

Planarizable push–pull oligothiophenes: in search of the perfect twist†

Cite this: *Chem. Sci.*, 2014, 5, 2819

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The concept to couple fluorophore planarization and fluorophore polarization for the construction of innovative fluorescent membrane probes is elaborated comprehensively in the context of oligothiophenes. Increasing length with different degree of twist from ter- to quinquethiophenes results in increasing extinction coefficients, decreasing quantum yields and relatively minor red shifts. Quaterthiophenes show maximal Stokes shifts and are thus preserved to further elaborate on deplanarization. Increasing quaterthiophene deplanarization results in increasing blue shifts and decreasing quantum yields in solution, whereas planarization in solid-ordered lipid bilayer membranes gives the respective red shifts with fluorescence recovery. An extensive screening reveals that intermediate global deplanarization with strong individual twists near the membrane interface are best. Weaker and stronger global twisting and strong individual twists deeper in the membrane are less convincing because planarization becomes either too easy or too difficult. The best probe reports decreasing membrane fluidity with a red shift of 44 nm and a fluorescence increase of almost 500%. These insights are important because they cover significant chemical space to help improving our understanding of chromophore twisting and promise bright perspectives with regard to biological applications and refined probe design.

Received 31st March 2014

Accepted 1st May 2014

DOI: 10.1039/c4sc00939h

www.rsc.org/chemicalscience

Introduction

For the design of fluorescent probes, the combination of fluorophore planarization and polarization has been largely ignored.¹ This is surprising because this coupled mechanism is abundant in nature² and could be of interest to image membrane environments^{3–5} including membrane tension, and also membrane potentials at maximal temporal resolution.⁴ The expectation is that twisted push–pull fluorophores could be planarized either by lateral forces, *e.g.*, lateral pressure in lipid bilayer membranes, or by axial forces, *e.g.*, dipole–potential interactions in polarized membranes.^{4,6} Taking place in the ground state, this planarization of twisted push–pull probes is reported by the shift in the absorption and excitation maxima.^{1,2} This is different from molecular rotors and planar push–pull chromophores that report the viscosity and the polarity of their environment by changes in quantum yield and emission, respectively.⁵

Oligothiophenes^{7–9} were initially selected to elaborate on the concept of planarizable push–pull probes because their polarization⁸ and their planarization⁹ are well explored as isolated

phenomena, and their synthesis is very well established. In quaterthiophenes **1–3**, methoxy groups serve as donors and cyanovinyl groups as powerful acceptors (Fig. 1). The choice of these donors and acceptors are the result of a systematic evaluation, better donors such as alkylamines are not applicable because of the onset of oligothiophene oxidation at the donor

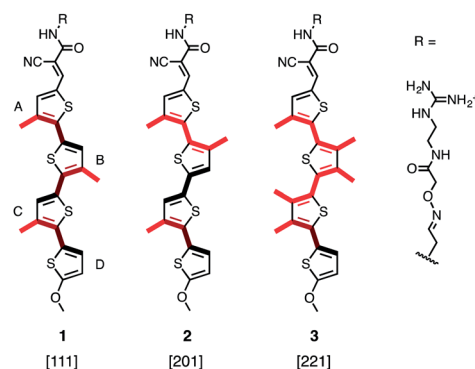


Fig. 1 The original triad of planarizable push–pull probes with a weak [111]-twist in quaterthiophene **1**, an intermediate [201]-twist in quaterthiophene **2** and a strong [221]-twist in quaterthiophene **3**. The numbers in brackets [abc] indicate the number of methyl groups next to thiophene–thiophene bonds A–B, B–C and C–D. With intermediate [201]-twist, decreasing membrane fluidity is reported as red shift of up to 34 nm, sufficient for detection with the naked eye.

