One-Step Synthesis of Novel Flavylium Salts Containing Alkyl Side Chains in Their 3-, 4′-, 5- or 6-Positions and Their Photophysical Properties in Micellar Media

Ana C. Fernandes,*[a] Carlos C. Romão,[a] Carla P. Rosa,[a] Vera P. Vieira,[a] António Lopes,[a] Palmira F. Silva,[b] and António L. Maçanita[a]

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A one-step preparation of several flavylium salts containing alkyl side chains in their 3-, 4′-, 5- or 6-positions is described. Flavylium salts with alkyl side chains in positions 3 or 4′ were isolated from reactions between 2,4-dihydroxybenzaldehyde and decanophenone, dodecanophenone and 4′-hexyl- or 4′-dodecylacetophenone. Flavylium salts with alkyl side chains in positions 5 or 6 were prepared through reactions between benzoylacetone and 4-hexyl-, 4-dodecyl- or 5-pentylresorcinol. The new compounds are insoluble or sparingly soluble in water, but readily incorporate into aqueous dispersions of anionic (SDS), cationic (CTAB) or neutral ($C_{12}E_{10}$) surfactants above their critical micellar concentrations. They also present interesting spectroscopic properties – namely, ultra-fast proton transfer in the excited state – and the 4′ derivatives also exhibit photochromic behaviour, which might have several applications in the field of self-assembled systems.

Introduction

Anthocyanins are natural pigments of the flavonoid family (polyphenols), largely responsible for red and purple colours in the plant world, in particular in flowers and fruits.[1] In naturally occurring anthocyanins, the flavylium chromophore is substituted in various ways with OH, OMe and β-glycosyloxy groups (Figure 1).

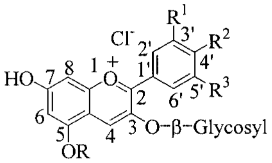

Figure 1. The flavylium cation form of common natural anthocyanins R = H, β-glycosyl; R^1, R^2, R^3 = H, OH, OMe, *O*-β-glycosyl

Anthocyanins are used as food colorants,[2,3] laser dyes,[4] sensitizers for electrophotographic recordings[5,6] or photovoltaic TiO_2 cells[7] and as models for optical memory systems.[8–12] Recent studies have revealed two unusual properties of the coloured flavylium cation forms of anthocyanins in the excited state. Firstly, flavylium cations undergo proton transfer to water in 5–20 ps (depending on the specific anthocyanin); that is, they are "super-photoacids" with excited state $pK_a \approx -1$.[13] Secondly, flavylium cations are also powerful oxidants (excited state reduction potential ca. 2.5 V vs. H^+/H_2 electrode).[14] Consequently, electron transfer to anthocyanins competes with ultra-fast proton transfer, even when the electron donor possesses a relatively high ionization potential (8–9 eV), as in the case of benzoic and cinnamic acid derivatives.[15]

From the biochemical point of view, anthocyanins also exhibit anti-inflammatory,[16] vasoprotective,[17] neuroprotective[18] and anti-hyperglycemic[19–20] activities in animal models, and have been shown to exert anti-proliferative effects in cell cultures.[21–23] In addition, they also seem to play a role in preventing human pathologies related to oxidative stress.[24–28] Nevertheless, it is not yet established which form or forms of the anthocyanin is or are involved. Finally, the photooxidative properties of the flavylium form[13] pose some puzzling questions as to the in vivo role of anthocyanins, which in plant vacuoles are associated with natural electron donors (IP ≈ 7.5 eV)[29] such as quercitrin.

Attachment of a long aliphatic (lipophilic) chain may confer interesting attributes on a (hydrophilic) flavylium cation, such as surfactant behaviour, water insolubility and solubility in low-polarity solvents. Specifically, it might be expected that such functionalized flavylium salts in aqueous dispersions of micro-heterogeneous media (i.e., micelles, microemulsions and vesicles) should exclusively incorporate

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[a] Instituto de Tecnologia Química e Biológica da Universidade Nova de Lisboa,
Quinta do Marquês, EAN, Apt 127, 2781-901 Oeiras, Portugal
Fax: (internat.) + 351-214411277
E-mail:anacris@itqb.unl.pt
[b] Instituto Superior Técnico da Universidade Técnica de Lisboa,
Av. Rovisco Pais, 1049-001, Lisboa, Portugal
Fax: (internat.) + 351-218419606
E-mail: macanita@ist.utl.pt

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into the interfaces of these microaggregates. This anticipated property opens routes to two planned studies in which anthocyanins seem to be appropriate, provided that they remain in the interface: anthocyanin/antioxidant electron transfer in confined media, mimicking plant vacuoles, and proton transfer for probing proton/water structure and mobility at charged interfaces. Such studies cannot be carried out with the non-functionalized flavylium salts, because they are soluble in water and do not preferentially bind to neutral or positively charged micelles.[30,31]

