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Development of Self-Organizing, Self-Directing Molecular Nanowires: Synthesis and Characterization of Conjoined DNA−2,5-Bis(2-thienyl)pyrrole Oligomers

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ABSTRACT: Specifically designed conducting polymers were prepared from monomers that are covalently linked to duplex DNA. These materials combine the self-assembly properties of DNA with those of conducting polymers and may be valuable in the development of self-directing molecular nanowires. Single-strand DNA oligomers having 2,5-bis(2-thienyl)pyrroles (SNS monomers) covalently linked at every other nucleobase along one strand form stable duplexes with their complementary strands. The duplex DNA serves as a scaffold that aligns the SNS monomers within its major groove. The reaction of these SNS-containing duplexes with horseradish peroxidase and H_2O_2 (an oxidant) results in the conversion of the SNS monomers to a conjoined (covalently linked) polymer having the optical properties of a conducting polymer. Examination of radiolabeled oligomers confirms bond formation between SNS monomers, and that conclusion is supported by AFM images. The conjoined polymers have structures that are determined and controlled by the DNA template.

Introduction

The creation of nanometer-sized molecular electronic devices requires the development of molecular nanowires that can effectively transport charge between functional components. The creation of such devices would be greatly facilitated if the nanowires were capable of self-directed connection enabling the efficient and scalable assembly of circuits. It has been widely recognized that the self-recognition and self-organizing properties of DNA may provide a means for the preparation of such self-directed nanowires and related structures.[1−4] However, because of its inherent low conductivity,[5] DNA itself is not useful for this purpose.

Remarkable progress has been made in recent years on various schemes to modify DNA to take advantage of its unique properties for application to molecular electronics.[6] For example, metal ions (e.g., Ag^+) electrostatically bound to the DNA phosphate groups may be reduced chemically to form metal clusters that serve as nucleation sites for the formation of a metallic wire along the length of the DNA.[7] Recently, this approach has been extended to enable the controlled positioning of nucleation sites along a DNA oligomer[8] and the formation of bimetallic Ag−Au nanowires.[9] Similarly, DNA has been used as a scaffold to form site-selective arrays of tetraphenylporphyrins that permit electronic tuning of the resulting nanostructure.[10] And the special advantage of sequence programmability enabled by DNA scaffolds has been demonstrated by the creation of molecular photonic wires with linearly arranged, unique chromophores.[11] We are pursuing a related approach for the preparation of conducting nanowires from DNA oligomers that have covalently linked monomers that are subsequently converted chemically or electrochemically to conjoined DNA-conducting polymers.[12−15]

Polyanilines (PANI) and related conducting polymers have been studied extensively because of their ease of synthesis, the wide range of electronic properties they exhibit, and their application to various important technologies.[16] Of particular relevance to the work reported here is the ability of DNA to act as a template that organizes anilinium ions and facilitates their conversion to PANI.[17,18] The negative charge of the phosphate groups attract and order the anilinium ions in the major groove of DNA, and that unique environment facilitates their conversion to PANI when the assembly is treated with an oxidant such as horseradish peroxidase (HRP) and H_2O_2. We have demonstrated that DNA can be both a template and a scaffold for the formation of PANI-like oligomers that are formed from covalently linked aniline-like monomers.[14] Treatment of these assemblies with HRP/H_2O_2 yield oligomers with the properties of PANI that are conjoined (i.e., attached covalently) to the DNA. Using this approach, conducting polymers of precisely defined length and composition have been prepared by taking advantage of both the self-organizing properties of DNA and of its specific sequence of nucleobases.[13]

There are limitations to this application of aniline-like monomers. One limitation results from destabilization of the DNA when it is modified by the covalent attachment of the monomers. The melting temperature (T_m) of the duplex is depressed by each additional monomer, which leads eventually to denaturation at room temperature. This limitation has been overcome by placing the aniline monomers on interior nucleobases of a longer DNA oligomer, but this isolates the conducting polymer and may make it unsuitable for some applications. A second limitation is that the three-dimensional structure of PANI is incommensurate with that of DNA. That is, the rise and the twist of PANI and the

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DNA are not the same. This limits the possible length of the conducting polymer because of distortions to the DNA scaffold. We report here experiments with 2,5-bis(2-thienyl)pyrrole monomers (SNS, see Figure 2) covalently linked to DNA. These monomers overcome the limitations of the aniline-like monomers. The T_m of these SNS-containing constructs increase with increasing length and the conducting polymer formed on their treatment with HRP/H_2O_2 appears to be structurally commensurate with duplex DNA.

Experimental Section

Materials. All reagents were used as received without further purification. Aluminum chloride, succinyl chloride, thiophene, 1,3-diaminopropane, and *p*-toluenesulfonic acid were obtained from Sigma-Aldrich (St. Louis, MO). The O4-triazolyldeoxyuridine phosphoramidite along with PAC phosphoramidites (phenoxyacetyl dA, isopropyl-phenoxyacetyl-dG, and acetyl-dC) were purchased from ChemGenes Corp., Wilmington, MA. T4 polynucleotide kinase (PNK) enzyme and terminal transferase (TdT) enzyme was purchased from New England Biolabs Inc. $\gamma[^{32}P]$ ATP and $\alpha[^{32}P]$ ATP were purchased from MP Biomedicals. Horseradish peroxide (HRP), type II (200 units/mg), was purchased from Sigma-Aldrich, St. Louis, MO. A stock solution of HRP was prepared by dissolving 1 mg of HRP in 1 mL of nanopure water. Hydrogen peroxide was purchased from Fischer Scientific, Pittsburgh, PA, and was diluted with nanopure water to 0.15% before use.

Synthesis of SNS and of 5,5′-Dimethyl-Substituted SNS Monomer. The synthesis of the SNS monomer with a 4-aminopropyl linker followed the previously reported method.[19,20] Flash column chromatography (silica gel column, elution with dichloromethane/methyl alcohol (100:5) afforded the desired compound as a brown oil. ^{1}H NMR: δ H($CDCl_3$): 7.3 (d, 2H, thienyl), 7.1 (dd, 4H, thienyl), 6.35 (d, 2H, pyrrolyl), 4.25 (t, 2H, CH_2), 2.45 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 0.95 (s, 2H, NH_2). Similarly, of 5,5′-dimethyl-substituted SNS monomer was prepared from 2-methylthiophene. ^{1}H NMR: δ H($CDCl_3$): 6.9 (dd, 2H, thienyl), 6.75 (dd, 2H, thienyl), 6.3 (d, 2H, pyrrolyl), 4.2 (t, 2H, CH_2), 2.5 (m, 8H, CH_2, CH_3), 1.65 (m, 2H, CH_2), 1.2 ppm (s, 2H, NH_2).

