THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

pubs.acs.org/JPCB

A Chiroptical Photoswitchable DNA Complex

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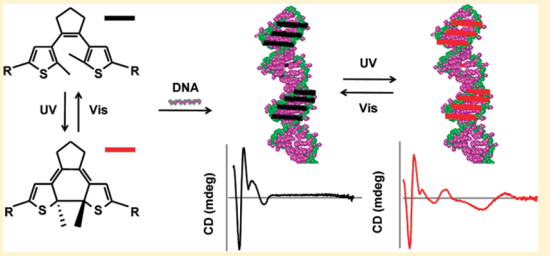
Supporting Information

ABSTRACT: The interesting structural, electronic, and optical properties of DNA provide fascinating opportunities for developing nanoscale smart materials by integrating DNA with opto-electronic components. In this article we demonstrate the electrostatic binding of an amine-terminated dithienylethene (DET) molecular switch to double-stranded synthetic polynucleotides. The DET switch can undergo photochemical ring-closure and opening reactions. Circular dichroism (CD) and UV−vis spectroscopy show that both the open, **1o**, and the closed, **1c**, forms of the switch bind to DNA. Upon addition of DNA to a solution of **1o** or **1c**, the UV−vis spectrum displays a hypochromic effect, indicative of an interaction between the switch and the DNA. The chirality of the DNA double-helix is transmitted to the switching unit which displays a well-defined CD signal upon supramolecular complexation to the DNA. Additionally, the CD signal of the DNA attenuates, demonstrating that both components of the complex mutually influence each other's structure; the DNA induces chirality in the switch, and the switch modifies the structure of the DNA. Modulation of the chiroptical properties of the complex is achieved by photochemically switching the DET between its ring open and closed isomers. A pH dependence study of the binding shows that when the pH is increased the switches lose their binding ability, indicating that electrostatic interactions between protonated amines and the negatively charged phosphate backbone are the dominant driving force for binding to the DNA. A comparison of poly(deoxyguanylic-deoxycytidylic) acid [poly(dGdC)$_2$] polynucleotides with poly(deoxyadenylic-deoxythymidylic) acid [poly(dAdT)$_2$] shows distinct differences in the CD spectra of the complexes.



INTRODUCTION

Natural systems utilize self-assembling molecules to build chiral nanoscale structures that respond to external stimuli, imbuing a living organism with a myriad of essential properties including sensing capabilities, memory storage, and self-replication.[1−4] The supramolecular assembly of stimuli-responsive molecules into chiroptical smart materials[5−9] has attracted considerable interest toward the development of synthetic nanoscale devices for a variety of applications including optoelectronics, logic gates, and memory storage.[10−15] DNA provides a versatile information-rich nanoscale building block with a well-defined helical structure that can be folded into complex two- and three-dimensional topologies.[16−19] The ability of DNA to undergo conformational changes and conduct long-range electron transfer[20,21] furthers the possibilities for integration into advanced DNA-based nanotechnologies[22−25] including nanomechanical devices,[26,27] nanocircuits,[28−30] and photonic wires.[31]

Conjugating DNA with small molecules provides potential for fueling new devices and applications that combine the topological control afforded by DNA assembly with the ability to tailor the chemical and physical properties of the resulting material.[32] Both covalent[33−35] and noncovalent[13,36−38] strategies to modify DNA provide opportunities to harness the chirality of the DNA double-helix to create well-defined hybrid chiroptical responsive systems. For example, porphyrins have been covalently attached to DNA by the synthesis of porphyrin−deoxyuridine conjugates that incorporate into DNA.[39] The marriage of stimuli-responsive chromophores to the DNA backbone provides fertile ground for introducing novel optical properties to DNA assemblies, developing new model nanoscale systems for exploring high-density information storage, and exploring the fundamental paradigms of chirality transfer to conformationally addressable molecules. Switchable supramolecular DNA devices that respond to temperature or external chemical reagents have previously been reported.[13,40−42] Photochromic molecules provide particularly interesting candidates for smart DNA systems because they can be triggered using light energy, a clean and tunable fuel that can be spatially delivered.