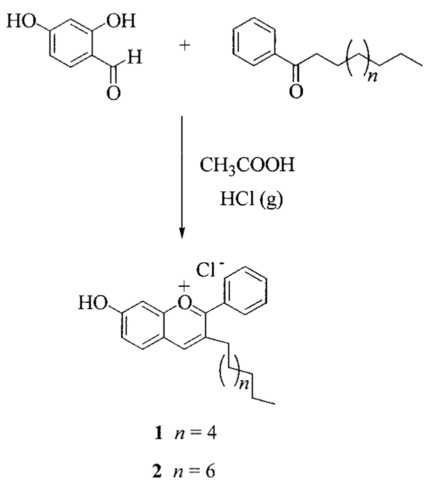
Several pyrylium salts with long alkyl chains were prepared by S. Balaban.[32−36] Introduction of an alkyl side chain at the 4-positions of flavylium (benzopyrylium) cations − involving the addition of sodium benzotriazolate to the flavylium salts, deprotonation by butyllithium at low temperature, treatment with an alkyl halide and final loss of benzotriazole anion − has been studied previously.[37,38]

Here we report an easy one-step procedure for the synthesis of several flavylium salts containing alkyl side chains in their 3-, 4′-, 5- or 6-positions. These positions cover all possible orientations of the alkyl group around the molecule, which also enables different orientations of the hydroxy group (which can be titrated) towards water when the compounds are included in the microaggregates. We also address some relevant photophysical properties of the synthesized compounds.

Results and Discussion

Synthesis

Introduction of alkyl side chains with eight and ten carbon atoms in the 3-positions of the flavylium salts **1** and **2** was possible by means of a reaction between 2,4-dihydroxybenzaldehyde and decanophenone or dodecanophenone (Scheme 1). Compounds **1** and **2** were isolated in 36% and 43% yields, respectively.



1 $n = 4$

2 $n = 6$

Scheme 1. Synthesis of flavylium salts containing an alkyl side chain in position 3

The presence of the alkyl side chains in the flavylium salts **1** and **2** was confirmed by analysis of their ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum of **1**, for example, the resonances corresponding to the protons of the alkyl side chain were observed as two triplets at $\delta = 0.43$ (8′′-H) and 2.59 ppm (1′′-H), one multiplet at $\delta = 0.81-0.92$ ppm (3′′-H-7′′-H) and one broad singlet at $\delta = 1.31$ ppm (2′′-H) (see Exp. Sect.). In the ^{13}C NMR spectra the signals corresponding to the carbon atoms of the alkyl chain were observed between $\delta = 14.4$ and 32.9 ppm (Figure 2).

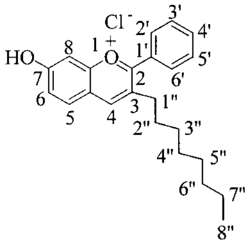
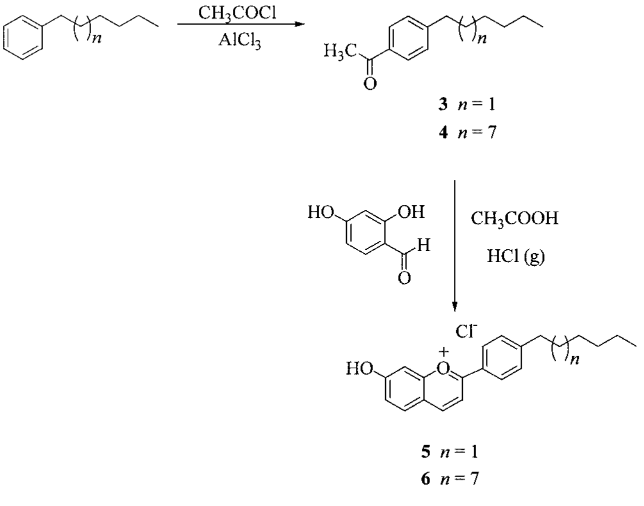


Figure 2. Labelled carbon atoms of the flavylium salts

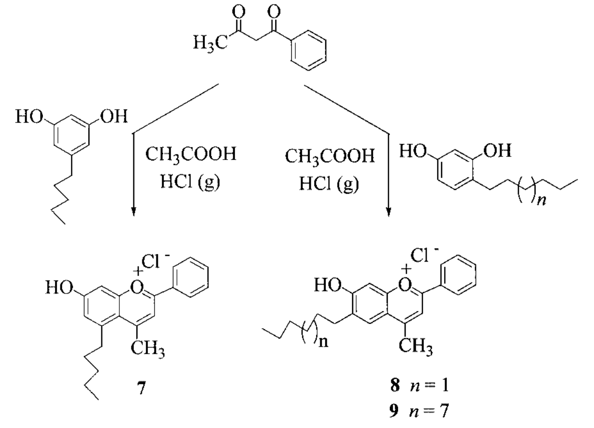
The 4′-hexyl- and 4′-dodecylacetophenone **3** and **4** (for use in the synthesis of the flavylium salts **5** and **6**) were prepared by Friedel−Crafts acylation of phenylhexane or phenyldodecane with acetyl chloride in the presence of aluminium chloride (Scheme 2). The singlets at $\delta = 2.55$ ppm (CH_3) in the ^1H NMR spectra of the compounds **3** and **4**, and vibrations corresponding to the C=O group in the infrared spectra, at 1682 cm^{-1} for **3** and 1679 cm^{-1} for **4**, confirmed the insertion of the acetyl group.



