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Abstract

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Reference

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3,4-Ethylenedioxythiophene in planarizable push-pull oligothiophenes†

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We report design, synthesis and evaluation of a push-pull quaterthiophene amphiphiles containing one
5 3,4-ethylenedioxythiophene (EDOT) and a single strong twist in the scaffold. Planarizable push-pull
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15 The combination of chromophore planarization and polarization is of functional relevance in many
important biological processes. Examples reach from the chemistry of vision to lobster pigmentation.¹
We wondered whether or not the same strategy could be used to create conceptually innovative
fluorescent probes.² This question was important because the potential of combining planarization and
polarization in the ground state has not been explored so far with fluorescent probes.³

20 The deplanarization of push-pull fluorophores in the excited state has received much scientific
attention in the context of molecular rotors.⁴ Also, the isolate phenomena of chromophore polarization⁵⁻
9 and planarization¹⁰⁻¹² in the ground state are understood in detail for several fluorophores. For
oligothiophenes,^{5,6,9,10,12} push-pull systems of various length and with various donors and acceptors have
been reported.^{5,6} As other fluorophores, push-pull oligothiophenes are sensitive to the polarity of the

environment and exhibit an impressive solvatochromism. Realized applications of these properties include the detection of membrane potentials and of amyloid fibrils.

The deplanarization of oligothiophenes has been investigated in detail as well.^{10,11} Oligothiophenes are planar in the excited state, unsubstituted oligothiophenes are also planar in the ground state. The α, α' dihedral angle of oligothiophenes with a methyl group in β position is 21° from *anti* conformation in the gas phase and 0° in the crystal (Figure 1). The α, α' dihedral angle of oligothiophenes with methyl groups in β and β' position varies from 0° to 46° from *anti* conformation in the solid state.

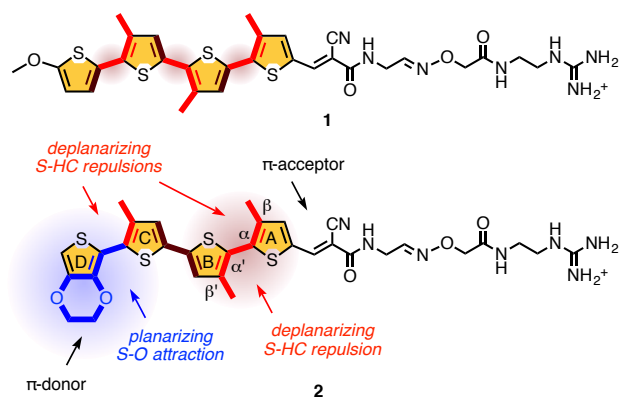


Fig. 1. Structure of planarizable push-pull probes. Compared to the original probe **1**, the new oligothiophene contains an EDOT unit as π -donor in ring D. To compete with the planarizing S-O interaction, a deplanarizing methyl group is placed in β position of ring C. The adjacent B-C dihedral angle without β methyls should be near 0° from *anti* conformation, whereas the following A-B twist with two S-HC repulsions should be large.

The 3,4-ethylenedioxythiophene (EDOT) unit is best known from PEDOT, the hole-transporting polymer that is widely used on organic solar cells.¹² When inserted as isolate units in oligothiophenes, EDOT units are co-planar with the adjacent thiophene rings. Their *anti* conformation is stabilized by close contacts between oxygen and sulfur atoms. Hindered rotational freedom due to this S-O attraction accounts a characteristic, partially resolved vibrational finestructure of their absorption and emission

