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Self-Organizing Oligothiophene–Nucleoside Conjugates: Versatile Synthesis via "Click"-Chemistry

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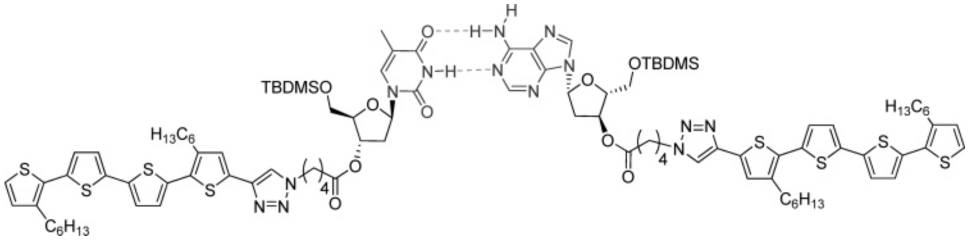
ABSTRACT



A versatile synthesis of novel oligothiophene–nucleoside conjugates based on Cu(I)-catalyzed alkyne–azide cycloaddition ("click-reaction") has been developed. Complementary thymidine- and adenosine-functionalized quaterthiophenes form recognition-driven superstructures via hydrogen bonding and other competing intermolecular forces. Self-aggregated fibers up to 30 μm in length were characterized with atomic force microscopy.

During the last decades, oligo- and polythiophenes have become one of the best investigated classes of organic semiconductors.[1] Their application covers all fields of organic and molecular electronics, which ranges from light-emitting diodes and field-effect transistors to materials for solar cells. Especially for oligomers, the formation of well-defined superstructures is of great significance for the device properties, and many approaches have been discussed in literature.[2] Typically, these nanoarchitectures are formed and held together by intermolecular forces such as van der Waals, electrostatic, or $\pi-\pi$ interactions. With the directed formation of hydrogen-bonding, nature offers an efficient tool to self-assemble artificial systems when they are combined with biological systems.[3] These functionalizations of biological building blocks not only allow the formation of nanoscale materials by molecular recognition and hydrogen-bonding, they also transduce these events into electronic signals.[4] First examples were presented[5] of nucleobase oligo- and polythiophene conjugates, which allowed the selective detection of a hybridization event with a complementary base by

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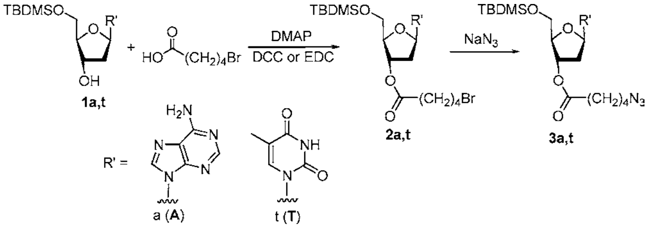
cyclic voltammetry and spectroelectrochemistry as well as the possibility to post-functionalize polythiophene films with longer oligonucleotide strands for application as DNA sensors (which can visualize even single-nucleotide polymorphisms[6]). Recently, Barbarella et al. published water-soluble dinucleotide conjugates that can form aggregates both in the solid state and aqueous solution at high ionic strength.[7] This example indicated the possibility to transform the molecular recognition of base pairs via hydrogen bonding into a molecular recognition-driven self assembly. Meijer et al. already demonstrated the successful application of this principle by the formation of helical stacks from thymidine-functionalized oligo(phenylenevinylene) and polyadenosine strands.[8]

Here, we describe the synthesis of thymidine (T)- and 2′-desoxyadenosine (A)-functionalized oligothiophenes as first examples of a versatile protocol using Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes, frequently referred to as "click-reaction".[9] The general procedure includes the connection of the important building blocks, oligothiophene and nucleoside, through a flexible alkyl spacer that should provide more flexibility and might benefit the self-assembling properties. The conjugates comprise highly amphiphilic character and can exert various competing intermolecular forces, such as π-stacking, van der Waals interactions, H-bonding, and solvent effects. The combination of all of these interactions may allow fine-tuning of the self-aggregating behavior and lead to the rational design of supramolecular assemblies of bio-inspired organic semiconductors.

