Bio-Inspired Multistate Networks Responsive to Light, pH and Thermal Inputs – An Example of a Multistate System Operating Through Different Algorithms

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Two multistate networks based on 4′-acetamidoflavylium and 4′-aminoflavylium, possessing six- and sevenfold multistates, respectively, and that can be reversibly interchanged by inputs of light, pH jumps and heat, are characterized. The two networks are connected irreversibly, the 4′-acetamidoflavylium being transformable into the 4′-aminoflavylium by means of a heat input in extremely acidic solutions. The possibility of performing several different *write-read-erase* cycles, as models for optical memories operating by different algorithms, is discussed. An upper level of operation of these photochromic devices in which the algorithms are used as inputs to switch between the several memory cycles is proposed.

Introduction

The idea of using photochromic reactions as a "photochemical erasable memory" was introduced by Hirshberg in 1956.[1] Since then, a vast investigation into the properties of photochromic compounds has been carried out by various research groups spread all over the world.[2–8] An obvious extension of the "erasable memory" concept is the use of families of molecules, the chemical structures of which respond reversibly or irreversibly to inputs other than light. The study of molecules capable of responding chemically both to light and also to other different external inputs, creating a network of chemical responses, is the basic aim of this work.

In the context of supramolecular chemistry, the bottom up approach can be associated with the building of more or less complex molecular entities, starting from simple molecules.[9] The objective of this strategy is to obtain new properties and functions not present in the building blocks. However, the search for new properties and functions through increasing complexity can also be achieved through the use of a simple molecule capable of chemical transformations upon input of different external stimuli, such as light (photochromism),[2,3] pH variations (acidichromism),[6a,10] electric current (electrochromism),[11] or heat (thermochromism):[12] the so-called multistate molecules.[6a,13] The *cis-trans* photochromic molecules are examples of a dual-state system responding to light, while a diacid can be viewed as a triple-state molecule responding to a pH input. On this basis, the stimuli can be regarded as inputs of energy, resulting in some chemical response of the multistate molecule, such as a a change of colour. The different responses of a multistate molecule can be employed to accomplish particular functions, such as writing upon a light input or erasing after a pH jump, and in such a case a multistate/multifunctional system can be envisaged.

The need for complex multistate/multifunctional chemical systems that can be actuated to process multiple information through colour changes is in step with the predictions of a third wave of computing, usually referred as ubiquitous computing.[14] Ubiquitous computing will take place in computers imbedded in walls, chairs, clothing – in everything – and is fundamentally characterized by interconnection of everyday objects with computation, which will take place at many scales, including the microscopic.

One fascinating class of molecules are the synthetic flavylium salts.[15] These molecules have the same basic structures as anthocyanins, the ubiquitous colorants of flowers and fruits. Even more interesting is the fact that the complex pH-dependent network of chemical reactions that occur in anthocyanins, study of which was triggered in the last century by the need to understand the colouring phenomena in plants, is also mirrored in synthetic flavylium salts. In this sense the synthetic flavylium salts can be viewed as *bio-inspired* molecules, the multistates of which, and their respective kinetic processes of interconversion,

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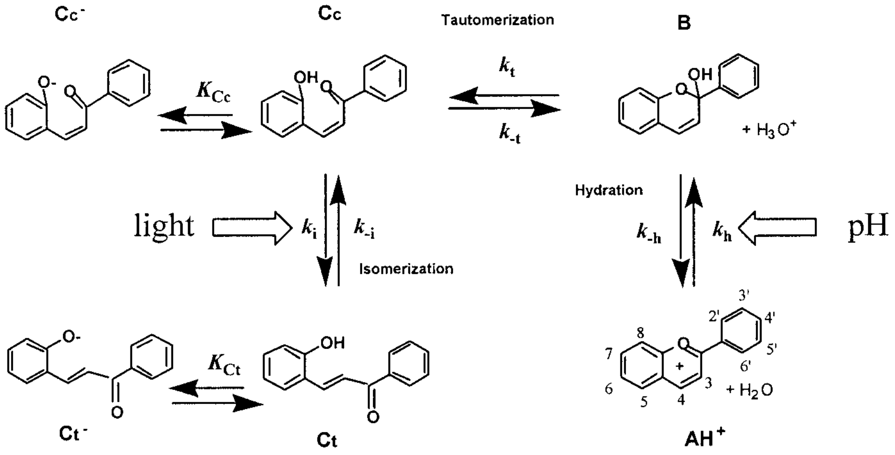
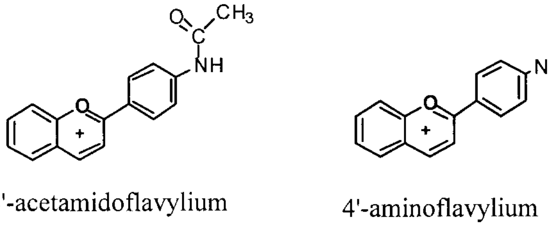


Scheme 1.

should be tuneable by careful choice of substituents to insert in the 2-phenylbenzo[*b*]pyrilium (flavylium) backbone (Scheme 1).

Scheme 1 shows the species expected for both flavylium compounds, on the basis of the anthocyanin pattern. The flavylium salt **AH**$^+$ is the thermodynamically stable species at acidic pH values; with increasing pH a hydration reaction occurs, producing the hemiketal species **B**. The rate of the hydration reaction is highly dependent on the pH, and typically occurs in timescales of seconds or fractions of a second. The hemiketal can open its ring to afford the *cis*-chalcone **Cc**. This reaction also occurs on subsecond timescales, and is only slightly dependent on the pH. Finally, the *trans*-chalcone **Ct** is obtained from its *cis* isomer on a timescale that can vary from several minutes to days (even months), depending on the substituents. In the case of anthocyanins, the benzopyrylium is substituted by at least two hydroxy groups, necessarily in positions 4′ and 7, and, in consequence, quinoidal bases **A**, or ionized quinoidal bases, are formed (kinetic products) immediately after a suitable pH jump. The network of reactions is reversible, but usually the kinetic pathways are not the same, which is an additional challenge offered by the system. In basic media the ionized chalcones **Cc**$^-$ and **Ct**$^-$ are also formed, Scheme 1.

In previous works we have described several flavylium-based multistate systems.[6] A further step, providing an increase in complexity and allowing the definition of more functions, is the design of a multistate system able to evolve into a different one upon a specific input, each system operating by its own kinetic and thermodynamic rules. The achievement of this goal is the immediate objective of this work, and it can be accomplished through the design of two networks based on 4′-acetamidoflavylium and 4′-aminoflavylium (Scheme 2) and through the fact that 4′-acetamidoflavylium hydrolysis forms the 4′-aminoflavylium in highly acidic solutions.



Scheme 2.

Results and Discussion

The 4′-Acetamidoflavylium Network

Pseudoequilibrium 1

The pH-dependent absorption spectra of the compound 4′-acetamidoflavylium, obtained immediately after a pH jump from a stock solution at pH = 1.5, are represented in Figure 1<yigr1>.[16] Absorption spectra were also measured with pH jumps from [HCl] = 12 M up to pH 1.0 (not shown) without significant variations, indicating a lack of protonation of the amide nitrogen, in contrast with the behaviour observed in the parent compounds containing amino substituents,[6e] in particular with 4′-aminoflavylium (see below).

The spectra shown in part A of Figure 1 are dominated by the orange absorption of the flavylium cation, with a maximum at 438 nm ($\varepsilon = 28700\ \mathrm{cm^{-1}\,M^{-1}}$). Increasing of the pH results in the disappearance of the flavylium absorption to give the hemiketal **B**, in equilibrium with the *cis*-chalcone species **Cc**. Because a *cis-trans* kinetic barrier is present in this compound (see below), a *pseudoequilibrium state* involving the species **AH**$^+$, **B** and **Cc** is established, as illustrated by Equations (1), (2) and (3).

$$\mathbf{AH^+} + H_2O \rightleftharpoons \mathbf{B} + H^+ \qquad K_h \qquad (1)$$

$$\mathbf{B} \rightleftharpoons \mathbf{Cc} \qquad K_t \qquad (2)$$

This set of equations can be simplified by a single acid-base equilibrium as follows:[6a]

$$\mathbf{AH^+} \rightleftharpoons \mathbf{CB} + H^+ \qquad K_a \qquad (3)$$

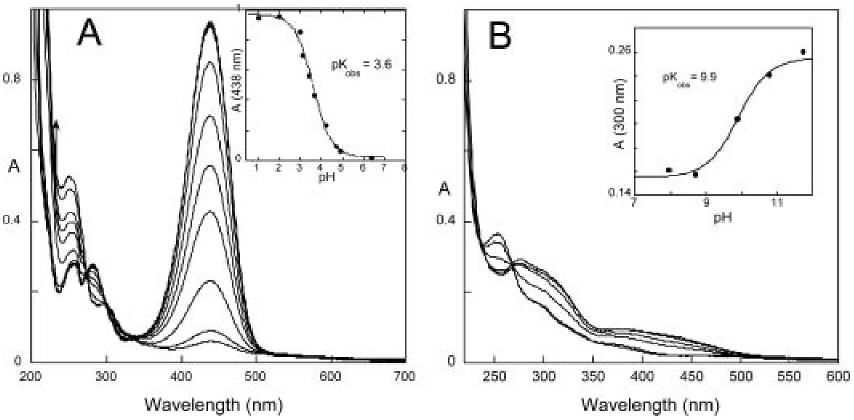


Figure 1. Absorption spectra of the compound 4′-acetamidoflaylium (3.3×10^{-5} M), in the acidic (A) and basic (B) regions, taken immediately after a pH jump from a freshly prepared stock solution at pH = 1.5.

where [**CB**] = [**B**] + [**Cc**], and $K_a = K_h + K_hK_t$.