Scheme 2. Synthesis of flavylium salts containing an alkyl side chain in position 4′

The reaction between the 4′-hexyl- and 4′-dodecylacetophenone and 2,4-dihydroxybenzaldehyde allowed the preparation of the flavylium salts **5** and **6** in 48% and 73% yields, respectively (Scheme 2). Analysis of the ^1H and ^{13}C NMR spectra confirmed the presence of the alkyl chains in the structures of the flavylium salts **5** and **6** (see Exp. Sect.).

Flavylium salts **7−9** with alkyl side chains in their 5- and 6-positions were isolated from reactions between benzoylacetone and 4- or 5-alkylresorcinol derivatives (Scheme 3). The flavylium salt **7**, containing an alkyl side chain with five carbon atoms, was prepared in 67% yield from 5-pentylresorcinol, while the flavylium salts **8** and **9**, containing alkyl side chains with six and twelve carbon atoms, respectively, were obtained from 4-hexyl- or 4-dodecylresorcinol in 71% and 99% yields, respectively.



Scheme 3. Synthesis of flavylium salts containing an alkyl side chain in positions 5 and 6

Relevant Physical and Spectroscopic Properties

All the flavylium salts (**1**, **2**, **5−9**) are insoluble or sparingly soluble in water, but dissolve in water/non-aqueous mixtures when the non-aqueous solvent (e.g., methanol, polyethylene glycol, acetonitrile) is above 20−30% (v/v). For compounds with alkyl side chains containing more than 10 carbon atoms (**6** and **9**), the fraction of non-aqueous solvent had to be raised above 40% in order to make them soluble in these mixtures. Additionally, there is some evidence for self-aggregation (micelle formation) of these compounds in the above mixtures. Specifically, there is a decrease in the surface tension with increasing concentration of the flavylium salt, which is now under detailed study. Along with that, and regardless of the pH, all of the newly synthesized compounds readily incorporate into aqueous dispersions of anionic (SDS), cationic (CTAB) or neutral (Triton X-100, $C_{12}E_{10}$) surfactants above their critical micelle concentrations.

Absorption spectra of **8** in aqueous solutions of SDS and CTAB micelles (Figure 3, a and b) show the flavylium cation $\mathbf{AH^+}$ absorption at low pH values ($\lambda_{max} \approx 430$ nm), while this is progressively replaced by the spectrum of the deprotonated base form A ($\lambda_{max} \approx 480$ nm) at higher pH values. The isosbestic point indicates that only these two forms are present. Predominance of the base form at less acidic pH values is typical of 4-methyl-substituted flavylium salts.[39] This is an advantage for study of the acid-base equilibrium with little interference from the other equilibria of flavylium salts (Scheme 4): hydration (K_h), tautomerisation (K_t) and isomerisation (K_i).

The effect of the micelle charge on the acid-base equilibrium of **8** can be appreciated in Figure 3, c [pK_a(CTAB) = 2.05 and pK_a(SDS) = 7.05]. The five orders of magnitude change in the acidity constant K_a is much larger than the variation in the effective proton concentration at the micelle surface between CTAB and SDS.[40] Instead, it reflects the strong effect of the micelle charge on the deprotonation rate constants, the flavylium cation being stabilised by the negatively charged SDS micelle and destabilised by the positively charged CTAB micelle.[31] The proton-transfer rate constants of these compounds can be evaluated from light-

