

Switchable Fluorescent and Solvatochromic Molecular Probes Based on 4-Amino-*N*-methylphthalimide and a Photochromic Diarylethene

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New fluorescent photochromic compounds (**1-H** and **1-Boc**) have been synthesized and characterized in different solvents. The fluorescence emission can be switched "on" and "off" with visible light and UV, respectively, by means of the photochromic reaction. The emission wavelength and efficiency strongly depend on the polarity of the solvent. The compounds show a positive solvatochromic effect in the emission maxima, and their fluorescence quantum yield decreases as the solvent's polarity increases (from cyclohexane to dioxane). In solvents more polar than dioxane the emission is too weak and therefore undetectable, and thus **1-H** and **1-Boc** behave as "normal" photochromic compounds. The photochromic reaction is also sensitive to the environment. A decrease of more than an order of magnitude was found for the quantum yield of the colouring reaction ($\Phi_{\text{OF} \rightarrow \text{CF}}$) for **1-H** in ethanol compared with cyclohexane, and an about threefold decrease in $\Phi_{\text{OF} \rightarrow \text{CF}}$ was observed for the compound **1-Boc** in polar solvents (compared with apolar solvents). For both compounds the ring-opening reaction was found not to depend on the solvent. The novel fluorescent molecular switches **1-H** and **1-Boc** are able to probe the polarity of their microenvironment.

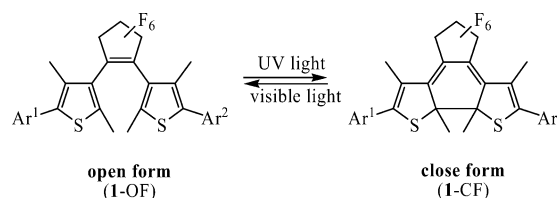
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Introduction

Photochromic materials are receiving an increasing interest as opto-addressable rewritable memory devices and reversible optical switches.^[1] One of their main advantages is the possibility to miniaturize devices to the size of a single molecule, resulting in very fast response times in the picosecond range.^[2] The light-induced changes of different physicochemical properties can be used as a readout signal. Absorption (color) changes are most evident, thus giving the name to this class of compounds.^[3] Other properties such as refractive index^[4] or infrared absorption^[5] have also been used with the aim to perform a non-destructive readout. Particular effort has been made to obtain more complex and useful devices with multiple readout signals. Modulation of other properties such as fluorescence,^[6] redox potentials,^[7] chiroptical^[8] or magnetic^[9] properties has been successfully achieved, as well as photoinduced supramolecular control of a self-assembled material.^[10] Fluorescence is of particular interest due to its high sensitivity and selectivity in one side, and the ability to provide non-invasive readout with high spatial information on the other.

The diarylethene family has been by far the preferred group of photochromic compounds (PC) in the preparation

of optical devices due to the thermal irreversibility of the ring-closing reaction and their photochemical and photo-physical fatigue resistance.^[11] In particular, 1,2-bis(3-thienyl)perfluorocyclopentenes can be reversibly switched between a colorless open form (OF) and a colored closed form (CF), with UV and green light, respectively (Scheme 1).



Scheme 1. Photochromism of 1,2-bis(thiophen-3-yl)hexafluorocyclopentenes.

The common lack of fluorescence of most PC compounds was overcome by binding them with various fluorophores whose signal can be modulated by the PC moiety through various mechanisms. The most commonly used mechanism relies on a resonance energy transfer (RET) from the fluorophore selectively to the CF of the photochromic switch.^[12] The two residues may be attached without any linker^[13] or through a spacer. Another interesting strategy is to use the changes in the electron density distribution between the OF and the CF to directly influence the fluorescent properties of the fluorophore.^[14]

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Derivates of 4-aminophthalimide show a very efficient blue fluorescence with relatively large Stokes shifts.^[15,16] They are commonly used as environmentally sensitive molecular probes,^[17] because their emission maxima and quantum yields are influenced by the medium polarity and its hydrogen-bond-donating capability.^[15,18,19] For instance, fluorescent quantum yields of compounds **2a–c** (Figure 1) strongly depend on the solvent polarity: in less polar solvents these values increase dramatically (from 1% in chloroform up to 56% in hex-1-ene for compound **2c** and from 0.5% in ethyl acetate up to 44% in hex-1-ene for **2b**).^[15] Moreover, the emission maxima (λ_{em}) and the Stokes shift depend on the solvent polarity as well.

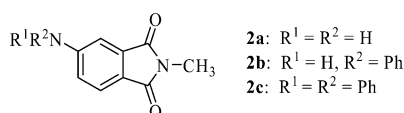
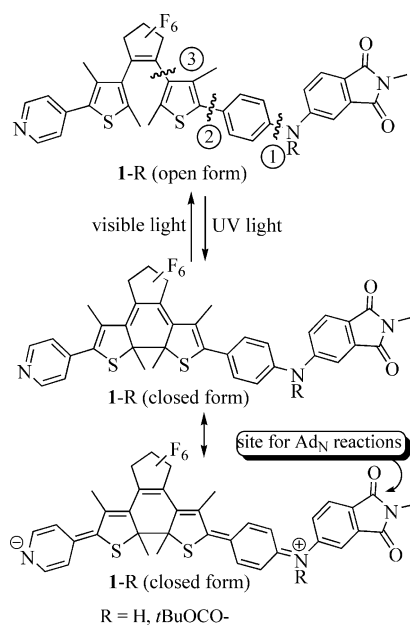


Figure 1. Fluorescent derivatives of 4-amino-*N*-methylphthalimide.