This article describes the facile preparation of a photoswitchable self-assembled chiroptical material by the electrostatic binding of *bis*-ammonium dithienylethene (DET) moieties (**1o**/**1c**-2H$^+$) to the polyanionic backbone of double-stranded polynucleotides (Figure 1).

DETs are interesting chromophores that can be photochemically switched between open and closed forms with generally high fatigue resistance and thermal irreversibility.[11] In the open form, **1o**, the switch interconverts between two dynamic helices. Photochemical ring-closure to form **1c** locks the conformation of the switch with a fixed chirality. The versatility of DET photoswitches has been demonstrated through their use in controlling

Received: June 23, 2011
Revised: August 31, 2011
Published: August 31, 2011

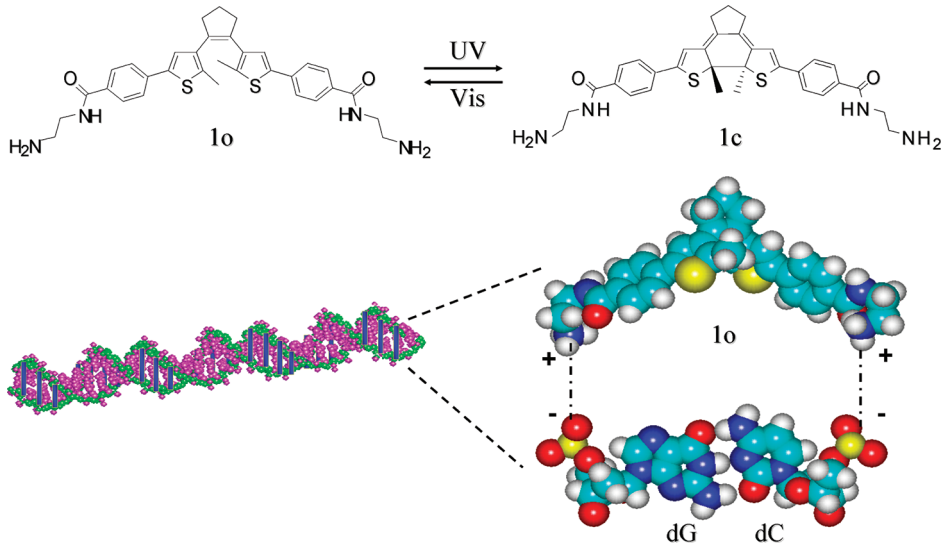


Figure 1. (a) Structure and photoswitching of an amine-terminated dithienylethene (DET) switch in the open (**1o**) and closed (**1c**) forms. (b) Space-filling model of the proposed electrostatic binding of protonated terminal amines of **1o** to a GC base pair of a DNA double-helix.

the surface morphology[43] and shape[44] of crystals, the modulation of conductance in break-junctions,[45] molecular electronic devices,[46] electropolymerization,[47] supramolecular assembly and chirality,[48] and a host of other processes. The chirality of the DNA double-helix is transmitted to the orientation of the switch which displays a well-defined chiroptical response upon binding to the DNA. Modulation of the chiroptical properties of the complex is achieved by photochemically switching the DET between its ring open and closed isomers. Our system utilizes simple electrostatic interactions between positively charged ammonium groups and the negatively charged phosphate groups exposed at the outer surface of the DNA double-helix. DNA modification through such a facile approach has precedence in biological systems. For example, endogenous oligoamines such as spermine and spermidine bind electrostatically to DNA.[13,49] We demonstrate that both **1o** and **1c** bind to DNA predominantly through electrostatic interactions. The binding results in an induced chirality of the switch. Importantly, the switch retains its photochemical switching properties when bound to the DNA and shows a very clear change in its response to circularly polarized light. This provides a novel chiroptical material that can be photochemically switched between the UV (open) and the visible light (closed) absorbing isomers as well as multiple states consisting of combinations of the two by simply changing the dosage of photons.

