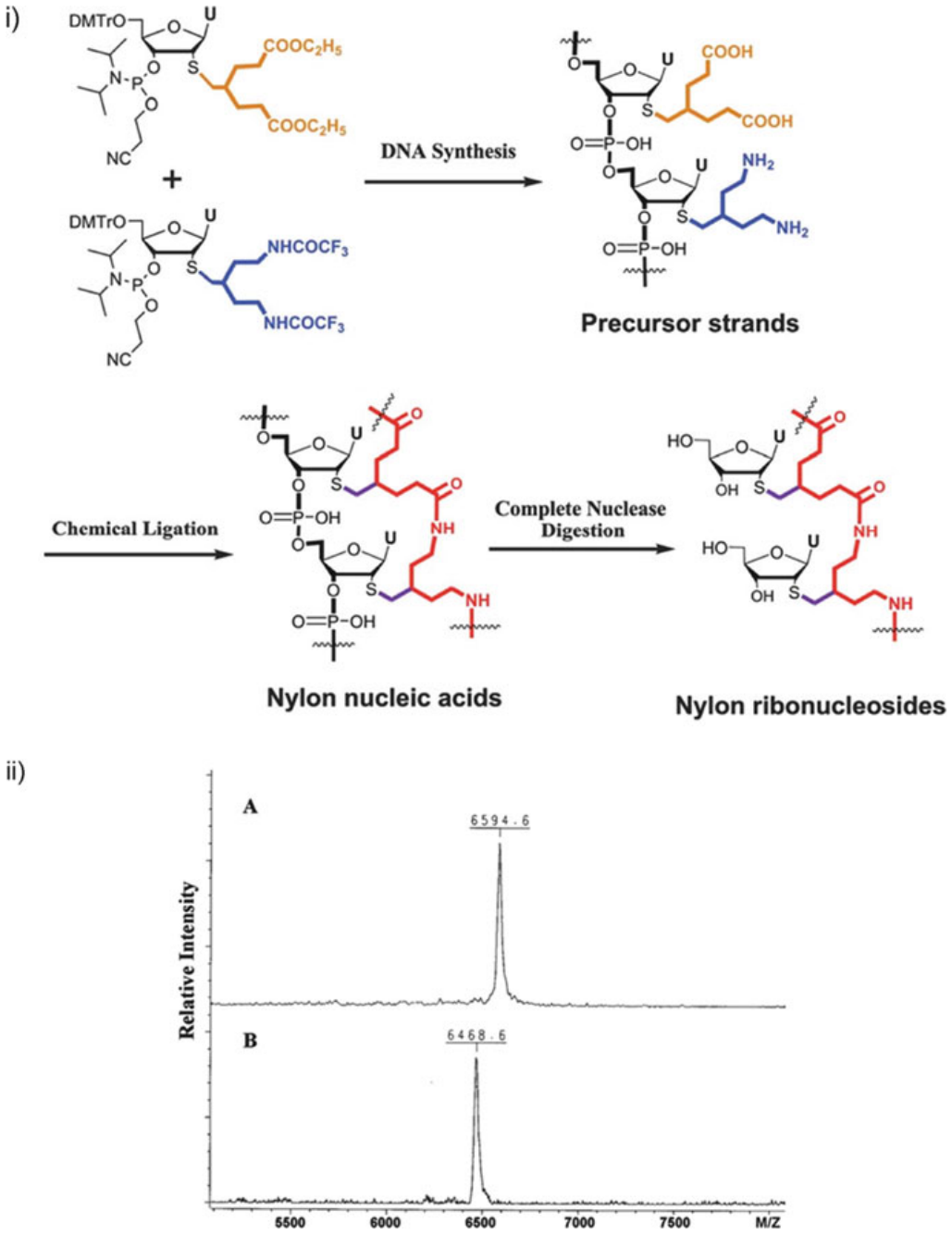

Fig. 6 (**i**) Nylon nucleic acid synthesis; monomers (*top left*), conventional DNA synthesis (*top right*), condensation/coupling using a dehydrating agent (*bottom left*) and complete nuclease digestion to produce nylon ribonucleotides (*bottom right*). (**ii**) MALDI-MS showing clean synthesis of a nylon nucleic acid from precursor containing eight contiguous monomers (*top spectrum* labeled A), clearly showing mass differential corresponding to a deficiency in seven water molecules (*bottom spectrum* labeled B). Image used with permission from Liu et al. (2012)