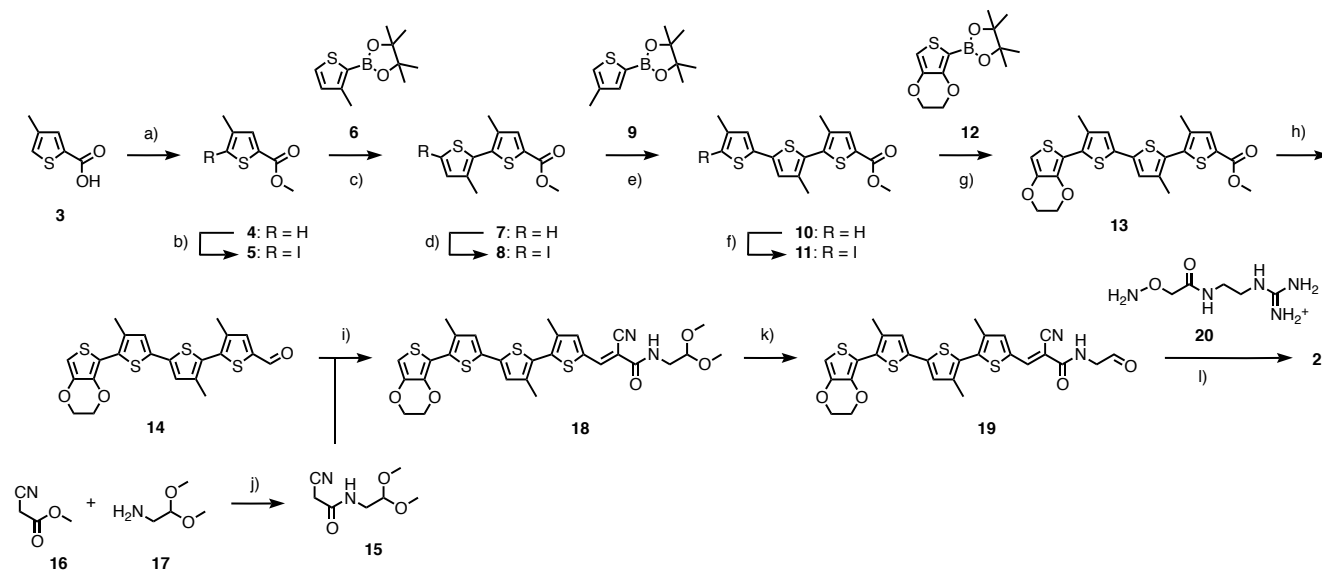
spectra.¹²

The conflicting combination of S-O attraction and S-HC repulsion from a repulsive β alkyl group has been used previously to maximize environmental sensitivity of polythiophenes.¹³ Particularly strong thermochromism has been reported. Other applications of this unique situation of conflicting interactions include the sensing of ions, nucleotides, oligonucleotides and polysaccharides.¹³

Last year, we introduced planarizable push-pull oligothiophenes such as **1** as fluorescent probes that sense membrane fluidity and potential with a new mode of action (Figure 1).² Current probes to sense membrane fluidity and heterogeneity operate by selective partitioning or sensitivity toward the polarity of the environment.⁹ Polarity-sensitive push-pull fluorophores work because more fluid membranes in liquid-disordered phase contain more water and are thus more polar. Classical probes to sense membrane potential are either electrochromic or solvatochromic, changing their environment by partitioning deeper into polarized membranes.⁵ More recent probes explore fluorescence resonance energy transfer (FRET) or photoinduced electron transfer (PET) to respond to membrane potentials in very elegant ways.⁷ Probes for membrane fluidity and heterogeneity are of interest to study rafts in biomembranes, probes for membrane potentials to image neural activity.^{5,7,9} There is much interest in developing conceptually innovative probes, particularly for the latter topic.⁷ Moreover, the mode of action of planarizable push-pull probes promises access to the detection of membrane tension, a phenomenon that is thought to be of high importance in biological transport but difficult to study because dedicated fluorescent probes are rare.¹⁴

Before considering any possible applications of planarizable push-pull probe **1** in biology, the conclusions made have to be validated and the so far modest effects have to be increased. For this purpose, the structure of oligothiophene **1** is currently modified with regard to length, twist and polarization. The objective with the new oligothiophene **2** was to explore the usefulness of a) the

conflicting S-O attraction and S-HC repulsion^{12,13} and b) a highly twisted α,α' dihedral angle with two repulsive methyl groups in β and β' position. We report that the inclusion of EDOT units weakens solvatochromism, adds thermochromism and introduces unique vibronic finestructure for the ratiometric sensing of membrane environments, including thermal phase transitions.