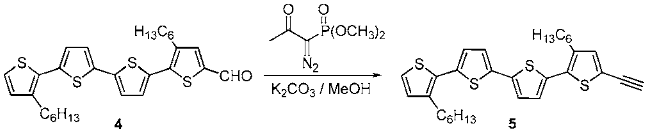
A flexible alkyl spacer bearing a terminal azide group was first attached to the nucleosides which subsequently were "clicked" to ethynylated oligothiophenes. In order to couple the spacer selectively at the 3′-OH group of the nucleoside, thymidine (T) and desoxyadenosine (A) were protected at the primary OH group with bulky *tert*-butyl-dimethylsilylether (TBDMS) under common basic conditions.[10] The resulting TBDMS-protected nucleosides **1a**,**t** were reacted with 5-bromovaleric acid under Steglich conditions to form esters **2a**,**t** in 72% and 81% yield, respectively, with either dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-diisopropylamino-carbodiimide (EDC) as activating agent. Azido-functionalized "bio"-components **3a,t** were obtained in 87% and 82% yield, respectively, by nucleophilic substitution of the terminal bromine in **2a,t** with sodium azide (Scheme 1).

Scheme 1



"Semiconductor" block ethynyl-quaterthiophene **5** was synthesized from corresponding carbaldehyde **4** via Ohira−Bestmann reaction[11] with dimethyl-diazooxopropyl-phosphonate in 89% yield (Scheme 2).

Scheme 2



Coupling of the two different moieties to oligothiophene−nucleoside conjugates **6a,t** was achieved by "click"-reaction of alkyne **5** and azido-nucleosides **3a,t** with the catalytic system $Cu(CH_3CN)_4PF_6/Cu^0$ in THF.[10] This optimized protocol gave much better results than the standard Cu^{2+}/ascorbic acid system.[12] 2-Desoxyadenosine−quaterthiophene **6a** was obtained in 77% and thymidine−quaterthiophene **6t** in 54% yield. As a reference quaterthiophene−triazole **7** without a nucleoside unit has been synthesized by the same protocol in 79% yield by cycloaddition of alkyne **5** and 5-azidovaleric acid methylester (Scheme 3).

Investigation of the optoelectronic properties of conjugates **6a,t** and reference **7** gave only small differences compared to the parent quaterthiophene core. The absorption spectra showed identical intense $\pi-\pi^*$ transitions at 394 nm due to an excitation parallel to the conjugated π-system. Compared to α-quaterthiophene this absorption is slightly red-shifted by 5 nm due to the additional double bond in the adjacent 1,2,3-triazole ring. The second, smaller band at 257 nm which is due to a perpendicular excitation and independent of the length of the oligomer is only evident for **7**, because for conjugates **6a,t** this absorption band is overlaid by the specific absorption of the nucleoside. Enhanced bands with maxima at 258 nm for adenosine **6a** and at 264 nm for thymidine **6t** were found. The fluorescence behavior was identical for all three compounds, and emission bands with maxima at 473 and 500 nm were found (Table 1, Figure S1).

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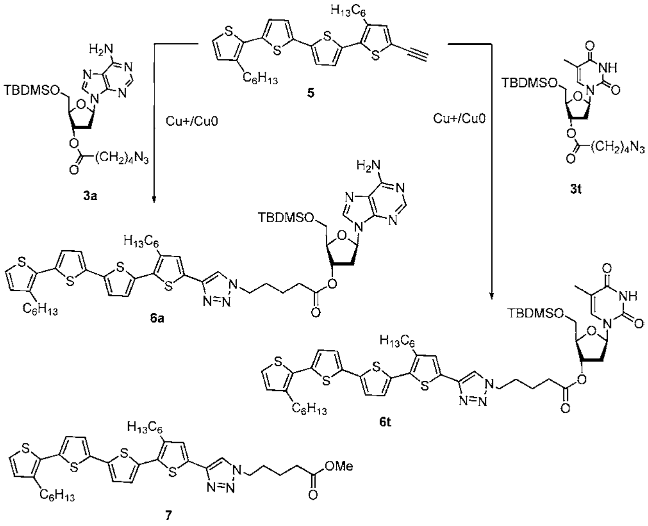
Scheme 3



The redox behavior of conjugates **6a,t** and ref **7** were determined by cyclic voltammetry (CV) in dichloromethane and tetrabutylammonium hexafluorophosphate (0.1 M) as electrolyte. Typical first (quasi)reversible oxidations indicating the formation of fairly stable quaterthiophene radical cations were found at $E^\circ = 0.37-0.39$V vs Fc/ Fc$^+$. In the back scan, small second waves at around 0.2 V were visible, pointing to the formation of dimers, due to one reactive α-position in the quaterthiophene unit (Table 1, Figure S1).

