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Binding of the five multistate species of the anthocyanin analog 7-β-D-glucopyranosyloxy-4′-hydroxyflavylium to the β-cyclodextrin derivative captisol

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Abstract

The host-guest chemistry of the anthocyanin analog 7-β-D-glucopyranosyloxy-4′-hydroxyflavylium (GHF) was studied in the presence of the β-cyclodextrin derivative captisol by stopped flow, UV–visible spectroscopy, flash photolysis, circular dichroism and isothermal titration calorimetry. The equilibrium and rate constants of the multistate of chemical species derived from the flavylium ion were calculated and compared with those in the absence of the host. A new procedure to obtain the host-guest association constants of the multistate (including the transient species) by superimposing the two energy level diagrams, in the presence and absence of the cyclodextrin, was developed. The results indicate that the magnitude of the association constants follows the order, trans-chalcone = cis-chalcone = hemiketal > quinoidal base > flavylium cation. The hydration equilibrium constant increases ca. 42 times in the presence of captisol as the hydration and dehybridation rate constants respectively increases and decreases. The other equilibrium constants are modestly affected: the rate constants of ring closure and opening are significantly decreased in the complex and the isomerization rate constants increase in both directions. The quantum yield of the photochromic system in the presence of captisol is 0.3, i.e. 3 times higher than in the absence of the host.

1. Introduction

The flavylium cation is a common feature of natural pigments, such as anthocyanins and 3-deoxyanthocyanins, and many other synthetic dyes including styrylflavylium and naphthoflavylum ions. However, the flavylium cation (AH+) is only one of the species of a more general multistate of chemical species, reversibly interconverted by external stimuli, such as pH modifications and light [1–3]. The flavylium cation is generally the stable species of the multistate in a narrow and very acidic pH window. Upon raising the pH to moderately acidic/neutral solutions, four other different species are formed according to the sequence, quinoidal base (A), hemiketal (B), cis-chalcone (Cc) and trans-chalcone (Ct) (Scheme 1).

The chemical reactions reported in Scheme 1 are accounted for by Eq. (1)–(4)

\[ \text{AH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{A} + \text{H}_3\text{O}^+ \quad K_a \quad \text{acid} – \text{base} \]  (1)

\[ \text{AH}^+ + 2\text{H}_2\text{O} \rightleftharpoons \text{B} + \text{H}_3\text{O}^+ \quad K_h \quad \text{hydration} \]  (2)

\[ \text{B} \rightleftharpoons \text{Cc} \quad K_i \quad \text{tautomeration} \]  (3)

\[ \text{Cc} \rightleftharpoons \text{Ct} \quad K_i \quad \text{isomerization} \]  (4)

The addition of base to equilibrated acidic solutions of the flavylium cation is defined here as the direct pH jump. After a direct pH jump, two competitive reactions take place, proton transfer, Eq. (1), leading to the quinoidal base, and hydration, Eq. (2), leading to the hemiketal. Proton transfer is by far the faster reaction of the multistate (μs timescale) and thus the first species to be formed is the quinoidal base. Flavylium cation and quinoidal base are
multistates exhibiting a high cis-trans isomerization barrier. Three kinetic steps can be differentiated: 1- Proton transfer which occurs in the μs time scale; 2- rate limiting hydration (seconds-minutes time scale) followed by fast and therefore kinetically silent tautomerization and 3- slow isomerization in the hours time scale.

\[
\text{AH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{CB} + \text{H}_3\text{O}^+ \quad K_a^\prime
\]

When the system reaches the equilibrium, the mole fraction distribution of the species is dependent on pH and can be expressed by a simple acid-base reaction involving the flavylum cation (AH\(^+\)) and an apparent conjugated base CB defined as the sum of the concentrations of quinoidal base (A), hemiketal (B) cis-chalcone (Cc) and trans-chalcone (Ct), Eq. (8).

\[
\text{AH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{CB} + \text{H}_3\text{O}^+ \quad K_a
\]

Due to the fact that the isomerization is much slower than the other kinetic steps, it is possible to define a pseudo-equilibrium, i.e. a transient state where the species \(\text{AH}^+, \text{A}, \text{B} \) and \(\text{Cc}\) can be considered in equilibrium before formation of significant amounts of \(\text{Ct}\), Eq. (10).

\[
\text{AH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{CB} + \text{H}_3\text{O}^+ \quad K_a
\]
energy level diagram of 7β-D-Glucopyranosylsoxy-4’-hydroxy-flavylium (GHF) in the absence [4] and presence of captisol. In particular, captisol has been tested as the best host (in comparison with other cyclodextrin derivatives) for anthocyanidins, improving storage stability and facilitating formulation [18]. The aim of this work is to investigate the effect of the host on the equilibrium and rate constants of the flavylium multistate. This knowledge could help to define new strategies of color stabilization and find more efficient flavylium-based photochromic systems.

