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TTF-Modified DNA

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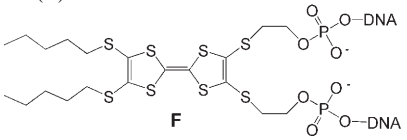
Ever since its first description,[1] tetrathiafulvalene (TTF) has taken an eminent role in the field of materials sciences. Due to their specific π-donor properties, TTFs have been incorporated into a number of macrocyclic, molecular, and supramolecular systems to create multifunctional materials with desired structure, stability, and physical properties.[2–8] As a consequence, they are frequently used as donor units in donor–acceptor (D–A) ensembles that are of prime interest due to their potential applications in molecular electronics and optoelectronics.[9–13] In addition, their tendency to form π-stacked aggregates renders them attractive objects for the construction of supramolecular assemblies with applications in liquid-crystalline materials and organogels.[14,15] DNA represents a highly developed, yet very practical scaffold for the construction of complex assemblies.[16] Due to the existence of well-developed and versatile methods for oligonucleotide synthesis, the use of modified nucleic acids has become an attractive way for the generation of functionalized nanostructures.[17] During the past decade, non-nucleosidic aromatic hydrocarbons, such as phenanthrene,[18–20] pyrene,[21–28] and perylene,[29–33] have been developed as building blocks for modified nucleic acids.[34–37] They were explored as hairpin replacements,[38–44] as units for conformational control in DNA,[45–47] or as replacements of the natural nucleotides maintaining helical organization.[48–50] Further efforts are aimed at the development of advanced functional building blocks with a high level of structural organization. Interest in TTF–oligonucleotide conjugates is documented in patents describing the use of redox-active labels for the development of oligonucleotide-based sensors.[51] So far, however, a single report on the preparation of such a construct exists, in which Neilands and co-workers describe the introduction of pyrimido-TTF nucleosides into a phosphorothioate oligoribonucleotide.[52] Due to the interesting electronic properties of TTF and its excellent stacking properties, we have explored the generation of TTF-modified DNA. Here, we present the synthesis of a non-nucleosidic TTF building block (**F**, see Table 1), its incorporation into oligonucleotides, as well as the properties of several modified hybrids.

Table 1. Hybridization data of TTF-modified DNA duplex.[a]

	Hybrid	T_m [°C]	ΔT_m [°C]
5	(5′) AGC TCG GTC ATC GAG AGT GCA	72.5	–
6	(3′) TCG AGC CAG TAG CTC TCA CGT		
7	(5′) AGC TCG GTC A**F**C GAG AGT GCA	77.4	+4.9
8	(3′) TCG AGC CAG T**F**G CTC TCA CGT		



F

[a] Conditions: 1.0 μM oligonucleotide concentration (each strand), 10 mM phosphate buffer (pH 7.4) and 100 mM NaCl.

The synthesis of the tetrathiafulvalene phosphoramidite building block is shown in Scheme 1. Starting from the known 2,3-bis(2-cyanoethylthio)-6,7-bis(pentylthio)tetrathiafulvalene (**1**),[53] bis-diol **2** was prepared by treatment with sodium in ethanol followed by alkylation with 2-chloroethanol. Reaction with 4,4′-dimethoxytrityl chloride gave the mono-protected intermediate **3**, which was subsequently converted into the phosphoramidite derivative **4**.

Building block **4** was used for the synthesis of modified oligonucleotides. Despite the known susceptibility of TTF towards strong acids and oxidants, the standard phosphoramidite protocol[54] was successfully applied. Although some fragmentation of the TTF-modified oligonucleotides was observed during ammonia deprotection, oligomers **7**–**9** were easily purified by reverse phase HPLC.[55]

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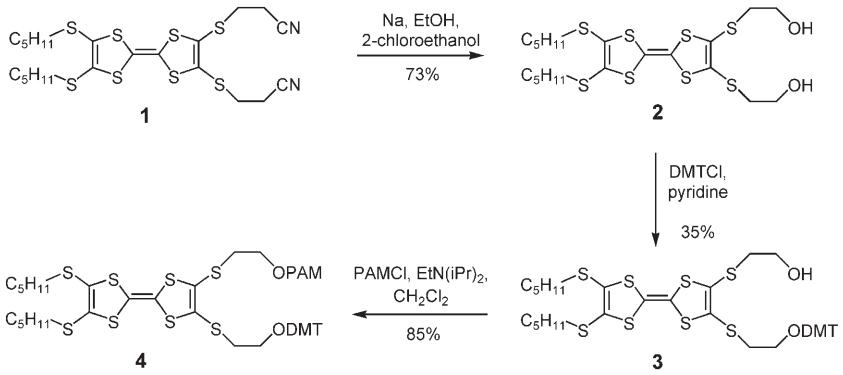


Scheme 1. Synthesis of TTF phosphoramidite **4**; DMT = 4,4′-dimethoxytrityl; PAM = 2-cyanoethyl *N*,*N*-diisopropyl-phosphoramidite.

