During the past half-century the known functions of nucleic acids have expanded from genetic information carriers and messengers to include catalysis and regulation of a number of cellular processes.1 In addition, many nucleic acid-based structures have been developed with medicinal applications, catalytic properties, and prebiotic chemistry implications.1 Notable examples are antisense agents2, e.g., peptide nucleic acid (PNA),3 deoxynucleic guanidine (DNG),4 and locked DNA (LNA).3 DNAzymes have been developed with functionalized nucleotidyl groups to enhance catalytic abilities.6 TNA, (3′,2′)-α-threo nucleic acid, has been suggested as an evolutionary progenitor of RNA or DNA or both.7

We wish to develop new nucleic acid-based materials to expand the applications and scope of DNA nanotechnology.8 A number of topological targets, objects, devices, and two-dimensional (2D) arrays have been prepared from conventional DNA molecules with defined sequences and unusual structural motifs.9 Analogous DNA/organic polymer conjugates of these structures offer practical interest. For example, DNA 2D arrays10 may serve as platforms, to assemble molecular electronic devices with nanometer precision, or as templates to synthesize non-DNA polymeric 2D networks that would enjoy the stability and other favorable properties of organic materials. Single-stranded DNA has been used to direct polymerization of DNA oligos with unnatural linkages,11,19 Our goal would be to harness the full power of DNA nanotechnology, which depends on both secondary and tertiary DNA structural motifs, to assemble organic materials with unique structures. Our approach also entails regioselective chemistry between non-DNA entities.

Here, we report the first nucleic acid-based structure in which a DNA backbone has been covalently linked to an organic polymer, nylon. The synthesis was accomplished in three stages: preparation of 2′-β-substituted phosphoramidites, synthesis of oligonucleotides (ODNs) with appended amine and carboxylate groups, and coupling of the pendent groups to form oligopeptide strands covalently linked at each base pair to give a nylon/DNA ladder polymer (Figure 1). The strategy is general and could be used to generate a variety of nylon-based materials, or to direct the assembly of other organic polymers.

Initial synthetic protocols attempted 2′-OH alkylation of a protected ribonucleoside, but this approach was inefficient for hindered electrophiles.12 However, 2′-deoxy-2′-mercaptopuridine13 was alkylated with 1a and 1b to afford 2′-S-alkylated nucleosides exclusively (Scheme 1). Tritylation and phosphorylation of 2b afforded the modified phosphoramidite 4b. Two extra steps were taken to replace the stable phthlimidyl groups in 3a with DNA synthesizer-friendly trifluoroacetyl groups.14 Phosphitylation of the resulting nucleoside 3e afforded amino-modified phosphoramidite 4e. Monoamino and carboxyl-modified phosphoramidites 4d and 4f were prepared by similar methods. The respective nucleotidyl groups are shown in deprotected form in Figure 2.

Modified phosphoramidites were incorporated into 16-mer ODNs through conventional ODN synthesis. The sequences are shown in Table 1. Methanolic NaOH was used to deprotect and remove the strands from the CPG support. The conventional concentrated ammonium hydroxide treatment could not be used due to aminolysis between NH3 and the ester moieties.15 Deprotection with prevention of the Michael addition between acrylonitrile and deprotected amines16 was accomplished by including 10% piperidine in methanolic NaOH. To prevent acetate ions (from hydrolysis of the 5′-acetyl groups of the capped failure strands) from competing as alternative coupling partners, they were eliminated by triple ethanol precipitation prior to being subjected to amide-coupling conditions. The concurrent deprotection of amino and carboxyl groups and the removal of ODNs from CPG support was therefore achieved with this customized protocol. The ODNs were characterized by MALDI-TOF mass spectrometry17 (Table 1).
The foregoing results should be extensible using additional bases to more complex systems in which the self-assembling properties of DNA can be exploited. Aside from obvious applications in the antisense and gene therapy areas, we anticipate significant utility in nanotechnology.

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Supporting Information Available: Synthesis and characterization of compounds 2–4 and all the ODNs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

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(21) These estimates are lower limits, as small amounts of sodium in the spectra obscure and artificially inflate the starting material peak.
(22) In 5C, a less likely topological isomer is possible under these reaction conditions. Control experiments were performed to study the distance dependence of the coupling reaction between amino and carboxyl groups separated by a spacer. Strands 5′-(dT)_{5}U_{3}(dT)_{n}U_{5}(dT)_{5} (x + n + y = 14, n = 0, 1, 2, 3, 6, 10) were subjected to amide-bond promoting conditions. It was found that the coupling yield was highly dependent upon the length of the spacer (dT)_{n}. When n ≥ 2, the yield was less than 50%; when n = 6 or 10, coupled products were barely detectable. Therefore, the amide bonds were biased to form between amino and carboxyl groups on adjacent nucleotidyl residues.