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Increasingly twisted push–pull oligothiophenes and their planarization in confined space†

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A series of systematically deplanarized push–pull oligothiophenes is designed and synthesized to determine the perfect twist for maximal spectroscopic response to their planarization within lipid bilayer membranes. Weak deplanarization naturally gives weak shifts, but strong deplanarization also gives weak shifts because planarization becomes impossible. Intermediate deplanarization turns out to be ideal. The shifts found in response to chromophore planarization are not as dramatic as with lobsters during cooking but sufficient to discriminate solid-ordered and liquid-disordered membranes with the naked eye.

Introduction

In nature, the combination of chromophore planarization and polarization occurs in processes ranging from the chemistry of vision to the pigmentation of lobsters.[1] Increased conjugation and thus improved communication between the polarizing groups are responsible for a dramatic red shift upon flattening of these chromophores. With fluorescent probes, the same coupled process is poorly explored,[1,2] although fluorophore planarization[3] and polarization[4] as isolated phenomena have received extensive attention, and the twisting of the push–pull fluorophore in the excited state is known in the context of molecular rotors.[5] Recently, we have introduced the [111]-trimethyl-quaterthiophene **1** as a planarizable push–pull probe (Fig. 1).[1] Decreasing the fluidity of lipid bilayer membranes caused bathochromic shifts in the excitation but not the emission spectra, suggesting that [111]-probe **1** can be planarized in the ground state but is already planar in the excited state. Here, we report that [201]-trimethyl-quaterthiophene **2** gives highly twisted probes that can be planarized in both ground and excited states, whereas [221]-pentamethyl-quaterthiophene **3** is already too twisted for planarization in confined space.

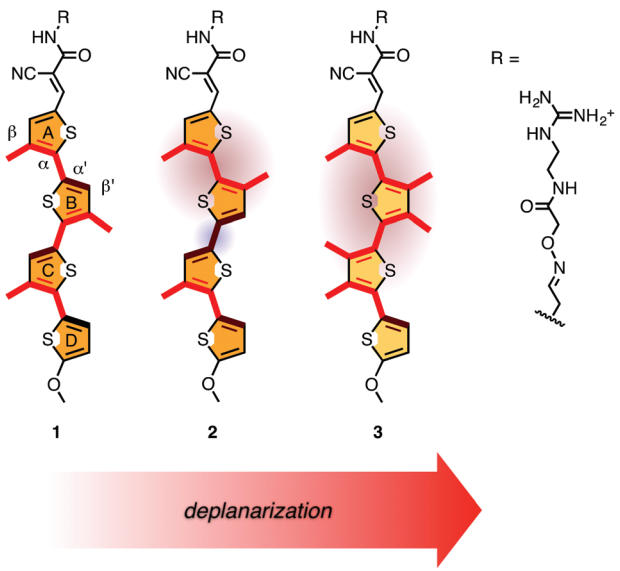

Fig. 1 Systematic deplanarization of the original [111]-oligothiophene amphiphile **1** leads to [201]-probe **2** and [221]-**3**. Numbers in brackets indicate the number of methyl groups on β,β′-positions of each thiophene–thiophene bond.

Results and discussion

In [111]-trimethyl-quaterthiophene **1**, the push–pull system is created with a methoxy donor and a cyano acceptor, and partial chromophore deplanarization is achieved with one methyl group in β-position per α,α′-ring junction.[1] The probe further contains a positive charge, attached *in situ* by oxime formation, to ensure its delivery to and orientation in lipid bilayer membranes. To systematically increase the twist of the oligothiophene scaffold, we first envisioned probe **2**, the [201]-regioisomer of probe **1** with two proximal methyl substituents to cause a strong twist between rings A and B. The [221]-pentamethyl-quaterthiophene **3** with A–B and B–C twists was considered next to achieve full deplanarization.