The effect of TTF incorporation on duplex stability was analyzed by thermal denaturation experiments (Table 1). Incorporation of one TTF moiety in each strand (duplex **7***8**) results in a considerable increase in stability ($\Delta T_m = +4.9\,°C$) in comparison to the unmodified duplex **5***6. The increase in stability can be due to stacking interactions between the TTF units with the neighboring nucleobases as well as to hydrophobic interactions of the pentyl chains. Cooperativity of the melting process in the natural and the modified part of duplex **7***8 was shown by monitoring the denaturation process at 290 as well as at 330 nm (hyperchromicity of TTF absorption, see the Supporting Information).

The circular dichroism (CD) spectrum of the duplex **7***8 (Figure 1) is consistent with an overall *B*-conformation with a maximum at 280 nm and a minimum at 251 nm, indicating that the TTF units are structurally well integrated into a *B*-type DNA. Despite the high duplex stability, no signs of exciton coupling were detected in the TTF region from 300 to 400 nm. A weak CD signal was observed, which is explained by chiral induction by the nucleic acid environment. This signal disappears upon duplex melting (Figure 1, inset).

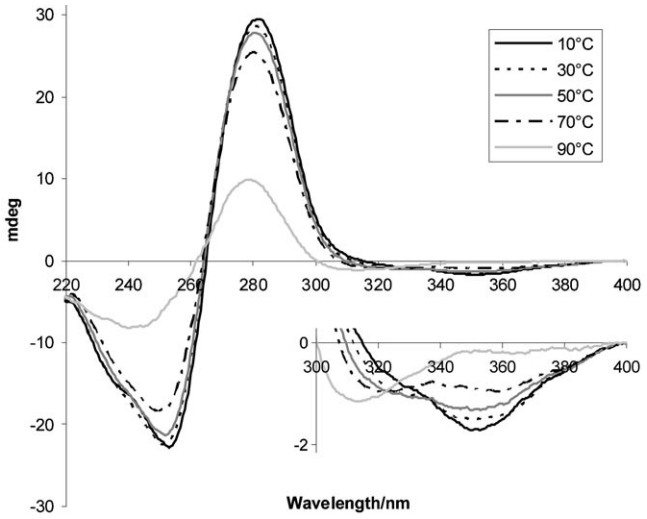
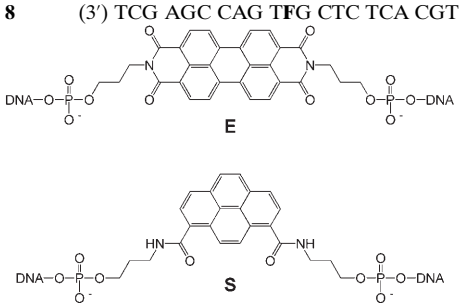


Figure 1. Temperature-dependent CD spectrum of TTF-modified duplex **7***8. Conditions: 5.0 μM oligo concentration (each strand), 10 mM phosphate buffer (pH 7.4) and 100 mM NaCl; inset shows enlarged view of the region from 300–400 nm.

The structural and electronic effects resulting from TTF modification were further studied in mixed DNA hybrids (Table 2). Non-nucleosidic perylene diimide (PDI, building block **E**) or pyrene (**S**) units were placed opposite TTF. PDI was selected due to its high sensitivity towards conformational changes in CD spectroscopy,[29] and pyrene for its diverse fluorescence properties.[56] TTF-modified strands form stable hybrids with all other modified strands. The T_m values are generally somewhat lower than the one of the reference duplex **5***6 (72.5 °C, Table 1), except for the PDI/TTF-mixed hybrid **9***10, which has a comparable T_m value (72.1 °C). In the same duplex, CD spectroscopy (Figure 2) revealed strong exciton coupling of the PDI chromophores. This shows that the PDI units are oriented in a twisted conformation and that a well-ordered helical structure is maintained in the modified region of the duplex.[57]