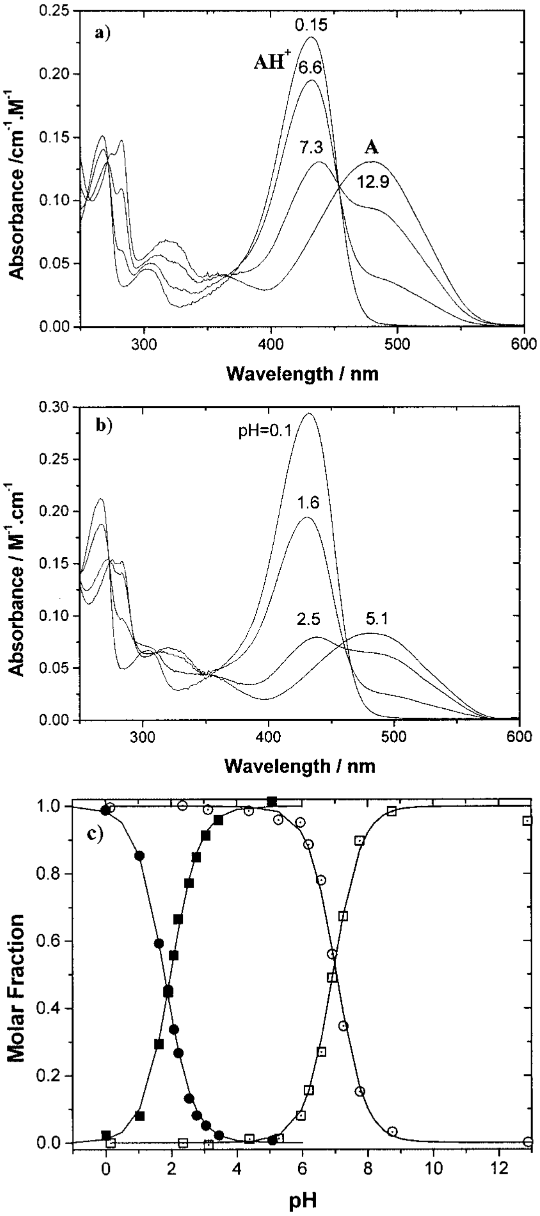
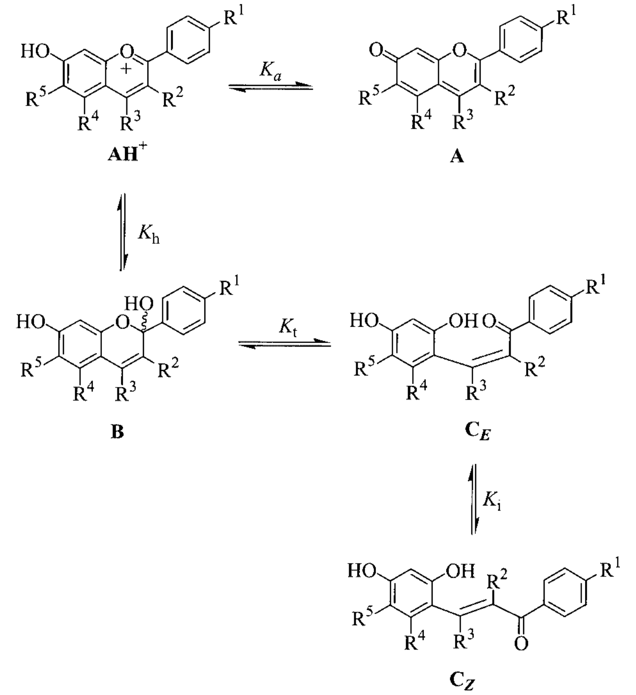


Figure 3. Absorption spectra of **8** in aqueous solutions of: (a) SDS 20 mM micelles, and (b) CTAB 20 mM micelles, at the labelled pH values, and (c) Hendersson−Hasselbach plots for the titration of **8** in the same micelle solutions of SDS (filled symbols) and CTAB (open symbols)



Scheme 4

jump experiments,[41] and so compound **8** (and probably **7** and **9**) can be regarded as useful probes of interfacial effects on the kinetics and energetics of proton transfer.

In Figure 4, fluorescence spectra of **8** in SDS (see a in Figure 4) and CTAB (see b in Figure 4) micelles show, in addition to the emission of the flavylium cation ($\lambda_{max} \approx$ 480 nm), the emission of the base form ($\lambda_{max} \approx$ 580 nm). The emission spectrum of **8** in CTAC, at pH = 0.01, shows strong emission of the base form, even though this form does not exist in the ground state at that pH (see b and c in Figure 3). This observation demonstrates the occurrence of ultra-fast excited-state proton transfer (ESPT) from the flavylium cation to water, as observed with all studied synthetic and natural anthocyanins.[13,39,42] In water, excited state deprotonation of 4-methyl-substituted flavylium salts is actually controlled by the Debye relaxation time of water (ca. 6–7 ps).[12] Compound **8** can thus be used to examine the effect of interfaces (micelle, membrane, etc.) on water mobility (water structure) in the interface vicinity, by measurement of the excited state deprotonation rate constant in such media. Such studies are not possible with water-soluble non-functionalised flavylium salts, due to the low efficiency of incorporation into the interface.[31]

A second interesting example of the spectroscopic properties of the synthesized compounds is illustrated with **5**. The predominant form of this compound (as well as **6**) at less acidic pH values is the $\mathbf{C_Z}$-chalcone form[43] ($\lambda_{max} \approx$ 380 nm), rather than the base (spectrum in SDS, at pH = 7.74, in Figure 5). The apparent pK_{app} is heavily dependent on the surfactant, as found with **8** (5.1, and 0.5 in SDS and $C_{12}E_{10}$ micelles). The predomination of the $\mathbf{C_Z}$ form, at less acidic pH values, is typical of 4′-substituted flavylium salts.[44] Excitation of the $\mathbf{C_Z}$, in the near UV, displaces the equilibrium towards the flavylium cation, through excited state $\mathbf{C_Z}/\mathbf{C_E}$ isomerisation,[43] thus converting the solution colour from pale yellow to deep orange (i.e., **5** is photochromic).[44] Tuning of this photochromic effect in microaggregates is now possible with the aid of the functionalised compounds **5** and **6**.