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† Electronic supplementary information (ESI) available: Detailed procedures and results for all reported experiments. See DOI: 10.1039/c4sc00939h



side. All quaterthiophenes are also equipped with a guanidinium cation to assure delivery to the bilayer, directional partitioning into the bilayer and the potential of ligand-directed assembly and cellular uptake with polyanions such as DNA or RNA.¹⁰ These cations are introduced by oxime formation *in situ* to minimize synthetic work with troublesome amphiphiles.^{1,10}

In quaterthiophenes 1–3, methyl substituents are placed along the scaffold to gradually increase the twist of the push-pull probes. In the original quaterthiophene 1, one methyl group next to each thiophene–thiophene bond causes a weak and regular deplanarization of the entire scaffold. This twist is referred to as [111], indicating the presence of one methyl group each next to the bonds connecting ring A and B, ring B and C, and ring C and D. In the constitutional [201]-isomer 2, two methyl groups next to the bond connecting ring A and B twist the chromophore a bit more. The [221]-pentamethyl-quaterthiophene 3 with two methyl groups next to the bonds connecting ring A and B and the ring B and C is most strongly deplanarized. In solution, increasing deplanarization in quaterthiophenes 1–3 is reflected in increasing blue shifts of absorption maxima as expected. In solid-ordered (So) lipid bilayer membranes, the excitation maximum of the intermediately twisted quaterthiophene 2 shifted by $\Delta\lambda_{\text{ex}} = +34$ nm to the red compared to the same probe in liquid-disordered (Ld) membranes. Weaker and stronger twists in quaterthiophene 1 and 3 gave less significant red shifts because planarization is either too easy or too difficult. The red shift in response to the planarization of the intermediately twisted quaterthiophene 2 was already sufficient to discriminate Ld and So membranes with the naked eye.^{1c}

These results suggested that further improvements in this series could be achieved either by finetuning of the twists around quaterthiophene 2 or with shorter or longer oligomers. In this report, we first compare twisted push-pull oligothiophenes of different length and then fully cover the chemical space around intermediately twisted quaterthiophene to identify the optimal twist with highest possible precision.

Results and discussion

To explore the dependence of planarizable push-pull probes on their length, the [111]-series around the original quaterthiophene 1 was completed with terthiophene 4 and quinquethiophene 5 (Fig. 2). Their synthesis – accomplished from the acceptor terminus by repeated Suzuki coupling of thiophene monomers to the iodinated oligomers – followed the protocols developed for 2 and 3 and is thus not further noteworthy.^{1c} Their planarization in So membranes was assessed in large unilamellar vesicles (LUVs) composed of 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylcholine (DPPC). These vesicles form So membranes at room temperature that undergo phase transition into liquid disordered (Ld) membranes at 41 °C.

In DPPC LUVs at 55 °C, *i.e.*, in Ld membranes, the excitation maximum of the shortened [11]-terthiophene 4 was $\Delta\lambda_{\text{ex}} = -14$ nm blue-shifted compared to the original [111]-quaterthiophene 1 at $\lambda_{\text{ex}} = 467$ nm (Table 1, entries 1 and 2). The elongated [1111]-quinquethiophene 5 did not absorb at longer wavelength

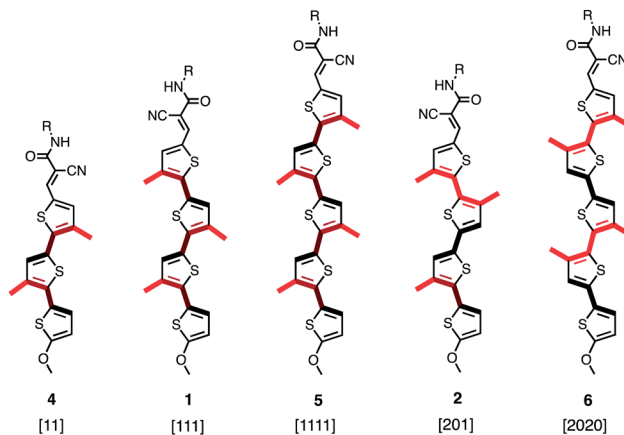


Fig. 2 Planarizable push-pull oligothiophenes with different length (R shown in Fig. 1).

