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Self-organizing Carbohydrate-Oligothiophene-Hybrids for Eukaryotic Membrane-labelling

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We report synthesis and photophysical characterization of D-(+) and L-(-) mannose terminated oligothiophene hybrids. In polar environment fluorescently quenched suprastructures were formed. Fluorescence was recovered by integration of the hybrids into phospholipidic bilayers of artificial vesicles as well as membrane compartments of myeloid cells, a defined hematopoetic lineage.

Among the number of π-conjugated polymers, polythiophenes (PT) are unique due to their excellent optoelectronic and charge transport properties [1] and have been extensively employed in organic electronics, in particular for application in organic photovoltaics. More recently, carbohydrate-functionalized PT, [2] as well as poly (aryleneethynylenes), [3] poly(*p*-phenyleneethynylene)[4] poly(*p*-phenylenevinylenes),[5] and oligo(ethynylenes) [6] have attracted interest as optical probes for monitoring biological processes. Specifically, poly- or oligothiophenes have been described for monitoring interactions with nucleobases,[7] DNA,[8-10] or peptides.[11] Well-defined oligothiophenes (OT) equipped with entities of biological relevance offer the avenue to create specifically interacting self-assembled superstructures[12,13] due to the interplay of noncovalent interactions such as highly efficient π-stacking (0-50 KJ/mol).[14]

Thus, in an aqueous environment, a clustering of biologically active ligands such as carbohydrates might be favored and increase binding affinities to transmembrane receptor proteins similar as natural archetype lipopolysaccharides (LPS) endowed with a hydrophobic aglycon.[15] Contrary to an intracellular fluorescent staining of the cytoplasm region which requires the involvement of smaller, more polar fluorophores,[16,17] we pursued to enforce a permanent localization of the OT-chromophor within the hydrophobic region of the plasma membrane or other hydrophobic cell compartments. As various non-charged alkylglycosides such as octylglucoside are well-known to form at sublytic concentrations stable co-assemblies with phospholipidic membrane constituents [18] we decided to combine fluorescent linear OTs with a pyranose moiety such as mannose. The unique sensitivity of the photophysical properties of the quaterthiophene (4T)-scaffold towards slight conformational alterations [19,20] should enable to use carbohydrate-functionalized "rods" as specific fluorescent membrane probes to track cellular uptake or cell trafficking. Depending on the number of thiophene rings and substituents tailored OT-based fluorophores with good photostability, widely tunable emission, absorbance and large Stokes shifts can be afforded.[17] In addition, self-assembling nanostructures formed by π-conjugated OT-biohybrids should offer an ideal platform for supramolecular π-π-stacking interactions with aromatic drugs such as doxorubicin (DOX) in order to develope nano-carriers for drug-delivery.[21] Recently, we described a series of branched D-(+)-mannose-functionalized OT-hybrids, which were capable to recognize specifically the tetrameric protein Concanavalin A under aqueous conditions.[22,23] For a better understanding of the biological identity of the carbohydrate-functionalized OT-hybrids now the pair of mirror image D-(+) and L-(-)-4T-enantiomers **D7**

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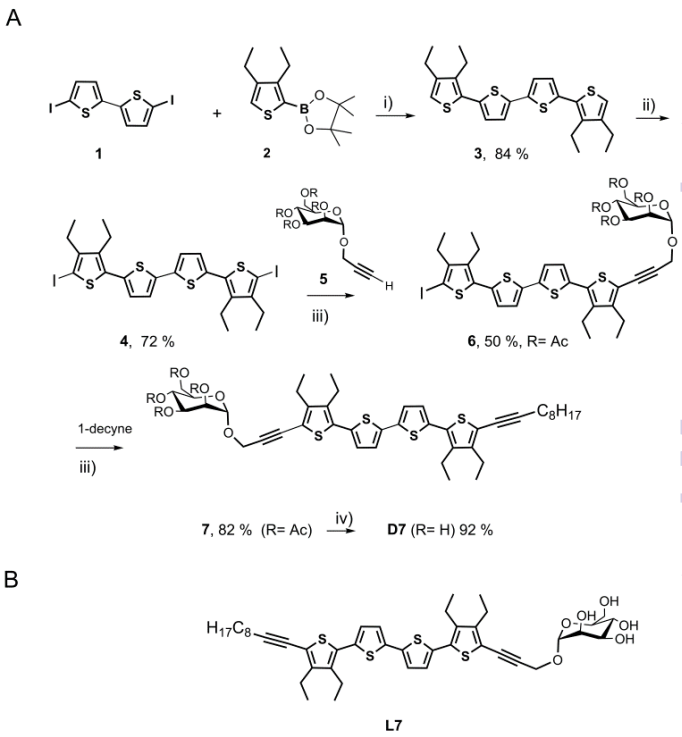
and **L7** (Chart 1) were synthesized which should exhibit different reactivity towards biological systems such as enzymes and proteins.[24] Functionalization of the carbohydrates with the rod-like quaterthiophene scaffold was performed at the anomeric position of the pyranoses as the mannosidic hydroxyl groups in 2,3 and 4 position are implicated to bind to either C-type lectin receptors such as CD 207, 208, 209, and others.[25] In addition, the introduction of the long decyne chains at the terminal α-position of the OT-rods was expected to assist self-assembly of the chiral rod-coil amphiphiles into stable bilayers,[26] but also to facilitate anchoring of the hybrids within phospholipid membranes.[27]