SNS Containing Modified DNA Oligomers. SNS modified DNA oligomers were synthesized according to a previously published report.[14] The solid support containing oligonucleotides with the triazole modified uridine was treated with 200−500 μL of 5 M SNS monomer in acetonitrile solution for 40 h at 60 °C. The supernatant was removed, and the solid support was washed with acetonitrile and then treated with concentrated aqueous ammonium hydroxide solution at room temperature for 12 h. The ammonium hydroxide solution was dried on Speed Vac at 50 °C, and samples were reconstituted with water and purified by reverse phase HPLC on a Hitachi preparative HPLC system using Dynamax C18 column. Purified DNA was desalted using Waters Sep Pak cartridges and characterized by ESI-mass spectrometry. The concentration of the modified DNA oligomers was determined in solution by measuring the absorption of the SNS group at 320 nm where its extinction coefficient is 1.37×10^4 M^{-1} cm^{-1}. Mass spectra of the oligomers are reported in the Supporting Information.

Preparation of Radiolabeled DNA. The oligonucleotides were labeled at the 5′-terminus with $[^{32}P]$ ATP and PNK enzyme and at the 3′ terminus with $[^{32}P]$ ATP and TdT enzyme. The radiolabeled DNA samples were purified by 20% PAGE. The desired bands were excised from the gel and eluted with 800 μL of elution buffer (Poly-Gel Elution buffer, OMEGA biotek) at 37 °C for 12 h. The DNA was precipitated from the supernatant by addition of cold ethanol (800 μL for 400 μL of the supernatant) and 2 μL of glycogen solution. The mixture was vortexed, placed on dry ice for 60 min, and centrifuged for 45 min at 13 000 rpm. The supernatant was removed, and the residual DNA was washed three times with 100 μL of 80% ethanol and dried in Speed Vac at medium heat. Suitable volumes of water were added for further experimentation.

UV−vis Absorption Measurements. Samples were prepared by hybridizing 2 μM of the desired single-strand DNA in 10 mM citrate buffer (pH 4.5) containing 500 mM of NaCl. Hybridization was achieved by heating the samples at 90 °C for 10 min followed by slow cooling to room temperature. Polymerization was carried out at 10 °C by addition of 2 μL of HRP (1 mg dissolved in 1 mL of nanopure water) followed by 2 μL of H_2O_2 (0.15%). Spectra were recorded at 10 °C before and after initialization of polymerization at 10 min intervals.

Thermal Denaturation and CD Measurements. Samples for T_m and CD spectral measurements were prepared by hybridizing 2 μM of the DNA strands in 10 mM citrate buffer (pH 4.5) containing 500 mM of NaCl. The thermal denaturation profiles were recorded with a heating and cooling rate of 0.5 °C min^{-1}. UV−vis absorption spectra were recorded on a Cary 1E spectrophotometer; UV melting and cooling curves were recorded using a multicell block and temperature controller on the spectrophotometer. CD spectra were recorded on a JASCO J-715 spectropolarimeter.

PAGE Experiments. Samples for the gel experiments were prepared by hybridizing a mixture of unlabeled (0.5 μM) and radiolabeled (30 000 cpm) SNS-modified DNA oligonucleotides with the complementary strand in 10 mM citrate buffer (pH 4.5) containing 500 mM NaCl (total volume 200 μL). The reaction with HRP/H_2O_2 was carried out at 5 °C for 30 min. The pH was increased to 7 by adding 1 M NaOH, and this solution was mixed with 200 μL of denaturing loading buffer (formamide and water in 4:1 ratio). The samples were electrophoresed on a 20% 19:1 polyacrylamide gel containing urea (7 M) at 300 W for 3 h in a Hoefer Vertical Slab gel unit model SE400 (Hoefer Scientific Instruments, San Francisco, CA). The gels were dried and the bands were visualized by autoradiography.

Atomic Force Microscope (AFM) Imaging. Tapping mode AFM images were acquired in air on a Veeco Nanoscope IV system with SSS-NCH super sharp tips (Nanosensors). The typical tip radius is 2 nm. The typical tapping frequency is 204−497 kHz. The nominal force constant of the tip is 42 N/m. A freshly cleaved mica surface was coated with 10 μL of 10 mM magnesium chloride solution for 30 min. Then the surface was washed thoroughly with nano pure water and dried with nitrogen gas stream. A 10 μL solution of duplex DNA oligomer (1 μM in pH 4.5 citrate buffer containing 500 mM NaCl) was deposited dropwise on the Mg-treated mica surface. After 30 min of incubation, the DNA solution was washed from the mica surface with nanopure water.

Results and Discussion

Polythiophene and its derivatives are among the most extensively studied conducting polymers.[21,22] They are relatively easy to synthesize, and they exhibit a wide range of readily adaptable properties. Moreover, oligothiophenes are described as forming "good" molecular wires characterized by having β values equal to 0.1 $Å^{-1}$.[23] Monomers comprised exclusively of thiophenes cannot be easily linked to DNA, but their analogue, 2,5-bis-(2-thienyl)pyrrole, contains a nitrogen atom suitable for linking. Such monomers have been prepared previously, their electrochemistry and polymerization mechanism studied, and their electrochromic properties described.[24,25] First, we assessed computationally the ability of these SNS monomers to form commensurate, conjoined polymers with DNA.

Molecular Modeling Studies. It is well-known that the nucleobase pairs of B-form duplex DNA are stacked ca. 3.4 Å apart with a helical twist of ca. 36°.[26] For the SNS monomer, the linear distance from the pyrrole nitrogen atom to the hydrogen atom attached to the 5-carbon is estimated

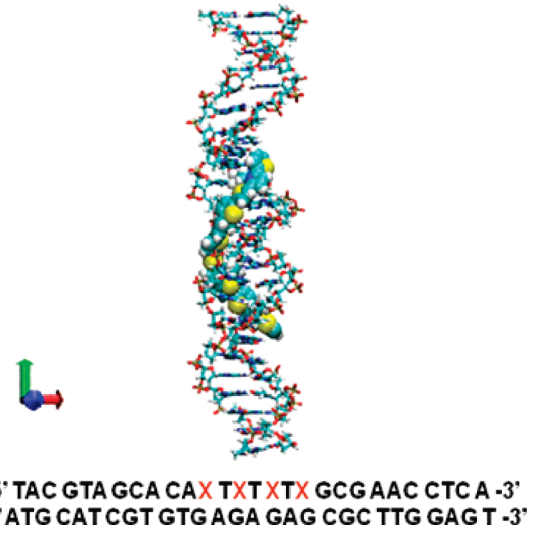


Figure 1. Computer-generated structural model for conjoined duplex DNA−SNS oligomer comprised of four SNS monomer units (symbolized as X) placed on alternating nucleobases of the modified strand in the DNA major groove. The structure was calculated by means of Hyperchem software.