(Table 1, entries 2 and 3). Cooled down into So membranes, the excitation maximum of [11]-terthiophene 4, [111]-quaterthiophene 1 and [1111]-quinquethiophene 5 shifted all by $\Delta\lambda_{\text{ex}} \sim +20$ nm to the red (Table 1). These shifts were consistent with planarization of the weakly twisted fluorophores in the confined space within So membranes. Similar shifts were not observed in 1,2-dioleoyl-*sn*-glycero-3-phosphatidylcholine (DOPC) LUVs which are in Ld phase at 25–55 °C.

In Ld DPPC, increasing twist with quaterthiophenes blue shifted the $\lambda_{\text{ex}} = 467$ nm for [111]-1 by -18 nm to $\lambda_{\text{ex}} = 449$ nm for [201]-2 (Table 1). Correspondingly, red shift upon planarization in So DPPC increased from $\Delta\lambda_{\text{ex}} = +20$ nm for [111]-1 to $\Delta\lambda_{\text{ex}} = +34$ nm for [201]-2 (Table 1). Intermediately twisted quinquethiophene [2020]-2 gave roughly the same red shift of $\Delta\lambda_{\text{ex}} = +30$ nm in response to Ld to So transition (Table 1). Independent of their twist, the red shift for planarization of push-pull oligothiophenes was thus roughly independent on their length.

This finding was interesting because other chemical and physical properties showed strong length dependence. Most importantly, sensitivity toward oxidation increased significantly with length and twist. Whereas the stability of quaterthiophenes was still unproblematic, [1111]-quinquethiophenes 5 and particularly the more twisted [2020]-isomers 6 were oxidized within hours without precaution. This is understandable considering that HOMO energy levels of oligothiophenes increase with length and increasing twists further accumulate electron density near the donor terminus.

In chloroform, extinction coefficients of the absorption maxima increased with increasing length (Table 2). Quantum yields decreased complementarily from $\Phi = 63\%$ for [11]-terthiophene 4 to $\Phi = 46\%$ for [111]-quaterthiophene 1 and $\Phi = 11\%$ for [1111]-quinquethiophene 5. This decrease can be attributed to increasing rotational quenching with increasing number of twistable bonds (Table 2). Quantum yields in chloroform also decreased with increasing twist from $\Phi = 46\%$ for weak [111]-twists in 1 to $\Phi = 20\%$ for intermediate [201]-twists in 2 and $\Phi = 9\%$ for strong [221]-twists in 3 (Table 2). Decreasing quantum yield with increasing twist was meaningful



Table 1 Spectroscopic data in DPPC LUVs^a

Entry	Cpd ^b	Twist ^c	λ_{ex}^d (nm) 55 °C	λ_{ex}^e (nm) 25 °C	$\Delta\lambda_{\text{ex}}^f$ (nm)	λ_{em}^g (nm) 55 °C	λ_{em}^h (nm) 25 °C
1	4	[11]	453	472	+19	624	624
2 ⁱ	1	[111]	467	487	+20	650	650
3	5	[1111]	468	487	+19	621	619
4 ^j	2	[201]	449	483	+34	562	600
5	6	[2020]	465	495	+30	600	610

^a DPPC = 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylcholine, LUVs = large unilamellar vesicles. ^b Compounds, see Fig. 2. ^c [*abcd*] = number of methyl groups next to thiophene–thiophene bonds A–B, B–C, C–D and D–E. ^d Excitation maximum at 55 °C, in wavelength (in nanometers). ^e Excitation maximum at 25 °C. ^f Shift of excitation maximum upon cooling from 55 °C to 25 °C. ^g Emission maximum at 55 °C. ^h Emission maximum at 25 °C. ⁱ Data from ref. 1a. ^j Data from ref. 1c.