2. Methods

All solutions were prepared in Millipore water, 0.2 mM GHF [19] and 0.2 M captisol stock solutions were prepared using 0.1 M HCl and water, respectively. Any pH adjustment was achieved by addition of HCl, NaOH or Theorell and Stenhagen’s universal buffer, pH was recorded on a Radiometer Copenhagen PHM240 pH/ion meter (Brønshøj, Denmark). Direct pH jumps were carried out mixing stock GHF, neutralized with the same amount of NaOH (0.1 M), buffer (desired pH), stock captisol solution and water. Reverse pH jumps were achieved by addition of conc. HCl to equilibrated slightly acidic or neutral GHF + captisol solutions.

UV–Vis spectra were recorded on a Varian-Cary 100 Bio or 5000 spectrophotometer (Palo Alto, CA, USA). The stopped flow experiments were conducted on a SX20 (Applied Photochemistry; Surrey, UK) spectrometer equipped with a PDA1/UV photodiode array detector. Irradiation was carried out at 365 nm. Quantum yields were measured based on the total absorbed light. Flash photolysis experiments were performed on a Varian Cary 5000 spectrophotometer with a Harrick fiber-mate (Pleasantville, NY, USA) coupled to an Ocean Optics 4-way cuvette holder (Dunedin, FL, USA). The compartment was isolated from daylight and a commercially Achiever 630AF camera flash (Hong Kong, China) was used as a pulsed white light source (placed in close contact with the quartz cuvette).

For host-guest association constant calculations, different concentrations of captisol solutions were used. In the case of the AH+/ captisol couple (pH 1), the same procedure as for direct pH jumps was performed but with variations in captisol concentration (0–0.04 M). In the case of the A/captisol couple, the constant was calculated from the UV–Vis spectra recorded after a direct pH jump (from pH 1 to pH 8) in 2.6 × 10⁻⁵ M GHF solutions containing captisol (0–16 mM).

Circular dichroism absorption spectra were recorded on a Chirascan qCD spectrometer (Applied Photochemistry; Surrey, UK) at 298 K under constant nitrogen flush. The GHF concentration was kept constant (6.93 × 10⁻³ M) and the captisol concentration increased from 0 to 8.33 × 10⁻³ M. A quartz cell (optical path-length = 1 cm) was used for irradiation in the range 220–550 nm with an interval of 1 nm. Two scans were averaged with baseline correction during all measurements.

Isothermal Titration Calorimetry (ITC) measurements were performed on a Nano ITC (TA Instruments; New Castle, DE, USA) with standard volumes. The solutions were thoroughly degassed before use by stirring under vacuum. The sample cell was loaded with a 0.288 mM GHF solution (pH = 6) and a 250 µl autopipette was filled with a 4 mM captisol solution. GHF was titrated in a sequence of 25 injections of 10 µl aliquots after achievement of baseline stability.

3. Results and discussion

3.1. UV–visible spectroscopy, stopped flow and flash photolysis

In a previous work, the equilibrium and rate constants of the GHF multistate, Scheme 1, were reported [4]. The pH-dependent absorption spectra of the pigment in the presence of 50 mM of captisol, taken immediately after a direct pH jump, at pseudo-equilibrium and at equilibrium, are shown in Fig. 1. The absorption spectra of Fig. 1a only reflect the flavylium-quinoidal base equilibrium, Eq. (1). Indeed, the proton transfer is very fast (complete during the mixing time of the stopped flow device), whereas the subsequent reaction (hydration) is fully negligible during the few milliseconds after the pH jump. The acid dissociation constant in the presence of captisol, pK_a = 4.95, is higher than in the absence of cyclodextrin, pK_a = 5.4, indicating that the quinoidal base binds captisol more tightly than the flavylium cation does.