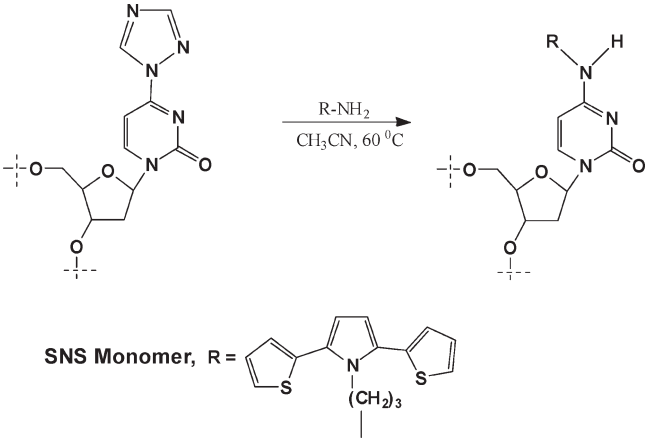


Figure 2. Outline of the method used for the preparation of oligonucleotides modified to contain 2,5-bis(2-thienyl)pyrrole (SNS) monomers. The DNA strands having triazole-modified uridine were prepared by standard phosphoramidite-based machine synthesis.

from structural models to be ca. 5.6 Å. Consequently, modified DNA oligomers were modeled that have an SNS monomer linked at every other nucleobase along one strand of the duplex. A similar arrangement was shown experimentally to be appropriate for related thieno[3,2-*b*]pyrrole monomers.[15] Accordingly, we carried out simple molecular mechanical modeling studies of an oligomer having an SNS monomer attached to every other nucleobase of B-form DNA by a $-(CH_2)_3-$ (trimethylene) linker between the N4 nitrogen of cytosine and the pyrrole nitrogen atom of SNS (see Figure 1). These studies showed that the SNS monomers appear to line up "head-to-tail" in the major groove and that bond formation between the 5-positions of thiophenes on adjacent monomers can form a polymer with rise and twist approximately commensurate with that of B-form DNA. On the basis of these studies, we prepared and undertook the study of the series of DNA oligomers, shown in Figure 3, that are modified by covalent attachment of SNS monomers.

SNS-Containing DNA Duplex Oligomers: Preparation and Characterization. The SNS monomers were incorporated into DNA oligomers by triazole displacement from a uridine

DNA(**1**)	5' TCT CTC TCT CTCTCT CTC TCT CTC TCT CTC T3' 3' AGA GAG AGA GAG AGA GAG AGA GAG AGA GAG A5'
DNA(**2**)	5' TXT XTX TXTXTX T3' 3' AGA GAG AGA GAG A 5'
DNA(**3**)	5' TXT XTX TXT XTX TXT XTX TXT 3' 3' AGA GAG AGA GAG AGA GAG AGA5'
DNA(**4**)	5' TXT XTX TXTXTX TXT XTX TXT XTX TXTXTX T3' 3' AGA GAG AGA GAG AGA GAG AGA GAG AGA GAG A5'

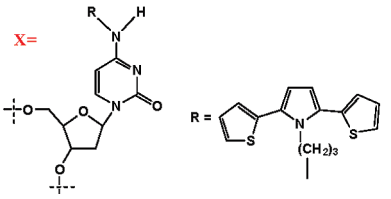


Figure 3. Structures of the DNA duplex oligomers. DNA oligomers 1−4 are covalently linked to the SNS monomer X.

precursor with 1-aminopropyl group linked 2,5-bis(2-thienyl)-pyrrole following standard phosphoramidite-activated oligonucleotide synthesis (see Figure 2).[27] The DNA oligomers were purified by standard methods and characterized by optical and mass spectrometry (see Supporting Information). One strand (the "complementary" strand) of these duplex DNA oligomers is comprised of a repeating sequence of adenine and guanine nucleotides; i.e., 5′-$(AG)_n$A-3′. The second strand (the "modified" strand) is comprised of thymines, which are opposite the adenines of the complementary strand, and a cytosine or an SNS-linked cytosine (symbolized as "X") opposite the guanines of the complementary strand; i.e, 3′-$(TX)_n$T-5′. Duplex oligomer DNA(1) (see Figure 3) is a 31-mer comprised of standard nucleobases. DNA(2) is similar to DNA(1) except that each of the six cytosines on the modified strand is replaced with the SNS-modified nucleobase X. DNA(3) and DNA(4) are 21- and 31-mers, respectively, following the same pattern with 10 and 15 SNS monomers attached to the modified strands. The melting behavior of each of these oligomers was determined by standard optical methods in citrate buffer solution containing 500 mM NaCl at pH 4.5.

SNS-linked duplex oligomers DNA(2), -(3), and -(4) each exhibit a single, reversible melting transition with T_m = 24, 34, and 49 °C, respectively. In contrast, under these conditions unmodified duplex DNA(1) shows two transitions, one at 38 °C and the second at 85 °C, suggesting the presence of noncanonical structures in addition to the normal duplex, which is typical of homopurine/homopyrimidine sequences like DNA(1) in acidic solution.[28] Apparently, the covalently linked SNS monomers of the modified DNA duplex oligomers block the formation of these alternative structures by occupying the major groove.

Clearly, these melting data show that replacement of cytosines with the SNS-modified nucleotides reduces the stability of the duplex; for example, the T_m of DNA(4) is 36 °C below that of DNA(1). But, the T_m of the modified duplexes increases as the number of SNS modifications increases. For example, the T_m of duplex DNA(4), which has 15 SNS-linked nucleobases, is more than 25 °C greater than duplex DNA(2), which has six SNS-linked nucleobases. The increase in T_m is a consequence of the larger number of Watson−Crick base pairs that are present in SNS-linked duplexes of greater length, which evidently overcomes the destabilization caused by the additional SNS modifications. In principle, this property will enable the preparation of stable SNS-modified duplexes of any desired length.