Table 2 Spectroscopic data in CHCl₃^a

Entry	Cpd ^b	Twist ^c	λ_{abs}^d (nm)	ϵ^e (mM ⁻¹ cm ⁻¹)	Φ^f (%)
1	4	[11]	463	14.7	63
2	1	[111]	461	19.9	46
3	5	[1111]	481	22.9	11
4	2	[201]	409	17.1	20
5	3	[221]	375	12.2	9

^a Measured at 25 °C. ^b Compounds, see Fig. 1 and 2. ^c [*abcd*] = number of methyl groups next to thiophene–thiophene bonds A–B, B–C, C–D and D–E. ^d Absorption maximum. ^e Extinction coefficient. ^f Fluorescence quantum yields measured in comparison to rhodamine G6 as standard.

because out of conjugation, thiophene monomers are not fluorescent. The planarization of twisted push–pull oligothiophenes will thus occur not only with a red shift but also with an increase in quantum yield, *i.e.*, fluorescence recovery.

The emission spectra of push–pull oligothiophenes showed strong solvatochromism, whereas the excitation spectra were essentially independent of the polarity of the solvent.^{†1} This is not surprising because solvatochromism of push–pull systems originates from the stabilization of the “charge-separated” excited state after intramolecular charge transfer (ICT) by polar solvents, thus shifting the emission to longer wavelength.^{3,8,11} Similar emission of probes 1–6 in So and Ld membranes demonstrated that the red-shifted excitation spectra in So membranes are not due to drastic polarity changes in their environment (*e.g.*, probe ejection from the membrane, Table 1). The length dependence of the solvatochromism of twisted push–pull oligothiophenes was not linear (Fig. 3). In a series of hydrophobic derivatives with a methyl ester in place of the cyanovinyl acceptor, the largest Stokes shifts up to 174 nm were found for the derivative of [111]-quaterthiophene 1 in DMSO. According to Lippert analysis,¹ this calculated to a transition dipole moment of $\Delta\mu = 16.1$ D. Smaller transition dipole moments were found for both the shorter derivative of [11]-terthiophene 4 with $\Delta\mu = 10.6$ D and the longer derivative of [1111]-quinquethiophene 5 with $\Delta\mu = 12.0$ D. In agreement with results from other push–pull systems, this suggested that $\Delta\mu$ increases from ter- to quaterthiophenes because of the increased π conjugation length, whereas $\Delta\mu$ decreases from quater- to quinquethiophene because of the distance between

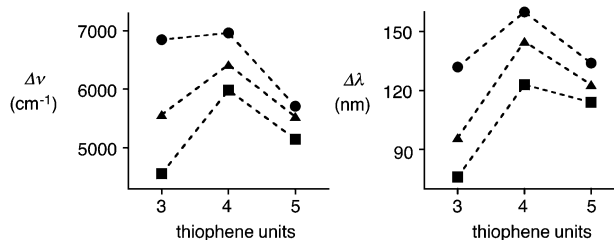


Fig. 3 Dependence of Stokes shifts $\Delta\nu$ (left) or $\Delta\lambda$ (right) on chromophore length (number of thiophene units) determined from absorption and emission maxima in acetone (●), diethyl ether (▲) and hexane (■) for derivatives of [11]-terthiophene 4, [111]-quaterthiophene 1 and [1111]-quinquethiophene 5 with a methyl ester in place of the cyanovinyl acceptor.

donor and acceptor is becoming too large for ICT. This non-linear length dependence of the solvatochromism thus provided the decisive argument in favor of twisting studies on the quaterthiophene level.