In this work we present two novel fluorescent molecular switches (Scheme 2) with a multifunctional response: these compounds possess both a photoswitchable fluorescent signal and an environment sensing ability. The switches are based on a 4-amino-*N*-methylphthalimide fluorophore, and a “push-pull” diarylethene compound. The latter was prepared by introducing an electron-acceptor group in one of the aryl substituents (Scheme 1, Ar^1 = pyrid-4-yl as a “pull” group) and an electron-donor group in the other one (Ar^2 = *p*-aminophenyl as a “push” group). In the resulting diarylethene **1** the direct polar conjugation of both groups is only possible in the CF.^[20] This means that the electron density distribution can be modulated through the photochromic reaction. In the molecular switches **1**, the amino



Scheme 2. Target compounds **1-R** (wavy lines denote strategical bonds for construction of the whole molecule).

group of Ar^2 is also a part of the aminophthalimide fluorophore. Therefore, its fluorescence properties may be perturbed by the strong acceptor group – the pyridine ring – only in the CF, because the electron density on the amino group is substantially reduced. In the OF, the push and pull groups are electronically disconnected, and therefore different emission properties are expected (quantum yields, spectra, etc.), as well as a different chemical reactivity (e.g. hydrolytic stability of the phthalimide ring). As a result, the fluorescence signal of the molecular switches can be reversibly modulated with light stimuli. Moreover, the solvent dependence of the emission properties of the aminophthalimide fluorophore is conserved in the prepared adducts, which may serve as molecular probes for environmental conditions.

Results and Discussion

1. Synthesis

The target molecule **1** could be built-up in several ways. The easily available starting compounds **4**^[21] and **5**^[21,22] (Figure 2) offer two synthetic pathways: the sequential construction of the bonds 1, 2 and 3 (in that order), or in the order 1, 3 and then 2 (Scheme 2).

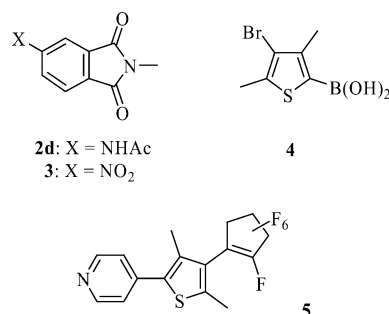
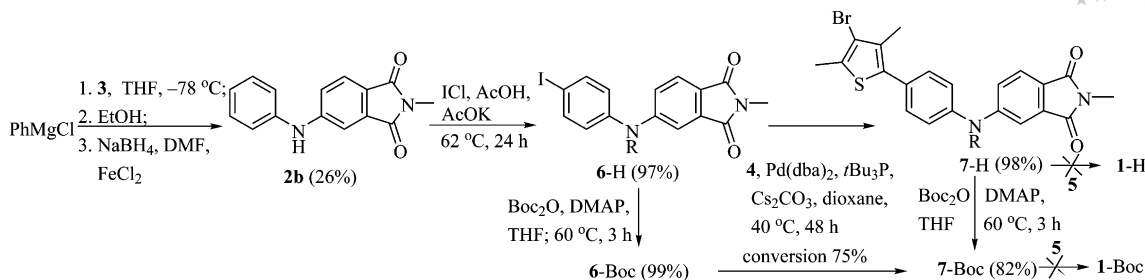


Figure 2. Starting materials and building blocks **2d**, **3–5**.

The bond 1 may be formed either by the Ullmann^[23] or by the Knochel reaction.^[24] Preparation of the intermediate **2b** (Scheme 3) according to Ullmann required iodobenzene and 4-acetylamino-*N*-methylphthalimide (**2d**).^[23] The latter was synthesized from compound **3** by the reduction^[25] and acylation of the intermediately formed **2a**.^[23] Under various arylation conditions, either 4-(diphenylamino)-*N*-methylphthalimide (**2c**) or its mixture with **2b** was obtained. Therefore, we decided to use the Knochel reaction for the synthesis of the iodide **6-H**. The Grignard reagent *p*- $\text{IC}_6\text{H}_4\text{MgCl}$ and the nitro compound **3** may give the required compound **6-H** directly and save the iodination step, but the monoiodide **6-H** was not detected in this reaction mixture. Substitution of *p*- $\text{IC}_6\text{H}_4\text{MgCl}$ by PhMgCl afforded the amine **2b**, which, even after optimization, was isolated only in low yield (Scheme 3).^[26]

Bond 2 was constructed by the Suzuki reaction^[27] of the iodide **6-H** (prepared from **2b**) with the boronic acid **4**, but the substance **7-H** was isolated in a very low yield (probably because of the hydrolysis of the phthalimide cycle with hot

Scheme 3. Synthesis of compounds **2b**, **6-R** and **7-R** (1–2–3 strategy).

aqueous Na_2CO_3). Unfortunately, the next bond (3) did not form, if the heptafluoride **5** reacted with the lithiation product of the thiophene **7-H**.^[22] Protection of the free NH group, which could slow down the Suzuki reaction and inhibit the next step ($\text{7-H} + \text{5} \rightarrow \text{1}$) afforded the compound **6-Boc**^[28] but, quite unexpectedly, it did not react with the boronic acid **4** in the presence of $\text{Pd}(\text{dba})_2$, Ph_3P , and aqueous Na_2CO_3 in THF. Another catalytic system, in dioxane proved to be extremely efficient in the Suzuki reaction.^[29] In this case, the reaction proceeded faster, with 75% conversion, but we were not able to separate the initial substance **6-Boc** from the product **7-Boc** (or to reach the full conversion). Luckily, the compound **6-H** was transformed into **7-H** in the presence of $\text{Pd}(\text{dba})_2$, $t\text{Bu}_3\text{P}$ and Cs_2CO_3 , with 98% conversion (Scheme 3). However, the protected bromide **7-Boc** (obtained from **7-H**) could not be further transformed into the target compound **1-Boc** with the heptafluoride **5**.

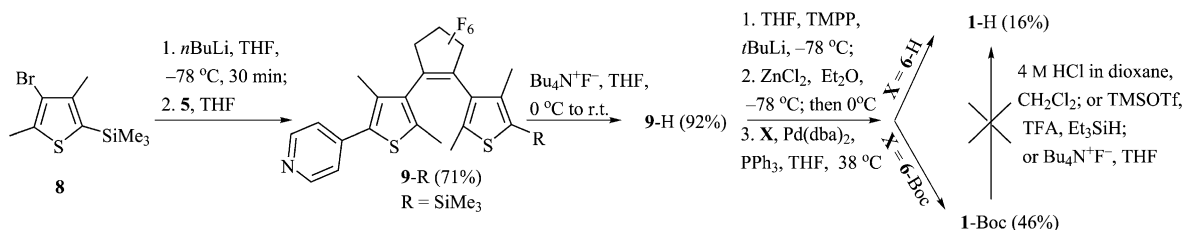
Therefore, the second strategy for the preparation of the target substances **1**, by forming the bonds 1, 3 and then 2 (Scheme 4), was used. For that, an intermediate **9-SiMe₃** was synthesized from **8**^[30] and **5**, the silyl group was removed, and, finally, the two building blocks (**9-H** and **6-Boc**) were connected in the course of the multistep procedure. As a result, the desired compound **1-Boc** was isolated with satisfactory yield. At the very end it was necessary to remove the Boc group, but all deprotection protocols (HCl in dioxane,^[31] TMSOTf , CF_3COOH with Et_3SiH ,^[32] $\text{Bu}_4\text{N}^+\text{F}^-$ in THF^[33]) failed. Therefore, the same procedure was applied for the direct coupling of substances **9-H** and **6-H**, without any protection of the amino group. Thus, both target substances **1-H** and **1-Boc** were obtained by the Negishi coupling reaction^[34] at the key step.