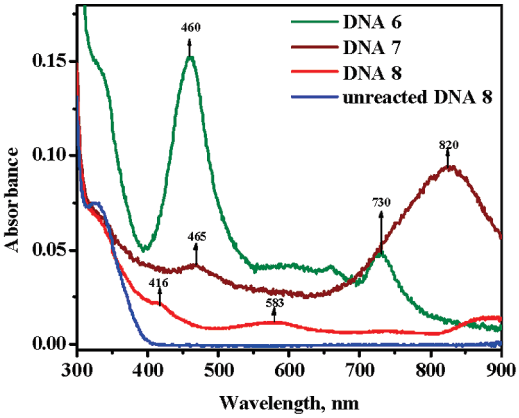
We carried out a series of circular dichroism (CD) experiments to confirm formation of heteroduplex DNA from SNS-modified oligomers and their complementary strands. Separate solutions of single-strand 5′-$(AG)_{15}$A-3′ and of 5′-$(TX)_{15}$T-3′ exhibit characteristic CD signals in the UV spectral region (the CD spectra are included in the Supporting Information). The CD spectrum of a 1:1 mixture of these two strands gives a unique CD spectrum that neither is like that of either single strand nor is it the sum of the two single strands, which indicates formation of duplex DNA(4).

These melting and spectroscopic experiments show that the SNS-linked oligomers form duplexes with their complementary strands, and that theses duplexes have structures similar to that of B-form DNA. This suggests that a polymer resulting from conversion of the monomers linked to 31-mer DNA(4) would be ca. 10 nm long and would be comprised of 45 "aromatic" rings, which is a length sufficient to convey the properties of conducting polymers.[29] We carried out a series of experiments to probe for the formation of a conducting polymer from the oxidation of these covalently linked SNS monomers.

Optical Properties of Conjoined SNS Oligomers. Unique optical absorption spectra are one of the characteristic features of conducting polymers.[30] At the one-electron approximation level, the allowed optical transitions for SNS-like polymers can be identified as arising from valence band to conduction band transitions and transitions between bonding and antibonding levels for both polaronic and bipolaronic structures.[31] The essential characteristics of these absorptions are maintained in more sophisticated multiconfiguration analyses.[32] We prepared a series of SNS-substituted oligomers and examined their optical spectra to determine whether their oxidation results in spectral properties that are typical of conducting polymers.

A series of SNS-containing duplex oligomers (see Figure 4) was prepared, purified, and analyzed. DNA(5) is a duplex 27-mer that contains only standard nucleobases. DNA(6) is similar to DNA(5), except that it has a single SNS group at the central position of the modified strand. At pH 4.5, DNA(6) has a T_m = 71 °C, which is 3 °C lower than that of unmodified DNA(5) under the same conditions. The circular dichroism (CD) spectra of DNA(5) and DNA(6) are essentially identical, which indicates that the global structure of DNA(6) remains B-form DNA. Similarly, DNA(7) contains two SNS monomers on the modified strand and DNA(8) has four. The T_m of DNA(7) and DNA(8) are 6 and 15 °C less than DNA(6), respectively, and their CD spectra indicate that they are also B-form like DNA duplexes. The melting data are summarized in the Supporting Information.

The reaction of duplex DNA(5) with HRP/H_2O_2, as expected, results in no meaningful change to its absorption spectrum because it does not contain an SNS monomer. In contrast, the addition of HRP/H_2O_2 to an aqueous buffer solution at pH 4.5 of duplex DNA(6) results in the rapid appearance of new absorption bands (within the recorded range from 300 to 900 nm) with apparent maxima at 460 and 730 nm (see Figure 4). These absorption features are essentially identical with the reported absorption spectrum of the SNS radical cation ($SNS^{\bullet+}$).[33] The thermodynamic and kinetic stabilization of oligoaniline radical cations by encapsulation has been recently reported and linkage to duplex DNA appears to similarly stabilize the SNS radical cation.[34] Importantly, one-electron oxidation of the SNS-modified single strand of DNA(6) does not give a spectrum characteristic of the SNS radical cation. Instead, very broad, relatively weak bands with apparent maxima 575 and 822 nm appear in the absorption spectrum. These bands indicate that



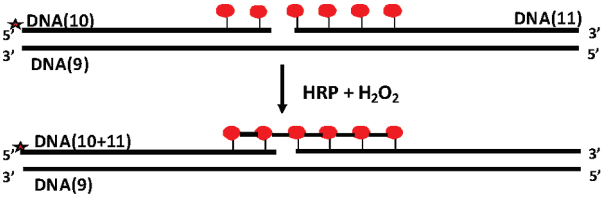
DNA(**5**)	5' TGA GGT TCG CGA GAG AGT GTG CTA CGT A 3' 3' ACT CCA AGC GCT CTC TCA CAC GAT GCA T5'
DNA(**6**)	5' TGA GGT TCG CGA GAG AGT GTG CTA CGT A 3' 3' ACT CCA AGC GXT CTC TCA CAC GAT GCA T5'
DNA(**7**)	5' TGA GGT TCG CGA GAG AGT GTG CTA CGT A 3' 3' ACT CCA AGC GXT XTC TCA CAC GAT GCA T5'
DNA(**8**)	5' TGA GGT TCG CGA GAG AGT GTG CTA CGT A 3' 3' ACT CCA AGC GXT XTX TXA CAC GAT GCA T5'

Figure 4. Optical absorption spectra observed from the reaction of SNS-containing duplex DNA oligomers with HRP/H_2O_2 in buffer solution at pH 4.5. The curves are color-coded as shown in the legend. The structures of the duplex DNA oligomers are shown; "X" has the same meaning as in Figure 3.

oxidation of SNS linked to single-stranded DNA results in an optical spectrum having the characteristics of short SNS oligomers (i.e., $SNS{-}SNS^{\bullet+}$, see below) that are formed by intermolecular reactions. Thus, it appears that the SNS radical cation ($SNS^{\bullet+}$) is stabilized when it is linked to duplex DNA, in which case the ensuing intermolecular reaction with SNS monomers is inhibited, but not when linked to single-strand DNA. This finding is supported by the results of additional optical and "ligation" experiments that are reported below.

The addition of HRP/H_2O_2 to a solution of duplex DNA-(7), which contains two covalently linked SNS monomers, results in new prominent absorption bands at 465 and 820 nm that are formed essentially immediately on mixing (see Figure 4). These bands are very similar to those observed for the hexathiophene radical cation,[29] and thus this indicates that the oxidation of duplex DNA(7) results in the intramolecular formation of a dimer $(SNS{-}SNS)^{\bullet+}$, which also has six contiguous aromatic rings. Reaction of the single modified strand of DNA(7) results in spectral changes similar to that of oxidation of the modified single strand of DNA(6). The oxidation of duplex DNA(8), which contains four SNS monomers, results in two relatively weak absorption bands with maxima at 416 and 583 nm and the tail of a band that has an apparent absorption maximum in the near-IR (see Figure 4). This finding is consistent with the expectation that the polaronic $(SNS)_4^{\bullet+}$ or bipolaronic $(SNS)_4^{2+}$ absorption bands of an oligomer that is 12 aromatic rings long will absorb primarily in the near-IR region.