As mentioned in the introduction, in the case of flavylium multistates with a high cis-trans isomerization barrier, a pseudo-equilibrium involving all the species except trans-chalcone can be considered. The spectral variations at pseudo-equilibrium are represented in Fig. 1b and the data fit with a single acid-base equilibrium with pK_a = 3.25. The higher pK_a value (4.7) in the absence of captisol [4] shows that the macrocycle has a higher affinity for CB (essentially, a mixture of B and Cc) than for AH+.
same trend is observed at full equilibrium, comparing $pK_a = 0.8$ (with captisol) with $pK_a = 2.3$ (no captisol), in this case pointing to the preferential stabilization of the trans-chalcone, Fig. 1c, a result already observed for other flavilium multistates [20]. It is especially remarkable that in the presence of captisol the flavilium ion almost behaves as a strong acid.

The $AH^+\text{-captisol}$ binding constant was estimated from spectra collected a few seconds after addition of the host at pH = 1.0. These measurements were thus carried out at pseudo-equilibrium (before significant formation of Ct), where $AH^+$ is still the dominant species at this pH [21]. On the other hand, the A-captisol binding was monitored by stopped flow immediately after a direct pH jump in the presence of captisol, see experimental part, Fig. 2. In both cases, captisol brought about significant spectral differences permitting the estimation of the corresponding binding constants from absorbance vs. captisol concentration plots. At pH = 1, the binding constant, 200 M$^{-1}$, is much higher than those reported with native $\beta$-cyclodextrin in similar compounds [20,22]. A likely explanation for this enhanced affinity is the additional electrostatic attraction between the flavilium cation and the negatively charged captisol.

![Fig. 1](image1.png)

**Fig. 1.** (a) Spectral modifications observed for GHF in presence of 0.05 M of captisol 10 ms after a direct pH jump followed by stopped flow ([GHF] = 3.33 × 10$^{-5}$ M); (b) the same at pseudo-equilibrium ([GHF] = 3.33 × 10$^{-5}$ M); (c) the same at equilibrium ([GHF] = 3.33 × 10$^{-5}$ M). The experimental value of this acidity constant presents a larger error due to the very acidic range required for its estimation. However, it was possible to assess all other equilibrium constants of the multistate in less acidic conditions (see below), and thus to also calculate the $pK_\alpha$ value from its definition in Eq. (9).

![Fig. 2](image2.png)

**Fig. 2.** (a) Spectral variations of the visible spectrum of GHF 3.3 × 10$^{-5}$ M at pH = 1 as a function of added captisol; (b) the same for GHF 4 × 10$^{-5}$ M at pH = 7.7 followed by stopped flow.
The quinoidal base – captisol binding constant is close to the one previously reported with β-cyclodextrin [22].

A series of direct pH jumps (followed by stopped flow) from equilibrated solutions at pH = 1.0 to higher pH values, in the presence of captisol, was carried out (Fig. 3a and b). On Fig. 3a (pH = 2.35), the flavilyum cation disappears to give the hemiketal and cis-chalcone, the formation of trans-chalcone being much slower. At this pH, the quinoidal base is negligible. In contrast, for a final pH = 6.9 (Fig. 3b), practically all of the flavilyum cation is converted into the quinoidal base and the spectral variations refer to the disappearance of this species. Here again, no trans-chalcone is formed. At high pH values, the fraction of electrophilic AH⁺ (the only species undergoing water addition) is weak and hydration is slower than tautomerization and rate-determining, see Eq. (6).

Finally, the system reaches the equilibrium through a slower process yielding the trans-chalcone, as shown in Fig. 4 for a direct pH jump to pH = 2.8. A plot of the isomerization rate constants as a function of pH gives the expected sigmoid curve (Eq. (7)), with an inflexion point at pK^a = 3.2, in agreement with the previous estimation (Fig. 1b). Moreover, the two well defined limits of this curve at low and higher pH values leads respectively to k_i = 6 × 10⁻⁶ s⁻¹ and k_s,K_{k/K_a} = 1.4 × 10⁻³ s⁻¹.

Fig. 3. (a) Spectral variations after a direct pH jump to 2.35 followed by stopped flow (GHF 3.33 × 10⁻⁵ M, Captisol 0.05 M); (b) the same with final pH = 6.9; (c) pH dependence of the apparent rate constant of hydration in the presence of captisol. (●) direct pH jumps fitted with Eq. (6), inset; (○) reverse pH jumps from pseudo-equilibrium fitted with Eq. (12); Curve-fitting was achieved for the following parameters: k_h = 0.67 s⁻¹; k_{h/(1+K_t)} = 1.1 × 10⁻³ M⁻¹ s⁻¹ and k_{i/a} = 1.9 × 10⁸.