2. Physical Properties

Photochromism of Compounds **1-H** and **1-Boc**

The photochromic properties of the target compounds were studied in diluted solutions ($\approx 10^{-5}$ M) in different solvents. The solutions were placed in 1 cm cuvettes, irradiated with UV or visible light whilst stirring, and the changes in the absorbance were recorded in a UV/Vis spectrophotometer. The solutions were not degassed. The initial solutions with the pure open isomers had a different appearance: the solutions of compound **1-H** were pale yellow due to the absorption band of the 4-aminophthalimide residue centred at 370 nm in cyclohexane (Figure 3); in compound **1-Boc** this band is blue-shifted, and appears as a shoulder at about 335 nm. The absorption band of the photochromic moiety in the open form is not shifted and is found at 283 and 285 nm in **1-Boc** and **1-H**, respectively. Irradiation in the UV (313 nm) resulted in a rapid appearance of the characteristic absorption band of the closed form in the visible region, and the solutions became coloured. The absorption maximum of the closed form was observed at 573 nm for **1-H** and 577 nm for **1-Boc**, respectively, with a larger absorption coefficient in the case of **1-H**. In both cases nearly a full conversion in the photostationary state of ($\approx 95\%$ determined by HPLC) was reached in cyclohexane. Subsequent irradiation of the solutions with visible green light (550 nm) resulted in a complete conversion to the corresponding open isomer. This process could be repeated several times (>10) with no sign of photochemical damage.

Similar photochromic behaviour was observed for both compounds in other solvents. The absorption bands of the CF were slightly red-shifted in polar solvents, to a maximum of 10 nm in ethanol (compared with cyclohexane), but

Scheme 4. Assembling of the target compounds **1-R** according to the 1–3–2 strategy (TMPP = 2,2,6,6-tetramethylpiperidine; TMSOTf = trimethylsilyl trifluoromethylsulfonate; TFA = trifluoroacetic acid).

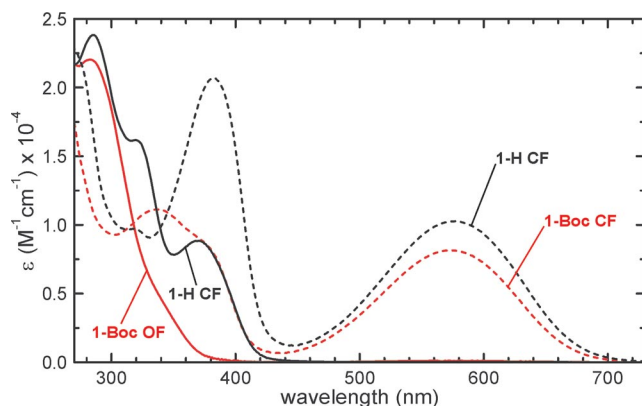


Figure 3. Absorption spectra of the open (full lines) and close (dashed lines) forms of compounds **1-H** (black lines) and **1-Boc** (red lines) in cyclohexane.

the position of the absorption band of the OF was rather insensitive to the solvent. The most distinct changes were observed in the cyclization quantum yields ($\Phi_{\text{OF} \rightarrow \text{CF}}$). An increase in the solvent polarity resulted in a drastic decrease of $\Phi_{\text{OF} \rightarrow \text{CF}}$ for compound **1-H**: in ethanol this value was found to be 28 times lower than in cyclohexane. A less pronounced (2.5-fold) decrease was observed for compound **1-Boc** in the same solvents. On the contrary, the quantum yield for the ring-opening reaction ($\Phi_{\text{CF} \rightarrow \text{OF}}$) was found to be almost the same for both compounds (within an experimental error) in all the solvents. The results obtained for compounds **1-H** and **1-Boc** are summarized in Table 1.

Fluorescence Properties and Switching

The photochromic reaction not only resulted in the colour changes mentioned above (mainly governed by the visible absorption band of the CF), but also in a drastic change in the fluorescence signal. Figure 4 shows the fluorescent modulation observed for compounds **1-H** and **1-Boc** in cyclohexane. A contrast in the signal of about 20 was found for both compounds between the pure OF (spectra normalized to one at the maximum wavelength) and the photostationary state reached under irradiation with UV light, indicating that the emission efficiency of the close isomer is negligible. Unlike most of the reported com-

pounds,^[12] in this case the emission occurs at wavelengths between the absorption of the OF and the CF, where neither one of the isomers have a significant absorption. A perfect correlation between the emission and the absorption of the close form (visible band) can be observed for compound **1-Boc** in Figure 5. At least ten complete cycles were performed for both compounds in this solvent without signs of fatigue in the absorption, or the emission spectra. In more polar solvents some signs of photoinduced decomposition were observed after a few irradiation cycles, evidenced by the presence of increasing amounts of blue fluorescent product(s) (emission maxima at 430–460 nm). In all the cases, compound **1-Boc** was more resistant to this irreversible photobleaching than compound **1-H**. However, a decrease of the maximum absorption in the visible band of the CF in the photostationary state under irradiation with UV light was not observed, indicating that the amount of photoproduct is relatively small, but the product(s) emit with a high efficiency as compared with the studied compounds **1**.