The knowledge that the twist of [111]-quaterthiophene 1 is insufficient and that of [221]-quaterthiophene 3 is too strong for planarization in lipid bilayer membranes suggested that the optimal twist should be found between these two dysfunctional extremes. To cover this intriguing chemical space comprehensively, *i.e.*, the full “twistome,” we prepared quaterthiophenes 7–14 (Fig. 4). Their synthesis, a significant effort, followed the protocols developed for 2 and 3.^{†1c}

The deplanarization of quaterthiophenes 7–14 was assessed in MeOH. The absorption maxima of all [2XX]-probes, *i.e.*, 8, 9, 11, 12 and 14, clustered at $\lambda_{\text{abs}} = 364 \pm 6$ nm (Table 3). This blue-shifted absorption was consistent with significant twisting. The red-shifted $\lambda_{\text{abs}} = 456$ nm of [111]-probe 7 confirmed that the only one methyl group per thiophene–thiophene junction does not cause significant deplanarization (Table 3, entry 1). The similarly red-shifted $\lambda_{\text{abs}} = 438$ nm of the [X2X]-probes 10 and 13 suggested that the twisting of dimethylated thiophene–thiophene junctions far from the cyanovinyl acceptors is either spectroscopically less influential or occurs to a lesser extent. The latter explanation, that is reduced twisting of [X2X]-probes compared to [2XX]-probes, was meaningful considering that the electron density of the partially conjugated thiophene–thiophene junctions increases with increasing distance from the acceptor.



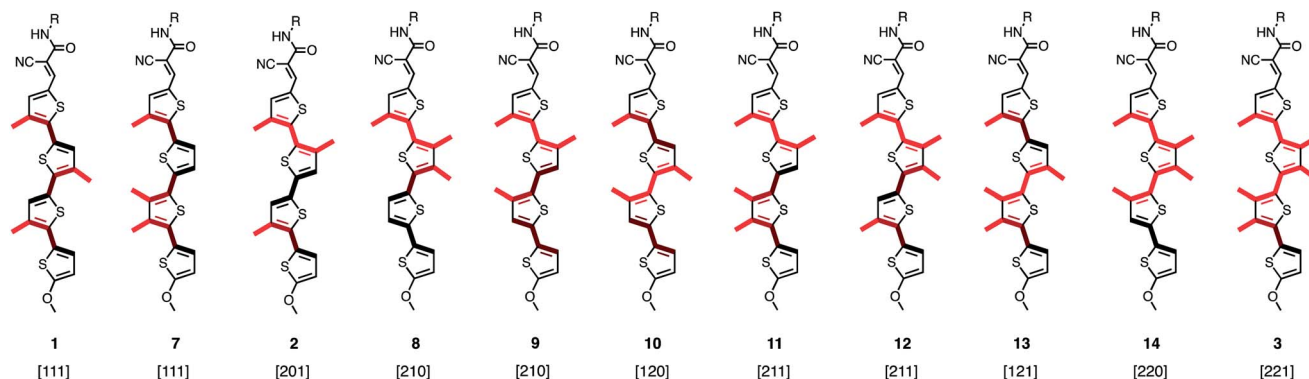


Fig. 4 Planarizable push-pull quaterthiophenes with different twist (R shown in Fig. 1).

Table 3 Excitation and emission data in solid-ordered DPPC and liquid-disordered DOPC membranes and absorption in MeOH^a

Entry	Cpd ^b	Substitution ^c	λ_{abs} (nm) MeOH ^d	λ_{ex} (nm) DPPC ^e	λ_{ex} (nm) DOPC ^f	$\Delta\lambda_{\text{ex}}^g$ (nm)	$\Delta F_{\text{ex}}/F_{\text{ex}}^h$ (%)	λ_{em} (nm) DPPC ⁱ	λ_{em} (nm) DOPC ^j	$\Delta\lambda_{\text{em}}^k$ (nm)
1	7	[111]	456	460	450	+10	50	550	570	-20
2	8	[210]	367	462	415	+47	89	550	545	+5
3	9	[210]	370	470	430	+40	183	560	550	+10
4	10	[120]	438	463	440	+23	176	555	555	0
5	11	[211]	362	465	440	+25	273	560	575	-15
6	12	[211]	362	460	416	+44	487	550	535	+15
7	13	[121]	438	440	435	+5	181	550	555	-5
8	14	[220]	358	410 ^l	366	+44 ^l	111	540	555	-15