It is clear that the optical spectra of the products formed from reaction of HRP/H_2O_2 with the SNS-modified DNA duplexes are consistent with the formation of $(SNS\text{-}SNS)_n^{\bullet+}$. We carried out a series of experiments using [^{32}P]-labeled DNA to demonstrate that the intramolecular bond formation required for the generation of these oligomers does occur between SNS monomers when they are linked to duplex DNA.



DNA(**9**)	5'CGATGCATCACAGCTAGAGAGTGAGAGAGTCATCTACTACGAGC 3'
DNA(**10**)	5' GCTCGTAGTAGATGAXTXT 3'
DNA(**11**)	5' XTXAXTXTCTAGCTGTGATGCATCG 3'
DNA(**12**)	5'GCTCGTAGTAGATGAXTXTXTXAXTXTCTAGCTGTGATGCATCG3'
DNA(**13**)	5' GCTCGTAGTAGATGAYTYT 3'
DNA(**14**)	5' YTYAYTYTCTAGCTGTGATGCATCG 3'

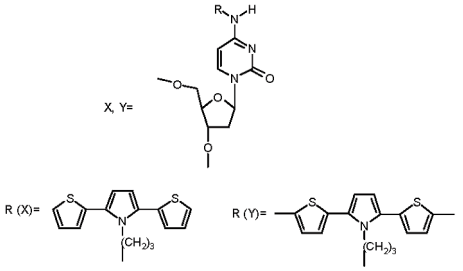


Figure 5. Three single-strand DNA oligomers assemble to make a three-part duplex DNA that contains six SNS-modified nucleobases, the red circles and symbolized by "X". Reaction with HRP/H_2O_2 in buffer solution at pH 4.5 results in ligation (bond formation) forming the longer oligomer DNA(10 + 11), which is detected by PAGE and autoradiography both when DNA(10) and when DNA(11) are labeled with [^{32}P] (indicated by the red star) as is shown in Figure 6A,B.

Oligomer "Ligation" through SNS to SNS Bond Formation. A series of "ligation" experiments were carried out on SNS-linked single- and double-stranded DNA oligomers to investigate covalent bond formation between neighboring SNS monomers. The logic of the ligation experiments is shown in Figure 5. There are three DNA strands: ssDNA(9), which is a 44-mer comprised of standard nucleobases; ssDNA(10), which is a 19-mer that contains two SNS-modified bases near its 3′-terminus and is complementary to the first 19 bases (from the 3′-end) of ssDNA(9); and ssDNA(11), which is a 25-mer containing four SNS-modified bases near its 5′-terminus and is complementary to 25 bases from the 5′-terminus of ssDNA(9). These three single strands are expected to assemble to form duplex DNA(9,10,11) as shown in Figure 5, which has six aligned SNS-modified oligomers: two on one side of a gap (nick) and four on the other side. Separate experiments were carried out in which samples of ssDNA(10) were radiolabeled with [^{32}P] at the 5′-end (indicated by asterisk) or ssDNA(11) was labeled at its 3′-end. If reaction with HRP/H_2O_2 results in oligomerization of the SNS monomers of DNA assembly (9,10,11), the "gap" between DNA(10) and (11) will be bridged, and these two oligomers will be covalently linked (ligated) to form the 44-mer ssDNA(10 + 11), which can be detected and identified by means of denaturing polyacrylamide gel electrophoresis (PAGE) and autoradiography.

The melting behavior of a 1:1:1 mixture of DNA(9), -(10), and -(11) shows transitions indicating the formation of the expected three-part assembly (the melting curves are included in the Supporting Information). The addition of HRP/H_2O_2 to this assembly results in an optical absorption spectrum indicative of the formation of an $(SNS-SNS^{\bullet+})_n$ oligomer; specifically, the tail of the expected near-IR band is observed at ca. 900 nm. The results of a preliminary set of ligation experiments for this assembly using radiolabeled oligomers are shown in Figure 6A. Lane 1 shows [^{32}P]-labeled ssDNA(9),