Fig. 4. (a) Spectral modifications from pseudo-equilibrium to equilibrium after a direct pH jump to 2.8 (GHF 3.33 × 10⁻⁵ M, Captisol 0.05 M); (b) plot of the apparent rate constant of the slowest process (controlled by isomerization) as a function of pH. Curve-fitting was achieved with Eq. (7) for the following parameters: k_i = 6 × 10⁻⁶ s⁻¹ and K_{k/k/K_a} = 1.4 × 10⁻³ s⁻¹.
Table 1 summarizes the kinetic and thermodynamic parameters obtained experimentally from Figs. 1, 3 and 4.

The coherence of these data can be tested considering that the value of $K_h(1 + K_t)$ obtained from $K_a - K_a$ is equal to the ratio between column 4 and column 3 in Table 1 ($6.1 \times 10^{-4}$).

In order to obtain all the rate and equilibrium constants, one more relation is necessary. When the flavlylium multistate exhibits a cis-trans isomerization barrier, it is possible to carry out a reverse pH jump from the pseudo-equilibrium to acidic pH values, Fig. 5 [3,23].

The use of reverse pH jumps was reported by McClelland and co-workers [3,23]. When the final pH is sufficiently acidic, the hydration step, due to its dependence on $[H^+]$, becomes faster than tautomerization, the so-called change of regime. Consequently the equilibrium between B and Cc is disrupted, B disappears to give $AH^+$ in a first kinetic step, according to Eq. (12), followed by a slower reaction that converts Cc in more flavlylium cation via B, Eq. (13). The pH dependence of the faster observed rate constant is represented in Fig. 3c (open circles). Curve-fitting was achieved with the parameters reported in Table 1.

In the flash photolysis experiments (Fig. 6), the trans-chalcone is excited and converted into cis-chalcone during the lifetime of the flash ($\mu$s), as shown by the bleaching at 362 nm, a wavelength where Cc is expected to absorb less than Ct [6,23]. Considering that hydration is faster than tautomerization at very acidic pH values, the rate-determining step should be the tautomerization reaction, as observed in Fig. 5.

### Table 1

| Parameter | Value |
|-----------|-------|
| $K_a$     | $10^{-3.25}$ |
| $K_a$     | $10^{-4.95}$ |
| $k_h/(1+K_t)$ | $1.1 \times 10^7$ M$^{-1}$ s$^{-1}$ |
| $k_i$     | 0.67 s$^{-1}$ |
| $K_hK_b/K_a$ | $1.4 \times 10^2$ s$^{-1}$ |
| $k_4$     | $6 \times 10^{-6}$ s$^{-1}$ |
| $k_6$     | 0.025 s$^{-1}$ |
| $K_t$     | 0.74 |

**Fig. 5.** Reverse pH jump from a solution at pseudo equilibrium ($pH = 6.0$) to $pH = 2.4$, followed by stopped flow. The first process is due to hydration, Eq. (12), and the second to tautomerization, Eq. (13).

**Fig. 6.** (a) Time dependence of A(362 nm) (absorption of chalcones) after a light flash at pH = 1.05; (b) Curve-fitting was achieved according to Eq. (13) for $k_t = 0.02$ s$^{-1}$ and $k_i$. $[C]_0 = 4.2$ M$^{-1}$ s$^{-1}$; (○) data from the slowest process in Fig. 5.
The two sets of experimental data regarding the slowest process in Fig. 5 and the one of Fig. 6, express the same trend, confirming that both kinetic steps refer to the tautomerization reaction. The relatively small differences observed in Fig. 6b, may be attributed to chalcone photochromism brought about by the very intense lamp used for analysis in the stopped flow apparatus. Such interferences do not occur in the flash photolysis experiments as analysis is carried out by a standard spectrophotometer.

The data reported in Table 1 permit to calculate all the rate and equilibrium constants presented in Table 2. Inspection of Table 2 allow to emphasize some properties of the multistate in the presence of captisol. The thermodynamic constant of hydration increases ca. 39 times due to the increase of the hydration rate constant and decrease of the dehydration rate constant. Although the other equilibrium constants are only modestly affected by captisol, this is not the case for the tautomerization rate constants, showing that it is more difficult to open and close the ring in the presence of the host. The decrease of the ring-opening/ring-closure rate constant can be explained by the geometric constrains brought about by the host. However, such constrains do not seem to operate in the isomerization. We still do not have a reliable interpretation for this behavior.