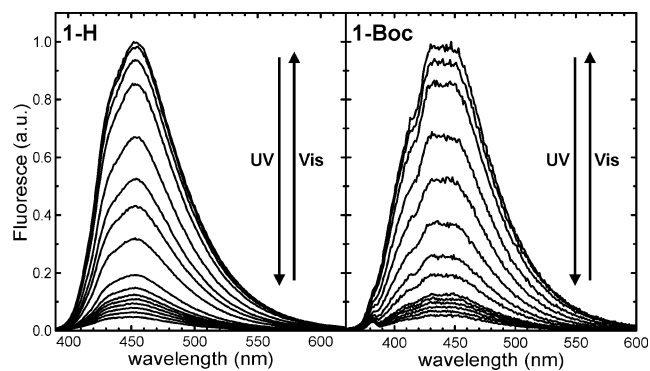


Figure 4. Fluorescence changes upon irradiation with UV (313 nm) and visible light (550 nm) for compounds **1-H** (left) and **1-Boc** (right). The arrows indicate the directions of the changes. The highest spectra correspond to the pure OF, and the lowest to the photostationary state (PSS). Excitation was performed at 370 nm for **1-H**, and at 350 nm for **1-Boc**.

Both compounds displayed a marked positive solvatochromic effect in the emission spectra, accompanied by a reduction of the fluorescence quantum yield (Φ_{FLUO}) with

Table 1. Physical properties of compounds **1-H** and **1-Boc** in different solvents. Quantum yield for the cyclization ($\Phi_{\text{O} \rightarrow \text{c}}$) and ring-opening reaction ($\Phi_{\text{CF} \rightarrow \text{OF}}$), absorption maximum of the visible band of the closed form (λ_{CF}), fluorescence switching ratio (*SR*), maximum of fluorescence emission (λ_{EM}), and fluorescence quantum yield (Φ_{FLUO}). The empirical parameter $E_{\text{T}}(30)$ defining solvent's polarity is also provided.^[a]

Solvent	$E_{\text{T}}(30)^{[a]}$ [kcal mol ⁻¹]	$\Phi_{\text{OF} \rightarrow \text{CF}}^{[b]}$		$\Phi_{\text{CF} \rightarrow \text{OF}}^{[b]}$		Switching ratio (<i>SR</i>)		λ_{CF} [nm]		λ_{EM} [nm]		% $\Phi_{\text{FLUO}}^{[b]}$	
		1-H	1-Boc	1-H	1-Boc	1-H	1-Boc	1-H	1-Boc	1-H	1-Boc	1-H	1-Boc
Cyclohexane	30.9	0.50	0.63	0.011	0.016	20	20	577	573	452	440	23.0	4.5
Tetrachloromethane	32.4	— ^[c]	0.57	— ^[c]	0.013	— ^[c]	17	— ^[c]	577	478	462	12.8	10.2
<i>p</i> -Xylene	33.1	0.13	0.48	0.009	0.013	10	17	588	581	501	474	8.6	5.7
Toluene	33.9	0.13	0.50	0.009	0.013	13	20	589	582	508	482	5.5	4.7
Benzene	34.3	0.09	0.38	0.008	0.012	7	17	587	581	514	487	4.4	4.4
Dioxane	36.0	0.046	0.30	0.013	0.015	4	17	586	581	526	498	1.6	3.6
THF	37.4	0.026	0.21	0.009	0.014	— ^[d]	— ^[d]	589	582	— ^[d]	526	<0.5	0.8
Acetonitrile	45.6	0.022	0.28	0.009	0.015	— ^[d]	— ^[d]	589	578	— ^[d]	— ^[d]	— ^[d]	— ^[d]
Ethanol	51.9	0.018	0.26	0.008	0.014	— ^[d]	— ^[d]	588	575	— ^[d]	— ^[d]	— ^[d]	— ^[d]

[a] From ref.^[36]. [b] Uncertainties are about 5%. [c] Photoinduced irreversible secondary reaction. [d] Non or very poorly fluorescent.

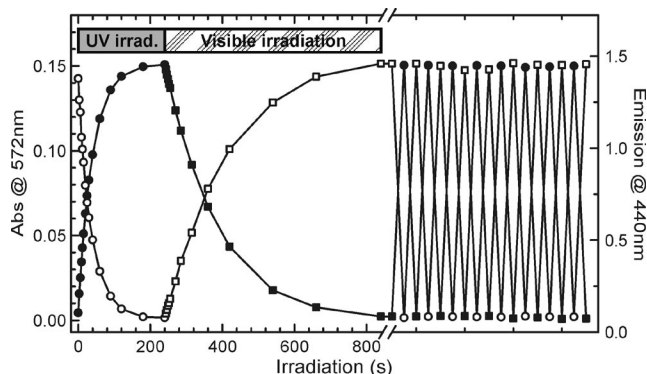


Figure 5. Photoswitching of compound **1-Boc** in cyclohexane. The absorption in the visible band (filled symbols, left axis) and the emission at the maximum (hollow symbols, right axis) are plotted as a function of the irradiation time during the complete first cycle, and then only in the photostationary states after irradiation with UV (circles) and visible light (squares), for a total of 10 cycles.

increasing solvent's polarity, in agreement with the data for other 4-aminophthalimides^[15,16,35] (Table 1), the only exception being the increase observed in Φ_{FLUO} for compound **1-Boc** from cyclohexane to tetrachloromethane [$E_{\text{T}}(30) = 30.9$ and $32.4 \text{ kcal mol}^{-1}$ respectively]. Red shifts in the emission maxima of 75–85 nm were observed for both compounds with a relatively small change in polarity of $6.5 \text{ kcal mol}^{-1}$ measured in the one-parameter [$E_{\text{T}}(30)$] empirical scale, derived from the absorption of Reichardt's betaine dyes.^[36]

The emission in more polar solvents [$E_{\text{T}}(30) > 37 \text{ kcal mol}^{-1}$] becomes too weak ($\Phi_{\text{FLUO}} < 0.003$) for both compounds. The absorption band of the aminophthalimide (AP) residue was also red-shifted for compound **1-H**, but this shift is smaller (maximum 20 nm by changing cyclohexane to ethanol). In the case of compound **1-Boc**, the AP band (shoulder at 335 nm) did not experience any significant change with the variation of the solvent.