According to Equation (3) the mol fraction distribution of the flavylium cation as a function of pH – and consequently its absorption – follows a typical acid-base sigmoid curve, the inflection point of which is attained for $[H^+] = K_a = 10^{-3.6}$, as shown in the inset of Figure 1, part A.

In order to obtain the equilibrium constant K_t, stopped-flow experiments were carried out (Figure 2, A). The pH of the stock solution ($\mathbf{AH^+}$ species at pH = 1.5) was changed to ca. 7 and the species **Cc** and **B** formed. Because of the *cis-trans* thermal barrier, formation of **Ct** is very slow, and the pseudoequilibrium is maintained for a long period of time (lifetime 15.4 hours, at room temperature, Figure 3, A). A reverse pH jump back to acid was performed on the solution containing the species **B** and **Cc** (pseudoequilibrium), and followed by stopped flow. The traces monitored at 438 nm indicate the formation of the $\mathbf{AH^+}$ species at the expense of **B** and **Cc**. As previously reported for similar flavylium compounds possessing identical thermal barriers,[6d,15] the $\mathbf{AH^+}$ species is formed through two consecutive processes, both following first-order kinetics. The first one is faster and its rate constant highly dependent on pH. It can be assigned to the (reverse) process reported in Equation (1), $k_{obs1} = k_h + k_{-h}[H^+]$. The second (slower) process is the formation of flavylium cation from **Cc** through **B** [Equation (2)], the observed rate constant of which should be $k_{obs2} \approx k_{-t}$, because there is no reversibility: the **B** formed from **Cc** (rate k_{-t}) is not accumulated and immediately produces $\mathbf{AH^+}$, and in consequence the step of **Cc** formation from **B** is not observed. On the other hand, the equilibrium constant K_t = [**Cc**]/[**B**], can be calculated from the amplitudes of the two exponentials, the first proportional to the equilibrium concentration of **B** and the second to the equilibrium concentration of **Cc**, giving K_t = 0.19. This value permits the calculation of $K_h = 2.1 \times 10^{-4}$ M, from $K_a = K_h + K_hK_t$ obtained through the fitting of Equation (3), see inset Figure 1, A.

Additional information can be obtained from the stopped-flow experiments by representing the two rate constants as a function of proton concentration (Figure 2, B).

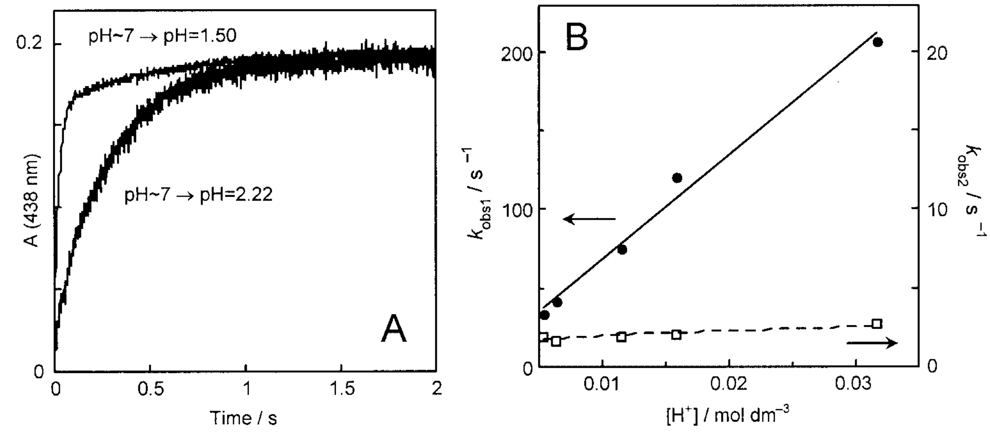


Figure 2. Reverse pH jumps, followed by stopped flow, from freshly prepared solutions of 4′-acetamidoflavylium at pH ca. 7 to several acidic pH values (A); observed rate constants from the biexponential fitting of the kinetic traces (B).

With regard to the hydration reaction, the slope of the curve and the intercept give $k_{-h} = 6.6 \times 10^3\ \mathrm{s^{-1}\,M^{-1}}$, and $k_h = 2.0\ \mathrm{s^{-1}}$, respectively, which compares with $k_h = 1.4\ \mathrm{s^{-1}}$ calculated from the product $k_{-h}K_h$.[17] The data shown in Figure 2 also allow the ring-closure constant to be measured, giving a pH-independent component equal to $k_{-t} = 1.5\ \mathrm{s^{-1}}$, as well as another component dependent on pH, equal to $34 \times [\mathrm{H^+}]\ \mathrm{s^{-1}}$. From the equilibrium constant K_t, the value for the rate constant $k_t = 0.29\ \mathrm{s^{-1}}$ can also be calculated. In a second series of pH jumps (direct pH jumps) the stock solution was subjected to a pH jump from pH = 1.5 to the basic region. The traces (not shown) are compatible with a first-order kinetic process in which the rate constant changes with pH according to $k_{obs} = 1.5 + 4 \times 10^5 \times [\mathrm{OH^-}]\ \mathrm{s^{-1}}$. The first term of this equation is due to the hydration and tautomerization reactions giving a mixture of **B** and **Cc** (see Table 2).[18] At higher pH values $\mathrm{OH^-}$ attack takes place and the associated rate constant is equal to $4 \times 10^5\ \mathrm{s^{-1}\,M^{-1}}$. The final product is the $\mathbf{Cc^-}$ species, which further isomerizes very slowly (see below).

Figure 1 (B) shows the spectra obtained immediately after a pH jump to the basic region. In this case Equation (4) has to be added to the system in order to account for the formation of the ionized *cis*-chalcone.

$$\mathbf{Cc} \rightleftharpoons \mathbf{Cc^-} + \mathrm{H^+} \qquad K_{Cc} \qquad (4)$$

It is easy to show that the inflection point of the inset of Figure 1 (B) is reached for $[\mathrm{H^+}] = K_{Cc}K_t/(1 + K_t) = 10^{-9.9}$, allowing calculation of $K_{Cc} = 10^{-9.1}$.

Thermodynamic Equilibrium

When the system is allowed to reach equilibrium, two more equations have to be added in order to account for the formation of the *trans*-chalcones [Equation (5) and Equation (6)].

$$\mathbf{Cc} \rightleftharpoons \mathbf{Ct} \qquad K_i \qquad (5)$$

$$\mathbf{Ct} \rightleftharpoons \mathbf{Ct^-} + \mathrm{H^+} \qquad K_{Ct} \qquad (6)$$

Figure 3 provides the spectral variations after four days in basic and acidic media. Comparison of Figure 3 with Figure 1 shows the characteristic absorption of the *trans*-chalcones of flavylium compounds, which are known to have higher molar absorption coefficients than the *cis* analogues.

In acidic media, Equations (1), (2) and (5) account for the observed equilibria. As previously reported, these three equilibria can be simplified as a single one as presented in Equation (7).[19]

$$\mathbf{AH^+} \rightleftharpoons \mathbf{CB} + \mathrm{H^+} \qquad K'_a \qquad (7)$$

where $[\mathbf{CB}] = [\mathbf{B}] + [\mathbf{Cc}] + [\mathbf{Ct}]$, and $K'_a = K_h + K_hK_t + K_hK_tK_i$

As in the pseudoequilibrium, the variation of the flavylium absorption as a function of pH follows a sigmoid curve in this case with inflection for $[\mathrm{H^+}] = K'_a$. The difference between $K'_a - K_a = K_hK_tK_i$ allows K_i to be calculated from the values of K_h and K_t previously obtained from the pseudoequilibrium and stopped-flow experiments. In the current compound the 4′-acetamidoflavylium is not stable at more acidic pH values and formation of the analogous compound 4′-aminoflavylium occurs (see below). This behaviour impedes the definition of the thermodynamic state at lower pH values and for this reason the calculated value of $K_i = 14$ is given with some uncertainty.

In basic media the *trans*-chalcone (**Ct**) species and its ionized form ($\mathbf{Ct^-}$) prevail. The spectrum corresponding to the thermodynamic equilibrium reached after four days (Figure 3, B) is slightly different from the spectrum obtained from the pH titration of the thermally equilibrated $\mathbf{Ct^-}$ species (Figure 3, C), due to the existence of a thermal barrier to *cis-trans* isomerization. In other words, the spectra shown in Figure 3 (C) exclusively concern the species **Ct** and $\mathbf{Ct^-}$, the protonation constant of which is $K_{Ct} = 10^{-8.55}$, while the spectra shown in Figure 3 (B) represent the thermodynamic equilibrium, in which, depending on pH, there is a mixture of **Ct**, $\mathbf{Ct^-}$ and the minor species **B(Cc)**.