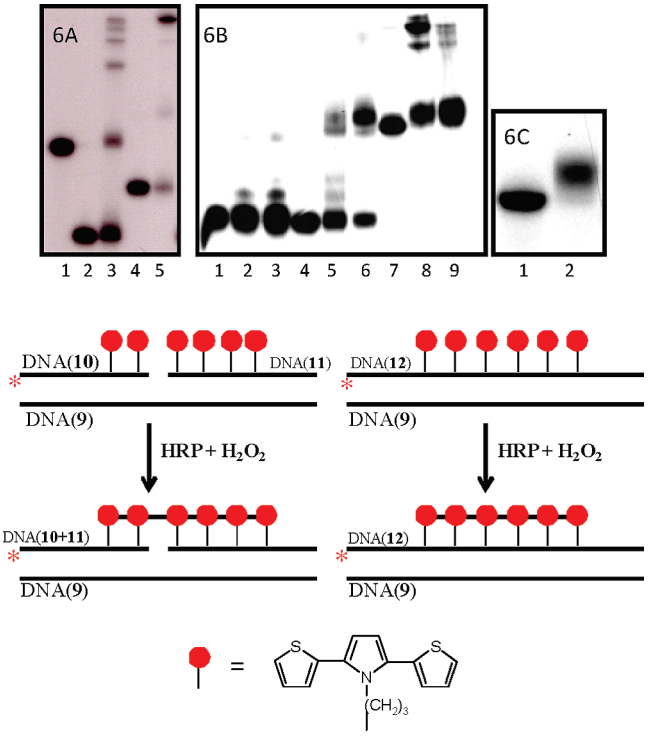


Figure 6. Oligomerization reactions of assembly DNA(9,10,11) and duplex DNA(9/12) by reaction with HRP/H_2O_2. The red circles represent the covalently linked SNS monomers (X), and the red star indicates the position of the [^{32}P] radiolabel. PAGE results are shown in 6A, 6B and 6C, which indicate that reaction forms the conjoined oligomeric $(SNS)_6$ indicated by the horizontal red line through the red circles. (6A) PAGE results from the ligation experiment of DNA oligomers 9, 10, and 11. Lane 1 is [^{32}P]-labeled single-strand (ss)DNA-(9), lane 2 is [^{32}P]-labeled (ss)DNA(10), lane 3 is the result of reaction of [^{32}P]-labeled ssDNA(10) with HRP/H_2O_2, lane 4 is [^{32}P]-labeled (ss)DNA(11), and lane 5 is the result of reaction of [^{32}P]-labeled ssDNA(11) with HRP/H_2O_2. (6B) Lanes 1−3 are PAGE results from [^{32}P]-labeled DNA(9, 13, 14) where the SNS monomer is modified by 5,5′-dimethyl substitution. Lane 1 is [^{32}P]-labeled DNA(13), lane 2 [^{32}P]-labeled DNA(13) and DNA(14) after reaction with HRP/H_2O_2, and lane 3 [^{32}P]-labeled DNA(13), DNA(14), and DNA(9) after reaction with HRP/H_2O_2. Lanes 4−7 are the three-part ligation experiment of the duplex assembly of three DNA single strands formed from DNA(9), DNA(10), and DNA(11). Lane 4 is a control for [^{32}P]-labeled ssDNA(10) before reaction with HRP/H_2O_2, and lane 6 is the result of [^{32}P]-labeled DNA(10), DNA(11), and DNA(9) after reaction of the assembly with HRP/H_2O_2; note in particular the slow moving band that corresponds in approximate position to the band for [^{32}P]-labeled DNA(12) shown in lane 7. Lane 5 is a 1:1 mixture of single-stranded [^{32}P] labeled DNA(10) and DNA(11) without complementary DNA(9) after reaction with HRP/H_2O_2. Lanes 8 and 9 are the results of reaction of ssDNA(9) and duplex DNA(9/12) with HRP/H_2O_2. (6C) Lane 1 is [^{32}P]-labeled ssDNA(12), and lane 2 is the result of reaction of duplex DNA(9/12) with HRP/H_2O_2; DNA(12) is labeled with [^{32}P].

which indicates the approximate position on the gel for a ssDNA 44-mer. Lane 2 is [^{32}P]-labeled DNA(10), which being shorter than DNA(9) migrates farther on the gel (compare lanes 1 and 2). Lane 3 shows the result of oxidation of ssDNA-(10) alone (i.e., no complementary strand) with HRP/H_2O_2. Clearly, the oxidation of ssDNA(10) results in the formation of a mixture of SNS-containing oligomers comprised of dimers, trimers, tetramers, etc., formed presumably from the intermolecular reaction of the SNS monomers on separate single-stranded DNA oligomers. Lanes 4 and 5 show ssDNA(11) and its reaction with HRP/H_2O_2, respectively. DNA(11) is longer than DNA(10) and shorter than DNA(9) and thus it falls between these two on the gel. The HRP/H_2O_2 oxidation of DNA(11) also shows that intermolecular formation of dimers,

trimers, etc., results when SNS monomers are linked to single-strand DNA.

The results of HRP/H_2O_2 oxidation experiments with the three-strand duplex assembly DNA(9,10,11) with DNA(10) radiolabeled are shown in Figure 6B. Bond formation between the SNS monomers linked to DNA(10) and -(11) will form the ligation product DNA(10 + 11) which is approximately equivalent in length and structure to DNA(12), which is a 44-mer containing six covalently linked SNS monomers. Lane 4 in Figure 6B is a control that shows the position of DNA(10) on the gel before its reaction with HRP/H_2O_2. Lane 6 of Figure 6B shows the results the reaction of HRP/H_2O_2 with the entire three-part assembly of ssDNA(10), ssDNA(11), and complementary strand ssDNA(9). This reaction results in new band that migrates just a bit slower than the band for DNA(12), which is shown in lane 7. We assign the new band in lane 6 to the ligation product DNA-(10 + 11). DNA(10 + 11) is expected to migrate just a bit slower than DNA(12) in the electric field of the PAGE analysis because the latter has one more phosphate group than DNA(10 + 11). Also, DNA(10 + 11) may migrate a bit more slowly than DNA(12) because the polaronic or bipolaronic form of the conjoined SNS polymer of DNA(10 + 11) may include one or two positive charges (see below). The ligation product DNA(10 + 11) appears to be formed in good yield with just a trace of the apparent homodimer product DNA(10 + 10), which appears to be the faint band below that assigned to DNA(10 + 11). In a related experiment, DNA(10 + 11) is similarly formed from reaction of the three-part assembly in which ssDNA(11) is labeled with [^{32}P], which confirms its identity. In contrast, reaction of a 1:1 mixture of ssDNA(10) and ssDNA(11) with HRP/H_2O_2 in the absence of complementary ssDNA(9), lane 5 in Figure 6B, shows that this reaction gives low yields of apparent homodimer and DNA(10 + 11). It should be noted that homodimer DNA(11 + 11), if formed, will not appear on the gel because it does not contain a radiolabel. Also, the density of the image on the gels is only roughly proportional to the amount of product present. In particular, minor products, such as homodimer DNA(10 + 10) in lane 6, are typically over-represented because the photographic images of the major products are saturated. Finally, experiments conducted on a four-part assembly formed from a single complementary strand and three SNS-containing oligomers give two-bond ligation to form a conjoined (SNS) oligomer (see Supporting Information).

These ligation experiments confirm the formation of bonds between neighboring SNS monomers when they are part of duplex DNA and support the observations from the optical spectroscopy experiments that HRP/H_2O_2 oxidation of SNS monomers covalently linked to DNA results in formation of SNS oligomers. It should also be noted that the formation of dimers, trimers, etc., is inhibited in the reaction of SNS when it is part of duplex DNA. This was similarly indicated in the optical absorption experiments described above.

Further evidence for specific bond formation between the thiophene groups of the SNS monomers linked to duplex DNA comes from experiments with the 5,5′-dimethyl-substituted SNS (see Figure 6B, lanes 1−3). As in the previous ligation experiment, a duplex assembly of three DNA single strands is formed from DNA(9), [^{32}P]-labeled DNA(13), and DNA(14). DNA(13) and DNA(14) are equivalent to DNA-(10) and DNA(11), except that in this case they are linked to 5,5′-dimethyl-substituted SNS monomers ("Y") (see Figure 5). If the oligomerization of the SNS monomers in the DNA(9,10,11) assembly occurs as expected by bond formation between the 5-positions of SNS monomers,[24] then the methyl groups on the methyl-substituted monomer will block reaction between the SNS monomers and inhibit the ligation of DNA(13) and DNA(14). The 5,5′-dimethyl-substituted SNS monomer modified DNA is easily oxidized to form a stable radical cation that shows characteristic absorption bands at 754 and 491 nm, respectively.[33] The results of reaction of assembly DNA(9,13,14) with HRP/H_2O_2 give an optical absorption spectrum characteristic of the dimethyl-SNS radical cation but show no ligation of DNA(13) with DNA(14) under the conditions where ligated DNA(10 + 11) is readily formed from DNA(9,10,11). In particular, comparison of lanes 3 and 6 in Figure 6B shows that essentially none of the ligated product DNA(13 + 14) can be detected. This result confirms that bond formation between SNS monomers covalently linked to duplex DNA occurs intramolecularly between the 5-carbon atoms of adjacent SNS monomers only when that position is not blocked by a substituent such as a methyl group.

