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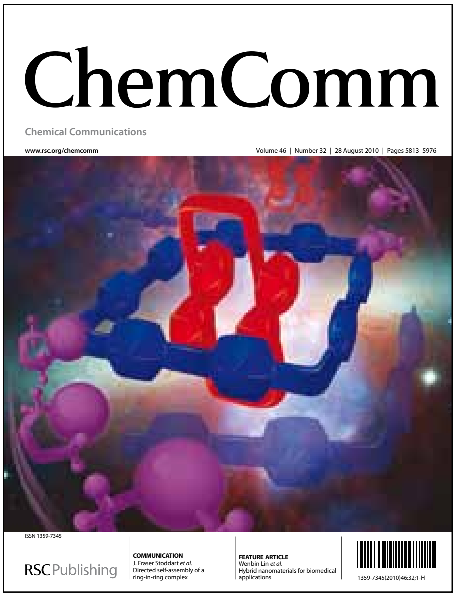

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ARTICLE TYPE

Chiral suprastructures of asymmetric oligothiophene-hybrids induced by a single proline

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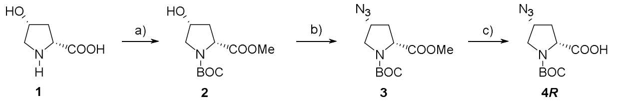
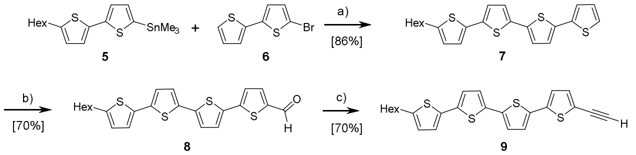
Oligothiophene-proline hybrids were synthesized via click-reaction showing intriguing self-assembly behavior in aqueous environment by forming chiral superstructures, whose helicity is controlled by the configuration of the amino acid moiety.

Poly- (PT) and oligothiophenes (OTs)[1,2] have gained immense interest in the field of organic electronics and find versatile application as organic light emitting diodes (OLEDs), organic field effect transistors (OFETs),[3] and organic solar cells (OSCs).[4] As the performance of the electronic devices depend directly on the self-organization of the active material in the bulk, chiral PT and OTs were reported as promising scaffolds for the construction of functional nano-architectures.[5-9] A more recent approach combines various π-conjugated segments with biological motifs such as peptides[10-18] or carbohydrates [19,20], most of them in a symmetric A-B-A structure, capable to interact via a broad variety of non-covalent forces such as π–π, van-der-Waals, dipole-dipole, and hydrogen bond interactions. The resulting nano-structures were reported to follow the secondary structure motifs of the incorporated biosegments, e.g., α-helices or β-sheets.[21,22] Our approach to avoid the often tedious synthesis and isolation of larger peptides consists of introducing a single amino acid such as enantiomerically pure (2*R*,4*R*) or (2*S*,4*S*) 4-azidoproline into the hybrid resulting in novel non-symmetrical A-B structures. Mild and regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition ("click"-reaction)[23,24] was employed for the biofunctionalization[25] of a quaterthiophene. Furthermore, the terminal alkylation of the OT should preserve solubility of the hybrids in organic solvents and prevent oxidation of the conjugated backbone. The physical and self-assembling properties of the asymmetric and chiral oligothiophene hybrids will be addressed.

Synthesis of azido-(2*R*,4*R*)-proline **4*R***[17] started from commercially available (2*R*,4*R*)-hydroxyproline **1** (Scheme 1). Esterification of the amino acid in methanol and subsequent protection of the secondary amine with *tert*-butyloxycarbonyl(BOC)-anhydride afforded hydroxyproline derivative **2**. Activation of the hydroxyl group was carried out via a mild Mitsunobu reaction of proline **2** with methane sulfonic acid. After S_N2 reaction with sodium azide the BOC-protected, azido-functionalized (2*R*,4*R*)-ester **3** was isolated. Subsequent saponification under basic conditions afforded the free amino acid **4*R***[18] (Scheme 1) with retained stereochemistry in 98 % yield. The hexyl-terminated quaterthiophene scaffold **7** was synthesized via Stille cross-coupling reaction of stannylated 5-hexylbithiophene **5** and brominated bithiophene **6** in 86% yield in the presence of $Pd(PPh_3)_4$.[28,29] The quaterthiophenic aldehyde **8** was prepared by subsequent formylation of **7** in 70% yield. Subsequently, aldehyde **8** was converted to ethynylated quaterthiophene **9** via Ohira-Bestmann-reaction with dimethyl(2-oxopropyl-phosphonate) and azidotosylate under basic conditions.[30] The new alkynylated building block **9** was afforded in a satisfying yield of 70 % (Scheme 2).