Photoswitching of the fluorescence signal was also observed in different solvents for both compounds upon light irradiation. The results are summarized in Table 1, defined as the ratio between the fluorescent signal of the pure open isomer ($I_{\text{F-0}}$) and the one obtained in the photostationary state ($I_{\text{F-PSS}}$) after irradiation with UV light ($SR = I_{\text{F-0}}/I_{\text{F-PSS}}$). In the case of compound **1-Boc**, an excellent signal modulation of 17 to 20-fold was obtained independent of the solvent polarity, from cyclohexane to dioxane (Figure 6). On the contrary, compound **1-H** showed a large decrease in the switching ratio, i.e. from 20 (95% of signal modulation) in cyclohexane to 4 (76% modulation) in dioxane. These results can be explained by the changes observed in the conversion in the photostationary state (a_{PS}), which are also in agreement with the behaviour of $\Phi_{\text{OF} \rightarrow \text{CF}}$ observed in different solvents. While a_{PS} remains approximately constant in all the solvents for compound **1-Boc** ($a_{\text{PS}} = 0.93\text{--}0.97$), a decrease from 0.95 in cyclohexane to 0.55 in ethanol was observed for **1-H**. A decrease in $\Phi_{\text{OF} \rightarrow \text{CF}}$ and a_{PS} with increasing solvent polarity was ascribed to the presence of two conformations in the excited state (a reac-

tive planar and an inactive twisted one); the relative energies of these conformations depend on the solvent polarity.^[37] The same tendency was found for the compounds presented here (see Table 1), with a more pronounced change in $\Phi_{\text{OF} \rightarrow \text{CF}}$ in the case of **1-H**. We attribute the differences observed between **1-H** and **1-Boc** to the different electron-donor properties of the *p*-aminophenyl substituent in the diarylethene. The urethane group in the compound **1-Boc** decreases the electron density on the nitrogen atom, making this compound less sensitive to changes in the polarity of the environment.

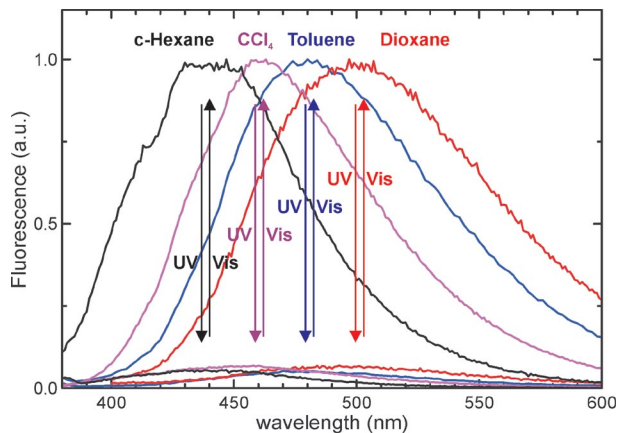


Figure 6. Photoswitching of the fluorescence of compound **1-Boc** in different solvents (excitation wavelength: 370 nm). The switching contrast obtained in the signal between the pure OF and the photostationary state (PSS-313) was for all cases greater than 17 ($I_{\text{F-0}}/I_{\text{F-PSS}}$).

The mechanism of fluorescence modulation may be rather complex and probably more than one effect contributes to it. In principle, at least two effects can be considered. First, the changes in the charge density on the nitrogen at the position 4 of the phthalimide, between the two isomers (see Scheme 2) should result in a very important contribution. Second, a possible energy transfer process from the emissive state, centred at the aminophthalimide part of the molecule (in the CF), to the state responsible for the red absorption band of the CF, centred in the diarylethene moiety may also have a contribution. The latter should be of lower incidence because the emission maxima is located at a wavelength of minimal absorbance of the CFs (see Figures 3 and 4), but it cannot be completely ruled out due to the close proximity between the donor and the acceptor. Moreover, the red-shifts experimented in polar solvents by the emission maxima are higher than the one observed in the absorption of the CF. Therefore the energy transfer efficiency from the fluorophore (donor) to the closed form (acceptor) should increase with solvent polarity, and this effect should be more pronounced for amine **1-H** (emission shift from 452 nm in cyclohexane to 526 nm in dioxane) than for the *N*-protected **1-Boc** (emission shift from 440 nm to 498 nm in the same solvents). The observed changes for *SR* point in the opposite direction. Therefore, energy transfer cannot be the main mechanism responsible for the fluorescence modulation of compounds **1**.

Conclusion and Outlook

We have designed and characterized new compounds that display environmentally dependent emission colors (fluorescence spectra), that can be optically modulated between “on” and “off” states with a high signal ratio between the fluorescent and non fluorescent states. Thus, these molecular switches may be used for probing the microenvironment, e.g. intracellular objects, organelles, or in particular, used as membrane potentials probes. Their switching behavior makes the probes also useful in intracellular tracking experiments, to individualize the structure to be followed, or to provide subdiffraction resolution in far field microscopy based on the use of the molecular states of the fluorescent probes.^[38] For that, the *N*-methyl group of the phthalimide fragment should be transformed into the CH₂COOR group and bound with a ligand, which should serve as a recognition site for the (biological) object, the polarity of which is to be probed. The key intermediate of the present study – the organo-zinc compound prepared from the thiophene **9-H** – is compatible with a *tert*-butyl ester group (R = *t*Bu in CH₂COOR mentioned above). The *N*-(*tert*-butoxycarbonyl)methyl derivative of the iodide **6** may easily be synthesized and used as a starting material for the preparation of the (amino) reactive modifications of the environmentally sensitive probes presented here.