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Scheme 1. Synthesis of probe 2. a) MeOH, H₂SO₄, μ W, 100 °C, 15 min, 71%; b) NIS, CH₂Cl₂, AcOH, rt, 16 h, 73%; c) Pd(PPh₃)₄, CsF, DMF, 80 °C, 16 h, 77%; d) NIS, CH₂Cl₂, AcOH, rt, 16 h, 51%; e) Pd(PPh₃)₄, CsF, DMF, 80 °C, 16 h, 74%; f) NIS, CH₂Cl₂, AcOH, rt, 16 h, quantitative; g) Pd(PPh₃)₄, CsF, DMF, 80 °C, 16 h, 42%; h) 1. DIBAL, CH₂Cl₂, 2. MeOH, 3. MnO₂, CH₂Cl₂, 58% ; i) piperidine, MeCN, rt, 16 h, 80%; j) neat, rt, 48 h, 92%;¹⁶ k) TsOH · H₂O, CH₂Cl₂, 24%; l) AcOH, 16 h, 50%.

Results and Discussion

The scaffold of push-pull oligothiophene 1 has been synthesized from the donor terminus by repeated Suzuki couplings. This approach has been successful although the more electron-rich intermediates required attention to avoid oxidation. To overcome this problem, a revised synthetic strategy was

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developed for push-pull oligothiophene **2** (Scheme 1). Namely, the synthesis was executed from the acceptor rather than the donor terminus to avoid working with easily oxidizable intermediates. First, the carboxylate **3** was esterified, and the obtained methyl ester **4** was iodinated in α -position with *N*-iodosuccinimide (NIS). Suzuki coupling of the iodothiophene **5** with boronic ester **6** gave the twisted bithiophene **7**. Iodination with NIS gave iodobithiophene **8** for Suzuki coupling with the regioisomeric boronic acid **9**. The obtained terthiophene **10** was iodinated, and the obtained product **11** was reacted with the EDOT terminus **12**.¹⁵ In the resulting quaterthiophene **13**, the ester was reduced to the primary alcohol, which in turn was oxidized with MnO₂ to afford aldehyde **14**. The acceptor terminus was installed by Knoevenagel condensation with the cyanoamide **15**, which was readily accessible from ester **16** and amine **17**.¹⁶ The quaterthiophene **18** was deprotected to afford the aldehyde **19**. The positive charge in **2** was added in situ by oxime formation with **20**. This in situ strategy was invented recently to secure access to molecules with difficult physical properties such as amphiphile **2**.¹⁷

Initial optical studies were conducted with quaterthiophene **18** without hydrophilic oxime tail, which was shown to be irrelevant for the property of the chromophore but causes aggregation in hydrophobic solvent.² Absorption spectra of the hydrophobic quaterthiophene **18** showed a distinct finestructure (Figure 2). Characteristic for alkoxy-substituted oligothiophenes, this finestructure has been attributed to vibrational bands.^{12,13} In DMSO, for example, the first, formally 0-0 transition appeared at $\lambda_{\max} = 427$ nm, the second, formally 0-1 transition at $\lambda_{\max} = 373$ nm. The energy of this vibrational mode calculated to 0.42 eV (3391 cm⁻¹). The original, EDOT-free quaterthiophene **1** did not exhibit this distinct finestructure. The vibrational finestructures found with alkoxy-substituted oligothiophenes has been attributed to hindered rotational freedom due to the planarizing S-O interaction.^{12,13} With continuing loss of rotational freedom at low temperature, this finestructure sharpens and a second vibrational progression at higher frequency appears. Importantly, the relative fluorescence intensity of the 0-0 band in absorption and excitation spectra, F_{00} , becomes very strong at low temperature, clearly more intense

than F_{01} , that is the 0-1 band that dominates at ambient temperature. Decreasing rotational freedom thus coincides with a ratiometric change from $\Delta F = F_{00}/F_{01} < 1$ to > 1 , i.e., $\Delta\Delta F > 0$.^{12,13}