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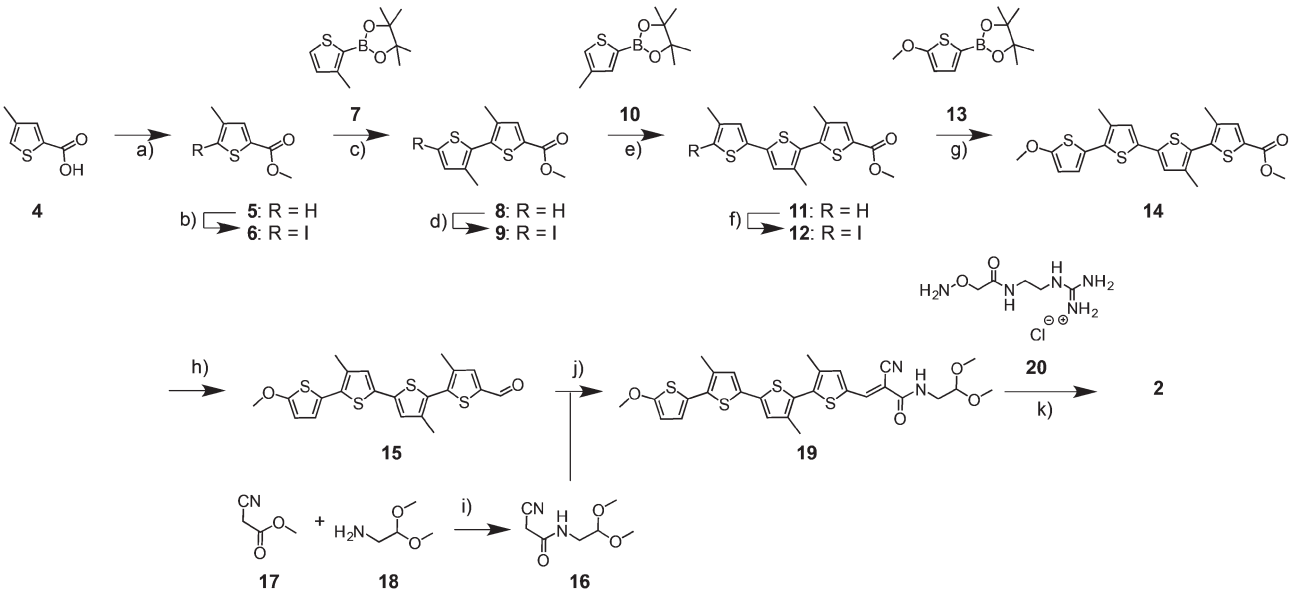

Scheme 1 Reagents and conditions: (a) MeOH, H_2SO_4, μW, 100 °C, 15 min, 71%; (b) NIS, $CHCl_3$, AcOH, rt, 16 h, 73%; (c) $Pd(PPh_3)_4$, CsF, DMF, 80 °C, 16 h, 77%; (d) NIS, $CHCl_3$, AcOH, rt, 16 h, 51%; (e) $Pd(PPh_3)_4$, CsF, DMF, 80 °C, 16 h, 74%; (f) NIS, $CHCl_3$, AcOH, rt, 16 h, quantitative; (g) $Pd(PPh_3)_4$, CsF, DMF, 80 °C, 16 h, 71%; (h) 1. DIBAL, CH_2Cl_2, −78 °C, 2. DMP, CH_2Cl_2, rt, 20 min, 57%; (i) neat, rt, 48 h, 92%; (j) piperidine, MeCN, 70 °C, 3 h, 82%; (k) 1. TsOH·H_2O, CH_2Cl_2, rt, 10 min, 55%, 2. DMSO, 60 °C, 10 min, 80%.

The new oligothiophenes were synthesized in strict analogy to the previously reported probes.[1,6] In brief, the carboxylic acid **4** was subjected to esterification under microwave conditions, and the resulting methyl ester **5** was regioselectively iodinated in the α-position with *N*-iodosuccinimide (NIS) (Scheme 1). Suzuki–Miyaura cross-coupling between the iodinated thiophene **6** with boronate ester **7** yielded the twisted bithiophene **8**. Iodination with NIS gave the halide compound **9** for Suzuki–Miyaura cross-coupling with the regioisomeric boronic ester **10**. The obtained terthiophene **11** was regioselectively iodinated, and the resulting product **12**[6] was subjected to Suzuki–Miyaura cross-coupling with the donor terminus **13**. The ester group of the quaterthiophene **14** was reduced to the corresponding primary alcohol, which was then oxidized under mild conditions with Dess–Martin periodinane (DMP) to afford aldehyde **15**. The strong cyano acceptor terminus was installed by Knoevenagel condensation with the cyanoamide **16**, which was readily accessible from ester **17** and amine **18**. Deprotection of acetal **19** followed by covalent capture of the guanidinium moiety **20** gave amphiphile **2**. The preparation of amphiphiles *in situ* by oxime or hydrazone formation has been introduced recently to secure synthetic access to membrane-based differential odorant sensors, biosensors, fluorescent membrane probes and siRNA transfection agents.[1,7] This dynamic covalent approach is important because the resulting amphiphiles are often problematic to purify and characterize due to self-assembly into micelles and reversed micelles in most solvents at already relatively low concentrations. Nevertheless, oxime **2** has been purified and characterized by RP-HPLC, ^1H and ^{13}C NMR spectroscopy, and ESI-MS (Fig. S4†). The same synthetic route was followed to prepare the fully twisted probe **3** (Fig. S5†).