An efficient route for the synthesis of the deprotected, D-(+)-mannose-functionalized 4T- scaffold **D7** is depicted in Scheme 1. Synthesis of the literature known α,α'-diiodobithiophene **1** was accomplished according to a modified protocol.[28] Suzuki cross-coupling reaction of the dihalogenated bithiophene **1** with 2 equivalents of 3,4-diethylthiophene boronic acid ester **2** [29] afforded the tetraethylated quaterthiophene **3** in 89 % yield. The following halogenation of **3** with iodine and mercury acetate provided the diiodinated quaterthiophene **4** in 72 % yields. Subsequently, mild Sonogashira cross-coupling conditions were applied for the reaction of the di-halogenated quaterthiophene **4** with 2,3,4,6-tetraacetylpropargyl-α-D-(+)-mannoside **5** [30] to obtain the D-(+)-mannosidic OT intermediate **6**. The D-(+)-mannosidic OT intermediate **6** served as starting material for a second Sonogashira cross-coupling reaction with 1-decyne and the OT hybrid **7** could be isolated in a 82 % yield. Subsequent removal of the mannosidic ester functions using basic "Zemplen" conditions [31] yielded 92 % of the non-protected, anomerically pure **D7**. The L-(-) enantiomeric counterpart **L7** (Chart 1) could be prepared according the same route but using the 2,3,4,6-tetraacetylpropargyl-α-L-(-)-mannoside,[12b] which was coupled to diiodoquaterthiophene **4**.

The deprotected D-(+) and L-(-) mannosidic quaterthiophene hybrids (**D7**, **L7**) revealed moderate solubility in various organic solvents; therefore, their optoelectronic characterization was accomplished in THF, DCM, and MeOH. In the UV-vis spectra of a 10^{-5} M solution of **D7** in MeOH the typical absorption bands of the bisethynylated OT-chromophore with a main absorption maximum at λ = 397 nm were observed (Fig. 1a). The molar extinction coefficient was determined to be 31407 L mol^{-1} cm^{-1}. In the emission data, the well resolved vibronic splitting with characteristic maxima at 492 nm and 524 nm was monitored, which well correlates with the stronger quinoid character of the oligothiophene-backbone in the excited state. The non-structured absorption bands and the high intensity of the emission implied a molecularly dissolved state of the mannosidic OT-hybrids in the investigated concentration range. In order to induce aggregation, a solution of **D7** in MeOH was titrated with water. Concomitantly, a strong alteration of the UV-spectra took place. λ_{max} of the absorption of **D7** was affected by a large, hypsochromic shift of 40 nm related to the absorption maxima measured in pure MeOH and appeared now at 359 nm. Additionally, the asymmetry of the main absorption band was supported by tail absorption at the low energy side. The large hypsochromic shift indicated the formation of H-aggregates, in which the π-conjugated skeletons interact by π-stacking.[32]



Scheme 1 A) Synthesis of amphiphilic D-(+)-mannosidic OT-hybrid D7 i) [Pd2dba3]·CHCl3/HP(tBu)3BF4/K3PO4/THF, ii) Hg(OAc)2/I2 iii) Pd(PPh3)2Cl2 (8 mole %) CuI (5 mole %), DIPA/ THF 16h iv) 3 M NaOMe/MeOH, RT, 1h. B) Chemical structure of L-(-)-mannosidic OT-hybrid L7.