Table 1. UV/Vis, Fluorescence, and Redox Data for Conjugates **6a,t** and Reference Compound **7** in Dichloromethane

	absorption				
compd	$\lambda_{\max1}$ [nm]	$\lambda_{\max2}$ [nm]	ϵ_2 [l·mol^{-1}·cm^{-1}]	emission $\lambda_{\max}$ [nm]	redox E°_{ox1} [V]
6a	258	394	28600	473, 502	0.39[a]
6t	264	394	27400	473, 502	0.37[a]
7	257	394	31100	473, 499	0.38[a]

[a] Quasi-reversible waves.

A common method to determine base−base interactions through H-bonding is the application of NMR spectroscopy.[13] In solution, several possibilities for the association of bases, such as Watson−Crick or Hoogsteen modes, are possible and lead to a downfield shift of the involved NH- or OH-protons.[9] Upon titration of **6t** with **6a** in CDCl$_3$ a remarkable shift of the thymidine imino protons from 8.3 to 11.8 ppm was noticed, while all other signals remained almost constant, clearly verifying the formation of H-bonds between the two nucleobases. Only slight differences of about 0.03 ppm for the protons at C2 and C8 of the adenine moiety were detected, which indicated both Hoogsteen and Watson−Crick base-pairing modes.[14] The maximum chemical shift (CIS) of the imino proton of **6t** at full complexation and K_a were determined with a nonlinear fit (Job Plot, Figure S2),[15] and only values within the *Weber's criterion*[14] were taken into account. The value of 14.2 ppm for full complexation of **6a**::**6t** in a 1:1 stoichiometry and of 33 M^{-1} for association constant K_a were in the expected range compared to other association constants of thymidine and adenosine derivatives.[16]

The self-organization properties of oligothiophene−nucleosides **6a,t**, reference compound **7**, and 1:1 mixtures of the complementary nucleosides **6a**::**6t** on solid substrates were investigated with atomic force microscopy (AFM). The results of drop-casted films from toluene solutions on highly oriented pyrolytic graphite (HOPG) before and after annealing at 120 °C are summarized in Table 2.

Table 2. Results of AFM Investigations of Drop-Casted Films of Conjugates **6a,t**, Reference Compound **7** and **6a::6b** (1:1 Mixture) on Graphite (HOPG) before and after Annealing

	fiber dimensions before annealing				fiber dimensions after annealing			
cmpd	*L* [μm]	*W* [nm]	*H* [nm]	other morphols.[a]	*L* [μm]	*W* [nm]	*H* [nm]	other morphols.[a]
7	–	–	–	ML	2 ± 0.5	40	~1.6	C
6a	–	–	–	ML+C	<5	100	~2.2	C
6t	2 ± 0.5	120	2.2	ML+C	<6	~120	~2.2	L
6a::6t	10 ± 2	100	2.2	ML	>30	~120	2.2−7	C

[a] ML = monolayer; L = multilayer, C = cluster.

For all three individual compounds **6a,t** and **7** we observed monolayer (ML) formation on the substrate with heights of 2.2 nm, which agree very well with the calculated length of the short molecular axis. Clustered aggregates (C) were only observed for layers of **6a,t** and not for **7** and the 1:1 mixture. The clusters are formed by partially fractured or fully collapsed monolayer and further growth in unordered structures perpendicular to the substrate. Additionally, for thymidine **6t** very small fibers of ca. 2 μm in length and 2.2 nm in height adsorbed onto the surface were observed. The 1:1 mixture of the nucleosides **6a**::**6t** showed the formation of much longer fibers (10 μm). In this case, the recognition of the complementary base pairs through H-bonds seems to be more efficient than self aggregation, which can take place for both thymidines and adenosines. It is well-known that the association constant for dimerization of adenosine bases in CDCl$_3$ (K_{AA} < 5 M^{-1}) is 4 times weaker than for corresponding thymines ($K_{TT} \approx 20$ M^{-1}) and 20 times weaker than the complementary recognition ($K_{AT} \approx 100$ M^{-1}).[17] This