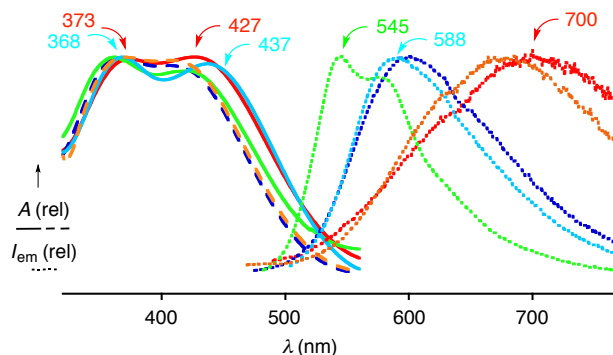


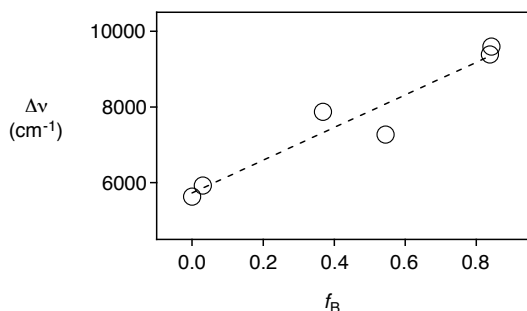
Fig. 2. Absorption (left) and emission (right) spectra of **18** in, with increasingly bathochromic emission, hexane (green), toluene (cyan), diethyl ether (blue), acetone (orange) and DMSO (red).

For EDOT probe **18**, $\Delta F \sim 1$ was found in most solvents (Figure 2). Minor exceptions include hexane with $\Delta F \leq 1$. Interestingly, the emission spectra of EDOT probe **18** did not show similar finestructure. The vibrational splitting seen in hexane appeared already with the probe **1** and can thus not be attributed to the presence of EDOT.

The absorption maximum of the probe **1** was between $\lambda_{\max} = 448$ - 460 nm for most solvents, although some exceptions were observed. The 0-0 absorption of **18** showed similarly weak solvatochromism. The position around $\lambda_{\max} = 430$ nm suggested that either the push-pull system in **18** is weaker, or the strong twist induced with two repulsive methyl groups in β and β' position reduces conjugation.

The emission spectra of EDOT probe **18** showed stronger solvatochromism than the absorption spectra (Figure 2). However, the solvatochromism was less pronounced than with the original push-pull probe **1**. The results were analyzed from dependence of the Stokes shifts on the solvent polarity function from Bakhshiev (Figure 3). The Bakhshiev-Kawski excited-state dipole moment $\mu_e = 16.9$ D found for EDOT probe **18** was slightly smaller than the $\mu_e = 18.8$ D found for the original probe **1**. This result was

consistent with the conclusion made from the less important red shift, i.e., that the push-pull system in **18** is weaker because of the less powerful EDOT donor or reduced conjugation at the site of twofold S-HC repulsion.



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Fig. 3. Bakhshiev plot of **18**, showing the dependence of the Stokes shifts on the solvent polarity function f_B . Data are taken from spectra in Figure 2.

The 0-1 transition in absorption and excitation spectra of **18** was nearly temperature independent (Figure 4). However, the 0-0 transition showed a significant bathochromism ($\Delta\lambda_{\text{max}} = +14$ nm) as well as a characteristic hyperchromism with decreasing temperature. As a result, the $\Delta F = 0.98$ at 20 °C decreased at higher temperature, and the resolution of the vibronic finestructure decreased as well. At 10 65 °C, $\Delta F = 0.92$ was measured, resulting in a $\Delta\Delta F = +6\%$ for cooling from 65 °C to 20 °C. This ratiometric thermochromism is characteristic for EDOT-containing oligothiophenes.^{12,13} The thermochromism of **18** is in sharp contrast with the temperature independence of the absorption spectrum 15 of the freely rotating EDOT-free oligothiophene **1**.²

Large unilamellar vesicles (LUVs) composed of DOPC (dioleoyl phosphatidylcholine) with two unsaturated tails remain in the same liquid-crystalline phase from 25 °C to 55 °C. At 25 °C in DOPC LUVs, the 0-0 transition occurred at 492 nm (Figure 5, solid). This excitation maximum is more than $\Delta\lambda_{\text{max}} = +60$ nm red-shifted compared to the absorption maximum in all solvents tested (Figure 5, dotted, 20 Figure 2; excitation spectra in solution were nearly superimposable with absorption spectra). This highly

significant red shift of the 0-0 transition suggested that in liquid-crystalline vesicles, the EDOT probe **2** is at least partially planarized in the ground state. This result differs from the original probe **1**, which was insensitive to liquid-crystalline membranes. The emission spectra showed negligible thermochromism.