Formation of Conjoined DNA−(SNS)$_n$ Conducting Polymers. The efficiency of oligomerization of the SNS monomers covalently linked to duplex DNA was assessed by denaturing PAGE analysis of the reaction of the duplex formed by DNA(12) and DNA(9). The 44-mer DNA(12) is fully complementary to DNA(9), containing six centrally located SNS monomers, one on every other nucleobase, and is labeled with [^{32}P] at its 5′-end (see Figures 5 and 6). The six SNS monomers of duplex DNA(12/9) are expected to be polymerized by reaction with HRP/H_2O_2. In Figure 6B, lane 7 shows DNA(12) before reaction. Lane 8 in Figure 6B shows that the reaction of single-stranded DNA(12) with HRP/H_2O_2 apparently gives its dimer, trimer, and tetramer formed from intermolecular reaction, which is consistent with the results of reactions carried out on other single-strand oligomers. Lane 9 shows the product formed by reaction in the presence of DNA(12) as a duplex with its complementary strand DNA(9). The intermolecular reaction is inhibited in the duplex. The main product from the intramolecular reaction of the covalently linked SNS monomers appears at a similar position on the gel as that of the DNA(10 + 11) (lane 6) but moves a bit more slowly than does unreacted DNA(12) in lane 7. This migration pattern is consistent with the formation of a structure having the polaronic $(SNS)_6^{\bullet+}$ or bipolaronic $(SNS)_6^{2+}$ oligomers linked to the DNA. That is, the DNA with conjoined, positively charged polymer having net negative charges one or two less than that with the unreacted monomers will migrate more slowly in the electric field of the gel. The high-resolution gel electrophoresis in Figure 6C shows the conversion of DNA(12) to the conjoined $(SNS)_6$ oligomer is nearly complete; very little unreacted DNA(12) is seen in the gel. The band in lane 2 of Figure 6C attributed to the conjoined polymer is a little "fuzzy", which may indicate incomplete oligomerization, but there is one primary product formed.

We carried out additional optical spectroscopy experiment on DNA(4), which has 15 consecutive SNS monomers linked to a duplex DNA 30-mer. The addition of HRP/H_2O_2 to a 30 μM solution of duplex DNA(4) in buffer at pH 4.5 yields a clear green solution with a strong absorption band at 630 nm and a band in the near-IR region with maximum beyond 1100 nm (see Figure 7A), which indicates that the HOMO−LUMO band gap for the SNS oligomer is ca. 1 eV. This spectral change is consistent with that expected for formation of a conjoined $(SNS)_{15}$ polymer.[29] The observed T_m of DNA(4) with conjoined $(SNS)_{15}$ oligomer formed from the reaction with HRP/H_2O_2 is 49 °C, which is the same as that before reaction. The CD spectrum of DNA(4)

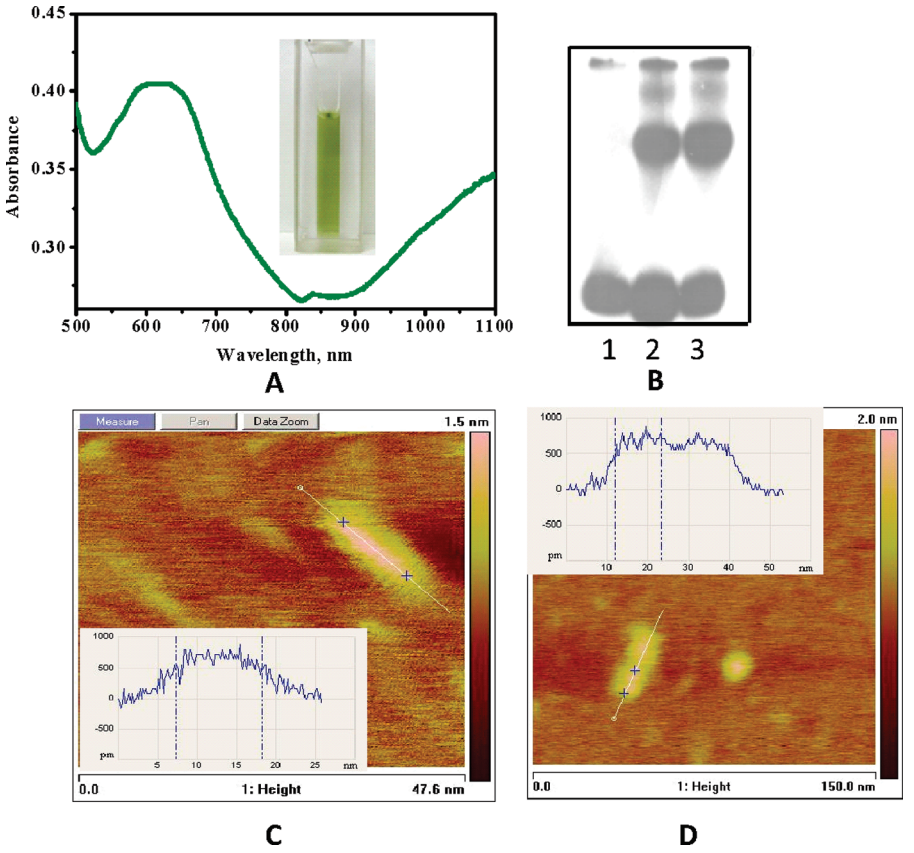


Figure 7. (A) Optical absorption spectrum resulting from the reaction of duplex DNA(4) with HRP/H_2O_2 in citrate buffer at pH 4.5. (B) PAGE of the reaction of DNA(4) with HRP/H_2O_2 in citrate buffer at pH 4.5. Lane 1 is the control of DNA(4) before reaction, lane 2 is the result from the reaction of the SNS-containing single strand, and lane 3 is the result from reaction of duplex DNA(4). AFM images of DNA(4). (C) Image recorded before reaction of DNA(4) with HRP/H_2O_2. The inset shows the height dimension. (D) Image recorded of DNA(4) after reaction with HRP/H_2O_2. Two objects are detected: one has approximately the same length as unreacted DNA(4), and the second is approximately twice as long. The inset shows the height dimension.

was also measured after the reaction with HRP/H_2O_2. There is little change to either the positive peak at 264 nm or the negative peak at 242 nm, but the shoulders at 290 and 330 nm decrease significantly after the reaction, which is attributed to the distortion of aromatic thiophene/pyrrole rings in the conjoined $(SNS)_{15}$ oligomers. This indicates that the oligomerization reaction does not extensively destabilize the duplex, which is a result consistent with the molecular modeling studies that show the approximate similarity of the rise and pitch of SNS oligomers and duplex DNA.