Isomerization Kinetics

Figure 4 shows the slow absorption variations occurring after a pH jump from the stock solution (pH = 1.5) to pH = 6.25 and 11.1. The spectra are compatible with the conversion of **Cc** and **B** to **Ct** (pH = 6.25) and $\mathbf{Cc^-}$ to $\mathbf{Ct^-}$ (pH = 11.1), and both processes follow first-order kinetics with

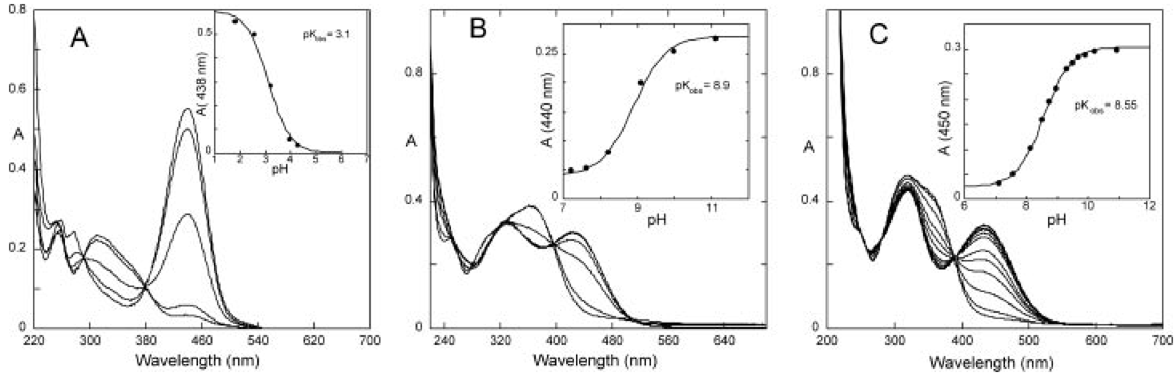


Figure 3. Spectral variations of the compound 4′-acetamidoflavylium (3.3×10^{-5} M) after 4 days at room temperature in the dark, as a function of pH: A) acid and B) basic region, C) titration of $\mathbf{Ct^-}$/**Ct** from an equilibrated solution of $\mathbf{Ct^-}$ at pH = 11.0.

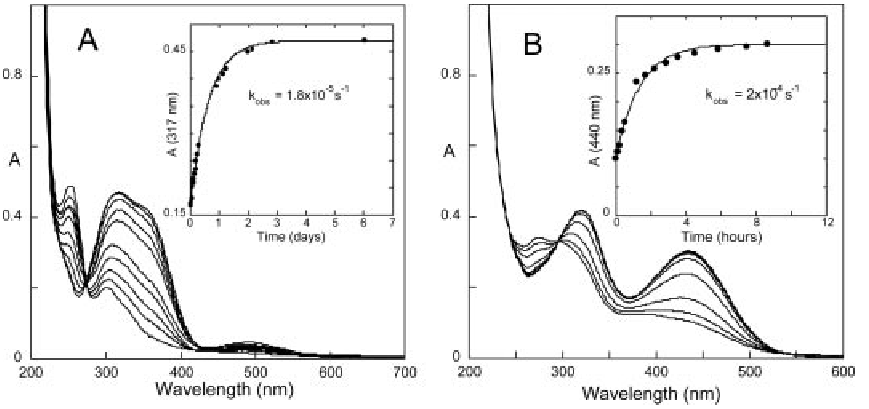


Figure 4. A) Spectral variations of the compound 4′-acetamidoflavylium (3.3×10^{-5} M) at pH 6.25, room temperature. B) The same at pH 11.1.

observed rate constants equal to 1.8×10^{-5} s^{-1} and 2.0×10^{-4} s^{-1}, respectively. On the other hand, the equilibriumconstant $K'_i = k'_i/k'_{-i} = 50$ can be calculated from Equations (4) to (6) into Equation (8).

$$\mathbf{Cc}^- \rightleftharpoons \mathbf{Ct}^- \qquad K'_i = K_i K_{\mathrm{ct}}/K_{Cc} \tag{8}$$

In order to measure the kinetic constants of the isomerization reaction, it must be assumed that the observed rate constant for the **Ct** formation is given by Equation (9), where $K_t/(1 + K_t)$ is the fraction of **Cc** in the tautomeric equilibrium.

$$k_{obs} = \frac{K_t}{1 + K_t} \tag{9}$$

Table 1 summarizes the equilibrium constants and Table 2 the rate constants calculated for the compound 4′-acetamidoflavylium, as well as for 4′-aminoflavylium (see below).

Table 1. Equilibrium constants of both networks at 25 °C, defined by Equations (1), (2), (4) and (5) – (7).

	4′-Acetamidoflavylium	4′-Aminoflavylium
K_h [M]	$(2.10\pm0.09)\times10^{-4}$	$(2.8\pm0.1)\times10^{-8}$
K_t	0.19 ± 0.01	212 ± 1
K_i	14 ± 2	130 ± 17
pK_{Cc}	9.1 ± 0.1	9.6 ± 0.1
pK_{Ct}	8.55 ± 0.05	8.55 ± 0.05
K'_I	50 ± 4	$(1.5\pm0.1)\times10^3$
K_{Ct+}	–	2.00 ± 0.05

Pseudoequilibrium 2

Pseudoequilibrium 2 is different from the previous one, because it originates from the thermally equilibrated **Ct**$^-$ species, which can give the **Ct** analogue [Equation (6)] with decreasing pH (and **Ct**$^+$ in the case of 4′-aminoflavylium; see below). The existence of this pseudoequilibrium is also a consequence of the *cis-trans* isomerization thermal barrier. It is worth noting the fact that at pH = 1.0 the metastable **Ct** species is very stable in the dark (ca. 7% of flavylium formation after 8 days).

Table 2. Rate constants of both networks, see Scheme 1, T = 25 °C.

	4′-Acetamidoflavylium	4′-Aminoflavylium
k_h [s^{-1}]	1.4 ± 0.3	$(2.8\pm0.6)\times10^{-5}$
k_{-h} [s^{-1} M^{-1}]	$(6.6\pm0.4)\times10^3$	$(1.00\pm0.06)\times10^3$
k_t [s^{-1}]	0.29 ± 0.02	80 ± 6
k_{-t} [s^{-1}]	1.5 ± 0.1	3.7 ± 0.2
k_i [s^{-1}]	$(7.8\pm0.6)\times10^{-5}$	$(4.8\pm0.5)\times10^{-6}$
k_{-i} [s^{-1}]	$(5.6\pm0.6)\times10^{-6}$	$(3.7\pm0.4)\times10^{-8}$
k'_i [s^{-1}]	$(2.0\pm0.2)\times10^{-4}$	$(4.3\pm0.4)\times10^{-6}$
k'_{-i} [s^{-1}]	$(3.9\pm0.4)\times10^{-6}$	$(3.0\pm0.3)\times10^{-9}$
k_h^{OH} [s^{-1} M^{-1}]	$(4.0\pm0.4)\times10^5$	$(9.3\pm0.5)\times10^4$

Photochemistry

Part A of Figure 5 shows the spectral variations obtained upon irradiation (365 nm) of the *trans*-chalcone form of the compound 4′-acetamidoflavylium at pH = 1.6 and room temperature. The *trans*-chalcone is metastable at this pH value, and no significant formation of flavylium is obtained after two days in the dark at room temperature, due to the existence of a *cis-trans* isomerization barrier. Upon irradiation, however, the orange colour of the flavylium cation is observed; the quantum yield of this photochemical reaction is 0.09. In Figure 5 (B) the irradiation was carried out with the **C**t species at pH = 6.1. In this case spontaneous formation of the flavylium cation is prevented for thermodynamic reasons, so only **Cc** and **B** are formed. However, the photochemical process is reversible because a photostationary state is reached, as can be shown by comparison of the absorption spectrum of the **Cc** and **B** species (recorded immediately after a pH jump from the stock solution to pH = 6.1; traced line in part B of Figure 5) with the absorption spectrum of the stationary state. In effect, the **Ct** species is not completely converted into **B** and **Cc**. The quantum yield for the *cis* to *trans* photoisomerization can be evaluated (Φ = 0.5), taking into account that in a photostationary state the product of the absorbed light by each species multiplied by the corresponding quantum yield should be equal. Irradiation of the **Cc**$^-$ species (formed upon a pH jump from