The 3-substituted flavylium salts (compounds **1** and **2**) mimic the behaviour of natural anthocyanins in the sense

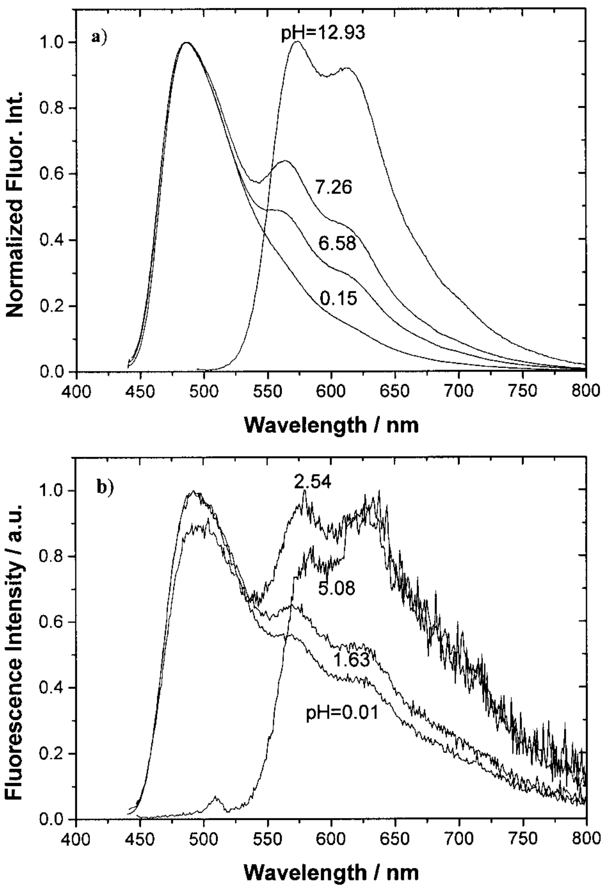


Figure 4. Normalised fluorescence spectra of **8** ($\lambda_{excitation}$ = 430 nm) in aqueous solution of: (a) SDS 20 mM micelles, and (b) CTAB 20 mM micelles at the labelled pH values; emissions of the flavylium cation and of the base form are observed at $\lambda_{max} \approx$ 480 nm and 580 nm, respectively

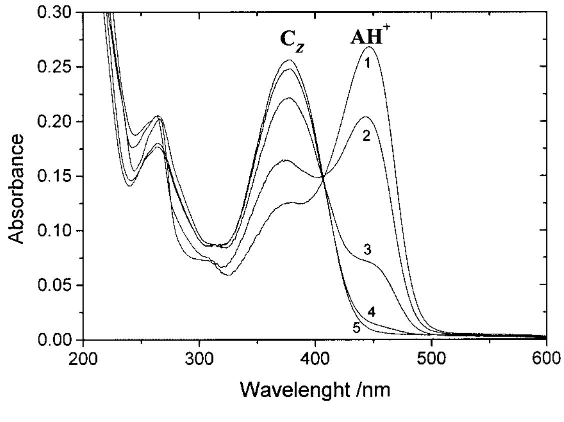


Figure 5. Absorption spectra of **5** in aqueous solution of $C_{12}E_{10}$ 20 mM at pH values: (1) 0.06; (2) 0.43; (3) 1.13; (4) 2.18; (5) 2.92

that the hemiacetal ($\lambda_{max} \approx 280$ nm) and the $\mathbf{C_E}$ forms are the most stable at less acidic pH values (Figure 6). Alkylation at the 3-position decreases the apparent pK_{app} (approximately equal to the hydration pK_h in the case of **1**) to ca. 4.8 in SDS micelles and 0.05 in $C_{12}E_{10}$ micelles. This property is convenient for study of co-pigmentation effects (colour stabilisation)[45] and excited state electron transfer[14] of hydrophobic co-pigments such as flavones, which solubilize in micelles.