Our approach contains several merits. First, the simplicity of the ammonium group provides a very general molecular design in comparison with intercalating or other specialized moieties that are in some cases photosensitive and susceptible to radical-generating processes.[50,51] Further, the ammonium groups do not give an absorption signal in regions that interfere with the signals related to the switch. Additionally, the ammonium groups confer water solubility at sufficient pH, allowing for complexation to occur under aqueous conditions that do not perturb the structure of the DNA or require the use of a secondary organic solvent. The system assembles in a chiral manner without the need to introduce asymmetric substituents into the structure of **1o** or resolve the enantiomers of **1c**. The chromophore itself is not the major constituent for binding, allowing for the photoswitching between two chemically distinct states of the switch without a drastic loss of binding upon conversion to a particular form. A considerable change in DNA binding was recently reported for a conformationally switchable spiropyran derivative.[52] A second distinction with the spiropyran system is that the DET switch absorbs at longer wavelengths than the DNA, allowing for the photoswitching to take place without direct irradiation of the DNA with 254 nm light, a condition that can damage the DNA.[53] In another spiropyran system, the switchable chromophore was tethered at the 5′ position and used to regulate hybridization through photochemical and thermal reactions.[54] DNA chains containing a single azobenzene photoswitch have been prepared by synthesizing a phosphoramidite-derivatized azobenzene, which can be covalently incorporated into a defined DNA sequence using an automated synthesizer.[55,56] The azobenzene DNA systems were shown to modulate duplex and triplex formation. In another report, a bifunctional naphthyridine carbamate azobenzene derivative was shown to bind to GG mismatches on separate single strands of DNA.[57] An advantage of the DET switch over azobenzene is a lack of thermal reversibility, which is essential for applications that involve memory storage and gating. Our system provides a noninvasive approach to assemble a chiral ensemble of photoswitchable DETs at a DNA double helix. Chemically and optically distinct states can be written and stored without dehybridization of the DNA or release of the switch.

RESULTS AND DISCUSSION

Design and Photochemical Switching of Amine-Terminated DETs. To use DNA as a scaffold for the chiral assembly of photoswitchable DET molecules, we designed a diarylthienylethene switch containing two terminal amino groups (Figure 1, see also the Supporting Information (SI)). Both **1o** and **1c** are expected to bind electrostatically to the negatively charged phosphate groups of the DNA backbone under conditions in which the primary amines are protonated. Diarylethenes **1o** and **1c** are sufficiently soluble in a buffer solution of 3-(*N*-morpholino)propanesulfonic acid (MOPS) at pH 6.5, which is below the pK_a of the switch (approximately 7.5, see below). The expected

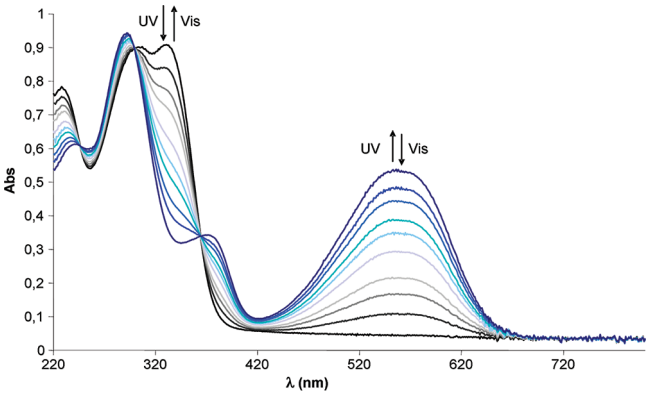


Figure 2. Irradiation of a solution of **1o** and **1c** (38 μM) in MOPS buffer (20 mM, pH 6.5) for varying amounts of time with UV light (>340 nm) and visible light (>520 nm) is accompanied by characteristic changes in the absorption spectra signifying ring-opening and closing photochemical reactions. **1o** has absorption bands with maxima at 303 and 331 nm which decrease upon illumination with UV light as **1c** is generated, which has absorption maxima at 292, 372, and 556 nm. Irradiation with visible light regenerates the spectrum of **1o**.