Aggregate formation was also corroborated by the emission spectra, as in the aqueous MeOH solutions a decreased intensity of the fluorescence was detected. Partial suppression of the 0-0 vibronic band implied H-aggregation, since this transition is forbidden in π-π-coupled aggregates.[33, 34] As expected, the absorption and emission spectra of the **L7** enantiomer were identical with those of **D7**.

In order to get insight into the chiral nature of the aggregates, CD measurements were performed (Figure 1b). In 10^{-5} M methanol solutions the hybrids **D7** and **L7** were found to be CD-silent in the π-π* region. Applying aqueous conditions [MeOH:H_2O, 2:1] the D-(+)-mannosidic derivative **D7** revealed a significant bisignate Cotton-Effect with a positive absorption maximum at higher wavelengths (λ_{max} 378 nm) and a strong negative absorption for higher energies (λ_{max} 349 nm) (Fig. 1b, black curve). The observed Davidov splitting [35, 36] of the π-π* transition band indicates excitonic interaction of the OT-chromophores of the **D7**-hybrid and implies the formation of helically arranged π-stacks with *P*-(+)-handedness. Structural evidence of the inherent opposite chirality of the synthesized L-(-)-enantiomeric hybrid **L7** was provided by the almost mirror-imaged CD-signal (Figure 1b, grey curve). Thus, the formation of helically arranged π-stacks guided by the respective handedness of the mannose segments was conclusive. To ascertain the self-assembly process under physiological conditions a larger amount of water was added to the sample of the OT-hybrid **D7** initially dissolved in MeOH: H_2O, (2:1). With increasing water content (MeOH: H_2O, 1:99 or DMSO: H_2O, 1:99) in the UV-spectra

of **D7** as well a remarkable alteration of the UV-signal was observed. λ_{max} absorption was affected by a moderate bathochromic shift related to the sample in the previously investigated [MeOH: H_2O, 2:1] mixture. Under more aqueous conditions only a weak hypsochromic shift related to the sample in pure methanol was detected and a slight low-energy absorption tailing was visible. (Supporting information, Fig.S1). The differences of the UV characteristics indicated disassembly of the π-conjugated segments of **D7** with a more loosely packing of the π-segments.[37] This assumption was supported by a decrease of the CD-intensity with increasing water content.

After these basic UV and CD-studies, we choose the L-(-)-mannosidic OT-hybrid **L7** to investigate the aggregation behavior of the OT-hybrids in various solvents and in presence of lipid vesicles by fluorescence spectroscopy. Fluorescence emission of **L7** dissolved in DCM or MeOH, respectively, showed only slight differences (Figure 1c). In contrast, the fluorescence properties of **L7** in aqueous DMSO/Hepes [1:99] buffer solutions changed dramatically, the characteristic vibronic fine structure was completely lost and only a non-structured emission band was observed, indicative for the formation of an excimer-type excited state.

To investigate whether the aggregates could be broken up in an aqueous environment, lipid vesicles of different lipid compositions (unilamellar or multilamellar) and membrane vesicles preparation of myeloid cells were prepared and tested. Firstly, large unilamellar vesicles from egg yolk phosphatidylcholine (EYPC LUV) were constructed.[38] The EYPC LUV in buffer solution alone did not show any fluorescence. After addition of a solution of the EYPC vesicles to a sample of the OT-hybrid **L7** dissolved in 1 % DMSO/Hepes buffer solution an increased intensity of the emission was detected (Figure 1d). In addition, λ_{max} of the emission was shifted hypsochromically from 597 nm to 523 nm related to **L7** in aqueous DMSO without EYPC LUV. The observed spectral changes were attributed to an improved dissolution of the **L7** OT-hybrid facilitated by the presence of the phospholipidic vesicles which might act as good solvents or surfactants. However, although the more hydrophobic microenvironment seemed to induce a partial disaggregation of the hybrids, the emission profile indicated that the mannosidic OT hybrids remained to exist as aggregates when the unilamellar EYPC vesicles were used. Subsequently, multilamellar vesicles from 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) were employed to study the optical behavior of the OT hybrids in a more viscous environment.[39] After addition of the OT-hybrids **L7** to the DMPC vesicle buffer solution a strong increase of the emission intensity was displayed. The pronounced hypsochromically shifted emission maxima (496 nm and 525 nm) relatively to the previously measured fluorescence spectrum of the hybrid **L7** with EYPC LUV indicated proceeding disaggregation.