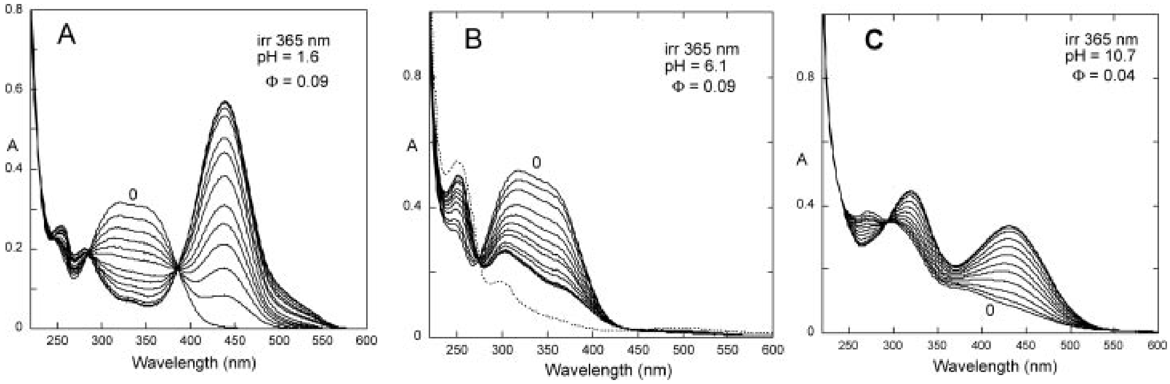


Figure 5. A) Irradiation (365 nm) of the *trans*-chalcone (**Ct**) form of the compound 4′-acetamidoflavylium (3.3×10^{-5} M) at pH = 1.6 (metastable; $I_0 = 2.98\times10^{-7}$ Einstein min^{-1}). B) The same at pH 6.1, **Ct** form, traced line the absorption spectrum of a freshly prepared solution of **Cc/B**. C) Irradiation of 4′-acetamidoflavylium at pH = 11.0, immediately prepared from the stock solution at pH = 1.6; **Cc**$^-$ form.

Table 3. Quantum yields[a] for the photochemical reactions reported in this work, λ_{irr} = 365 nm.

	Ct ⇒ AH$^+$	Ct ⇒ B + Cc	Cc ⇒ Ct	Cc$^-$ ⇒ Ct$^-$	Cc$^+$ ⇒ AH$^+$
4′-acetamidoflavylium	0.09	0.09	0.5	0.04	–
4′-aminoflavylium	–	–	0.4	0.2	0.06

[a] Estimated error of ±15%.

the stock solution to pH = 11.0) at 365 nm was also performed (Figure 5, C). The spectral variations indicate formation of the **Ct**$^-$ species with a quantum yield of 0.04. As reported above in Figure 4 (B), the *cis*-*trans* isomerization **Cc**$^-$ to **Ct**$^-$ also takes place thermally, and there is a coincidence between the spectrum obtained upon irradiation, and the spectrum of the thermal equilibrium. This result indicates the photostability of the **Ct**$^-$ species; otherwise a photostationary state would be attained as in the case of Figure 5 (B). Table 3 summarises the quantum yields for each process in both compounds.

Hydrolysis of 4′-Acetamidoflavylium

During our studies it was verified that strongly acidic solutions of 4′-acetamidoflavylium are not stable. Investigation of the reaction product revealed it to be the analogue 4′-aminoflavylium (see Exp. Section). The kinetics of the process are dependent on the proton concentration, the highest rate being observed in concentrated HCl (Figure 6). Figure 6 (A) shows the conversion of 4′-acetamidoflavylium into 4′-aminoflavylium in concentrated HCl at room temperature. The same reaction was carried out at pH = 1.0

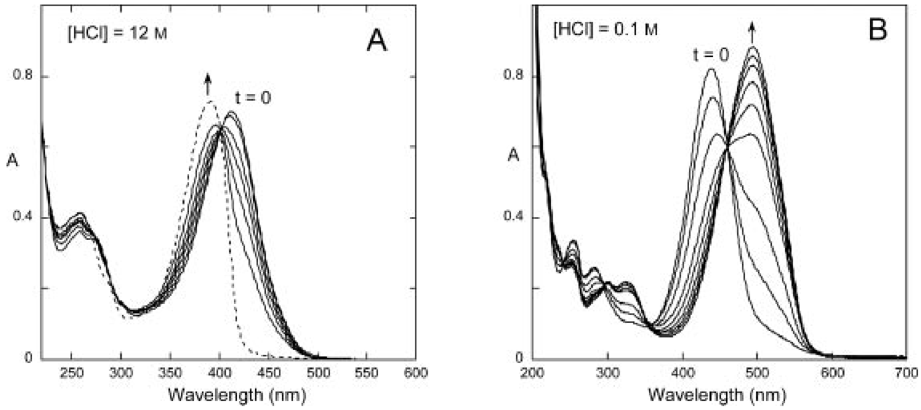


Figure 6. A) Absorption variations of 4′-acetamidoflavylium (3.3×10^{-5} M) in [HCl] = 12 M at room temperature, as a function of time: 0, 20, 90, 150, 240, 420, minutes (——), and 2 days (- - - -). B) The same at pH = 1.0 and 50 °C, for the following times: 0, 120, 365, 695, 925, 1170, 1280, 1480, 1740 min. The final product in both is the 4′-aminoflavylium analogue, protonated in A, and deprotonated in B.

and at 50 °C, with a rate constant equal to $2.5 \times 10^{-5}\,s^{-1}$ (see Figure 6, part B). At room temperature this reaction is very slow, and takes several weeks to reach completion, showing that the hydrolysis of the amido group is highly dependent on the proton concentration.

The conversion of the acetamido compound into the amino derivative can be explained by the occurrence of a hydrolysis reaction. In general, the hydrolysis of amides is a very slow reaction at room temperature, even under acidic or basic conditions, which are known to catalyse the reaction.[20] The reason for the rather efficient hydrolysis of 4′-acetamidoflavylium involves the very good properties of the 4′-aminoflavylium cation as leaving group, due to its delocalized positive charge. Efficient hydrolysis of similar amidoflavylium salts has also been observed in our group.

The 4′-Aminoflavylium Network

Pseudoequilibrium 1

Unlike 4′-acetamidoflavylium, the compound 4′-aminoflavylium can be protonated in extremely acidic solutions (see Figure 7, A), the inflection point being reached for [HCl] = ca. 2.5 м. Part B in Figure 7 shows the pH-dependent absorption spectrum of the compound 4′-aminoflavylium. The absorption spectra of the **AH**$^+$ species decreases with increasing pH, to give essentially the *cis*-chalcone in the neutral region (see below). In basic media (Figure 7, C) the spectra indicate the formation of ionized *cis*-chalcone species.

In order to provide more insight into the equilibrium between **Cc** and **B**, stopped-flow experiments were carried out. In a typical experiment, the solutions at pH = 8.2 (immediately prepared from the stock solution at pH 1.6), were subjected to a “reverse pH jump” back to acid (see Figure 8).

As shown in Figure 8A, the traces for **AH**$^+$ formation are compatible with the existence of two kinetic processes. At pH = 1.9 the faster process cannot be resolved by the apparatus, but its existence is confirmed by the fact that the extrapolated absorption for the initial time is not zero. In other words, there is a very fast process, the kinetics of which cannot be detected by the stopped flow, responsible for the initial absorbance at 497 nm (see inset of Figure 8, A). This process can be attributed to the transformation of

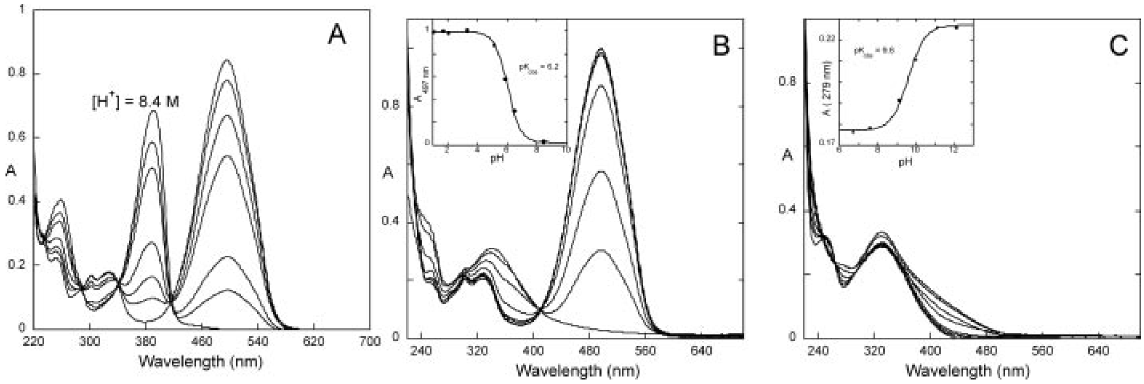


Figure 7. Spectral modifications of the compound 4′-aminoflavylium (3.3×10^{-5} м), obtained immediately after a pH jump from stock solutions at pH = 1.0 (A) to the very acidic region; [HCl](м) = 8.4, 4.2, 3.6, 2.4, 1.8, 1.2, 0.1 (B), neutral and acidic region: (C) basic region.