Table 2. Hybridization data of mixed DNA hybrids.[a]

	Hybrid	T_m [°C]
9	(5′) AGC TCG GTC **FF**C GAG AGT GCA	72.1
10	(3′) TCG AGC CAG **EE**G CTC TCA CGT	
9	(5′) AGC TCG GTC **FF**C GAG AGT GCA	67.5
11	(3′) TCG AGC CAG **SS**G CTC TCA CGT	
12	(5′) AGC TCG GTC A**S**C GAG AGT GCA	69.3
8	(3′) TCG AGC CAG T**F**G CTC TCA CGT	
13	(5′) AGC TCG GTC **SS**C GAG AGT GCA	66.7
8	(3′) TCG AGC CAG T**F**G CTC TCA CGT	



[a] Conditions: 1.0 μM oligonucleotide concentration (each strand), 10 mM phosphate buffer (pH 7.4) and 100 mM NaCl.

As expected for a neutral form of tetrathiafulvalene,[3,53,58,59] no fluorescence was observed for single-stranded TTF-modified oligonucleotides (**7**, **8**) nor duplex **7***8. On the other hand, the low oxidation potential of TTF may, in principle, favor fluorescence quenching via photo-induced electron transfer, as recently applied in the construction of

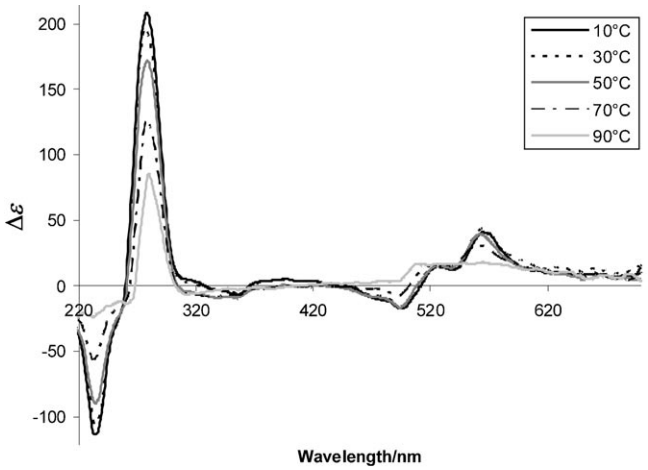


Figure 2. Temperature-dependent CD spectra of duplex **9*****10**. Conditions: 2.5 μM oligonucleotide concentration (each strand), 10 mM phosphate buffer (pH 7.4) and 100 mM NaCl; $\Delta\varepsilon$ ($mol^{-1}\,dm^3\,cm^{-1}$).

switchable fluorescent systems.[53,58,59] Indeed, quenching of pyrene fluorescence by TTF was observed in hybrids **12*****8** and **13*****8** containing one and two pyrenes, respectively (Figure 3, Table 3, and the Supporting Information). The

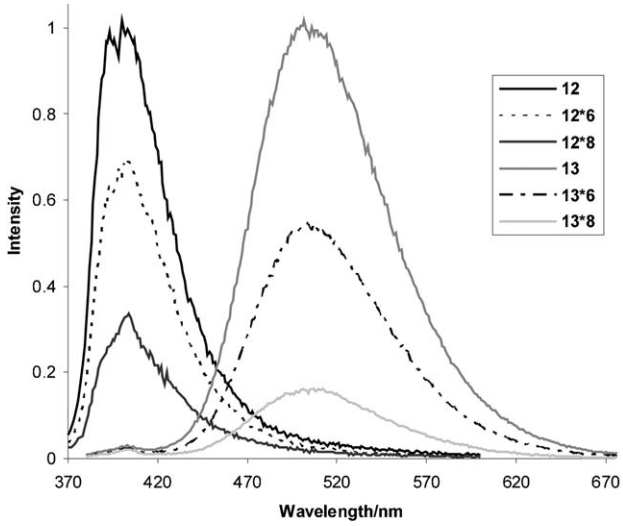


Figure 3. Normalized fluorescence spectra of pyrene modified single strands **12** and **13** and the respective hybrids formed with an unmodified single strand (**6**) and a TTF-containing strand (**8**). Conditions: 1.0 μM oligonucleotide concentration (each strand), 10 mM phosphate buffer (pH 7.4) and 100 mM NaCl; λ_{ex} at 354 nm.

fluorescence spectrum of **13** shows pyrene excimer emission with a maximum at 505 nm. This signal was decreased by 85% in duplex **13*****8**, which is considerably more than observed by a non-modified complementary strand (duplex **13*****6**). A slightly lower—but still significant—quenching effect (~70%) was observed in the case of monomer fluorescence (duplex **12*****8**). These data show that TTF can act as a quencher within a DNA duplex.