Membrane vesicle preparations of OT-hybrid treated myeloid cells exhibited emission maxima at 495 nm and 526 nm (Fig. 1d) similar to a sample of the hybrid **L7** in the pure organic solvent DCM. In addition, an increase of the emission intensity related to **L7** in DMPC vesicle buffer solution was detected. Namely, as the spectral profile of the hybrids in the presence of the cell vesicles is consistent with a nonpolar environment such as in DCM, it is evident that the mannosidic OT-hybrids experience the more hydrophobic internal environment of the vesicle membranes and the formation of transmembrane π-stacking assemblies was excluded.

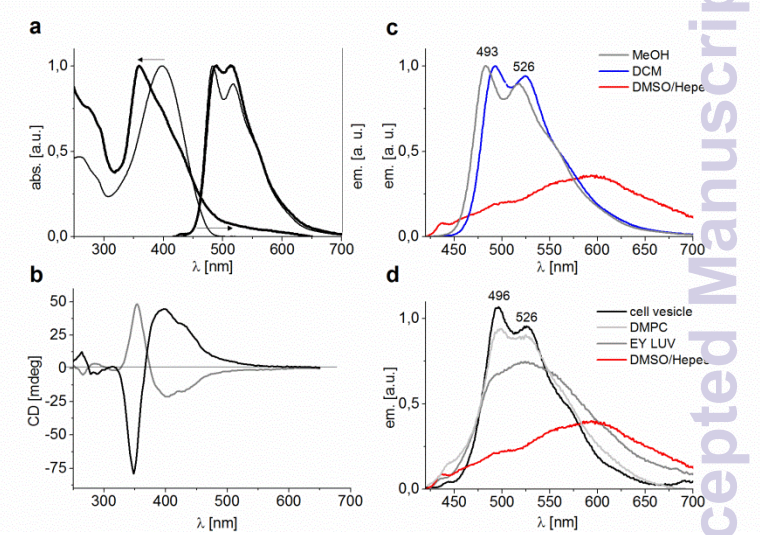


Fig. 1 a) Normalized UV-vis and fluorescence spectra of the deprotected D-(+)-mannosidic hybrid **D7** in MeOH (straight) and MeOH/H_2O 2:1 (bold) [1 * 10^{-6} M] λ_{exc} = 380 nm. b) CD-spectra of the mannosidic OT-hybrids **D7** (black) and **L7** (grey) [10^{-5} M] MeOH/H_2O, 2:1. c) Normalized emission spectra of **L7** [10^{-6} M] in MeOH (grey), in DCM (blue) and DMSO/Hepes [1/99] (red) d) normalized emission spectra of **L7** [10^{-6} M] with DMPC vesicles (light grey), with EYPC LUV (dark grey), in the presence of cellular bilayer membrane vesicles (black), and DMSO/Hepes [1:99] (red). For clarity emission of **L7** in DMSO/Hepes [1:99] normalized to 0.4 emission intensity.

In order to visualize localization of the fluorescent hybrids within the phospholipidic liposomal membranes, mixed micelles from DMPC and 2 mol- % of **L7** related to the phospholipid were constructed and studied via standard fluorescence microscopy equipped with an Argon-Krypton laser. Fluorescent spherical objects mostly with an average diameter of roughly 10 µm. (λ_{exc} 490 nm, λ_{em} >515 nm) (Figure 2a) could be observed. Fluorescence images showed the intact vesicle structure. Upon excitation at 509 nm the characteristic green emission of the OT-chromophor was observed (Figure 2b) and confirmed successful incorporation of the flourescent OT-hybrids into the membrane of the DMPC vesicles.

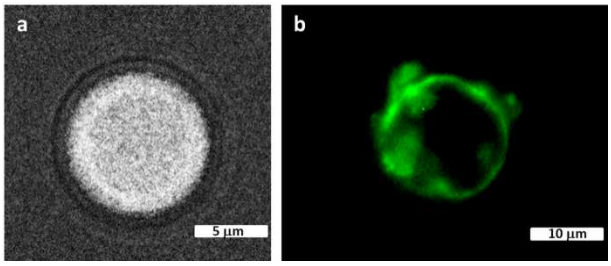


Figure 2 a) Fluorescence micrographs of DMPC vesicles modified with **L7** (2 mol % related to the phospholipid) b) Appearance of green emission indicated association of the hybrids with the DMPC membrane ($\lambda_{max\ exc}$ 509 nm). For clarity images are treated with Image J.