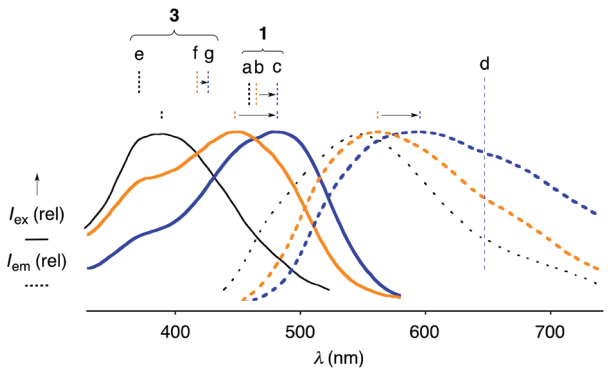

Fig. 2 Excitation (solid) and emission spectra (dashed) of **2** in DMF (black) and DPPC LUVs at 55 °C (gold) and 25 °C (blue), with an indication of excitation (a–c and e–g) and emission maxima (d) of **1** (a–d) and **3** (e–g) in DPPC LUVs at 55 °C (b, d and f) and 25 °C (c,d and g), and in DMF (a and e).

In the excitation spectra in DMF, the intermediately twisted [201]-isomer **2** showed a maximum at $\lambda_{ex} \sim 390$ nm (Fig. 2, black, solid; Table 1). This was $\Delta\lambda_{ex} = -71$ nm blue-shifted from the weakly twisted [111]-probe **1** at $\lambda_{ex} = 461$ nm (Table 1). The strongly twisted [221]-oligothiophene **3** shifted further to $\lambda_{ex} = 371$ nm ($\Delta\lambda_{ex} = -90$ nm, Fig. S1,† black, solid; Table 1). Increasing deplanarization in the ground state was thus correctly reflected in the increasing blue shifts of the excitation maxima.

In comparison to the original maximum of [111]-probe **1**, the emission maxima of both [201]-probe **2** and [221]-probe **3** were blue shifted by $\Delta\lambda_{em} \sim -165$ nm to $\lambda_{em} \sim 570$ nm (Fig. 2, black, dotted, Table 1). This result demonstrated that strongly deplanarized push–pull probes remain twisted also in the excited state. This finding was very important because it

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Table 1 Excitation and emission data in DMF[a]

Cpd[b]	λ_{ex} [c] (nm)	$\Delta\lambda_{ex}$ [d] (nm)	λ_{em} [e] (nm)	$\Delta\lambda_{em}$ [f] (nm)
1[g]	461	—	736	—
2	390	−71	569	−167
3	371	−90	572	−164

[a] Compare Fig. 2, S1, measured at 25 °C. [b] Compounds, see Fig. 1. [c] Excitation maximum, in wavelength (in nanometers). [d] Shift of the excitation maximum compared to **1**. [e] Emission maximum. [f] Shift of the emission maximum compared to **1**. [g] Data from ref. 1.

Table 2 Excitation and emission data in DPPC LUVs[a]

Cpd[b]	λ_{ex} [c] (nm) 55 °C	λ_{ex} [d] (nm) 25 °C	$\Delta\lambda_{ex}$ [e] (nm)	λ_{em} [f] (nm) 55 °C	λ_{em} [g] (nm) 25 °C	$\Delta\lambda_{em}$ [h] (nm)
1[i]	467	487	+20	650	650	0
2	449	483	+34	562	600	+38
3	413	423	+10	590	582	−8

[a] Compare Fig. 2, S1, DPPC = dipalmitoyl phosphatidylcholine, LUVs = large unilamellar vesicles. [b] Compounds, see Fig. 1. [c] Excitation maximum at 55 °C, in wavelength (in nanometers). [d] Excitation maximum at 25 °C. [e] Shift of excitation maximum upon cooling from 55 °C to 25 °C. [f] Emission maximum at 55 °C. [g] Emission maximum at 25 °C. [h] Shift of the emission maximum upon cooling from 55 °C to 25 °C. [i] Data from ref. 1.

suggested that the planarization of the new probes should be detectable not only in the excitation but also in the emission spectra.