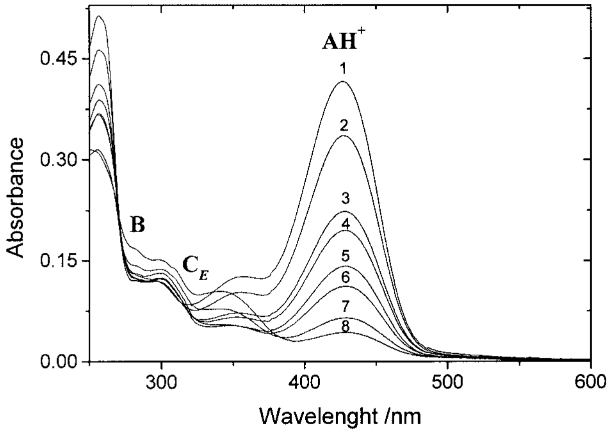


Figure 6. Absorption spectra of **1** in aqueous solution of $C_{12}E_{10}$ 20 mM at pH values: (1) −0.61; (2) −0.31; (3) 0.06; (4) 0.18; (5) 0.44; (6) 0.58; (7) 0.96; (8) 1.22

Conclusion

Flavylium salts with alkyl side chains in their 3-, 4′-, 5- or 6-positions can be prepared in moderate to excellent yields by an easy one-step method. These compounds have several potential applications in the area of self-assembled and interface systems, due to the remarkable chemical versatility of flavylium salts, both in the ground and in the excited states (multiequilibria, photochromism and ultrafast proton and electron transfer in the excited state).

Experimental Section

General Remarks: Melting points were determined with a Büchi 530 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX 300 spectrometer. IR spectra were recorded with a Unicam Mattson model 7000 FTIR spectrometer, UV/Vis absorption spectra with a Olis Cary-15 spectrophotometer conversion, and fluorescence spectra with a SPEX Fluorolog 212 in L conformation. The pH was measured at 20 °C with a Crison micropH 2002, with the exception of very acidic solutions (pH < 2), for which values of proton concentration ($HClO_4$) were used. Microanalyses were performed at the Elemental Analysis Service of ITQB and the mass spectra were recorded at the Mass Spectrometry Service of ITQB.

General Procedure for the Preparation of 4′-Hexyl- and 4′-Dodecylacetophenones (3 and 4): Acetyl chloride (2.3 mL, 32 mmol) was added dropwise over 5 min to a mixture of aluminium chloride (16 mmol) and phenylhexane or phenyldodecane (16 mmol). After having been heated at 50 °C for 1 h, the reaction mixture was cooled to room temperature and poured into ice and water (10 mL). The reaction mixture was extracted with dichloromethane (3 × 100 mL), dilute sodium hydroxide solution (2 × 50 mL) and water (2 × 50 mL), and was finally dried with sodium sulfate. After evaporation of the solvent, the product was purified by silica gel column chromatography with EtOAc/hexane (1:6) as eluent.

4′-Hexylacetophenone (3): Yellow oil. Yield 41% (1.34 g). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.86 (br. s, 3 H, 6′′-H), 1.28 (br. s, 6 H, 3′′-H to 5′′-H), 1.60 (br. s, 2 H, 2′′-H), 2.55 (s, 3 H, CH_3), 2.63 (t, J = 9.0, 6.0 Hz, 2 H, 1′′-H), 7.24 (d, J = 9.0 Hz, 2 H, 3′-H, 5′-H), 7.86 (d, J = 9.0 Hz, 2 H, 2′-H, 6′-H) ppm. IR (neat): $\tilde{\nu}$ = 1682 (C=O) cm^{-1}. $C_{14}H_{20}O$ (204.3): calcd. C 82.30, H 9.87; found C 82.62, H 9.93.

4′-Dodecylacetophenone (4): White solid. Yield 54% (2.49 g). M.p. 39−40 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.85 (t, J = 6.0 Hz, 3 H, 12′′-H), 1.18−1.27 (m, 18 H, 3′′-H to 11′′-H), 1.58−1.62 (m, 2 H, 2′′-H), 2.55 (s, 3 H, CH_3), 2.63 (t, J = 9.0 Hz, 2 H, 1′′-H), 7.24 (d, J = 9.0 Hz, 2 H, 3′-H, 5′-H), 7.85 (d, J = 9.0 Hz, 2 H, 2′-H, 6′-H) ppm. IR (neat): $\tilde{\nu}$ = 1679 (C=O) cm^{-1}. $C_{20}H_{32}O$ (288.5): calcd. C 83.27, H 11.18; found C 83.52, H 11.37.

General Procedure for the Preparation of 3- and 4′-Alkylflavylium Salts 1, 2, 5 and 6: Equimolar amounts of decanophenone, dodecanophenone, 4′-hexylacetophenone or 4′-dodecylacetophenone (2.4 mmol) and 2,4-dihydroxybenzaldehyde (2.4 mmol) were dissolved in acetic acid (20 mL). Gaseous hydrogen chloride was gently bubbled into the mixture (4 h). After stirring at room temperature for about 12 h, the reaction mixture was left at 0 °C for another 12 h. The precipitate was filtered off and washed with diethyl ether.