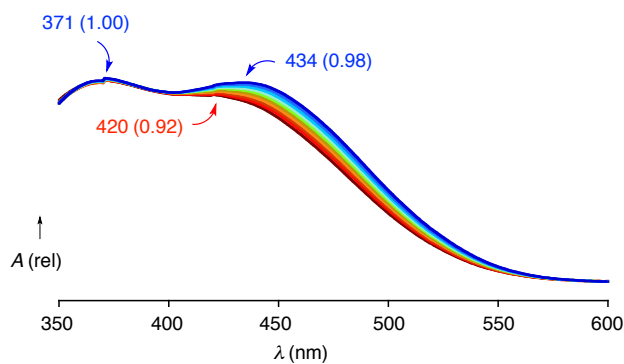


Fig. 4. Absorption spectra of **18** in DMSO with decreasing temperature from 65 °C to 20 °C (red to blue, with increasing intensity around 430 nm), normalized to 1.0 at the maximum at 371 nm.

At 25 °C in DOPC LUVs, the intensity of the 0-0 band exceeded that of the 0-1 band. Their ratio increased from $\Delta F = 0.98$ in DMSO to $\Delta F = 1.21$ in liquid-crystalline vesicles. This difference suggested that reduced rotational freedom in liquid-crystalline membranes is sensed by EDOT probe **2**. When heated from 25 °C to 55 °C in DOPC LUVs, the 0-0 transition showed hypsochromism ($\Delta\lambda_{\max} = -13$ nm) and hypochromism ($\Delta\Delta F = -12\%$) as in DMSO. These changes were thus likely to originate from thermochromism. However, ΔF remained always > 1 compared to $\Delta F = 0.92$ in solution at 55 °C, indicating that rotational freedom remains limited also in “hot” DOPC LUVs.

Contrary to DOPC LUVs, LUVs composed of DPPC (dipalmitoyl phosphatidylcholine) with two saturated tails have a phase transition at 41 °C. Liquid crystalline at higher temperature, they adapt a crystalline, gel or solid-ordered phase below phase transition. The 0-0 transition in the excitation spectrum of DPPC LUVs in fluid phase at 55 °C is red-shifted to $\lambda_{\max} = 477$ nm (as in “hot” DOPC, $\Delta\lambda_{\max} = +57$ nm compared to “hot” DMSO). This shift suggested that EDOT probe **2** is planarized in

fluid-phase DPPC, but not more planarized than in fluid-phase DOPC. However, compared to $\Delta F = 1.21$ and $\Delta F = 1.09$ in fluid-phase DOPC at 25 °C and 55 °C, respectively, a $\Delta F = 1.30$ suggested that, even in “hot” fluid-phase DPPC, rotational freedom is more limited than in “cold” fluid-phase DOPC.

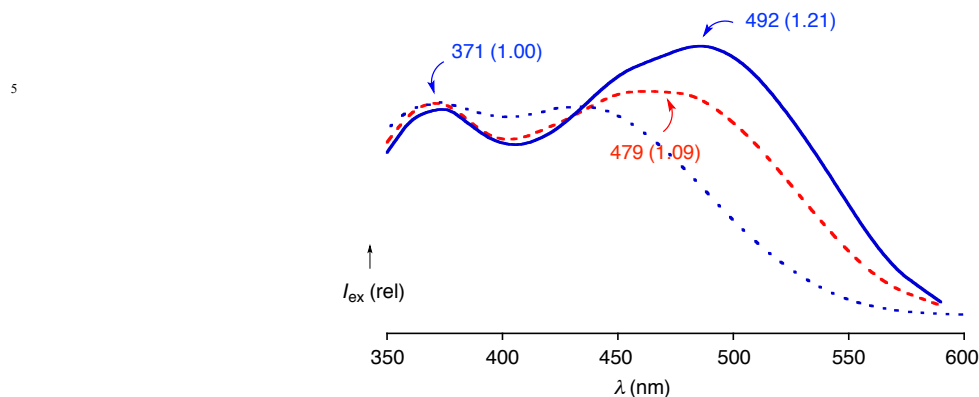


Fig. 5. Excitation spectra of **2** in DOPC LUVs at 25 °C (blue, solid) and 55 °C (red, dashed), normalized to 1.0 at the maxima around 371 nm and compared to the excitation spectrum of **2** in DMSO at 20 °C (blue, dotted; from Figure 4).