^a Compare Fig. 5 and S1. All measurements were done at 25 °C. Sample addition to DPPC LUVs was at 50 °C, followed by slow cooling to 25 °C, DOPC = 1,2-dioleoyl-*sn*-glycero-3-phosphatidylcholine. ^b Compounds, see Fig. 4 for structures. ^c [abc] = number of methyl substituents next to thiophene-thiophene bonds connecting rings A-B (a), B-C (b) and C-D (c), compare Fig. 1. ^d Absorption maximum in MeOH. ^e Excitation maximum in DPPC LUVs. ^f Excitation maximum in DOPC LUVs. ^g Difference of excitation maxima in DPPC and DOPC LUVs. ^h Increase in excitation intensity in DPPC compared DOPC LUVs. ⁱ Emission maximum in DPPC LUVs. ^j Emission maximum in DOPC LUVs. ^k Difference of emission maxima in DPPC and DOPC LUVs. ^l Broadened maximum, see Fig. 5.

Very similar absorption maxima of the strongly twisted [21X]-isomers **8**, **9**, **11** and **12** in MeOH suggested that the influence of number and position of the methyl groups does not strongly affect the electronic properties of the chromophore in solution. For instance, the [211]-isomer **12** contains one methyl donor in a position where hyperconjugation strengthens the push-pull system, whereas three methyl donors are positioned to weaken the push-pull system by hyperconjugation. The constitutional [211]-isomer **11** contains two supportive and two opposing methyl donors. However, the absorption maxima of isomers **11** and **12** in MeOH were identical (Table 3, entries 5 and 6). About the same could be said for the [210]-isomers **8** and **9** (Table 3, entries 2 and 3).

The planarization of the “twistome” **7–14** in So and Ld membranes was assessed by comparing spectroscopic data in DPPC and DOPC LUVs at 25 °C to avoid possibly confusion with contributions from thermochromism. However, the probes were added to Ld membranes at 50 °C and then cooled down because direct partitioning into So membranes was very slow. Measurements in membranes were done at high dilution and thus limited to the more sensitive fluorescence spectroscopy, higher vesicle concentrations were not considered because of increasing interference from light scattering. Thus, quantum yields in So and Ld membranes could not be determined.

In Ld membranes, all excitation maxima were found between 415–450 nm (*i.e.* $\lambda_{\text{ex}} = 432 \pm 18$ nm) except for the strongly twisted [220]-probe **14** at $\lambda_{\text{ex}} = 366$ nm (Table 3, entry 8). Compared to their absorption maxima in MeOH, significantly red-shifted excitation maxima ($\Delta\lambda_{\text{ex}} = +48 \sim +78$ nm) in Ld membranes were found for [21X]-isomers **8**, **9**, **11** and **12**. The bathochromic $\lambda_{\text{ex}} = 430\text{--}440$ nm of the [21X]-isomers **9** and **11** (compared to their constitutional isomers **8** and **12** at $\lambda_{\text{ex}} = 415\text{--}416$ nm) suggested that an increasing number of methyl donors strengthening the push-pull system by hyperconjugation also increases the electron density in the strong A-B twist and thus facilitates partial planarization already in Ld membranes (Table 3, entries 3 and 5). In other words, methyl donors hyperconjugated into the push-pull system increase the mechano-sensitivity of twisted push-pull probes, a characteristic that is essential for the detection of weak spacial confinement as in Ld membranes.