The reaction of DNA(4) with HRP/H_2O_2 was also studied by PAGE analysis with DNA(4) labeled at its 5′-end with [^{32}P]. The results are shown in Figure 7B where lane 1 is DNA(4) before reaction; lanes 2 and 3 are for DNA(4) after reaction with HRP/H_2O_2 in the absence and presence of the complementary strand, respectively. Apart from the band for DNA(4), the main bands in lane 2 and 3 are assigned to a conjoined $(SNS)_{30}$ dimer of DNA(4), which is supported by AFM imaging (see below). Unlike DNA(12), which has six central SNS monomer units and a 15-mer "overhanging" duplex at its 5′-side and a 18-mer overhang at 3′-side, DNA(4) has only one thymine at its 5′-end or 3′-end. Thus, the same dimer product is expected in either the presence or absence of the complementary DNA strand. Apparently, intermolecular reaction between the SNS monomers of duplex DNA(4) is not inhibited because it lacks long overhangs. Although the reaction is incomplete, the dimer is formed in more than 50% yield.

Finally, atomic force microscope (AFM) images of DNA(4) on a treated mica surface before and after its reaction with HRP/H_2O_2 were obtained. These images support the findings of the optical and PAGE experiments that a conjoined SNS oligomer is formed. The AFM image of unreacted DNA(4), Figure 7C, was acquired with a sample deposited from a pH 4.5 citrate buffer solution (containing 500 mM of NaCl) onto a mica surface that had been treated with $MgCl_2$ so that the DNA would adhere to the positively charged surface.[35] The sample was washed with water, and the image was recorded in tapping mode. Under these conditions, the image of DNA(4) indicates an apparent length of ca. 11 nm, which is within the experimental uncertainty of the expected length of the B-form DNA duplex 30-mer. The apparent diameter of unreacted DNA(4) is ca. 0.8 nm is considerably less than the 2 nm expected for natural DNA; however, such discrepancies have been observed by others and are attributed to the deformation of DNA by AFM tip, strong adhesion of the DNA to the surface, and to a background of buffer salts.[36,37] Figure 7D shows the image of DNA(4) after reaction with HRP/H_2O_2. The sample was purified by elution through a Sep Pak C18 column and dissolved in citrate buffer/NaCl solution before being deposited on a $MgCl_2$-treated mica surface. The image in Figure 7D shows two distinct structures. One is the $(SNS)_{15}$ duplex oligomer, which appears to be similar length to that of unreacted DNA(4), and a second that is ca. 30 nm long and 0.8 nm high which is assigned to a dimer of DNA(4) linked by bond formed between the two conjoined $(SNS)_{15}$ oligomers.

It appears from the AFM images that the dimers of the $(SNS)_{15}$ duplex oligomer are formed by "blunt ligation" between the SNS groups at the ends of the conjoined duplex

oligomers because the linear morphology of the oligomer is unchanged. This finding is consistent with the results of the PAGE analysis of the reaction of DNA(4) shown in Figure 7B, which also reveals dimer formation, and the optical spectroscopy that clearly shows absorptions characteristic of a linear conducting polymer. Blunt ligation to form a dimer likely occurs by reaction of two $(SNS)_{15}$ duplex oligomer radical cations, $(SNS)_{15}^{\bullet+}$, to form the $SNS_{15}-SNS_{15}$ dimer with the loss of two protons as suggested by mechanistic studies of the Tl^{3+}-catalyzed reaction of bis- and tetrathiophenes to form polythiophenes.[38]

Conclusions

The results reported above show that SNS monomers appropriately spaced and covalently linked to DNA oligomers react intramolecularly to form SNS-to-SNS bonds when they are components of duplex DNA assemblies. The conjoined $(SNS)_n$ oligomers that result have the optical properties expected for polarons or bipolarons in conducting polymers. The lengths of the SNS oligomers formed by this process are determined primarily by the DNA constructs used as their templates. In contrast, HRP/H_2O_2 oxidation of SNS monomers linked to single-stranded DNA results in an intermolecular reaction that yields short SNS oligomers of uncontrolled length. These finding may enable the construction of $(SNS)_n$ oligomers of specified length attached to DNA, which will allow the assembly of these oligomers into complex, unique arrays by taking advantage of the well-understood self-organizing properties of DNA.[39,40]

The conjoined $(SNS)_n$ oligomers reported here differ in important ways from the previously described PANI oligomers similarly formed from aniline-like monomers linked to duplex DNA.[13,14] First, the observation that the stability of $(TX)_nT/(AG)_nA$ duplexes increases with n means in principle that $(SNS)_n$ oligomers of any length may be prepared. In the results reported above, an oligomer ca. 10 nm long is described and observed, but there is no reason to expect that the process used here cannot be applied to prepare substantially longer oligomers. In fact, the blunt ligation (coupling reaction between the SNS at the 5′-end or 3′-end) observed in dimer formation from DNA(4) may provide a facile way to make longer oligomers. Second, unlike the constructs formed from aniline-like monomers, which require unmodified DNA ends for stability, conjoined SNS oligomers formed from SNS monomers can extend the entire length of the DNA duplex. This may enable the direct linkage of the conducting polymer to gold electrodes, for example, using the recently described reaction of thiocyanate or thioacetate groups[23,41] that may be appended to the SNS monomers at the 5′- and 3′-terminal of the DNA construct. We have previously described and executed the processes necessary to covalently link specific monomers at unique positions of the duplex DNA and convert them to conducting polymers,[13] and that process may be applicable to positioning unique SCN or SAc bearing monomers at the termini of $(SNS)_n$ oligomers. Another advantage of the $(SNS)_n$ oligomer conjoined on DNA template is that the oligomer has a structure that is commensurate with B-form DNA. As reported above, the stability of modified DNA is the same before and after polymerization. The $(SNS)_n$ oligomer formed will not affect the unique capability of DNA to self-organize and self-recognize.

The reality of using these DNA-conjoined conducting polymers as molecular nanowires in self-assembling circuits has not been demonstrated. This objective will require that these DNA-containing constructs retain the electrical conductivity of their parent polymers and that their self-directed, low-resistance linkage to electrodes is possible. Experiments to assess these requirements are underway in our laboratory.

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Supporting Information Available: Mass spectra of the oligonucleotides used, CD spectra, melting curves, and PAGE gel for the two bond ligation experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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