Table 3. Quenching properties of TTF-modified oligonucleotide **8** in pyrene containing hybrids.[a]

	Oligonucleotides	ϕ	Quenching in %
12	(5′) AGC TCG GTC A**S**C GAG AGT GCA	0.014	–
13	(5′) AGC TCG GTC **SS**C GAG AGT GCA	0.094	–
12 **6**	(5′) AGC TCG GTC A**S**C GAG AGT GCA (3′) TCG AGC CAG TAG CTC TCA CGT	0.008	35.6
12 **8**	(5′) AGC TCG GTC A**S**C GAG AGT GCA (3′) TCG AGC CAG T**F**G CTC TCA CGT	0.004	70.5
13 **6**	(5′) AGC TCG GTC **SS**C GAG AGT GCA (3′) TCG AGC CAG TAG CTC TCA CGT	0.062	46.0
13 **8**	(5′) AGC TCG GTC **SS**C GAG AGT GCA (3′) TCG AGC CAG T**F**G CTC TCA CGT	0.014	85.1

[a] Conditions: see Table 1; quinine sulfate was used as standard for quantum yield (ϕ) determination.

In conclusion, a non-nucleosidic tetrathiafulvalene building block suitable for incorporation into DNA has been described. TTF-modified oligonucleotides form stable hybrids, which were characterized by thermal denaturation, fluorescence, and CD spectroscopy. Exciton coupling revealed a high degree of structural organization in the modified region of a hetero-duplex formed by TTF and perylene diimide-containing strands. Furthermore, fluorescence quenching in TTF/pyrene modified hetero-hybrids was demonstrated. The finding presented here may help in the development of optical sensors or redox-active, oligonucleotide-based diagnostics.

Experimental Section

General: Reactions were carried out under N_2 atmosphere using distilled, anhydrous solvents. Flash column chromatography (CC) was performed by using silica gel 60 (63–32 μM, Chemie Brunschwig AG). If compounds were sensitive to acid, the silica was pre-treated with solvent containing 1% Et_3N. All NMR spectra were measured at room temperature on a Bruker AC-300 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are reported in ppm relative to the residual undeuterated solvent ($CDCl_3$: 7.27 ppm). ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are reported in ppm relative to the residual non-deuterated solvent ($CDCl_3$: 77.00 ppm). ^{31}P NMR spectra were recorded at 162 MHz. Chemical shifts are reported in ppm relative to 85% H_3PO_4 as an external standard. Electron ionization mass spectra (EI-MS) were recorded on an AutospecQ (Waters Micromass) instrument.

Synthesis of 2,3-bis(2-hydroxyethylthio)-6,7-bis(pentylthio)tetrathiafulvalene (2): A solution of sodium (0.17 g, 7.35 mmol) in ethanol (20 mL) was added to a suspension of the cyanoethyl-protected compound **1** (0.85 g, 1.47 mmol) in anhydrous degassed ethanol (80 mL) under nitrogen. After being stirred at room temperature for 4 h, the red-brown mixture was treated with 2-chloroethanol (1.78 g, 22.05 mmol). After a few minutes, the solution turned orange and a precipitate started to form. The mixture was then stirred overnight after which it was treated with water (50 mL) and extracted with dichloromethane. The extract was washed with water, dried with magnesium sulfate, and concentrated. The resulting solid was purified by chromatography (silica gel: CH_2Cl_2/EtOAc 8:2) to give compound **2** in 73% yield (0.60 g, 1.08 mmol). ^{1}H NMR

($CDCl_3$, 300 MHz): $\delta = 0.90$ (t, 6H), 1.36 (m, 8H), 1.65 (m, 4H), 2.81 (t, 4H), 3.01 (t, 4H), 3.76 ppm (t, 4H); EI-MS: m/z: 560 [M^+], $C_{20}H_{32}O_2S_8$, MW = 560.02; R_f (CH_2Cl_2/EtOAc 4:1) = 0.15.