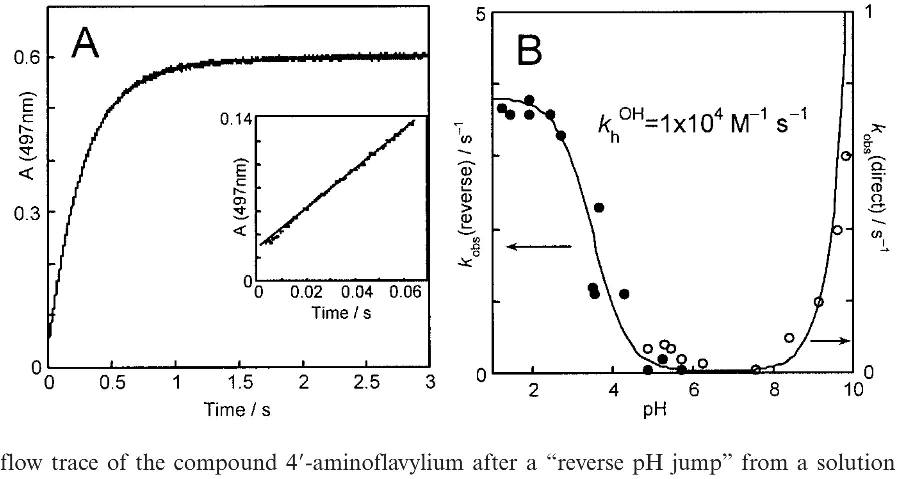


Figure 8. A) Stopped-flow trace of the compound 4′-aminoflavylium after a “reverse pH jump” from a solution at pH = 8.2 to pH = 1.9. Inset: detail of the curve for the initial times. B) Rate constants obtained by stopped flow as a function of proton concentration (○) direct pH jumps, from stock solutions at pH = 1.0; (•) reverse pH jumps, from “fresh” solutions at pH = 8.2 (obtained immediately after a pH jump from the stock solutions at pH = 1.0).

the small amount of **B** (in equilibrium with **Cc**) into **AH**$^+$. The second process can thus be assigned to the transformation of **Cc** into **AH**$^+$, through **B**. On this basis the tautomerization constant $K_t = 21.7$ can be calculated from the ratio between the amplitude of the exponential reported in Figure 8 (A) and the extrapolated initial absorbance. This value also permits the calculation of $K_h = 2.8 \times 10^{-8}$ M from the relationship $K_a = K_h + K_hK_t = 10^{-6.2}$.

Relevant information can be acquired from the pH dependence of the reverse pH jumps, as well as from the direct pH jumps carried out from the stock solution at pH = 1.0 to higher pH values (Figure 8, B). At low pH values (pH < 2.5) the rate constant of the reverse pH jumps reaches a plateau. This result can be interpreted in terms of the rate-determining step of the global process at these pH values being the tautomerization reaction, which is known to be only slightly pH-dependent.[6d,15] When the pH increases, the hydration reaction, which is highly dependent on the proton concentration, becomes slower and the rate-determining step. The proton dependence of these last kinetics allows the rate constant to be measured ($k_{-h} = 10^3$ s^{-1}M^{-1}), and consequently $k_h = 2.8 \times 10^{-5}$ s^{-1}. This low value of the rate constant k_h is the reason why it is possible to have coloured **AH**$^+$ species at higher pH values, almost to neutrality. This result contrasts with the behaviour of most flavylium compounds and anthocyanins, where the coloured flavylium cation disappears at relatively low pH values, typically between 2 and 4.[6,21] Actually, the easy hydration of anthocyanins is the great drawback for their use as food colorants.[22] In nature this problem is overcome by self-assembly processes involving anthocyanins, other polyphenols and metals, producing supramolecular structures, as reported by Goto, Kondo, Yoshida and co-workers.[23] On this basis, the current compound has proved to be a good colorant, due to its stability over a large range of pH values. Such stability towards hydration has been observed in other flavylium compounds bearing amines in position 4′,[24] and reflects the difficulty of hydration caused by the amine in this position. Other experimental findings corroborate this assumption: *i*) the single-crystal structures of 4′-amino-substituted flavylium compounds show planarity between the pyrylium ring and the benzene, and *ii*) the length of the N–C bond is shorter than in a simple aniline, showing some double character for this bond.[6e] These data are compatible with an extended conjugation throughout the molecule and involving the amine substituent, with a decrease in positive charge in position 2, which impedes the hydration reaction.

Stopped-flow experiments were also carried out from the stock solution at pH = 1.0 to the basic media. The final products formed during the stopped-flow experiments are the **Cc** species into **Cc**$^-$ species, the ionization constant being $K_{Cc} = 10^{-9.6}$ (Figure 7, C). The kinetics of the reaction reported in part B of Figure 8 involve a first-order rate constant, giving $k_h^{OH} = 9.3 \times 10^3$ s^{-1}M^{-1}, and can be interpreted, as in the case of 4′-acetamidoflavylium, as OH$^-$ attack on the flavylium cation in position 2, a hydroxylation at the same position at which hydration takes place.

Thermodynamic Equilibrium

The variations of the absorption spectra of the compound 4′-aminoflavylium as a function of pH over 12 days in the dark at room temperature are represented in Figure 9.

In the acidic region the spectra are compatible with an equilibrium involving the **Ct** species and the flavylium cation (Figure 9, A). As shown above for the amido analogue, the difference $K'_a - K_a$, allows calculation of $K_i = 130$. With regard to the basic region, the data reported in Figure 9 (B) allow the conclusion that $K_{ct} = 10^{-8.55}$. As previously shown above, the use of Equations (4) to (6) gives $K'_i = 73$. Moreover, both the spectra and the ionization constant were identical independently of whether the thermodynamic equilibria in the range 6 < pH < 12 was reached upon a pH jump from solutions at pH = 1.0 (after 12 days to reach

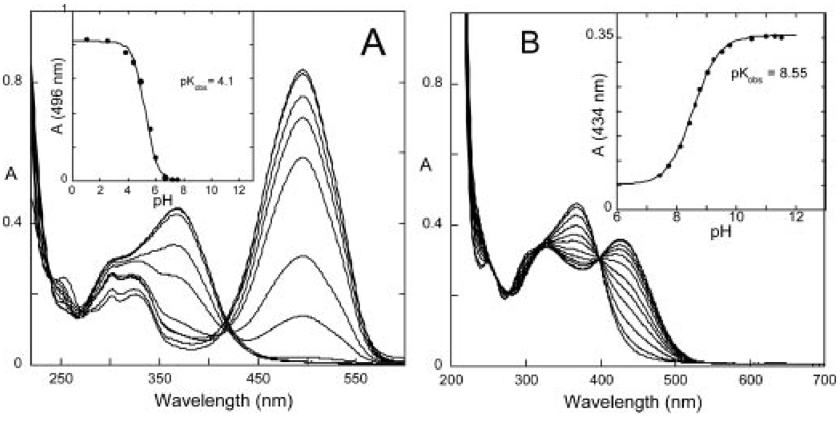


Figure 9. Absorption spectra of the compound 4′-aminoflavylium (3.3×10^{-5} M) over 12 days in the dark at room temperature; A) Acidic region; inset: fitting of the absorbance at 496 nm, vs. pH, in order to obtain the pK_{obs}. B) The same for the basic region; inset: fitting of the absorbance at 434 nm.

the equilibrium) or from solutions at pH = 12 containing the **Ct**$^-$ species.

Isomerization Kinetics

Thermal conversion of the *cis*-chalcones into the *trans*-chalcones occurs over a timescale of days, following first-order kinetics with observed rate constants of 4.6×10^{-6} s^{-1} at pH = 8.2 for conversion of **Cc** into **Ct** and 4.3×10^{-6} s^{-1} at pH = 11.1 for conversion of **Cc**$^-$ into **Ct**$^-$ (see Figure 1S in Supporting Information; see also the footnote on the first page of this article). It is important to emphasize that the thermal conversion of the *cis*-chalcones into the *trans*-chalcones is substantially slower in the 4′-aminoflavylium than in 4′-acetamidoflavylium. As in the case of the 4′-acetamidoflavylium compound, the *cis-trans* isomerization kinetic constants for the conversion of **Cc** into **Ct** and **Cc**$^-$ into **Ct**$^-$, can be evaluated. The respective values are reported in Table 2.

Pseudoequilibrium 2

As mentioned above, the pseudoequilibrium 2 is attained from the thermally equilibrated **Ct**$^-$ species, and involves **Ct** and **Ct**$^+$. In particular, **Ct**$^+$ is a very interesting metastable species: at pH = 1.0, for example, its thermal conversion in the dark follows a first-order kinetic process with rate constant $k_{obs} = 3 \times 10^{-7}$ s^{-1} (see below).