Experimental Section

General Remarks: UV/Vis absorption spectra were recorded on a Varian Cary 4000 UV/Vis spectrophotometer, and fluorescence spectra on a Varian Cary Eclipse fluorescence spectrophotometer. Sealed quartz cuvettes of 1 cm path length were used in all experiments. Photochromic reactions were performed with stirring by irradiation with a 200 W Mercury lamp (LOT-Oriel GmbH & Co. KG, Darmstadt, Germany) equipped with a monochromator and a system of filters to select the appropriate wavelengths. The analysis of the kinetic data to extract the values of the quantum efficiencies of the isomerization reactions ($\Phi_{O\rightarrow C}$ and $\Phi_{C\rightarrow O}$) is described elsewhere.^[39] As a reference, solutions of compound 1,2-bis(2,4-dimethyl-5-phenylthiophene-3-yl)perfluorocyclopentene^[40] in hexane were used. All reactions were carried out with magnetic stirring in Schlenk flasks equipped with septa under argon using a standards manifold with vacuum and argon lines. NMR spectra were recorded at 25 °C with Varian MERCURY 300 and Bruker AM 250 spectrometers at 300 (¹H) and 75.5 MHz (¹³C and APT), as well as at 250 (¹H) and 62.9 MHz (¹³C and DEPT), respectively. All spectra are referenced to tetramethylsilane as an internal standard (δ = 0) using the signals of the residual protons of CHCl₃ (δ = 7.26 ppm) in CDCl₃ or [D₅]DMSO (δ = 2.50 ppm) in [D₆]DMSO. Multiplicities of signals are described as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Multiplicities in the ¹³C NMR spectra were determined by APT (Attached Proton Test) measurements. Low resolution mass spectra (electro spray ionization, ESI) were obtained with LCQ spectrometer. High resolution mass spectra (ESI-HRMS) were obtained on APEX IV spectrometer. HPLC system (Knauer): Smartline pump 1000 (2 ×), UV detector 2500, column thermostat 4000, mixing chamber, injection valve with 20 and 100 μ L loop for the analytical and preparative columns, respectively; 6-ports/3-channel switching valve; analytical column: Eurospher-100 C18,

5 μ m, 250 × 4 mm, 1 mL/min; preparative column: Eurospher-100-5 C18, 5 μ m, 250 × 8 mm, 4 mL/min; solvent A: water + 0.1% v/v trifluoroacetic acid (TFA); solvent B: MeCN + 0.1% v/v TFA. Analytical TLC was performed on MERCK ready-to-use plates with silica gel 60 (F₂₅₄). Column chromatography: MERCK silica gel, grade 60, 0.04–0.063 mm; fraction collector RETRIEVER® II (ISCO). Elemental analyses were carried out at Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen. Organic solutions were dried with MgSO₄. All reactions were carried out with magnetic stirring.

***N*-Methyl-4-(phenylamino)phthalimide (2b):** In a dry 100 mL flask, a solution of PhMgCl (2.0 M in THF, 7.2 mL, 14 mmol) was diluted with dry THF (20 mL). Compound **3** (1.24 g, 6.00 mmol) in dry THF (30 mL) was added to the solution of PhMgCl at –50 °C. After stirring at –50 °C for 2 h, EtOH (4 mL) was added, followed by the freshly prepared solution of NaBH₄ (228 mg, 6.00 mmol) in dry DMF (10 mL), which was introduced dropwise. Then dry FeCl₂ (1.52 g, 12.0 mmol) was added. After stirring overnight at room temperature, the reaction mixture was poured into water (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic solutions were washed with brine (100 mL), dried and concentrated in vacuo. The residue was purified by chromatography on SiO₂ (100 g) with hexane/EtOAc mixture (2:1) as an eluent, and the title compound was isolated as a yellow solid (0.398 g, 26%); m.p. 178 °C (MeOH) (ref.^[15] 175 °C). ¹H NMR (200 MHz, CDCl₃): δ = 3.10 (s, 3 H), 6.31 (br. s, 1 H), 7.09 (dd, ³J = 8.3, ⁴J = 2.1 Hz, 1 H), 7.13–7.21 (m, 4 H), 7.28–7.37 (m, 2 H), 7.63 (d, ³J = 8.2 Hz, 1 H) ppm. ¹³C NMR (50.3 MHz, CDCl₃): δ = 23.7 (Me), 108.9 (CH), 118.6 (CH), 121.6 (2 × CH), 122.0, 124.4 (CH), 125.1 (CH), 129.9 (2 × CH), 135.0, 140.0, 150.0, 168.7 (CO), 168.9 (CO) ppm. MS (EI): *m/z* (%) = 252 (100) [M⁺].

4-(4'-Iodophenylamino)-*N*-methylphthalimide (6-H): To a stirred solution of **2b** (770 mg, 3.06 mmol) and AcOK (300 mg, 3.06 mmol) in glacial AcOH (40 mL), a solution of ICl (6.72 mL, 3.36 mmol, 0.5 M in AcOH) was added dropwise at room temperature. The reaction mixture was stirred for 30 h at 62 °C. After cooling, a half of AcOH was evaporated in vacuo, and the residue was poured into 2% aq. Na₂SO₃ (80 mL). The title product was filtered off, washed with water and air-dried; yield 1.12 g (97%), m.p. 220 °C (MeOH). ¹H NMR (200 MHz, [D₆]DMSO): δ = 2.98 (s, 3 H), 7.05 (d, ³J = 8.4 Hz, 1 H), 7.15–7.90 (m, 5 H), 9.24 (br. s, 1 H) ppm. ¹³C NMR (50.3 MHz, [D₆]DMSO): δ = 23.5 (Me), 85.5 (CI), 108.4 (CH), 118.6 (CH), 121.0, 122.0 (2 × CH), 125.0 (CH), 134.6, 138.3 (2 × CH), 140.8, 149.4, 168.0 (C=O), 168.2 (C=O) ppm. MS (EI): *m/z* (%) = 378 (100) [M⁺]. C₁₅H₁₁N₂O₂I (378.16): calcd. C 47.64, H 2.93, N 7.41; found: C 47.24, H 2.90, N 7.31.