The excitation maxima of [1XX]-probes **7**, **10** and **13** in Ld membranes at $\lambda_{\text{ex}} = 435\text{--}450$ nm were nearly identical with their red-shifted absorption in MeOH (Table 3, entries 1, 4 and 7). This poor responsiveness supported that [1XX]-probes are indeed already quite planar in MeOH, and that the twist



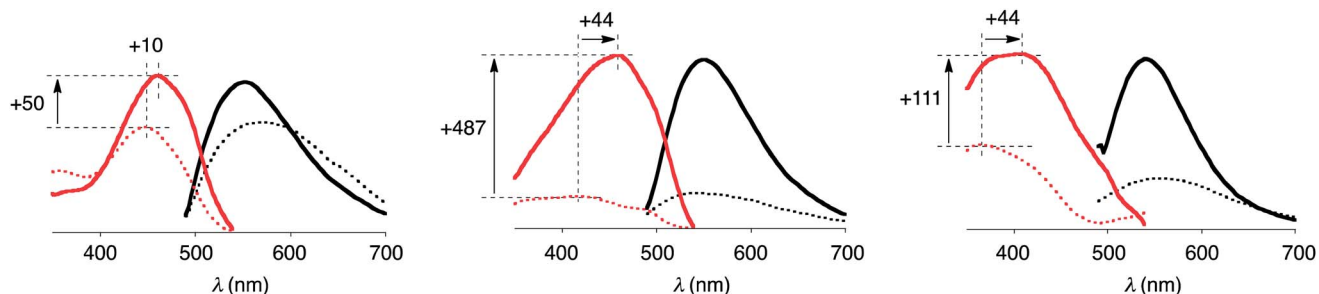


Fig. 5 Excitation (red) and emission spectra (black) of probes 7 (left), 12 (middle) and 14 (right) in DPPC (solid) and DOPC (dotted) LUVs at 25 °C, with red shift ($\Delta\lambda_{\text{ex}}$, in nm) and fluorescence recovery ($\Delta F_{\text{ex}}/F_{\text{ex}}$, in %) upon planarization (compare Table 3).

between ring A and B mostly determines their sensitivity to the environment.

In So membranes, the range of excitation maxima narrowed further to $\lambda_{\text{ex}} = 465 \pm 5$ nm except for the [121]-probe **13** at $\lambda_{\text{ex}} = 440$ nm and the most twisted [220]-probe **14** at $\lambda_{\text{ex}} = 410$ nm. Similarly, the emission maxima were mostly found between $\lambda_{\text{em}} = 550$ –560 nm. These results suggested that most of the probes adopt fully planar form in So membranes, and that these values are the excitation and emission maxima of fully planarized push-pull quaterthiophenes. The largest differences of the excitation maxima in Ld and So membranes are found with [210]-probe **8** and [211]-probe **12**, both with an [21X]-motif featuring only one methyl donor in support of the push-pull system (Table 3, entries 2 and 6). This finding implied that methyl donors hyperconjugated against the push-pull systems assure low mechanosensitivity because they keep the push-pull effect (macro-dipole, *etc.*) and the electron density at the strong A–B twist low and thus allow for planarization only in response to strong spacial confinement (*e.g.*, So membranes). This situation is complementary to high mechanosensitivity with methyl donors hyperconjugated into the push-pull system, thus increasing the push-pull effect including the electron density at the strong A–B twist, with planarization already in weak spacial confinement as the result (*e.g.*, **9** and **11** in Ld membranes). The $\Delta\lambda_{\text{ex}} = +44$ nm measured for the highly twisted [220]-isomer **14** was not considered as relevant because the excitation spectrum in So membranes is very broad (Table 3, entry 8, Fig. 5). Moreover, the maximum of [220]-probe **14** at $\lambda_{\text{ex}} = 410$ nm remains blue shifted compared to most other probes clustered at $\lambda_{\text{ex}} = 465 \pm 5$ nm in So membranes, fluorescence intensity was very weak and fluorescence recovery in So membranes with $\Delta F_{\text{ex}}/F_{\text{ex}} = 111\%$ comparably modest. All this indicated that the over-twisted [220]-isomer **14** is not fully planarizable in So membranes. The fluorescence recovery $\Delta F_{\text{ex}}/F_{\text{ex}}$ of the best [211]-probe **12** is near 500%, indicating that this excellent probe passes from nearly full deplanarization in Ld membranes to nearly complete planarization in So membranes (Table 3, entry 6 and Fig. 5). A quite remarkable $\Delta F_{\text{ex}}/F_{\text{ex}} = 273\%$ was also found for the second [211]-probe **11**, but the red shift of $\Delta\lambda_{\text{ex}} = +25$ nm was less convincing, presumably because of partial planarization in Ld membranes caused by a higher number of methyl substituents hyperconjugated into the push-pull system ($\lambda_{\text{ex}} = 440$ nm, Table 3, entry 5). The complementary [210]-