Photochemistry

Irradiation of the **Ct**$^-$ (pH = 11.5) and **Ct** (pH = 7.7) species at 365 nm does not produce any significant spectral variation, indicating that in the case of the 4′-aminoflavylium these species are not photoactive. In contrast, a photoreaction can be observed at pH < 2 (Figure 10). At these pH values, the nitrogen in position 4′ of the *trans*-chalcone can be protonated. This can be confirmed by the variation in the absorption spectra for pH < 2 (Figure 10A), from which the protonation constant **CtH**$^+$/**Ct** Equation (10) can be calculated ($pK_{Ct+} = 2.0$).

$$\mathbf{CtH}^+ \rightleftharpoons \mathbf{Ct} + \mathrm{H}^+ \qquad K_{Ct+} \qquad (10)$$

In conclusion, the **Ct** and **Ct**$^-$ species of 4′-aminoflavylium are photochemically stable, and only the **CtH**$^+$ species is photoactive.

In contrast, the photochemical behaviour of the *cis*-chalcones of 4′-aminoflavylium is very different (see spectral variations in Supporting Information). In effect, an efficient photochemical conversion of **Cc** into **Ct** (λ_{irr} = 365nm, pH = 8.2, Φ = 0.4) as well as of **Cc**$^-$ into **Ct**$^-$ (λ_{irr} = 365nm, pH = 12.4 Φ = 0.2) takes place. The *cis* to *trans* isomerization also occurs thermally at room temperature, but is slow, with lifetimes of 2.5 days (**Cc** to **Ct**) and 2.7 days (**Cc**$^-$ to **Ct**$^-$). The use of light is thus a much more efficient means to carry out the *cis-trans* isomerization.

The absence of *trans-cis* photochromism in flavylium salts containing amino derivatives in the 4′-position was previously interpreted[25] on the basis of a low-lying highly polarized excited state that competes with the photochemical pathway. It was suggested that the excited state of the *trans*-chalcone is strongly stabilized in water by its high dipole moment, resulting in the arrest of the *trans-cis* photochemical pathway. On the other hand, we observe the *cis-trans* photoisomerization, with a high quantum yield, in water. This is not incompatible with the above explanation but requires that the *trans* isomer in the excited state possesses a much higher dipole moment than the *cis* isomer.

In fact, molecular orbital calculations on the two isomers give the ground and excited state dipole moments presented in Table 4, and predict that the dipole moment of the *trans* isomer is higher than that of the *cis* isomer in both ground and excited states.

Pseudoequilibria and Thermodynamic Equilibrium

The existence of a kinetic barrier between the *cis* and *trans* chalcones in both compounds allows two different

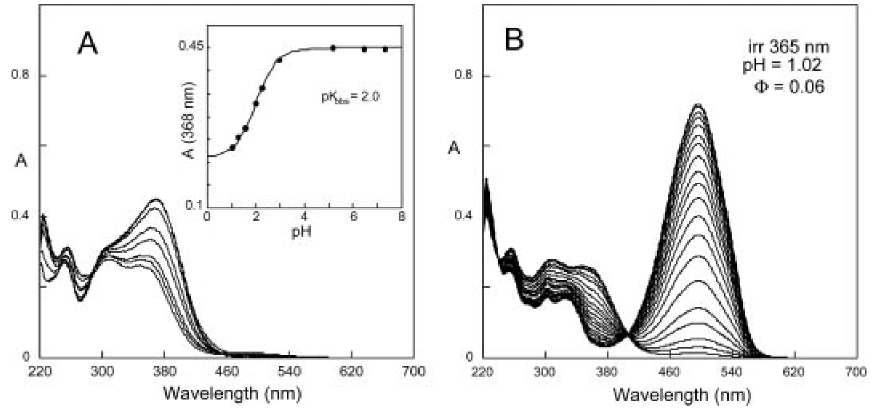
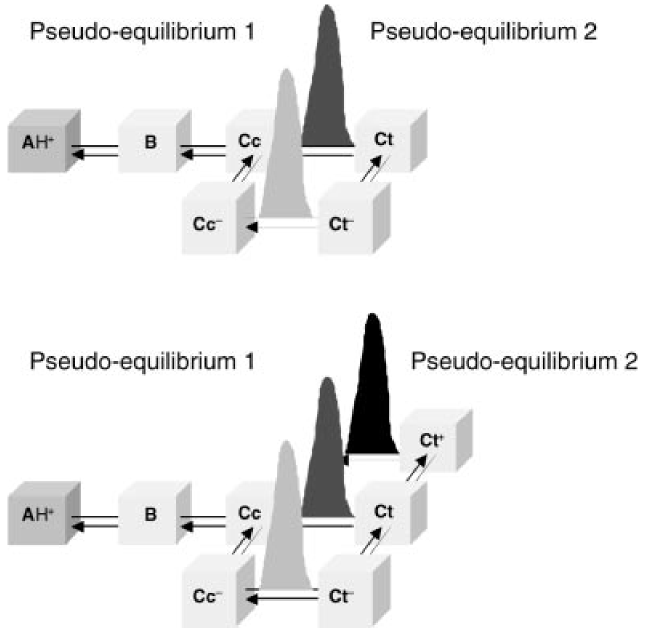


Figure 10. A) Spectral variations correspondent to the formation of the protonated *trans*-chalcone (**CtH**$^+$) from 4′aminoflavylium (3.3×10^{-5} M). B) Spectral variations resulting from the irradiation of the **CtH**$^+$ species at pH = 1.02.

Table 4. Dipole moments from molecular orbital calculations (AM1 method at RHF level) on geometries optimized by the semiempirical AM1 method at UHF level.

	Ground state dipole (D)	Excited state dipole (D)
trans-chalcone	3.91	4.51
cis-chalcone	2.05	1.80

pseudoequilibrium states to be defined for each compound, as represented in Scheme 3. Both pseudoequilibria are achieved from the thermodynamic equilibrium: *i*. pseudoequilibrium 1 is attained from addition of base to the thermally equilibrated **AH**$^+$ species, *ii*. pseudoequilibrium 2 is obtained from addition of acid to thermally equilibrated solutions of **Ct**$^-$. All the pseudoequilibria are thermally converted into the final equilibrium after a few days, as shown above. In some cases, the pseudoequilibrium 2 can be converted into the pseudoequilibrium 1 upon irradiation (of the *trans*-chalcones) and vice-versa (upon irradiation of the *cis*-chalcones), and the thermodynamic equilibrium into pseudoequilibria 1 (see below).



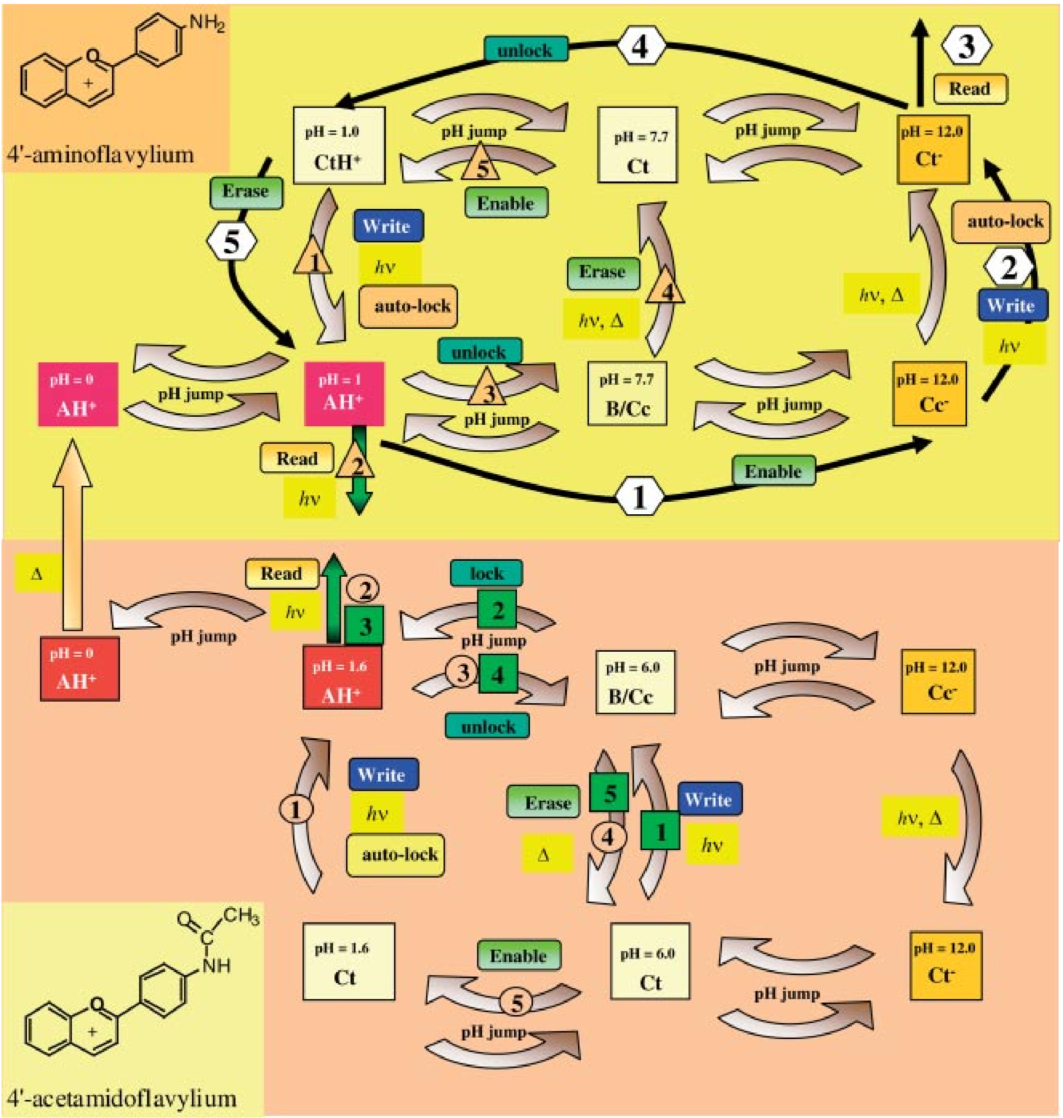
Scheme 3. For each compound two pseudoequilibria exist, on the left (pseudoequilibrium 1) and on the right (pseudoequilibrium 2) of the kinetic barriers that separate the *cis* and *trans* forms of the chalcones. Top: 4′-acetamidoflavylium, bottom: 4′-aminoflavylium.