Scheme1: Synthesis of the azido-functionalized-(2R,4R) proline a) (i) $SOCl_2$ (2 eq), MeOH, 0°C to reflux (ii) BOC_2O (1 eq), $KHCO_3$ (2.2 eq), H_2O, dioxane, RT; b) (iii) CH_3SO_3H (1.2 eq), PPh_3 (1.8), DIAD (2 eq), NEt_3 (0.4), toluene, 0°C to 70°C; (iv) NaN_3 (5 eq), DMF, 80°C; c) NaOH (2.1 eq), H_2O, CH_3OH, THF, RT.



Scheme2: a) $Pd(PPh_3)_4$, DMF; b) $POCl_3$, DMF, dichloroethane; c) NaH, THF, 0 °C, dimethyl(2-oxopropyl-phosphonate), azidotosylate, K_2CO_3, MeOH/THF.

The ethynylated hexyl-quaterthiophene unit **9** was reacted with the two azidoproline enantiomers, (2*R*,4*R*)-**4*R*** and commercially available (2*S*,4*S*)-**4*S*** in regioselective Cu(I)-catalyzed click-reactions. Quaterthiophene (2*R*,4*R*)-proline hybrid **10*R*** and enantiomeric (2*S*,4*S*)-hybrid **10*S*** were afforded in 90% and 89% yield, respectively (Scheme 3).

The physical properties of the enantiomeric oligothiophene proline hybrids **10*S*** and **10*R*** were investigated using cyclic voltammetry (CV), UV-Vis, fluorescence and circular dichroism (CD) spectroscopy. Self-assembly and the resulting suprastructures were investigated by dynamic light scattering (DLS), powder X-ray diffraction (XRD), and transmission electron spectroscopy (TEM).

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† Electronic supplementary information (ESI) available: Materials and methods, molecular characterization, XRD, CD and DLS

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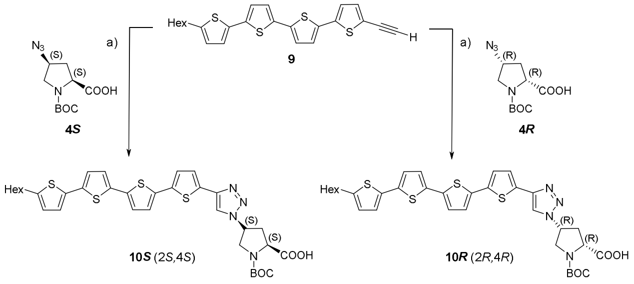

Scheme 3 Synthesis of oligothiophene (2*S*,4*S*)-hybrid **10*S*** and (2*R*,4*R*)-hybrid **10*R*** via click-reaction a) Cu(I)[CH_3CN]$_4$]PF_6, Cu(0), THF/DCM.

Firstly, the redox behavior of π-conjugated biohybrids **10** was determined by CV measurements (Fig. S1). Typical first and second reversible oxidations were found at $E°_{ox1}$ = 0.39 V and $E°_{ox2}$ = 0.69 V vs. Fc/Fc^+, characteristic for the formation of stable quaterthiophene radical cations and dications, whereas no signals were found in the reductive regime. Accordingly, we can assert that the redox activity of the oligothiophene is preserved in the enantiomeric hybrids.

Secondly, the photophysical properties of compounds **10*R*** and **10*S*** were analyzed in THF as good solvent, in which they molecularly dissolve. Because both enantiomers showed equivalent optical properties (Fig. S2) we will mostly report on results obtained for (2*S*,4*S*)-hybrid **10*S***. The absorption spectrum of **10*S*** in THF showed a broad unstructured band with a maximum at 416 nm, which corresponds to the π–π* transition of the quarterthiophene moiety (Fig. 1). The emission spectrum of **10*S*** showed a band with a maximum at 474 nm and a vibronic fine structure, which well correlates with a stronger quinoidal character of the oligothiophene backbone in the excited state.

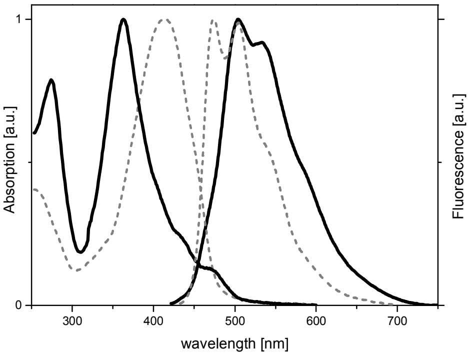

Figure 1: Normalized UV-Vis absorption and emission spectra of **10*S*** measured in THF (dashed line) and 10% THF-90% water (solid line).