The planarizability of push–pull probes **2** and **3** was tested in DPPC LUVs (large unilamellar vesicles composed of dipalmitoyl phosphatidylcholine). At room temperature, DPPC membranes are in solid-ordered (S_o) phase. At 41 °C, they undergo a phase transition to liquid-disordered (L_d) phase. Consistent with their planarization by a confining environment, the excitation spectrum of the weakly twisted [111]-probe **1** showed a red shift of +20 nm upon cooling from L_d to S_o DPPC LUVs (Fig. 2b and c; Table 2).[1] The emission maximum at 650 nm was insensitive to membrane fluidity because in the excited state, the fluorophore is already planar (Fig. 2d, Table 2).[1]

The excitation maximum of the intermediately twisted [201]-probe **2** in L_d DPPC LUVs was at λ_{ex} = 449 nm (Fig. 2, gold, solid; Table 2). The blue shift $\Delta\lambda_{ex}$ = −18 nm compared to the [111]-probe **1** demonstrated that [201]-probe **2** is more twisted in L_d phase. In S_o DPPC LUVs at 25 °C, the excitation maxima of both probes were at $\lambda_{ex} \sim 485$ nm. This suggested that the ground state of both probes is fully planarized in this highly confining solid-ordered environment. More ground-state twisting in L_d phase with identical planarization in S_o phase naturally meant that the [201]-probe **2** is more sensitive to L_d–S_o transition than the [111]-probe **1**. The bathochromic shift in response to pressure from the surrounding membrane increased from $\Delta\lambda_{ex}$ = +20 nm for **1** to $\Delta\lambda_{ex}$ = +34 nm for **2** (Table 2). Considering the experimental inaccuracy, it can be said that with optimized deplanarization, the sensitivity of the fluorescent membrane probes almost doubled (compare below for DOPC).

The emission maximum of probe **2** in L_d DPPC LUVs was at λ_{em} = 562 nm (Fig. 2, gold, dashed; Table 2). The strong hypsochromic shift of $\Delta\lambda_{em}$ = −88 nm compared to [111]-probe **1** suggested that the excited state of [201]-probe **2** remains partially twisted in L_d DPPC LUVs. Unlike the phase-insensitive emission of probe **1**, a bathochromic shift of $\Delta\lambda_{em}$ = +38 nm was observed with **2** in response to L_d–S_o transition of DPPC LUVs. These results suggested that also the excited state of [201]-probe **2** is deplanarized in L_d DPPC LUVs and provided corroborative evidence that the L_d–S_o transition can be sensed not only by ground-state but also by excited-state planarization.

The strongly twisted, weakly fluorescent [221]-probe **3** showed little difference in excitation and emission spectra in response to changes in membrane structure. The maximum in the excitation spectrum remained strongly blue-shifted compared to the maxima of probes **1** and **2**, suggesting that the ground state of the probe **3** is too twisted to be planarized in either L_d or S_o DPPC membranes (Fig. 2f and g, Table 2, Fig. S1†). The same is true for the excited state (Table 2, Fig. S1†).

Control experiments were performed in dioleoyl phosphatidylcholine (DOPC) LUVs. These membranes remain in L_d phase at 25 °C and at 55 °C. In DOPC LUVs at 55 °C, the fluorescence of the original [111]-probe **1** was almost the same as that in organic solvents or L_d DPPC LUVs and showed very little red shift upon cooling (λ_{ex} = 466 nm, $\Delta\lambda_{ex}$ = +2 nm, Table 3).[1] The excitation maximum of the hypersensitive [201]-probe **2** was at λ_{ex} = 436 nm under identical conditions, that is, $\Delta\lambda_{ex}$ = −30 nm compared to **1** and $\Delta\lambda_{ex}$ = −13 nm compared to **2** in L_d DPPC LUVs (Tables 2 and 3, Fig. S2†). These overall small shifts suggested that the ground state of **2** remains partially twisted also in "hot" DOPC LUVs.

The $\Delta\lambda_{ex}$ = +10 nm found upon cooling placed the excitation of **2** in "cold" DOPC LUVs together with that in L_d DPPC LUVs. This small shift could originate from partial ground-state planarization, although thermochromic effects cannot be excluded. In any case, the overall hypsochromic position and

Table 3 Excitation and emission data in DOPC LUVs[a]

Cpd[b]	λ_{ex} [c] (nm) 55 °C	λ_{ex} [d] (nm) 25 °C	$\Delta\lambda_{ex}$ [e] (nm)	λ_{em} [f] (nm) 55 °C	λ_{em} [g] (nm) 25 °C	$\Delta\lambda_{em}$ [h] (nm)
1[i]	466	468	+2	650	650	0
2	436	446	+10	557	557	0
3	367	367	0	607	595	−12

[a] Compare Fig. S2 and S3, DOPC = dioleoyl phosphatidylcholine, LUVs = large unilamellar vesicles. [b] Compounds, see Fig. 1. [c] Excitation maximum at 55 °C, in wavelength (in nanometers). [d] Excitation maximum at 25 °C. [e] Shift of excitation maximum upon cooling from 55 °C to 25 °C. [f] Emission maximum at 55 °C. [g] Emission maximum at 25 °C. [h] Shift of the emission maximum upon cooling from 55 °C to 25 °C. [i] Data from ref. 1.