7-Hydroxy-3-octylflavylium Chloride (1): Red solid. Yield 36% (0.32 g). M.p. 159−161 °C. UV/Vis (MeOH/HCl): λ_{max} = 260, 300, 357, 425 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): δ = 0.43 (t, 3 H, J = 6.6, 6.9 Hz, 8′′-H), 0.81−0.92 (m, 10 H, 3′′-H to 7′′-H), 1.31 (br. s, 2 H, 2′′-H), 2.59 (t, J = 7.2, 8.1 Hz, 2 H, 1′′- H), 7.05 (s, 1 H, 8-H), 7.11 (d, J = 9.0 Hz, 1 H, 6-H), 7.26−7.35 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.54 (d, J = 7.2 Hz, 2 H, 2′-H, 6′-H), 7.87 (d, J = 9.0 Hz, 1 H, 5-H), 8.98 (s, 1 H, 4-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): δ = 14.4, 23.6, 30.1, 31.2, 31.9, 32.9, 103.0, 122.3, 124.5, 130.4, 131.2, 131.3, 131.8, 134.3, 134.5, 158.6, 161.8, 171.9, 173.1 ppm. ESI-MS: m/z = 335 for $C_{23}H_{27}O_2$. $C_{23}H_{27}ClO_2$ (370.9): calcd. C 74.48, H 7.34; found C 74.65, H 7.28.

3-Decyl-7-hydroxyflavylium Chloride (2): Dark green solid. Yield 43% (0.41 g). M.p. 145−147 °C. UV/Vis (MeOH/HCl): λ_{max} = 263, 300, 360, 428 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): δ = 0.22 (t, J = 5.7, 6.9 Hz, 3 H, 10′′-H), 0.59 (br. s, 14 H, 3′′-H to 9′′-H), 1.10 (br. s, 2 H, 2′′-H), 2.38 (t, J = 7.2 Hz, 2 H, 1′′-H), 6.84 (s, 1 H, 8-H), 6.90 (d, J = 9.0 Hz,1 H, 6-H), 7.07−7.13 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.33 (d, J = 7.2 Hz, 2 H, 2′-H, 6′-H), 7.66 (d, J = 9.0 Hz, 1 H, 5-H), 8.77 (s, 1 H, 4-H). ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): δ = 14.4, 23.6, 30.1, 30.3, 30.5, 30.6, 31.2, 31.8, 33.0, 102.9, 122.3, 124.5, 130.4, 131.2, 131.3, 131.9, 134.3, 134.5, 158.5, 161.8, 171.9, 173.1 ppm. ESI-MS: m/z = 363 for $C_{25}H_{31}O_2$. $C_{25}H_{31}ClO_2$ (399.0): calcd. C 75.26, H 7.83; found C 75.47 H 7.95.

4′-Hexyl-7-hydroxyflavylium Chloride (5): Yellow-green solid. Yield 48% (0.39 g). M.p. 155−157 °C. UV/Vis (MeOH/HCl): λ_{max} = 268, 305, 363, 445 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25

°C): $\delta = 0.26$ (t, $J = 6.6$ Hz, 3 H, 6′′-H), 0.71 (br. s, 6 H, 3′′-H, 4′′-H, 5′′-H), 1.07 (t, $J = 6.6$, 6.9 Hz, 2 H, 2′′-H), 2.16 (t, $J = 6.6$ Hz, 2 H, 1′′-H), 6.86 (d, $J = 9.0$ Hz, 1 H, 6-H), 6.94−6.97 (m, 3 H, 3′-H, 5′-H, 8-H), 7.62 (d, $J = 9.0$ Hz, 1 H, 5-H), 7.77−7.86 (m, 3 H, 3-H, 2′-H, 6′-H), 8.64 (d, $J = 8.4$ Hz, 1 H, 4-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 14.6$, 23.8, 30.2, 32.2, 33.0, 37.4, 104.0, 114.3, 121.5, 123.8, 128.3, 130.9, 131.7, 134.7, 154.7, 156.4, 161.4, 171.7, 173.7 ppm. ESI-MS: $m/z = 307$ for $C_{21}H_{23}O_2$. $C_{21}H_{23}ClO_2$ (342.9): calcd. C 73.57, H 6.76; found C73.77, H 6.81.

4′-Dodecyl-7-hydroxyflavylium Chloride (6): Brown solid. Yield 73% (0.74 g). UV/Vis (MeOH/HCl): $\lambda_{max} = 268$, 305, 363, 445 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 0.33$ (t, $J = 5.4$, 6.3 Hz, 3 H, 12′′-H), 0.72−0.80 (m, 17 H, 3′′-H-11′′-H), 1.16 (br. s, 2 H, 2′′-H), 2.25 (t, $J = 7.2$, 7.8 Hz, 2 H, 1′′-H), 6.94 (d, $J = 9.0$ Hz, 1 H, 6-H), 7.02−7.05 (m, 3 H, 3′-H, 5′-H, 8-H), 7.70 (d, $J = 9.0$ Hz, 1 H, 5-H), 7.86−7.95 (m, 3 H, 3-H, 2′-H, 6′-H), 8.72 (d, $J = 8.7$ Hz, 1 H, 4-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 14.7$, 21.3, 23.9, 30.5, 30.9, 32.3, 33.3, 37.5, 104.1, 114.4, 121.6, 123.8, 128.3, 131.0, 131.8, 134.8, 154.8, 156.5, 161.5, 171.7, 173.8 ppm. ESI-MS: $m/z = 391$ for $C_{27}H_{35}O_2$. $C_{27}H_{35}ClO_2$ (427.0): calcd. C 75.94, H 8.26; found C 75.99, H 8.55.