***N*-Butoxycarbonyl-4-(4'-iodophenylamino)-*N*-methylphthalimide (6-Boc):** In a dry 50 mL flask, a mixture of **6-H** (750 mg, 1.98 mmol) and DMAP (97 mg, 0.79 mmol) was dissolved in dry THF (30 mL). *tert*-Butyl pyrocarbonate (578 mg, 2.65 mmol) was added dropwise at the room temperature, and the final solution was stirred for 3 h at 60 °C. The solvent was removed in vacuo; the residue was dissolved in CH₂Cl₂ (20 mL), washed 0.1 M aq. HCl (20 mL) and brine. After drying, the solvent was removed in vacuo, and the title compound was isolated by filtration through the silica gel (50 g) with hexane/EtOAc mixture (2:1) as an eluent (head fraction was discarded, as it contained excess of *tert*-butyl pyrocarbonate). After removing of the eluent, a white solid was obtained; yield 937 mg (99%); m.p. 171 °C (MeOH). ¹H NMR (200 MHz, CDCl₃): δ = 1.42 (s, 9 H), 3.13 (s, 3 H), 6.92 (d, ³J = 8.7 Hz, 2 H), 7.48 (dd, ³J = 8.1, ⁴J = 2.0 Hz, 1 H), 7.63 (d, ⁴J = 2.0 Hz, 1 H), 7.68 (d, ³J =

8.7 Hz, 2 H), 7.74 (d, $^3J = 8.1$ Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, CDCl_3): $\delta = 23.9$ (Me), 28.0 ($3\times\text{Me}$), 82.9 (C-O), 91.9 (CH), 120.6 (CH), 123.8 (CH), 128.2, 129.6 ($2\times\text{CH}$), 130.8 (CH), 133.3, 138.6 ($2\times\text{CH}$), 141.8, 148.3, 152.8 (C=O), 168.0 ($2\times\text{C=O}$) ppm. MS (CI/ NH_3): m/z (%) = 496 (100) [$\text{M} + \text{NH}_4^+$]. $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_4\text{I}$ (478.28): calcd. C 50.22, H 4.00, N 5.86; found C 50.10, H 4.34, N 5.60.

4-[2-[2,4-Dimethyl-5-(pyridin-4-yl)thiophen-3-yl]-3,3,4,4,5,5-hexafluorocyclopent-1-enyl]-3,5-dimethyl-2-(trimethylsilyl)thiophene (9-SiMe₃): To a solution of 3-bromo-2,4-dimethyl-5-trimethylsilylthiophene (**8**) (820 mg, 3.1 mmol) in anhydrous THF (4 mL), $n\text{BuLi}$ (2.5 M in hexanes, 1.26 mL, 3.15 mmol) was added slowly at -78°C , and the mixture was stirred at this temperature for 30 min. A solution of compound **5** (980 mg, 2.57 mmol) in anhydrous THF (4 mL) was added slowly at -78°C . After stirring for 20 min at -78°C , the reaction mixture was warmed-up to room temperature, stirred for 30 min, diluted with diethyl ether (100 mL), and washed with water (50 mL). The organic solution was dried and concentrated in vacuo. The residue was purified on silica gel (100 g) with hexane/EtOAc mixture (1:1), and the title compound was isolated as a yellow-red oil (1.00 g, 71%). ^1H NMR (300.5 MHz, CDCl_3): $\delta = 0.28$ (s, 9 H), 2.09–2.16 (m, 6 H), 2.29–2.38 (m, 6 H), 7.24 (dd, $^3J = 4.9$, $^4J = 1.6$ Hz, 1 H), 7.26 (dd, $^3J = 4.9$, $^4J = 1.6$ Hz, 1 H), 8.6 (d, $^3J = 4.9$, $^4J = 1.6$ Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = -0.3$ ($3\times\text{CH}_3$), 14.9 ($2\times\text{Me}$), 16.3 ($2\times\text{Me}$), 123.0 ($2\times\text{CH}$), 126.8, 127.0, 132.2, 133.1, 134.4, 140.8, 141.0, 141.7, 143.0, 144.5, 144.7, 150.1 ($2\times\text{CH}$) ppm. MS (ESI): m/z (%) = 546 (100) [$\text{M} + \text{H}^+$]. $\text{C}_{25}\text{H}_{25}\text{NF}_6\text{S}_2\text{Si}$ (545.65): calcd. C 55.03, H 4.62, N 2.57; found C 55.35, H 4.64, N 2.49.

4-[2-[2,4-Dimethyl-5-(pyridin-4-yl)thiophen-3-yl]-3,3,4,4,5,5-hexafluorocyclopent-1-enyl]-3,5-dimethylthiophene (9-H): To a solution of **9-SiMe₃** (1.0 g, 1.83 mmol) in anhydrous THF (10.0 mL), Bu_4NF (1.0 M in THF, 3.67 mL, 3.67 mmol) was added slowly at room temperature, and stirring was continued for 20 min. The mixture was diluted with diethyl ether (100 mL), washed with water (50 mL), dried and filtered. The solvents were removed in vacuo, and the residue was purified by filtration through silica gel (45 g) with hexane/EtOAc mixture (1:1) as an eluent. After removing of the solvent, an orange-red oil was obtained, which solidified in ca. one week; yield 800 mg (92%). ^1H NMR (300.5 MHz, CDCl_3): $\delta = 0.28$ (s, 9 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 2.25 (s, 3 H), 2.38 (s, 3 H), 6.67 (s, 1 H), 7.19 (dd, $^3J = 4.5$, $^4J = 1.7$ Hz, 2 H), 8.53 (dd, $^3J = 4.5$, $^4J = 1.6$ Hz, 2 H) ppm. ^{13}C NMR (50.3 MHz, CDCl_3): $\delta = 14.8$ ($2\times\text{Me}$), 17.0 ($2\times\text{Me}$), 119.7 (CH), 123.1 ($2\times\text{CH}$), 124.6, 127.0, 133.4, 134.5, 136.7, 141.0, 141.5, 150.2 ($2\times\text{CH}$) ppm. MS (EI): m/z (%) = 473 (100) [M^+]. $\text{C}_{22}\text{H}_{17}\text{NF}_6\text{S}_2$ (473.50): calcd. C 55.80, H 3.62, N 2.96; found C 56.13, H 3.84, N 3.09.