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poor sensitivity of the excitation spectrum of **2** in DOPC LUVs provided excellent general support that the large $\Delta\lambda_{ex}$ = +34 nm found for L_d–S_o transition in DPPC LUVs originates indeed from planarization of **2** in the ground state. Comparison of DOPC-LUV and DPPC-LUV samples at 25 °C demonstrated that the $\Delta\lambda_{ex}$ = +37 nm for planarization of [201]-probe **2** in S_o lipid bilayer membranes is sufficient to be seen with the "naked eye" (compare TOC graphic). This colorimetric detection of the nature of lipid bilayer membranes with the naked eye was not observed with the poorly twisted original [111]-probe **1**[1] and is thus unique for the almost perfect twist in the new [201]-probe **2**.

The sensitivity of the best probe **2** to liquid-ordered (L_o) phase was explored in the biologically relevant SM–CL LUVs (SM: sphingomyelin, CL: cholesterol; SM–CL = 3 : 1). Excitation was found at λ_{ex} = 488 nm, which is slightly red-shifted from that in S_o DPPC LUVs ($\Delta\lambda_{ex}$ = +5 nm, Fig. 3, blue, solid). The same trend was observed for emission, which maximized at λ_{em} = 619 nm ($\Delta\lambda_{em}$ = +19 nm, Fig. 3, blue, dotted). This suggested that further planarization of probe **2** might occur in L_o phase in both ground and excited states compared to that in S_o phase, although the effect is rather small.

Fluorescent properties of probe **2** were also measured in DOPC–SM–CL LUVs under conditions where L_o and L_d phases coexist in the same vesicle (DOPC–SM–CL = 1 : 1 : 1). The excitation maxima moved to λ_{ex} = 466 nm, which is nearly halfway between excitation in pure L_o and L_d phases (Fig. 3, grey, solid). This finding suggested that probe **2** partitions into both phases and can, in principle, report their coexistence in heterogeneous vesicles simultaneously. The emission in DOPC–SM–CL LUVs was roughly the same as in L_o phase (Fig. 3, grey, dashed). This difference in the behavior of the excitation spectra could possibly be explained by fluorescence resonance energy transfer from the twisted fluorophore in L_d to the flattened fluorophore in L_o phase.

Conclusions

In summary, ground- and excited-state planarization of intermediately twisted push–pull oligothiophenes in L_o, S_o, but not L_d lipid bilayer membranes causes significant red shifts in both excitation and emission spectra. With the best planarizable push–pull probe, L_d and S_o membranes can be discriminated with the naked eye (although the shifts are not yet as spectacular as the ones observed when cooking lobsters). In sharp contrast, highly twisted push–pull oligothiophenes resist planarization under the same conditions. These results provide systematic insights into the deplanarization of oligothiophenes as well as a solid basis for further fine-tuning and applications towards the sensing of more demanding, biologically relevant characteristics such as membrane tension.

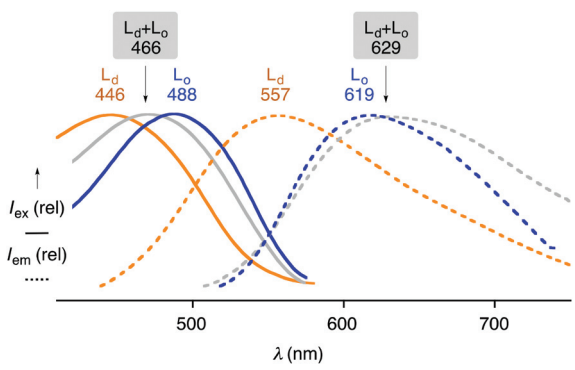

Fig. 3 Excitation (solid) and emission spectra (dashed) of **2** in DOPC (gold), SM–CL (blue), and DOPC–SM–CL LUVs (grey) at 25 °C (blue). Maxima are indicated in nanometers.

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