isomers **8** and **9** gave excellent red shifts ($\Delta\lambda_{\text{ex}} = +47 \sim +40$ nm), but the fluorescence recovery upon planarization in So membranes was not as significant as with the more twisted [211]-probes **11** and particularly **12** (Table 1, entries 2 and 3 vs. 5 and 6). The position of the methyl groups at various depth in the membrane and thus exposure to different lateral membrane pressure could further contribute to the observed characteristics, but these more complex effects are very difficult to specify.

Already approaching planarity in Ld membranes, the [1XX]-probes **7**, **10** and **13** naturally gave the weakest red shifts in So membranes. The best responsiveness in this group was found for [120]-probe **10** with $\Delta\lambda_{\text{ex}} = +23$ nm (Table 3, entry 4). The [121]-tetramethyl homolog **13** resisted further planarization in So membranes ($\Delta\lambda_{\text{ex}} = +5$ nm, Table 3, entry 7). The weakly deplanarized [111]-probe **7**, similar to the original probe **1**, gave very weak red shifts $\Delta\lambda_{\text{ex}} = +10$ nm and fluorescence recovery $\Delta F_{\text{ex}}/F_{\text{ex}} = 50\%$ (Table 1 and Fig. 5). The overall dramatic differences in fluorescence recovery in So membranes – from 50% for **7** to almost 500% for **12** – implied that reduced rotational quenching⁵ alone cannot explain the phenomenon and thus support key contributions from increasing conjugation of the push-pull system upon planarization. Although increased conjugation was expected to shift also the emission maxima to the red, comparably small changes were observed (Table 3). These results could be rationalized by the opposing blue shifts from solvatochromism in the less polar gel phase composed of saturated lipid.¹² Insensitivity of all significant trends in Ld and So membranes to probe dilution implied that probe aggregation does not occur under these conditions, *i.e.*, lipid-probe ratios > 10 : 1, usually 75 : 1, at probe concentrations <10 μM .

Conclusions

Comprehensive coverage of the “twistome” of the planarizable push-pull quaterthiophenes afforded a probe with the best degree of twist that reports planarization in confined space with a fluorescence recovery $\Delta F_{\text{ex}}/F_{\text{ex}} = 487\%$ and a red shift of $\Delta\lambda_{\text{ex}} = +44$ nm. This fine twisting was done with push-pull quaterthiophenes because they combine maximal excited state dipole moments with sufficient stability and acceptable quantum yields. The latter depend of course on the environment and should, considering $\Delta F_{\text{ex}}/F_{\text{ex}} = 487\%$, increase significantly upon planarization in confined space. [211]-Probes **12** and also



11 are currently being tested as the most promising candidates to sense membrane tension in model systems and cells. Future progress with planarizable push-pull probes is expected from the use of fluorescent monomers with high surface area for maximized mechanosensitivity.

Acknowledgements

We thank Normand Voyer (Laval University) for comments, the NMR and the Sciences Mass Spectrometry (SMS) platforms for their services, and the University of Geneva, the European Research Council (ERC Advanced Investigator), the National Centre of Competence in Research (NCCR) Chemical Biology and the Swiss NSF for financial support.

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