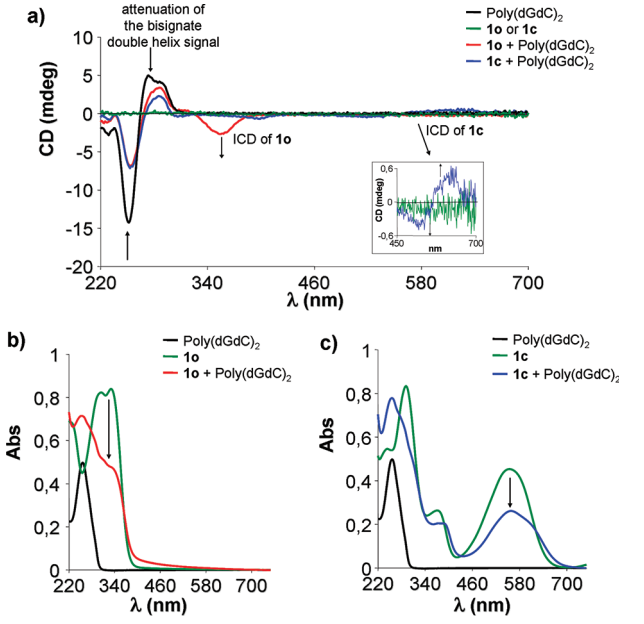


Figure 3. CD (a) and absorption (b, c) spectra of poly(dGdC)$_2$ 60 μM (black), **1o** 33 μM, or **1c** 35 μM (green) and the conjugates poly(dGdC)$_2$ + **1o** (red) and poly(dGdC)$_2$ + **1c** (blue). The inset in (a) shows the visible region at a smaller scale, revealing a bisignate ICD of **1c**.

photochemical ring closure and opening were found to occur in the buffer solution as shown in the UV−vis spectra taken at selected irradiation times (Figure 2). A solution of **1o** is colorless with absorption maxima at 303 and 331 nm and extinction coefficients of 23 254 M^{-1} cm^{-1} and 23 836 M^{-1} cm^{-1}, respectively (Scheme S1 of the SI). Irradiation with UV light results in a purple solution with a decrease in the absorption band at 331 nm and the growth of a band at 556 nm. Isosbestic points at 249, 299, and 366 nm indicate a clean conversion between two distinct states of the switch. The changes are reversible, demonstrating that **1o** and **1c** can function as photoactive molecular switches in the buffer solution.

Interaction of 1o and 1c with Poly(dGdC)$_2$. The ammonium groups of **1o** and **1c** are expected to bind to the negatively charged phosphate groups of DNA. The asymmetry of the double helix is expected to result in a chiral assembly with an induced circular dichroism (ICD) signal corresponding to the absorption band of the switch. Initially, we studied the interaction of the switch with a synthetic poly(deoxyguanylic-deoxycytidylic) acid [poly(dGdC)$_2$] nucleotide using CD and UV−vis absorption spectroscopy as shown in Figure 3.

The CD signal in the UV region indicates the B form of the polynucleotide (Figure 3a).[49] Achiral **1o** displays a strong signal in the UV region of the absorption spectrum but no CD signal by itself (Figures 3a,b). Upon addition of poly(dGdC)$_2$ to a solution of **1o** at pH 6.5, the UV spectrum displays a hypochromic effect, indicative of an interaction between the switch and the DNA. More interesting are the appearance of an ICD signal in the region where the switch absorbs and an attenuation of the CD signal of the polynucleotide, demonstrating that both components of the complex influence the structure of the other; the DNA induces chirality in the switch, and the switch somehow modifies the structure of the DNA. Similarly, the absorption band at 556 nm of **1c** undergoes a hypochromic effect upon addition of poly(dGdC)$_2$ (Figure 3c) and displays an induced bisignate CD signal corresponding to the absorption of the switch, although quite weak, in the visible region, and an attenuated DNA signal (Figure 3a). The ability of both forms of the switch to bind to DNA in a chiral manner suggests the utility of these molecules for creating dynamic chiroptical DNA-based materials that can be modulated with photons.

To study the stoichiometry of the complex, we titrated poly(dGdC)$_2$ into a solution of **1o** and followed the changes in the intensity of both the absorption (Scheme S2 of the SI) and the CD spectra (Figure 4).

The intensity of the absorption bands at 303 and 331 nm decreases upon the addition of the polynucleotide until the concentration of **1o** becomes approximately 79% of the concentration per base pair of the poly(dGdC)$_2$ (Figure 4). Further additions of polynucleotide cause only the increase of the band at 254 nm corresponding to the poly(dGdC)$_2$ absorption (S2). The titration was simultaneously followed with CD spectroscopy. As mentioned above, the switch alone shows no CD signal, however as DNA is added an ICD corresponding to **1o** interacting with the DNA appears as well as the bisignate signal corresponding to the B form of the polynucleotide.