In order to induce the self-aggregation of proline-functionalized hybrid **10*S***, titration of a pure THF solution with water was carried out. Upon titration a blue-shift of the absorption band was observed reaching a maximum (Δλ=53 nm) at a ratio of 1:9 THF/H_2O. The evident asymmetry of the absorption band with the strong blue-shifted component at λ_{max}=363 nm accounts for the formation of H-type aggregates in the solvent mixture. The characteristics of this type of aggregates involves the parallel alignment of the transition dipoles responsible for the observed electronic transition which corresponds in our case to the π–π* transition of the oligothiophene backbone. Accordingly, the weak absorption band at ~470 nm corresponds to the forbidden Davydov component (antiparallel alignment of the transition dipoles). Upon titration, the fluorescence spectra revealed a successive bathocromic shift from 474 nm to 504 nm (Fig. 1) and concomitantly a strong quenching (~70%) of the emission band (Fig. S3). Therefore, the formation of aggregates in the presence of water was assessed.

In order to analyze the nature of the self-assembled aggregates formed by both enantiomeric oligothiophene-proline hybrids **10*R*** and **10*S*** in the THF/H_2O solvent mixture, CD spectroscopy was carried out. With increasing water content, a bisignate Cotton effect for each of the hybrids **10*R*** and **10*S*** appeared which reached its maximum of intensity in 1:9 THF/H_2O (Fig. 2, bottom).

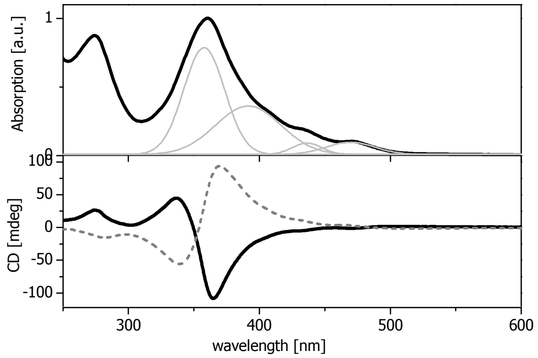

Figure 2 Absorption spectrum of (2*S*,4*S*)-hybrid **10*S*** in 1:9 THF/H_2O (black line) including Gaussian deconvolution for the π–π* transition, (grey curves), top. CD spectra of (2*S*,4*S*)- hybrid **10*S*** (solid line) and (2*R*,4*R*)-hybrid **10*R*** (dashed line) in 1:9 THF/H_2O, bottom.

As expected for the enantiomeric proline hybrids **10*R*** and **10*S*** (Fig. 2 bottom) mirror-image CD spectra were obtained. (2*S*,4*S*)-hybrid **10*S*** showed an intense exciton-coupled signal with negative first and positive second Cotton effect at 365 nm (-108 mdeg) and 337 nm (45 mdeg) which is indicative for the presence of chiral aggregates, in which π-π interacting conjugated backbones arrange in a left-handed helical way.[19] The correlation between the zero-crossing of the bisignated bands (350 and 354 nm for **10*R*** and **10*S***, respectively) and the maximum of the Gaussian curve deconvoluted from the absorption spectra in the solvent mixture (358 nm in the case of **10*S***; Fig. 2, top) evidences the exciton coupled character of the transition. Accordingly, (2*R*,4*R*)-enantiomer **10*R*** showed a positive couplet at 370 nm, (94 mdeg) and at 339 nm (-55 mdeg), corresponding to a right-handed helical arrangement of the chromophoric segments. CD spectra for both enantiomeric hybrids showed a second set of weaker CD signals in the region of 240-300 nm associated with the perpendicular excitation of thiophene and triazole units.

Preliminary XRD experiments on crystalline powders of (2*R*, 4*R*)-hybrid **10*R*** revealed three prominent diffraction peaks corresponding to *d* spacings of 0.45, 0.39, and 0.32 nm at the wide angle region (Fig. S4). Taking into account the wedge shape of the molecule (see Fig. 3, right), we ascribe the first reflection to the alignment of the most prominent proline heads and the other two reflections to the π–π stacking interaction distances of the thiophene backbones.[32] From the available data, we conclude that the chirality of the proline moiety is transferred to the helical organization of the quaterthiophene backbone in the aggregates.