General Procedure for the Preparation of 5- and 6-Alkylflavylium Salts 7−9: These compounds were obtained from reactions between benzoylacetone and 5-pentyl-, 4′-hexyl- or 4′-dodecylresorcinol according to the general procedure for the preparation of 3- and 4′-alkylflavylium salts.

7-Hydroxy-4-methyl-5-pentylflavylium Chloride (7): Orange solid. Yield 67% (0.54 g). M.p. 98−100 °C. UV/Vis (MeOH/HCl): $\lambda_{max} = 303$, 380, 438 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 0.45$ (t, $J = 6.9$ Hz, 3 H, 5′′-H), 0.91−0.93 (m, 4 H, 3′′-H, 4′′-H), 1.30 (t, $J = 7.2$ Hz, 2 H, 2′′-H), 2.41 (t, $J = 7.2$, 8.1 Hz, 2 H, 1′′-H), 2.61 (s, 3 H, CH$_3$), 6.69 (s, 1 H, 6-H), 7.14 (s, 1 H, 8-H), 7.25−7.38 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.98−8.03 (m, 3 H, 2′-H, 6′-H, 3-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 14.3$, 23.4, 31.2, 32.5, 37.7, 109.9, 115.7, 117.7, 129.8, 130.6, 131.2, 137.3, 157.7, 160.4, 160.7, 171.5, 175.6 ppm. ESI-MS: $m/z = 307$ for $C_{21}H_{23}O_2$. $C_{21}H_{23}ClO_2$ (342.9): calcd. C 73.57, H 6.76; found C 73.80, H 6.85.

6-Hexyl-7-hydroxy-4-methylflavylium Chloride (8): Yellow solid, yield 71% (0.60 g). M.p. 192−194 °C. UV/Vis (MeOH/HCl): $\lambda_{max} = 265$, 300, 425 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 0.10$ (t, $J = 6.9$ Hz, 3 H, 6′′-H), 0.53−0.63 (m, 8 H, 3′′-H-5′′-H), 0.86−0.96 (m, 2 H, 2′′-H), 2.07 (t, $J = 7.5$, 8.1 Hz, 2 H, 1′′-H), 2.28 (s, 3 H, CH$_3$), 6.79 (s, 1 H, 8-H), 6.90−7.03 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.42 (s, 1 H, 5-H), 7.63−7.68 (m, 3 H, 3-H, 2′-H, 6′-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 14.1$, 23.3, 30.0, 30.1, 31.1, 32.5, 102.6, 115.7, 120.6, 128.2, 129.6, 130.1, 130.8, 136.2, 138.5, 158.8, 169.2, 169.7, 170.1 ppm. ESI-MS: $m/z = 321$ for $C_{22}H_{25}O_2$. $C_{22}H_{25}ClO_2$ (356.9): calcd. C 74.04, H 7.06; found C 74.13, H 7.24.

6-Dodecyl-7-hydroxy-4-methylflavylium Chloride (9): Yellow solid. Yield 99% (1.03 g). M.p. 165−167 °C. UV/Vis (MeOH/HCl): $\lambda_{max} = 265$, 300, 425 nm. ^{1}H NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 0.29$ (t, $J = 6.0$, 7.5 Hz, 3 H, 12′′-H), 0.69−0.81 (m, 18 H, 3′′-H-11′′-H), 1.14 (br. s, 2 H, 2′′-H), 2.29 (t, $J = 7.8$, 7.5 Hz, 2 H, 1′′-H), 2.49 (s, 3 H, CH$_3$), 6.99 (s, 1 H, 8-H), 7.12−7.23 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.64 (s, 1 H, 5-H), 7.85−7.90 (m, 3 H, 2′-H, 6′-H, 3-H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol + DCl, 25 °C): $\delta = 14.4$, 21.0, 23.7, 30.3, 30.4, 30.5, 30.6, 30.7, 31.4, 33.0, 102.9, 116.0, 120.8, 128.5, 129.9, 130.3, 131.1, 136.5, 138.8, 159.0, 169.5, 169.9, 170.4 ppm. ESI-MS: $m/z = 405$ for $C_{28}H_{37}O_2$. $C_{28}H_{37}ClO_2$ (441.1): calcd. C 76.25, H 8.46; found C 76.47, H 8.63.

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