Analogous to the changes in the absorption spectra, the CD signals increase in a discontinuous fashion. The signal for the switch ultimately plateaus, whereas the signals corresponding to the DNA begin to increase with a steeper slope because the attenuating effect of the switch is no longer operating, indicating an excess of DNA relative to the switch−DNA complex. Plotting the CD intensity or UV absorption at specific wavelengths versus the concentration per base pairs of poly(dGdC)$_2$ shows a discontinuity that indicates that the maximum stoichiometry of the complex is, as mentioned before, approximately 79% of **1o** relative to the base pairs (Figure 4). Similar results were obtained when a solution of **1c** was titrated with poly(dGdC)$_2$ (Scheme S3 of the SI). Our results are in agreement with previous work that has shown that simple mono- and divalent cations bind to DNA with no more than 85% charge compensation.[58] The titrations were used to calculate the binding constants of the open and closed forms with poly(dGdC)$_2$.[59] Both were found to be approximately 2 × 10^5 (Scheme S4).

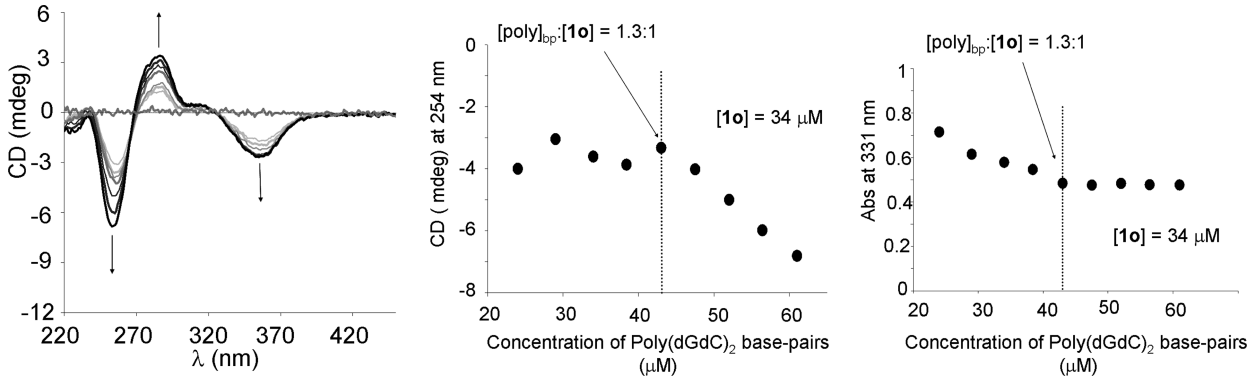


Figure 4. Titration of a solution of **1o** (34 μM in MOPS buffer 20 mM pH 6.5) with poly(dGdC)$_2$ shows an increase in the ICD signal at 360 nm (left). Plotting the CD intensity at 254 nm versus the concentration in base pairs of the poly(dGdC)$_2$ (middle) and the absorption at 331 nm versus the concentration in base pairs of the poly(dGdC)$_2$ (right) shows a discontinuity when the ratio of base pairs to **1o** is 1.3:1.

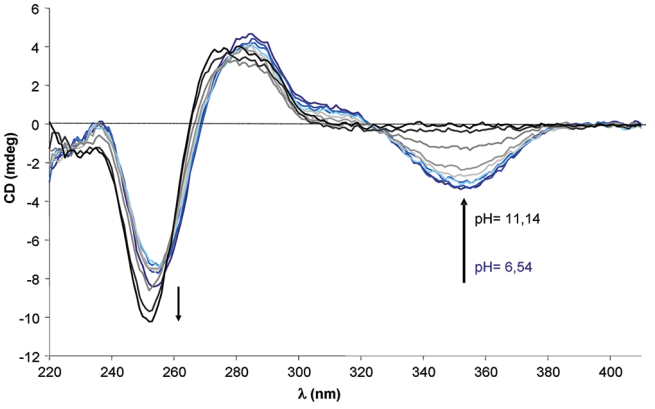


Figure 5. CD spectra obtained during pH titration of the poly(dGdC)$_2$ (45.5 μM)−**1o** (38 μM) complex show an attenuation of the ICD band corresponding to the switch as the pH is increased. The titration was performed by adding aliquots of NaOH (1 M) to a solution of switch−polynucleotide complex in MOPS buffer (20 mM).