4-[4-(4-[2-[2,4-Dimethyl-5-(pyridin-4-yl)thiophen-3-yl]-3,3,4,4,5,5-hexafluorocyclopent-1-enyl]-3,5-dimethylthiophen-2-yl)phenylamino]-N-(tert-butyloxycarbonyl)-N-methylphthalimide (1-Boc): 2,2,6,6-Tetramethylpiperidine (112.5 mg, 0.798 mmol) and anhydrous THF (1 mL) were introduced through a septum into a flame-dried flask (25 mL). $t\text{BuLi}$ (1.48 M in pentane, 0.532 mL, 0.785 mmol) was added slowly to this solution at -78°C , and stirring was continued for 10 min. Then a solution of the substance **9-H** (171 mg, 0.361 mmol) in anhydrous THF (1 mL) was added carefully at -78°C , and the mixture was stirred for 30 min. After that, a solution of anhydrous ZnCl_2 (1 M in Et_2O , 0.818 mL, 0.818 mmol) was added carefully, and simultaneously 10 mL of cold dry THF were added dropwise. Then a cooling bath was removed, and the reaction mixture was warmed-up to 0°C . In another dry flask, a mixture of **6-Boc** (50 mg, 0.105 mmol), $[\text{Pd}(\text{dba})_2]$ (7 mg, 12 μmol) and Ph_3P (14 mg, 52 μmol) was prepared under nitrogen. Anhydrous

THF (5 mL) was added through a septum, and the yellow solution was stirred at room temperature for 10 min. Then this solution was added dropwise with a syringe to the solution (or suspension) of the α -zink derivative in the first flask. The reaction mixture was stirred at 38°C for 16 h, until no spot of the starting iodide was detected on TLC. Then it was diluted with EtOAc (40 mL), washed with saturated aq. NH_4Cl (40 mL) and dried. After evaporation of the solvent, the residue was purified on silica gel (60 g) with hexane/EtOAc mixture (1:2), and the title product was isolated as a light yellow oil (40 mg, 47%). HPLC (see Supporting Information): $t_R = 18.9$ min (100%), A/B: from 50:50 to 0:100 in 25 min, 25°C , detection at 254 nm. ^1H NMR (300.5 MHz, CDCl_3 , two rotamers): $\delta = 1.40$ (s, 9 H), 2.04 (s, 3 H), 2.08 (s, 1.5 H), 2.11 (s, 1.5 H), 2.29 (s, 3 H), 2.31 (s, 1.5 H), 2.34 (s, 1.5 H), 3.09 (s, 3 H), 7.13 (d, $^3J = 8.5$ Hz, 2 H), 7.21 (m, 2 H), 7.29 (d, $^3J = 8.5$ Hz, 2 H), 7.49 (dd, $^3J = 3.6$, $^4J = 1.9$ Hz, 0.5 H), 7.52 (dd, $^3J = 3.6$, $^4J = 1.9$ Hz, 0.5 H), 7.57 (dd, $^3J = 3.8$, $^4J = 1.9$ Hz, 1 H), 7.69 (d, $^3J = 8.1$ Hz, 1 H), 8.53 (d, $^3J = 4.7$ Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 14.8$ ($4\times\text{Me}$), 24.0 (Me), 28.1 ($3\times\text{Me}$), 82.7 (C-O), 107.9 (CH), 120.6 (CH), 123.1 ($2\times\text{CH}$), 123.6 ($2\times\text{CH}$), 125.8, 126.7, 127.6 (CH), 128.1, 130.9, 129.8 ($2\times\text{CH}$), 132.2, 132.5, 133.1, 134.4, 135.4, 139.2, 139.4, 141.0, 141.8, 148.3, 149.8 ($2\times\text{CH}$), 152.9 (CO), 167.8 (CO), 167.9 (CO) ppm. MS (ESI): m/z (%) = 824 (100) [$\text{M} + \text{H}^+$]. HR MS (ESI): $m/z = 824.20468$ [$\text{M} + \text{H}^+$], calcd. for $\text{C}_{42}\text{H}_{36}\text{N}_3\text{F}_6\text{O}_4\text{S}_2$: 824.20514.

4-[4-(4-[2-[2,4-Dimethyl-5-(pyridin-4-yl)thiophen-3-yl]-3,3,4,4,5,5-hexafluorocyclopenten-1-yl]-3,5-dimethylthiophen-2-yl)phenylamino]-N-methylphthalimide (1-H): Compound **1-H** was prepared as described above for the substance **1-Boc** from the iodide **6-H** (40 mg, 0.106 mmol) and 4 mol-equiv. of the thiophene **9-H** (200 mg, 0.423 mmol). The crude product was purified on silica gel (60 g) with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ mixture (50:1) as eluent. Yield 12 mg (16%) of a yellow oil. HPLC (see Supporting Information): $t_R = 3.6$ min (95.6%), A/B: from 20:80 to 0:100 in 25 min, 25°C , detection at 254 nm. ^1H NMR (300.5 MHz, CDCl_3): $\delta = 2.04$ (m, 3 H), 2.11 (m, 3 H), 2.29 (s, 3 H), 2.34 (br. s, 3 H), 3.07 (s, 3 H), 6.40 (d, $^3J_{\text{H,H}} = 4.4$ Hz, 1 H), 7.09 (dd, $^3J_{\text{H,H}} = 8.2$, $^4J_{\text{H,H}} = 2.0$ Hz, 1 H), 7.11 (d, $^3J_{\text{H,H}} = 8.6$ Hz, 2 H), 7.22 (d, $^3J_{\text{H,H}} = 6.0$ Hz, 2 H), 7.28 (d, $^3J_{\text{H,H}} = 8.6$ Hz, 1 H), 7.36 (d, $^3J_{\text{H,H}} = 2.0$ Hz, 1 H), 7.60 (d, $^3J_{\text{H,H}} = 8.2$ Hz, 1 H), 8.54 (d, $^3J_{\text{H,H}} = 5.1$ Hz, 2 H) ppm. ^{13}C NMR (50.3 MHz, CDCl_3): $\delta = 14.8$ ($4\times\text{Me}$), 23.7 (Me), 108.0, 109.2 (CH), 119.2 (CH), 120.8 ($2\times\text{CH}$), 122.5, 123.2 ($2\times\text{CH}$), 125.1 (CH), 129.5, 130.5 ($2\times\text{CH}$), 133.4, 134.5, 135.1, 136.0, 139.5, 141.8, 149.3, 150.2 ($2\times\text{CH}$), 168.5 ($2\times\text{C=O}$) ppm. MS (ESI): m/z (%) = 724 (100) [$\text{M} + \text{H}^+$]. HRMS (ESI): $m/z = 724.15223$ [$\text{M} + \text{H}^+$], calcd. for $\text{C}_{37}\text{H}_{28}\text{N}_3\text{F}_6\text{O}_2\text{S}_2$: 724.15271.

Supporting Information (see also the footnote on the first page of this article): HPLC traces (**1-Boc** and **1-H**) and ^{13}C NMR spectrum of **1-H**.

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