Write-lock-read-unlock-erase

Some of the problems arising when a *cis*-*trans* photochromic system is considered as a model for an optical memory have been discussed in previous work.[6a] To obtain an optical memory it is necessary to use an input of light to **write**. This step corresponds to the photochemical reaction, and the higher the quantum yield, the better the performance of the memory. On the other hand, the write step gives rise to a different molecule exhibiting different properties. In order to **read** the information written, the output signal of the system can be selected among the different new characteristics and properties of the photoproduct obtained through the write step: its colour, for example. However, many photochromic systems do not show any thermal barrier between the *cis* and *trans* isomers, so the thermal back reaction occurs, spontaneously erasing the signal. The existence of a *cis*-*trans* thermal barrier is thus a necessary requirement of the system. Another problem can occur during the read step: if light is used to interrogate the system, the photoproduct should be photochemically inactive, otherwise the system erases while being read. This requirement is not common, and for that reason it was proposed to introduce a second input, such as a pH jump, as the **lock** step to leave the system in another species (another state of the molecule), allowing the photoproduct to close a ring, for example, followed by the dehydration reaction, as in the case of synthetic flavylium compounds.[6a] The species resulting from the lock step should be thermally and photochemically stable to allow the read step at will. Finally the **unlock** step, the reverse reaction of the lock process, should bring the system back to the photoproduct, in order to permit the **erase** step, which can be carried out by an input of heat or light. At this point the cycle is concluded, and the system ready for reuse. In some cases it is possible to choose a pH at which the lock step is spontaneous (autolock) and the erasing back to the initial state is carried out by heating the system (see Supporting Information for the procedure to obtain the best pH for autolock).

In the case of 4′-acetamidoflavylium (Scheme 4, bottom, numbers inside squares) the cycle starts from the **Ct** species in the equilibrium at pH = 6.0 (or from pseudoequilibrium 2, at the same pH value): i. the write step gives a mixture of **B/Cc** (as shown in part B of Figure 5, the system has the drawback of not being completely converted into **Cc/B** state), ii. the lock step results from the pH jump 6 → 1.6, forming **AH**$^+$, which is stable and can be read, iii. the unlock step corresponds to the pH jump 1.6 → 6 to give **Cc/B**, and 4) the erasing can be achieved by an heat input (Figure 4, A).

In the case of the compound 4′-aminoflavylium, such a cycle is not feasible from the **Ct** species because it is not photoactive. However, it is possible from the **Ct**H$^+$ species available in pseudoequilibrium 2 (Scheme 4, top, numbers inside triangles). In this case the system should start from this species, at pH = 1.0. Because of the low pH value of the system, the autolock step is spontaneous upon irradiation (1), the *cis*-chalcone (possibly protonated) evolving to **B** (possibly protonated) and finally to **AH**$^+$, which can be read (2). The unlock step (3), giving **Cc** (in this compound **B** is residual) is made by a pH jump 1 → 7. The erasing (4) can be done by an heat input (which is slow) or, better, by using light to allow the formation of **Ct**. At this pH value this compound is thermodynamically stable and photoinactive and the system can be stored. To allow the next cycle, it is necessary to use the **enable** step (5) through a pH jump 7 → 1.



Scheme 4. Thermal, pH-induced and light-induced interconverting pathways between all possible forms in 4′-acetamidoflavylium (bottom) and 4′-aminoflavylium (top) systems, allowing several *write-lock-read-unlock-erase* cycles involving different species.

One variation of the above cycle can be conceived for the 4′-acetamidoflavylium (Scheme 4, bottom, numbers inside circles). The starting point is the **Ct** species at pH = 1.6 (obtained from the pseudoequilibrium 2) to allow the write step, followed by auto-lock, permitting reading. A pH jump to 6.0 unlocks the system, which can be erased by the normal procedure. Finally, the pH jump back to 1.0 constitutes the enable step that will allow the auto-lock of the system after irradiation.

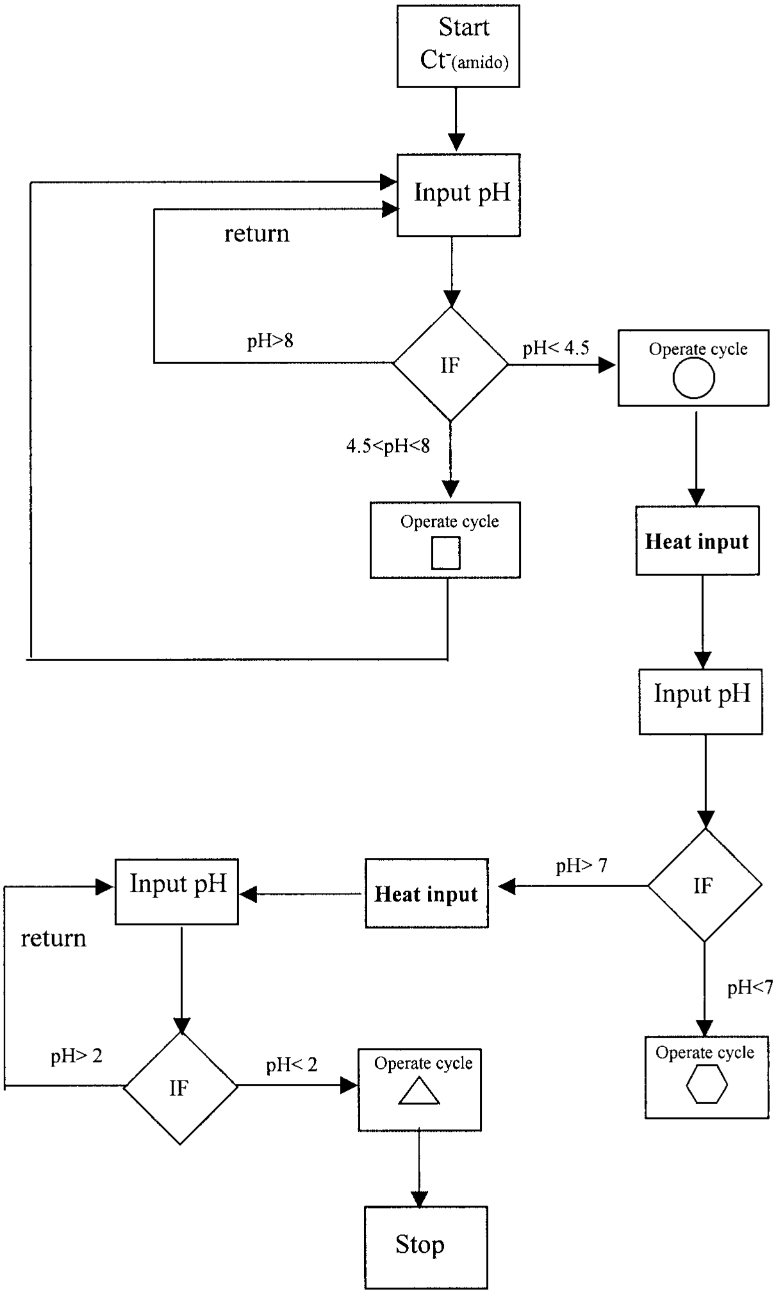
Writing and Erasing with Light

Other cycles involving the basic species can be conceived, passing through the ionized *cis*- and *trans*-chalcones. Usually the faster way to prepare the **Ct** species is to change the pH of the solution to pH > 10 because, as shown above, the attack of OH^- is very fast at these pH values, immediately resulting in the formation of the **Cc**$^-$ species, which forms **Ct**$^-$ either thermally or by irradiation. In some cases the ionized chalcones can also perform optical memory cycles, and such type of cycles can be proposed in the current network. This is particularly interesting in the case of the 4′-aminoflavylium compound (Scheme 4, top, numbers inside hexagons). The **Cc**$^-$ species can be prepared (pseudo-equilibrium 1, enable step) from the stock solution at acidic pH values. This species possesses a reasonable thermal stability, and can be used to write (the same is valid for the **Cc** species at pH = 7.7, for example). The curious behaviour of this cycle is that the photoproducts (**Ct**$^-$ or **Ct**) are thermally and photochemically stable, and the read step can be carried out (autolock conditions). The drawback of this cycle is that no visible colour is detected with this system, and if photochemical conversion is not complete the reading can erase (reagent and photoproduct have similar absorptions). In order to erase this cycle with light, an unlock operation should be made by means of a pH jump to 1.