Similarly to other flavylum-based systems, irradiation of the trans-chalcone leads to reversible formation of the flavylum cation/quinoidal base pair (Fig. 7). The photochromic system in the presence of captisol can operate at low pH values, gives a sharp color contrast and possesses a quantum yield (\( \phi = 0.3 \)) that is three times higher than in the absence of the host (\( \phi = 0.1 \)).

### 3.2. Isothermal titration calorimetry (ITC)

The isothermal titration calorimetry of GHF by captisol (Fig. 8) was carried out from an equilibrated GHF solution at pH 6.18, i.e. under conditions where the trans-chalcone is essentially the sole species in solution. The method permits the calculation of the thermodynamic parameters of \( \text{Ct} - \text{captisol binding: } \frac{K_b}{C_0} = 7700 \text{ M}^{-1}, \Delta H^0 = -21.6 \text{ kJ mol}^{-1}, \Delta S^0 = +4.83 \text{ J mol}^{-1} \text{ K}^{-1} \). The binding is essentially driven by a favorable (exothermic) enthalpic contribution. However, the weakly positive (favorable) entropic term suggests that the reduction in the degrees of freedom of both partners when they associate (\( \Delta S^0 < 0 \)) is largely compensated by their concomitant relative desolvation (hydrophobic effect, \( \Delta S^0 > 0 \)). The \( K_b \) value was used to superimpose (calibrate) the two energy level diagrams in the absence and presence of the host, see Scheme 3.

### 3.3. Circular dichroism

When a chiral transparent compound binds an achiral UV–Vis absorbing molecule, thereby causing a perturbation of its transition dipole moment, an induced circular dichroism (ICD) signal can form [24]. Such signals have been observed with host-guest complexes, e.g. with the inclusion complex of a trans-chalcone in \( \beta \)-cyclodextrin [25, 26]. Fig. 9 shows the circular dichroism spectra of GHF at pH 6.0 as a function of captisol concentration. The CD spectra can be attributed to the chiral trans-chalcone – captisol complex. The ICD signal permits the evaluation of the corresponding binding constant, through a fitting of the maximal ellipticity as a function of the host concentration assuming a 1:1 binding model: \( K_b = 8 \times 10^2 \text{ M}^{-1} \). This value is in good agreement with the one assessed by ITC (Fig. 8).

Taking into account the equilibrium constants of Table 1, it is possible to draw an energy level diagram of GHF in the absence (black) and presence (red) of captisol. The two independently constructed diagrams can be merged and correctly positioned to each other, owing to the experimental free energy of \( \text{Ct} - \text{captisol binding, } \Delta G^0 = -RT\ln K_b, (K_b \text{ value assessed by ITC, confirmed by ICD, Table 2). The association constants to captisol of all other species can thus obtained by simply calculating the corresponding } \Delta G^0 \text{ values (blue). It is satisfactory to note that the binding free energies of the quinoidal base and flavylum cation deduced from the independently determined binding constants (Fig. 2) are in reasonable agreement with the theoretical values.
calculated from the diagram. In particular, Scheme 3 is very useful to calculate the binding constants of the elusive species B and Cc.

The different \(K_b\) values (Table 3) show that the rigid tricyclic chromophores of the flavylum cation and quinoidal base have little affinity for captisol, probably because of steric hindrance. The distortions brought about by water addition (non-planar C-ring) and subsequent tautomerization (C-ring opening) strength the binding by one order of magnitude.

4. Conclusions

Cyclodextrins can modify the pH-dependent mole fraction distribution of the flavylum multistate, in particular by shifting the pH domain of trans-chalcone prevalence toward low pH values, where in general the stability of the multistate species is higher. Of interest is the 3-fold increase in photochromism efficiency in the presence of captisol. The superimposition of the energy level diagrams in the absence and presence of the host permits the calculation of the

![Diagram showing energy level diagrams and binding constants](image)
association constants of all the multistate species, provided that one of these constants is assessed by an appropriate experimental method. This general approach can be applied to any other types of 1:1 binding involving the flavilium multistate.

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