At 25 °C in solid-ordered DPPC, the 0-0 absorption maximum shifted to $\Delta\lambda_{\max} = 502$ nm ($\Delta\lambda_{\max} = +10$ nm compared to “cold” DOPC, $\Delta\lambda_{\max} = +68$ nm compared to DMSO), and the $\Delta F = 1.70$ was the highest ever observed. Dilution experiments suggested that light scattering does not contribute significantly to this impressive phenomenon. When cooling from 55 °C to 25 °C in DPPC LUVs, the 0-0 transition showed bathochromism ($\Delta\lambda_{\max} = +25$ nm) and hyperchromism ($\Delta\Delta F = +0.40$). Compared with the thermochromism of $\Delta\lambda_{\max} = +13$ nm for cooling DOPC LUVs from 55 °C to 25 °C, the $\Delta\lambda_{\max} = +25$ nm for DPPC LUVs suggested that additional planarization of the EDOT probe **2** in solid-ordered DPPC accounts for $\Delta\lambda_{\max} = +12$ nm. This is less than the $\Delta\lambda_{\max} = +20$ nm found for planarizing the original probe **1** in gel-phase DPPC. This reduced sensitivity to phase transition was consistent with the conclusion made above that the EDOT-probe **2** is already partially planarized in liquid-crystalline DOPC. However, thermal phase transition was better detected from the temperature dependence of ΔF

(Figure 7). In DOPC membranes without phase transition, ΔF decreased linearly with temperature (Figure 7, ○). The phase-transition in DPPC membranes at 41 °C was clearly detectable by a sharp change of ΔF beyond the underlying linear thermochromism (Figure 7, ●). Minor deviations from linearity were also observed in the ripple phase around 35-40 °C, but the effects were arguably too small to claim detectability of this phase.

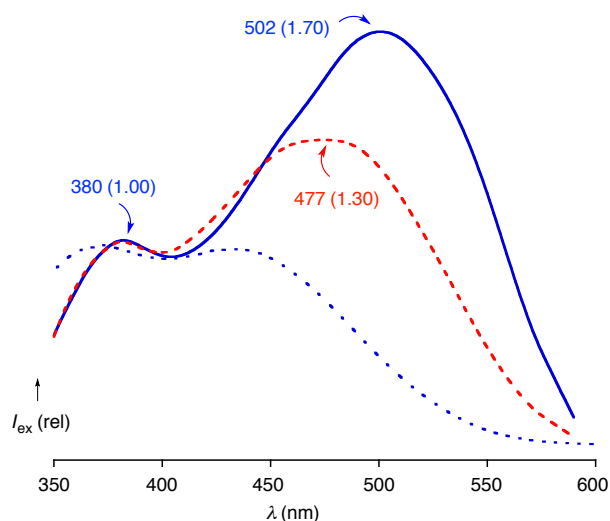


Fig. 6. Excitation spectra of **2** in DPPC LUVs at 25 °C (blue, solid) and 55 °C (red, dashed), normalized to 1.0 at the maxima around 380 nm and compared to the excitation spectrum of **2** in DMSO at 20 °C (blue, dotted; from Figure 4).

The responsiveness of EDOT probe **2** to membrane potentials was tested in polarized EYPC LUVs (*i.e.*, large unilamellar vesicles composed of egg yolk phosphatidylcholine).⁸ A potassium gradient was applied by exchanging external KCl with isoosmolar NaCl. The gradients were coupled by generating a small transmembrane current with the potassium selective carrier valinomycin. The emission spectra of **2** in polarized and unpolarized vesicles were superimposable (Figure 8b). The excitation spectra were almost superimposable (Figure 8a). However, a very small bathochromic shoulder became visible in polarized vesicles. Differential spectra produced a clear maximum at $\lambda_{\max} = 536$ nm in the excitation,

whereas no maximum was detectable in the emission spectra. Although the effect is weak, the maximum in the differential excitation spectrum suggested that EDOT probe **2** is indeed planarizable by dipole-potential interactions. However, much stronger effects were observed previously for probe **1**.² Having similar excited-state dipole moments, the main difference is that the new EDOT probe **2** is already partially planarized in unpolarized EYPC LUVs ($\lambda_{\max} = 486$ nm, $\Delta\lambda_{\max} = +52$ nm compared to DMSO). Reduced voltage sensitivity at reduced deplanarization was thus in good agreement with the concept that dipole-potential interactions can planarize twisted fluorophores.