In order to get insight into the stability and nature of the observed aggregates, temperature-dependent CD and UV-Vis investigations were carried out. Aggregates formed by both hybrids were stable until 60 °C. The temperature-dependent UV-vis spectra showed no influence, neither in intensity nor in the energy of the absorption maxima (Fig. S5, left). With increasing temperature no decrease of the magnitude of the bisignate CD signals for both enantiomeric hybrids **10*R*** and **10*S*** was detected (Fig. S5, right).

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These results account for the extraordinary stability of the aggregates in the solvent mixture.

Investigations on the aggregates in the solid state were performed by using TEM. In the TEM micrographs, the presence of circularly shaped aggregates was detected (Fig. 3). Two borderline dimensions have been analyzed: the large aggregates evidence a well-defined perimeter with a reflecting halo and strong contrast inside, which is indicative of a vesicle structure (Fig. 3, left). The size of the vesicles ranges from 0.5 to 1.7 µm diameter. The small structures (diameters between 25 to 75 nm) were randomly distributed in the micrographs and showed as well a brighter contrast inside (Fig. 3, middle). No evidence of intermediate aggregates was found. We attribute the inner contrast in the big vesicles to the enclosure of the solvent water in the structures.

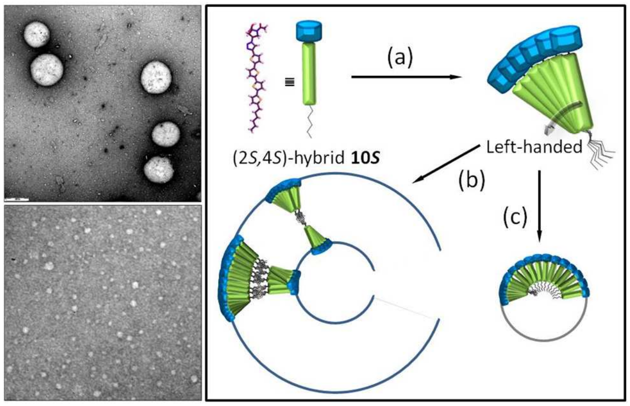

Figure 3 TEM micrographs left (9 x 9 µm^2, top and 2 x 2 µm^2, bottom) obtained from drop-casting of a 1:9 THF/H_2O solution of hybrid **10*S***. Proposed model for the aggregates of **10*S***, right: (a) π–π interacting ensemble formation, (b) vesicles and (c) unimolecular vesicles formation.

In addition, DLS measurements were taken from hybrid **10*S*** in THF/water 1:9 showing two different values for the averaged hydrodynamic diameter of the aggregates (Fig. S6). Particles of 21 nm and 70 nm in diameter were detected which is in good agreement with the size of the small features observed in the TEM micrographs. Scarcely bigger aggregates (175 nm and ~ 0.4 µm) were also determined.

The vesicle formation can be rationalized by taking the amphiphilic character of the oligothiophene-proline hybrids **10*R*** and **10*S*** into account. In the THF/H_2O solution, the molecules tend to aggregate leaving the hydrophilic proline part facing towards the water. In accordance with the results of the blue-shifted absorption band (H-aggregates) a slightly tilted face-to-face arrangement of the oligothiophene backbones is suggested (Fig. 3, right, (a)). As the CD results showed, the chirality of the proline moiety is transferred to the stacks of π–π interacting oligothiophene backbones leading to the formation of large chiral ensembles (Fig. 3, right, (a)). Thus, in the THF/H_2O solution, the molecules will preferentially form a stable bilayer structure with an all hydrophilic surface (Fig. 3, right, (b)). The molecular wedge shape, which is essential to form vesicles, most probably originates from the bulky dimension of the proline part compared to the flat rod-like structure of the alkylated oligothiophene backbone. The bilayer of the vesicles expresses as well the left-handed chirality of the molecular ensemble. The small structures could be interpreted as small vesicles formed by unimolecular walls (Fig. 3, right, (c)), which are as well chiral. In the solvent mixture, the THF might act as surfactant to stabilize the small vesicles and to overcome the entropic factor. The strong intermolecular interaction and the stabilization of the vesicles in the two borderline dimensions explain the observed high stability of the aggregates with temperature.

In conclusion, on the basis of our rational structural design, asymmetric oligothiophene-proline hybrids were synthesized. The hybrids revealed strong self-organizing behaviour in solution and in the solid state. It is demonstrated that a single amino acid with two stereocenters can induce a defined helical organization of the conjugated backbones, which is preserved in the nano- and micrometer-sized aggregates. The redox activity of the oligothiophene unit in the enantiomeric hybrids is fully preserved which allows for further application in electronic devices. In addition, L-proline and its derivatives are widely used as highly effective and selective molecular catalysts; therefore, nanometer sized self-assemblies of proline-functionalized oligothiophene hybrids in solution or on surfaces offer versatile possibilities for the generation of tailored catalytic microenvironments.