In the case of the compound 4′-acetamidoflavylium, formation of the $\mathbf{Ct}^-$ from the $\mathbf{Cc}^-$ can be achieved by irradiation (Figure 5, C). No photochemical (nor thermal) reaction of $\mathbf{Ct}^-$ was detected, so the system can also be stored in this state.

Memory Algorithm and Irreversible Interconversion of the Networks

The sequence of instructions necessary to carry out an optical memory cycle can be defined as its algorithm. On this basis, the write-lock-read-unlock-erase cycle starting with the **Ct** species of 4′-acetamidoflavylium at pH = 6.0 (Scheme 4, bottom, numbers in squares) is described by an algorithm consisting of the following sequence of instructions: 1) irradiation at 365 nm, 2) pH jump 6.0 to 1.0, 3) measurement of the absorption at 438 nm, 4) pH jump 1.0 to 6.0, and 5) thermal input. In the case of the compound 4′-aminoflavylium, the cycle starting with $\mathbf{CtH}^+$ at pH = 1.0 (Scheme 4, top, numbers in triangles) operates by the following set of instructions: 1) irradiation at 365 nm, 2) measurement of the absorption at 497 nm, 3) pH jump 1.0 to 7.7, 4) thermal input, and 5) pH jump 7.7 to 1. These examples show that each memory cycle operates according to a defined and unique algorithm. Moreover, it is possible



Scheme 5. Example of an upper level operation that can be executed, defining a sequence of algorithms to be operated in both 4′-acetamidoflavylium and 4′-aminoflavylium chemical networks.

to change from the 4′-acetamidoflavylium network to the 4′-aminoflavylium one by two instructions: 1) pH jump to pH = 0 (or even pH = 1.0), or 2) thermal input. This internetwork conversion is irreversible.

Example of an Upper Level Multistate Cycle

An upper level of operation can be executed by defining a sequence of algorithms to be operated within both networks (Scheme 5). As an example, if the **Ct**$^-$ species of 4′-acetamidoflavylium is regarded as the starting point of the upper level cycle, the first step would consist of a pH input to acid.[26] If $pH > 8$, the **Ct**$^-$ form remains unchanged and a further pH input is necessary (return). At $4.5 < pH < 8$, the squares cycle can operate, while for $pH < 4.5$ the autolock pH cycle (circles cycle) is available. After operation of the square cycle, the system is in the **Ct** multistate, and other inputs of pH can be made (return). On the other hand, after operation of the circles cycle, a heat input permits passage to the 4′-aminoflavylium network. At this point, a new pH input is needed to continue: *i.* if $pH < 7$ the hexagons cycle can be performed, and *ii.* if $pH > 7$, the system is in its pseudoequilibrium 3 and a heat input is necessary to produce the *trans*-chalcone species. The next step is a further pH input: *i.* if $pH > 2$ it is necessary to return in order to continue, and *ii.* if $pH < 2$, the triangles cycle can operate, and finally stop.[27]

Conclusions

In previous work we have reported on the possibility of using flavylium salts in solid matrices of water-permeable polymers, as well as in water/ionic liquid biphasic systems.[28] The cycles presented here could also be performed in such types of materials, opening the possibility of using these supramolecular systems in practical devices. However, the main scope of this work is the use of flavylium compounds as models to develop concepts and perspectives, linked to the idea that increasing of complexity can result in increasing of functionalities. This is not new, and follows the well established praxis of supramolecular chemistry. What is certainly less common is to accomplish a supramolecular strategy by use of a simple molecule.

Experimental Section

Synthesis: NMR spectra were run on a Bruker AMX 400 instrument, MS spectra were run on a Micromass GCT machine, and elemental analyses were obtained on a Thermofinnigan Flash EA 1112 Series device. All reagents and solvents used were of analytical grade.

4′-Acetamidoflavylium Tetrafluoroborate: This compound was prepared by condensation of 4′-aminoacetophenone (1.35 g, 0.01 mol) and 2-hydroxybenzaldehyde (1.06 mL, 0.01 mol) as described for similar compounds by Katritzky.[29] The reagents were dissolved in acetic acid (25 mL) and 48% tetrafluoroboric acid (5 mL) was added. Acetic anhydride (25 mL) was then added, with the temperature being kept below 60 °C (≈ 10 min). The solution was stirred overnight. Addition of ethyl ether resulted in the precipitation of a red solid that was filtered, washed with glacial acetic acid and ethyl ether, and dried in vacuo; 0.61 g (20%; not optimized). ^1H NMR (400 MHz, D_2O/DCl, pD ≈ 1.5, 30 °C; **AH**$^+$ species): $\delta = 2.16$ (s, 3 H, $COCH_3$), 7.78 (d, $J = 8.6$ Hz, 2 H, H3′ + H5′), 7.88 (t, $J = 7.3$ Hz, 1 H, H6 or H7), 8.14–8.24 [m, 3 H, H5 + H8 + (H6 or H7)], 8.45 (d, $J = 8.6$ Hz, 2 H, H2′ + H6′), 8.54 (d, $J = 9.1$ Hz, H3), 9.24 (d, $J = 9.1$ Hz, 1 H, H4) ppm. Mass spectrum (FD): $m/z = 264$ $[M - BF_4]^+$ (100%). Elemental analysis: $C_{17}H_{14}BF_4NO_2{\cdot}H_2O$ (369.13): calcd. C 55.32, H 4.37, N 3.79; found C 55.31, H 4.52, N 3.92.

4′-Aminoflavylium: This compound can be obtained by ageing a solution of 4′-acetamidoflavylium tetrafluoroborate acidified to pH = 1.0 at 50 °C. The ageing is followed by UV/Vis spectrophotometry until no more changes are observed (1–2 days). This solution can be used directly for the reported studies. For analytical purposes, this flavylium could be isolated by concentration of the solution, addition of sodium hexafluorophosphate and slow evaporation. Crystals were actually obtained and the structure is reported elsewhere.[6e] ^1H NMR (400 MHz, D_2O/DCl, pD ≈ 1.5, 30 °C; **AH**$^+$ species in equilibrium with some **AH**$_2^{2+}$ species): $\delta = 7.37$ (d, $J = 7.6$ Hz, 2 H, H3′ + H5′), 7.58 (t, $J = 7.2$ Hz, 1 H, H6 or H7), 7.84–7.94 [m, 3 H, H5 + H8 + (H6 or H7)], 8.07 (d, $J = 7.6$ Hz, 2 H, H2′ + H6′), 8.20 (d, $J = 9.2$ Hz, H3), 8.93 (d, $J = 9.2$ Hz, 1 H, H4) ppm. Mass spectrum (FD): m/z 222 $[M - PF_6]^+$ (100%). Elemental analysis: exp. (calcd. for $C_{15}H_{12}F_6NOP$; $FW = 367.23$ $g\,mol^{-1}$): C 49.14 (49.06), N 3.97 (3.81), H 3.25 (3.29).

Measurements: All experiments were carried out in aqueous solution. The pH was adjusted by addition of HCl and NaOH, or buffer, and was measured in a Meterlab pHM240 pH meter from Radiometer Copenhagen.

UV/Vis absorption spectra were recorded in a Shimadzu UV2501-PC spectrophotometer.

Light excitation was carried out by use of a medium-pressure mercury arc lamp (Helius), and the excitation bands were isolated with interference filters (Oriel). The incident light intensity was measured by ferrioxalate actinometry.[30]

The stopped-flow experiments were performed in a SFM-300 spectrophotometer, controlled by a MPS-60 unit (Bio-Logic) and the data were collected through a TIDAS diode array (J&M), with wavelength range between 300 and 1100 nm, all connected to a computer. The standard cuvette has an observation path length of 1 cm. For this experiments the dead time of each shot was previously determined to be 5.6 ms with a 8 $mL\,s^{-1}$ flow rate.

Semiempirical Calculations: Ground and excited states' dipole moments were calculated by the AM1 method at the RHF level.[31] Geometries were previously optimized by AM1 at UHF level.

Supporting Information Available (see footnote on the first page of this article): Kinetic and photochemical data for 4′-aminoflavylium; strategy to choose the suitable pH range to *write* in a cycle.

Acknowledgments

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[16] At this pH value the 4′-acetamidoflavylium is stable for a few days; if kept for several weeks it gives the 4′-aminoflavylium, as shown in the text.

[17] The intercept of the inset of Figure 2 is very small and the error large; in consequence, the value calculated from the equilibrium constant, $k_h = 1.4\ s^{-1}$, is in principle more reliable.

[18] In fact, assuming steady state conditions for **B** it is easy to prove that $d[\mathbf{Cc}]/dt \approx k_h[\mathbf{AH^+}]$ and thus the calculated value for the hydration rate constant is equal, within experimental error, to that reported in Table 2.

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