Effect of pH. To support the electrostatic binding model and understand the effect of pH on the complex, we titrated the system with an aqueous solution of NaOH. The effect of pH on both **1o** and **1c** alone and complexed with poly(dGdC)$_2$ was studied with UV−vis and CD spectroscopy. The UV absorption bands corresponding to **1o** and **1c** decreased with increasing pH for both the switch alone (Scheme S5 of the SI) and the switch−DNA complex (Scheme S6). Plotting the absorption at 331 nm for **1o** or 555 nm for **1c** against the pH shows, as expected, a sigmoidal curve with an inflection point at 7.45 that represents the pK_a (Scheme S5). The complex shows somewhat different behavior. The resulting curve does not show a clear sigmoidal shape with a quasi-inflection point at pH 9.9. The distortion in the shape of the curve relative to the switch alone is likely due to a more complicated process that includes both the deprotonation and the dissociation of the complex. Additionally, electrostatic complexes have been shown to change pK_a's, in some cases by up to 5 units.[60] A loss of the CD signal corresponding to the switch upon increasing the pH confirms the dissociation of the complex (Figure 5).

When a pH of 9.12 is reached, the intensity of the signal decreases drastically and ultimately disappears as the pH is further increased. The attenuation and loss of the CD signal with increasing pH support the hypothesis that both forms of the switch bind to DNA predominantly via electrostatic interactions.

Photochemical Switching of Poly(dGdC)$_2$−1o. From the results described above, it is apparent that both the open and the closed forms of the switch can bind to DNA and that the most likely reason for the ICD of the switch is that the chiral structure of the DNA imposes a specific chiral orientation to the switches. It is important to show that the chiroptical response of the complex can be modulated with light. Irradiation of a solution of **1o** complexed with poly(dGdC)$_2$ with UV light results in a decrease in the band at 331 nm and the growth of a band in the visible region at 556 nm (Figure 6).

As found for the switch alone, the colorless solution of the DNA switch complex becomes purple. Irradiation with visible light restores the open form of the complex, and subsequent irradiation with UV light restores the closed form. The switching is reflected in changes in both the CD and the UV−vis spectra (Figure 6). The complex can undergo several switching cycles; however, photochemical fatigue is evident from the reduction in the signal after each cycle. The amount of open and closed forms within the complex can be controlled by simply changing the dosage of photons as shown in the absorption spectra after irradiating for a selected period of time (Scheme S7 of the SI).

Photochemical switching of the chiroptical response of the complex is evident from the changes in the CD spectra upon alternating irradiation with UV and visible light. Irradiation with UV light results in a reduction of the signal in the UV region and the appearance of a bisignate signal in the visible region. Irradiation with visible light removes the signal in the visible region, while the signal in the UV region becomes larger. Additionally, the positive signal at 286 nm corresponding to the DNA attenuates when switching from the open to the closed form. The reduction in intensity is either an optical effect related to a difference in the CD signal between complexed **1c** and **1o** at this wavelength or a structural perturbation of the DNA induced by a conformational change in the bound switch upon photochemical ring closure.

Interaction with Poly(dAdT). Changing the sequence of the DNA can affect the structure of the helix and hence the structure of the supramolecular self-assembled switching system. To test the effect of changes in the polynucleotide structure and assess the binding capabilities of the switch to different sequences of DNA, we performed the same experiments using poly(deoxyadenylic-deoxythymidylic) acid [poly(dAdT)$_2$] (Figure 7). Again, the UV−vis absorption bands of **1o** and **1c** undergo a hypochromic effect. Additionally, the CD spectra show an ICD corresponding to the respective open and closed forms of the switch. The binding