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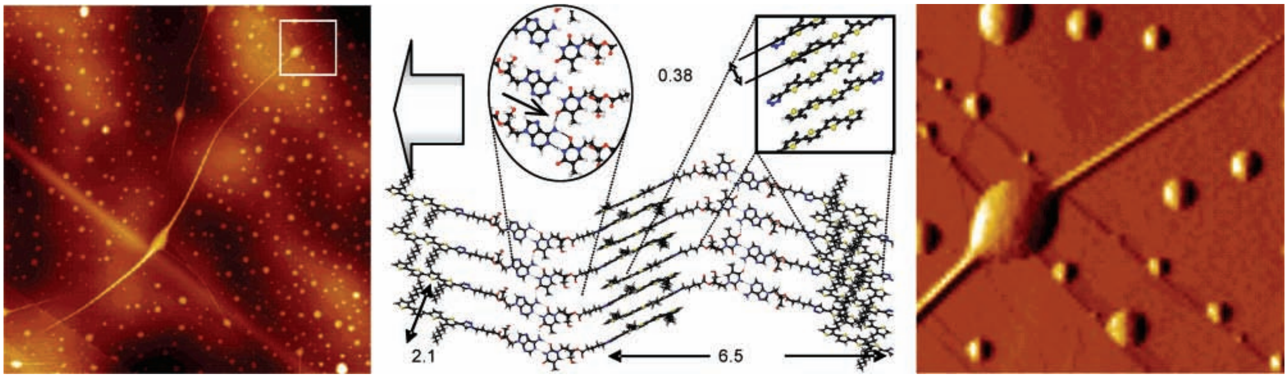

Figure 1. AFM tapping-mode images of a 1:1 mixture of adenosine−quaterthiophene **6a** and corresponding thymidine **6t** deposited from toluene on HOPG after annealing: topography representation (17 × 17 μm^2) (left) and detailed amplitude image (2.5 × 2.5 μm^2) (right). In the middle a calculated model for the fiber growth (gray arrow) is shown, including a detail of the molecular interactions involved (oval and square insets) and the molecular dimensions (see text for details).

trend agrees very well with the fact that in our study the adenosine-functionalized derivative **6a** did not show ribbon structures, whereas the thymidine **6t** formed smaller fibers, and the mixture, much longer aggregates.

After annealing of the deposited adsorbates, in all cases fiber formation on the graphite surface occurred, and the same trend as before was observed with respect to their lengths: very small fibers of ca. 2 μm can be identified for reference **7** and slightly bigger ones for pure **6a** and **6t** (up to 6 μm). In contrast, the 1:1 mixture of **6a**::**6t** exhibited the formation of very long fibers on HOPG, some of them even longer than 30 μm. In Figure 1 (left) a representative 22 μm long fiber is displayed in conjunction with smaller ones and round-shaped clusters. The image on the right is shown in amplitude mode and gives a detailed view of a fiber connected to a cluster. Interestingly, the right part of the ribbon exhibits some substructure, while the left part comprises no apparent structure. The analysis of several tens of fibers showed no preferred handedness, which can be explained by the influence of the underlying HOPG substrate.

In order to understand fiber formation and how the molecules are packed within the fibers, quantum chemical calculations were performed on two-dimensional stacks of interacting molecules. The model at the molecular level can shed light on the role of the different intermolecular interactions potentially involved in the stabilization of such supramolecular structures. Figure 1, middle, shows the most stable geometry for the 2D stacks of **6a**::**6t**. The base-pair recognition (**T**::**A**) is built on two H-bonds along the long molecular axis. In the perpendicular (or “upright”) direction the formed heterodimer is additionally stabilized by a third H-bond (arrow in oval inset) to the next base pair. The quaterthiophene parts of the molecules have a strong tendency to be almost planar and parallel to each other and interact at typical $\pi-\pi$ stacking distances of 0.38 nm (Figure 1, square inset). The calculations also showed that between interacting oligothiophenes a displacement of half of a thiophene unit along their long axis is favorable. This phenomenon was also found in single crystals of quaterthiophene molecules.[2d] Van der Waals interactions between the alkyl side chains on the thiophene units additionally stabilize the intermolecular interaction, which also explains the tendency of the model compound **7** to form fibers after annealing, although much less extended than for the **6a**::**6t** base-pair mixture.

In conclusion, we have shown that the combination of semiconducting oligothiophenes with complementary nucleosides leads to novel recognition-driven self-aggregated superstructures in solution and in the solid state.

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Supporting Information Available: Characterization data for all new compounds and experimental protocols as well as optical, redox, and NMR titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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