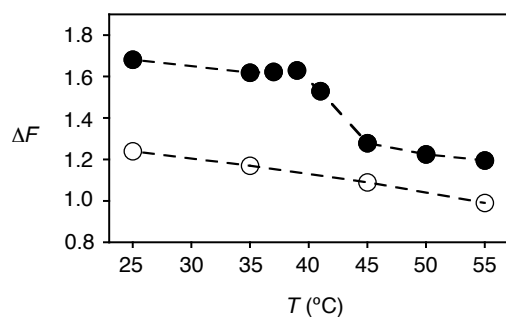


Fig. 7. Ratiometric detection of thermal phase transition: ΔF of the excitation maxima of **2** in DPPC (●) and DOPC (○) LUVs as a function of temperature (from Figures 5 and 6).

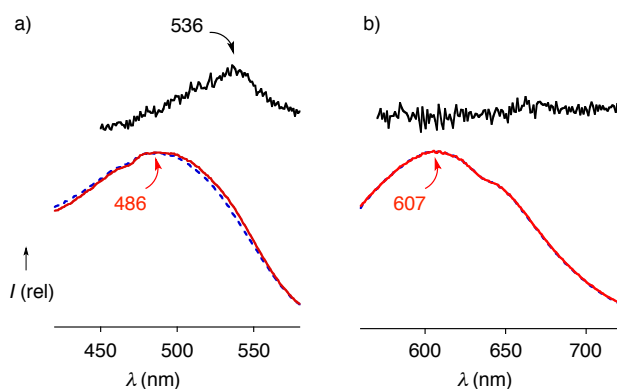


Fig. 8. Excitation (a) and emission spectra (b) of **1** in EYPC LUVs with (-180 mV, red, solid) and without (blue, dotted) inside negative membrane potential below their differential spectra (black).

Conclusions

In summary, a planarizable push-pull quaterthiophene with a planarizing EDOT donor and a strong single twist in the backbone is introduced. The results are compared to the best planarizable push-pull probe with a methoxy donor and an evenly deplanarized quaterthiophene. The applied changes reduce solvatochromism and thus the push-pull strength. The excited state dipole moment drops from $\mu_e = 18.8$ D to $\mu_e = 16.9$ D.

Most importantly, the presence of one rigidifying S-O interaction from EDOT to the adjacent thiophene is sufficient to generate thermochromic vibrational finestructure in the excitation spectrum. Compared to solution spectra, strong red shifts and increasing ΔF of the intensity ratios of the vibrational finestructure indicated that the new EDOT probe **2** is substantially planarized and suffers restricted rotational freedom already in liquid-crystalline lipid bilayers. In sharp contrast to the original planarizable push-pull probe **1**, this exquisite sensitivity allowed the ratiometric discrimination of fluid-phase DOPC and fluid-phase DPPC. Extreme $\Delta F = 1.70$ compared to $\Delta F \leq 1$ in solution revealed strongly restricted rotational freedom in solid-ordered DPPC membranes. With this high environmental sensitivity of the vibrational finestructure in the excitation spectrum, ratiometric detection of thermal phase transition, from solid-ordered to liquid-disordered DPPC membranes, became possible. Voltage sensitivity of the excitation spectrum is very weak, supporting that the chromophore is already partially planarized in unpolarized membranes.

In summary, these results suggest that planarizable push-pull oligothiophenes with EDOT donors are unique with regard to thermal as well as environmental sensitivity of the vibrational finestructure of the excitation spectrum, reporting on rotational freedom of the oligomer. This characteristic is particularly attractive for the ratiometric detection of subtle changes in membrane environments such as fluidity or possibly also tension.¹⁴ This important topic in need of fluorescent probes is currently investigated, together with unrelated applications in multicomponent photosystems.¹⁸ The probes reported in this

publication are part of an on going systematic effort to explore scope and limitations of conceptually innovative planarizable push-pull probes with regard to their nature, length, twist and polarization.

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