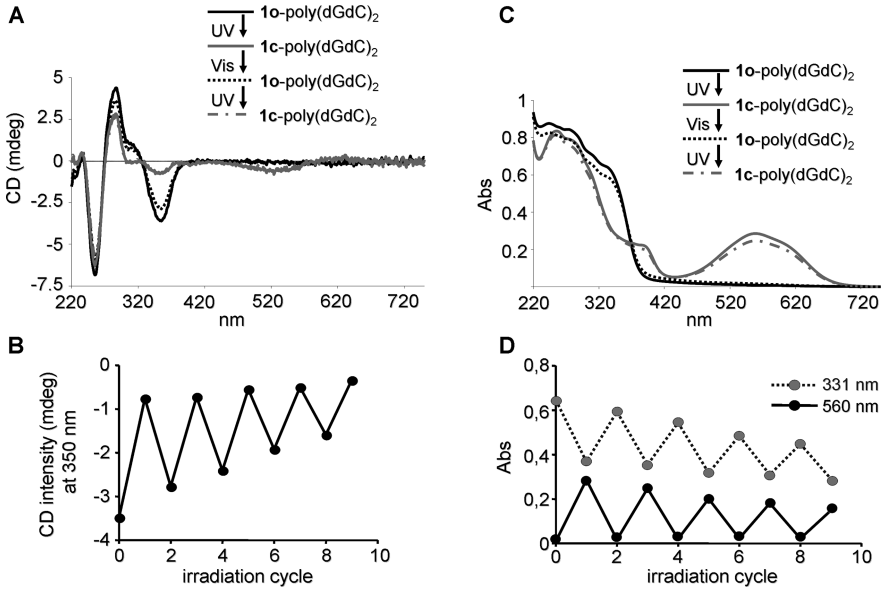


Figure 6. Irradiation of the DNA switch complex poly(dGdC)$_2$–**1o** (38 μM switch in MOPS buffer, 20 mM pH 6.5) with UV (20 min) and visible light (30 min) switches the bound DET between its open and closed forms. The photochemical changes are manifest in the CD (A) and absorption (C) spectra. On the bottom are shown the plots of the CD intensity at 350 nm (B) and UV-vis absorption at 331 and 560 nm (D) after each irradiation.

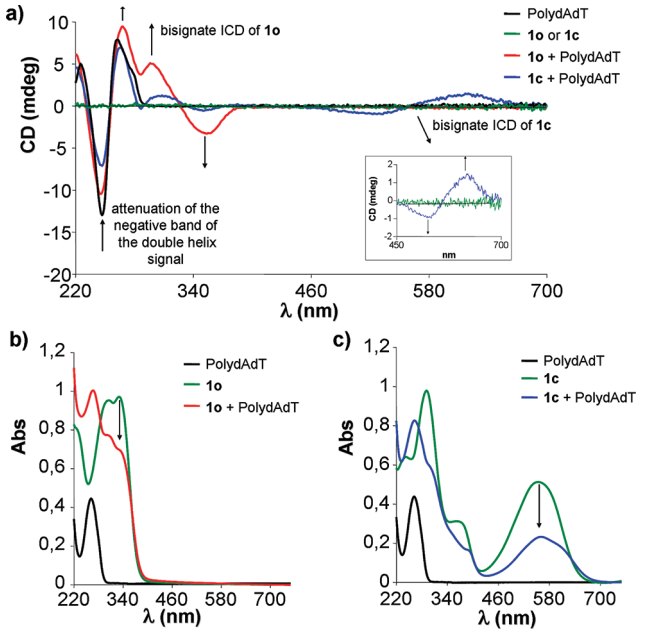


Figure 7. CD (a) and absorption (b, c) spectra of poly(dAdT)$_2$ 65 μM (black) and **1o** or **1c** 40 μM (green) and the conjugates poly(dAdT)$_2$ + **1o** (red) and poly(dAdT)$_2$ + **1c** (blue). The inset (a) shows the visible region at a smaller scale, revealing a bisignate ICD of **1c**.

constants of **1o** and **1c** with poly(dAdT)$_2$ are 2.2×10^5 and 3.0×10^6, respectively (Scheme S8 of the SI). Titrating the open form with poly(dAdT)$_2$ shows a slightly different trend than the poly(dGdC)$_2$ (Scheme S9). For poly(dGdC)$_2$, the ICD increased with the addition of DNA until a plateau was reached. For poly(dAdT)$_2$ a more complex relationship between the CD signal and ratio of switch/base pairs exists. After the first addition of poly(dAdT)$_2$, the ICD of **1o** shows very little change upon adding more polynucleotide, despite a clear continual hypochromic effect of the UV absorption band corresponding to the switch.