Subsequently, the interaction of the OT-hybrids with more complex biological systems was explored. A number of cell lines as well as peripheral blood derived leukocytes and bone marrow cells were screened for uptake and membrane labelling. Using dilutions of 10^{-4} to 10^{-6} of 5mg/ml stock solution of **D7** or **L7** in DMSO only myeloid cells showed a favorable integration of the OT-hybrids into their surface and intracellular membranes. Labelling of other cells of non-malignant origin such as endothelial cells, lymphocytes, red blood cells and granulocytes has been unsuccessful. In addition, a limited number of epithelial tumors were tested and were also found to be negative. In a typical procedure, K562 cell line cells were cultured in medium containing 0.5 µg/ml of the respective OT-hybrid for 48h at a cell density of $2x10^5$ cells / ml. After incubation, cells were washed once in phosphate buffered saline (PBS) with 0.25% fetal calf serum (FCS) and investigated via standard fluorescence microscopy. Membrane labelling of myeloid cells by **D7** or **L7** respectively occurred roughly after 24h of incubation. Orange light emitting particles seen in the cytoplasm already after 30 min of incubation demonstrated that both hybrids were taken up by endocytosis. After 24-48h, a homogenous green fluorescence of the surface and intracellular membranes was observed. Remnants of the phagocytozed and not (yet) membrane integrated OT-hybrids were still visible (arrows in Fig. 3a, b). Cells incubated with the D-(+)-mannosidic hybrid **D7** (Fig. 3a) and as well as with the L-(-)-mannosidic **L7** (Fig. 3b) revealed an intense green emissive staining ($\lambda_{max\ em}$ = 515 nm - 535 nm) of the plasma membrane. The membrane staining was attributed to hydrophobic interactions between the fluorescent OT-backbone and the lipid termini of the phospholipids of the plasma membrane. The time required for plasma membrane labelling of the L-(-)- mannosidic OT-hybrid **L7** was longer than for the D-(+)-mannosidic OT-hybrid **D7**, thus we concluded positive interaction of the latter one with the D-(+)-mannosidic scavenger receptors of these myeloid cells. Cell viability assays such as trypan blue exclusion and ^{51}chromium release assays (see SI, Table 1) evidenced that neither **D7** nor **L7** affected the cell viability at 10^{-6} – 10^{-8} M concentrations.

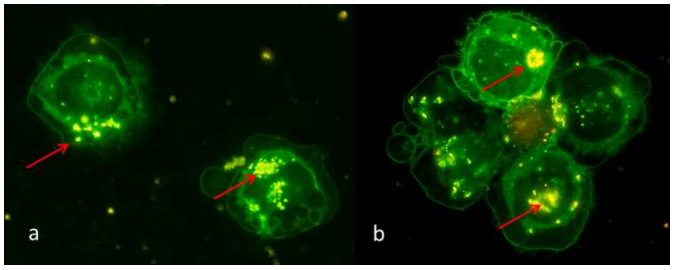


Fig. 3 Standard fluorescence microscopy images of endosomes of myeloid cell line K562 labelled a) with **D7** and b) with **L7**. In addition to unmodified OT particles in the center of the cytoplasm, a strong green emissive staining of the plasma membrane and cytoplasmic vesicles can be observed for both, **D7** as well as **L7** labelled cells.

In conclusion, we report the synthesis and comprehensive photophysical characterization of first non-symmetrical D-(+)- and L-(-)-mannose-functionalized OT-hybrids. Under aqueous conditions, the mannosidic OT-hybrids were observed to self-organize into helical arranged π-stacking suprastructures, indicating potential as drug delivery carriers. The observed high sensitivity of the OT-hybrids to the lipid composition of biomembranes enables for their application as efficient optical membrane probes. Unique labelling of surface as well as intracellular membranes of myeloid cells possibly due to their high endocytic function has been documented. Thus, the developed OT-hybrids are potential candidates for labelling of the myeloid cell lineage in leukemic isolates.

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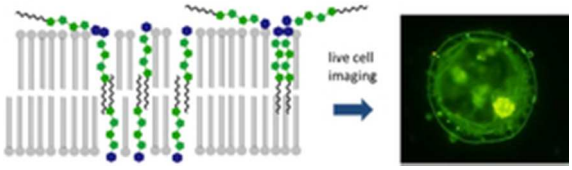

Self-assembling D-(+) and L-(-) mannose-functionalized oligothiophene hybrids were synthesized via Sonogashira cross-coupling reaction. The hybrids are taken up into live myeloid cells and offer an ideal platform for imaging of artificial and cellular membranes.
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