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Notes and references

1 D. Fichou, Ed. *Handbook of Oligo- and Polythiophenes*; Wiley-VCH: Weinheim, Germany, 1999; P. Bäuerle, In K. Müllen, G. Wegner, Eds.; Electronic Materials: *The Oligomeric Approach*; Wiley VCH: Weinheim, Germany, 1998; pp 105-197.
2 A. Mishra, C.-Q. Ma and P. Bäuerle, *Chem. Rev.* 2009, **109**, 1141-1278.
3 A. F. M. Kilbinger, A. P. H. J. Schenning, F. Goldoni, W. J. Feast and E. W. Meijer, *J. Am. Chem. Soc.*, 2000, **122**, 1820-1821; O. Henze, W. J. Feast, F. Gardebien, P. Jonkheijm, R. Lazzaroni, P. Leclere, E. W. Meijer and A. P. H. J. Schenning, *J. Am. Chem. Soc.*, 2006, **128**, 5923-5929.
4 K. P. R. Nilsson, A. Herland, P. Hammarstrom and O. Inganäs, *Biochemistry*, 2005, **44**, 3718-3724.
5 M. Melucci, G. Barbarella, M. Gazzano, M. Cavallini, F. Biscarini, A. Bongini, F. Piccinelli, M. Monari, M. Bandini, A. Umani-Ronchi and P. Biscarini, *Chem. Eur. J.*, 2006, **12**, 7304-7312.
6 H. A. Klok, A. Rösler, G. Götz, E. Mena-Osteritz and P. Bäuerle, *Org. Biomol. Chem.*, 2004, **2**, 3541-3544.
7 S. R. Diegelmann, J. M. Gorham and J. D. Tovar, *J. Am. Chem. Soc.*, 2008, **130**, 13840-13841.
8 D. A. Stone, L. Hsu and S. I. Stupp, *Soft Matter*, 2009, **5**, 1990-1993.
9 R. J. Kumar, J. M. MacDonald, Th. B. Singh, L. J. Waddington and A. B. Holmes, *J. Am. Chem. Soc.*, 2011, **133**, 22, 8564-8573.
10 J. A. Lehrman, H. Cui, W.-W. Tsai, T. J. Moyer and S. I. Stupp, *Chem. Commun.*, 2012, **48**, 9711–9713.
11 A. M. Sanders, T. J. Dawidczyk, H. E. Katz and J. D. Tovar, *ACS Macro Letters*, 2012, **1**, 1326-1329.
12 L. Tian, R. Szilluweit, R. Marty, L. Bertschi, M. Zerson, E.-C. Spitzner, R. Magerle and H. Frauenrath, *Chem. Sci.*, 2012, **3**, 1512-1521.
13 E.-K. Schillinger, E. Mena-Osteritz, J. Hentschel, H. G. Börner and P. Bäuerle, *Adv. Mater.*, 2009, **21**, 1562-1567; A. K. Shaytan, E.-K. Schillinger, P. G. Khalatur, E. Mena-Osteritz, J. Hentschel, H. G. Börner, P. Bäuerle and A. R. Khokhlov, *ACS Nano*, 2011, **5**, 6894-6909.
14 I.-B. Kim, J. N. Wilson and U. H. F. Bunz, *Chem. Commun.*, 2005, 1273–1275.
15 S. Schmid, A. Mishra and P. Bäuerle, *Chem. Commun.* 2011, **47**, 1324-1326.
16 A. J. Dirks, J. J. L. M. Cornelissen, F. L. van Delft, J. C. M. van Hest, R. J. M. Nolte, A. E. Rowan and F. P. J. T. Rutjes, *QSAR Comb. Sci.* 26, 2007, **11-12**, 1200–1210.
17 M. Kümin, L. S. Sonntag, H. Wennemers, *J. Am. Chem. Soc.*, 2007, **129**, 466-467.
18 R.S. Erdmann, H. Wennemers, *Org. Biomol. Chem.* **2012**, *10*, 1982-1986
19 S. A. Tucker, H. C. Bates, V. L. Amszi, W. E. Acree, Jr., H. Lee, P. Di Raddo, R. G. J. C. Fetzer and G. Dyker, *Anal. Chim. Acta*, 1993, **278**, 269-274.