Additionally, the CD signal corresponding to the DNA shows very little change upon adding more DNA up to a ratio of 1:1.3 switch/base pairs. The addition of higher amounts of poly(dAdT)$_2$ shows no further hypochromic effect of the UV absorption band of the switch; however, the ICD of the switch increases until a ratio of 1:1.7 switch/base pairs is reached. The UV and CD signals of the DNA increase steadily with increasing amounts of DNA. A few notable differences in the CD spectra of the poly(dAdT)$_2$ complex in comparison with the poly(dGdC)$_2$ complexes are worth pointing out. First, in general the ICD signal of the switch in the presence of poly(dAdT)$_2$ appears to be stronger and more defined than for the poly(dGdC)$_2$ system. The bisignate signal in the visible region corresponding to the closed form is more intense in the poly(dAdT)$_2$. The UV signal corresponding to the switch overlaps less with poly(dAdT)$_2$ compared to poly(dGdC)$_2$ due to a slight blue-shift of the poly(dAdT)$_2$ signal, revealing a clear bisignate ICD. The most intense ICD signal for **1o** occurs at a ratio of switch to base pairs of 1:1.7 in contrast to a ratio of 1:1.3 for the poly(dGdC)$_2$ system (Scheme S9 of the SI).

As noted above for **1o**, the ICD signal has a more delicate relationship to the molar ratio of switch to base pairs for the poly(dAdT)$_2$ complex. The closed form of the switch shows an even more intriguing behavior. For a ratio of 1:2.3 **1c**/base pairs, the CD spectrum corresponding to the switch shows a more intense bisignate curve in the visible region in comparison to other ratios tested (Scheme S10 of the SI). In addition, a positive band appears at 388 nm that is not present for other ratios tested. The differences in the CD spectra found for different ratios of the switch to base pairs indicates that the orientation of the switch may be influenced by the presence of other switches within proximity. The higher charge density of poly(dAdT)$_2$ relative to poly(dGdC)$_2$ may allow for more than one orientation of the switch at the double-helix, which is influenced by the presence of neighboring switches. Similar to the poly(dGdC)$_2$–switch complexes, the poly(dAdT)$_2$ complexes can be photochemically switched between the open and the closed isomers of the switch

dx.doi.org/10.1021/jp205893y |J. Phys. Chem. B 2011, 115, 11581–11587

with accompanying changes in the CD spectrum (Scheme S11). As found for the poly(dGdC)$_2$−switch complex, each switching cycle shows fatigue. The differences in the ICD signals that result when different polynucleotides are used indicates that the chiral assembly at the DNA helix is sensitive to changes in the structure of the helix or chemical constituents of the base pairs. The poly(dAdT)$_2$ may provide a more suitable geometry for the switch to form a chiral complex. The ability of **1o** and **1c** to bind to sequences of both GC and AT base pairs and remain photoactive indicates the potential of using simple primary amines in modifying a wide range of DNA-based materials with functional molecules.

CONCLUSIONS

We have shown that **1o** and **1c** bind to both poly(dGdC)$_2$ and poly(dAdT)$_2$ polynucleotides. ICD signals and hypochromic effects in the CD and UV−vis spectra show that both the open and the closed forms of the switch bind to DNA. The pH dependence of the binding suggests that electrostatic interactions are the predominant driving force for complex formation. The chiroptical response of the complexes can be modulated by photochemically switching the bound DETs between their ring open and closed isomers with UV and visible light. A comparison of poly(dGdC)$_2$ complexes with the poly(dAdT)$_2$ complexes shows distinct differences in the shape of the CD spectra and the dependence of the CD signal on the ratio of switch to base pairs. We expect that the facile methodology presented will be useful in decorating complex DNA-based structures with functional organic molecules to create new hybrid and addressable materials.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, calculation of extinction coefficients and binding constants, synthesis of switch, and additional CD and UV−vis spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank The Netherlands Organization for Scientific Research (NWO-CW), the European Research Council (ERC Grant 227897), and NanoNed (GMM 6977).

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