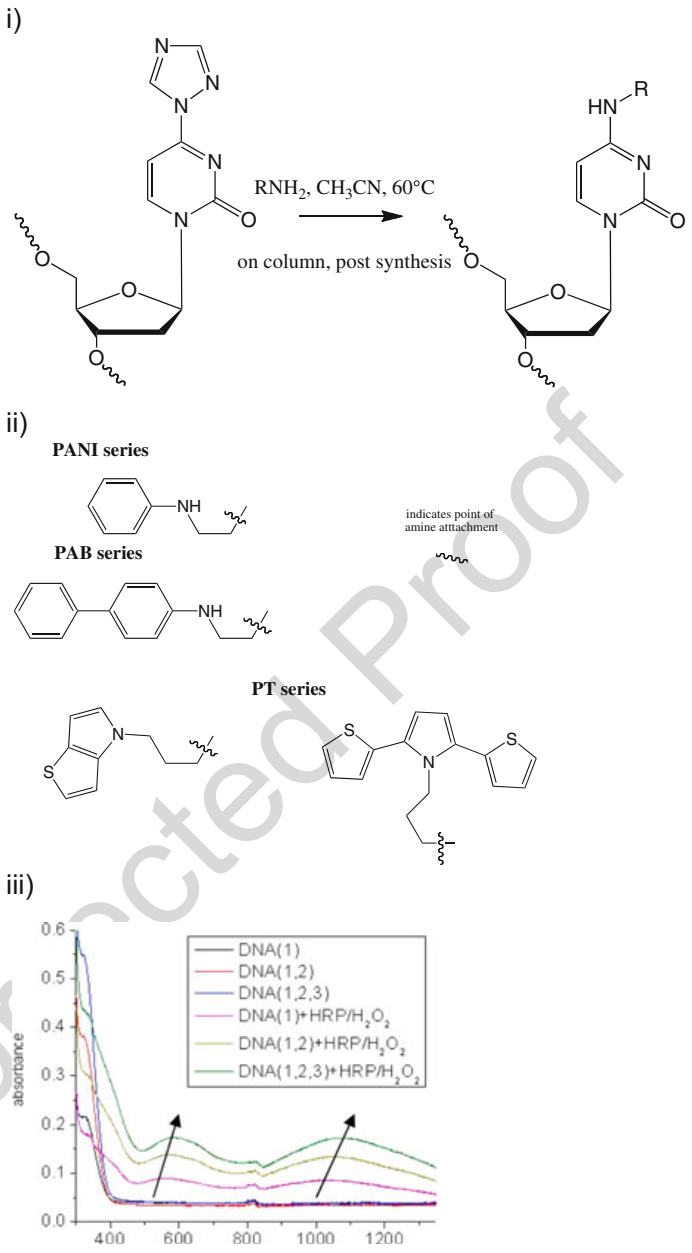

Fig. 7 (**i**) Oligomers displaying oxidizable aromatic rings can be synthesized using the convertible nucleotide approach. (**ii**) The oxidizable aromatic rings described in this chapter. (**iii**) UV–Vis–NIR absorption spectrum of DNA assemblies containing increasing lengths of PT monomers before and after reaction with HRP/H_2O_2. Before reaction with HRP/H_2O_2, all of DNA assemblies show absorptions that are the sum of those typical of the UV bands of DNA and the 320-nm band of these monomers. After reaction with HRP/H_2O_2, the absorption spectrum shifts revealing maxima at 560–580 nm and a band in the near IR region with a maximum at 1,030–1,070 nm. These spectral features are typical of the oxidized, conducting form of poly-2,5-bis (2-thienyl)-pyrrole

3.1 Future Directions for Topological Polymer Synthesis

The nylon-based chemistry described earlier is designed to be detached from the backbone via the liability of the carbon–sulfur linkage. Materials properties of catenanes and other topological objects constructed from a neutral polymer such as nylon will be open to investigation.

For the conducting polymer-based systems, if homogenous long conducting polymers can be generated, then signal transduction down these systems can be investigated using hole or electron injection as is done in conventional DNA

(Barton et al. 2011); new topologies should lead to a new understanding of electronic properties at this scale. As DNA-based electrochemical signaling is especially suited for detection in biofluids (Lubin and Plaxco 2010) (there are very few electrochemically active contaminants in human sera, for example), then applications involving, for example, fusions of aptamers with these conducting polymers might provide a new sensing platform.

4 Summary

What about the future of the field? As stated above, modified backbones are just beginning to be understood, and they are expensive compared to DNA. As one colleague pointed out "we need to do a better, exhaustive job with the molecule that we already understand and is dead cheap"; other chapters of this book describe such approaches. This caution need not preclude sensible research into things that generally cannot be done well with "vanilla" DNA, but like many "supramolecular" fields, there is a certain sense of intellectual "territory-marking" that drives this work.

Generally, the field of modified backbones "for and from" DNA nanotechnology is a sack of solutions pleading for a problem—a "killer app," to use terminology from the software world. While some suggestions have been made above, the scientific communities' discernment and drive is the ultimate arbiter of whether these assemblies move past their "curiosity" phase and live up to their evident potential in biomedicine and beyond.

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