Synthesis of 2-{2-[(4,4′-dimethoxytrityl)oxy]ethylthio}-3-(2-hydroxyethylthio)-6,7-bis(pentylthio)tetrathiafulvalene (3): The diol **2** (0.50 g, 0.89 mmol) was dissolved in dry pyridine (7.5 mL), and 4,4′-dimethoxytrityl chloride (0.30 g, 0.89 mmol) in dry pyridine (2.5 mL) was added dropwise. After the mixture had been stirred at room temperature for 6 h, a solution of sodium bicarbonate (25 mL) was added. The crude product was isolated by extraction with dichloromethane and dried with magnesium sulfate and concentrated. To avoid decomposition of the product on silica gel, the column was prepared with solvent containing 1% triethylamine. The crude was purified by chromatography (silica gel: hexane/EtOAc 2:1) to give compound **3** in 35% yield (0.27 g, 0.31 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.87$ (t, 3H), 0.90 (t, 3H), 1.30 (m, 8H), 1.63 (m, 4H), 2.76 (t, 2H), 2.82 (t, 2H), 2.87 (t, 2H), 3.02 (t, 2H), 3.34 (t, 2H), 3.62 (t, 2H), 3.79 (s, 6H), 6.83 (m, 4H), 7.19 (m, 1H), 7.28 (m, 2H), 7.31 (m, 4H), 7.43 ppm (m, 2H); EI-MS: m/z: 862 [M^+]; $C_{41}H_{50}O_4S_8$, MW = 862.15; R_f (hexane/EtOAc 2:1) = 0.4.

Synthesis of 2-[2-[(diisopropylamino)(2-cyanoethyl)phosphinoxy]ethylthio)-3-{2-[(4,4′-dimethoxytrityl)oxy]ethylthio}-6,7-bis(pentylthio)tetrathiafulvalene (4): The alcohol **3** (0.26 g, 0.30 mmol) and ethyldiisopropylamine (0.096 g, 0.75 mmol) were dissolved in dry dichloromethane (7.5 mL). 2-Cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (0.078 g, 0.33 mmol) dissolved in dry dichloromethane (2.5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The crude product was directly purified by chromatography (silica gel: hexane/EtOAc 2:1 +1% triethylamine). The fractions were combined and evaporated under high vacuum to furnish compound **4** in 85% yield (0.27 g, 0.25 mmol). ^{1}H NMR ($CDCl_3$ 300 MHz): $\delta = 0.88$ (t, 3H), 0.90 (t, 3H), 1.16 (m, 12H), 1.33 (m, 8H), 1.64 (m, 4H), 2.59 (m, 2H), 2.79 (t, 2H), 2.82 (t, 2H), 2.96 (t, 2H), 2.99 (t, 2H), 3.32 (t, 2H), 3.61 (m, 4H), 3.79 (s, 6H), 3.80 (m, 2H), 6.83 (m, 4H), 7.19 (m, 1H), 7.28 (m, 2H), 7.31 (m, 4H), 7.43 ppm (m, 2H); ^{31}P NMR ($CDCl_3$, 122 MHz): $\delta =$ 148.46 pm; EI-MS: m/z: 1063 [M^+], $C_{50}H_{67}N_2O_5PS_8$, MW = 1062.26; R_f (hexane/EtOAc 2:1) = 0.9.

Synthesis and analysis of oligonucleotides: Cyanoethyl phosphoramidites from Transgenomic (Glasgow, UK) were used for oligonucleotide synthesis. Oligonucleotides **5** and **6** were obtained from Microsynth (Switzerland) and were used without additional purification. Oligonucleotides **7**–**9** were prepared by automated oligonucleotide synthesis by a standard synthetic procedure ('trityl-off' mode) on a 394-DNA/RNA synthesizer (Applied Biosystems). Cleavage from the solid support and final deprotection was done by a treatment with 33% aqueous NH_3 at 55°C overnight. Oligonucleotides **7**–**9** were purified by reverse-phase HPLC (LiChrospher 100 RP-18, 5 μm, Merck, Bio-Tek instrument Autosampler 560); eluent A = (Et_3NH)OAc (0.1 M, pH 7.4); eluent B = 80% MeCN and 20% eluent A; gradient 5–80% B over 20 min at 25°C. ESI-MS (negative-mode, CH_3CN/H_2O/TEA) of oligonucleotides was performed with a Sciex QSTAR pulsar (hybrid quadrupole time-of-flight mass spectrometer, Applied Biosystems). Oligomers **10**[50] and **11**–**13**[22] were synthesized as described.

Acknowledgements

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Keywords: DNA · fluorescence · oligonucleotides · tetrathiafulvalene

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