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pH-Gated Photoresponsive Shuttling in a Water-Soluble Pseudorotaxane

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A fluorescent bistable pseudorotaxane was devised and shown to display pH-gated photoresponsive ring shuttling. At pH > 7.5 shuttling does not take place after light stimulation while at pH \approx 5 the macrocycle is quantitatively translocated.

Pseudorotaxanes, assembled from linear guest molecules (axle) and macrocyclic receptors, are precursors of mechanically interlocked molecules such as rotaxanes and catenanes that may be used as synthetic molecular machines and switches.¹⁻³ Bistable [2]rotaxanes, consisting of a linear molecule and a macrocycle that can be switched by means of external stimuli between two recognition sites, constitute a prototypical example of a synthetic molecular machine with potential applications in several fields such as molecular electronics, switchable catalytic systems, drug delivery systems, molecular muscles, molecular pumps, etc.⁴⁻⁹ Different chemical and physical external stimuli can be used to switch bistable rotaxanes, but probably light is one of the most appealing as it allows spatial and temporal control in a remote manner without introducing new reagents or producing chemical waste.¹⁰⁻¹³ In order to devise photoswitchable rotaxanes and pseudorotaxanes, light-responsive units such as azobenzenes, stillbenes, olefins, spiropyrans, hydrazones, etc can be introduced in the structures of the thread or macrocycle.¹⁴⁻²⁶ Alternatively, redox or pH-responsive units can also be used together with photosensitizers or photoacids, respectively, present in solution or chemically attached to the (pseudo)rotaxane components.²⁷⁻²⁹ Despite of the vast amount of work reported on this topic, there are several limitations, such as modest positional integrity movements, short-lived states and poor switching fidelity, that must be

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This article is dedicated to Prof. Fernando Pina on the occasion of his 70th birthday. † These authors contributed equally to this work

overcome in order to improve performance, as recently recognized by Leigh and co-workers.²⁵ Herein, we demonstrate the great, although unexplored, potential of the chalcone/flavylium photochromic system to devise photoresponsive pseudorotaxanes. The present system displays excellent switching fidelity, positional integrity and long-lived states that together with water solubility, pH-gated photoresponsive ring-shuttling and fluorescence emission properties make it potentially appealing for biological applications. Flavylium systems display highly attractive pHdependent photochemical properties that were previously explored to devise models for optical molecular memories and mimicking elementary properties of neurons.^{30–33} In this work, we have designed and synthesized trans-chalcone 1 (Scheme 1) in 3 steps from readily available starting materials (see Supporting Information, SI). The corresponding flavylium dication 2 (Scheme 1) is quantitatively formed after UV-light irradiation (366 nm) of 1 in acid media (pH = 1) as evidenced from ¹H NMR and UV-Vis absorption spectroscopy (see SI, Fig. S8 and Fig. S9). Both 1 and 2 were envisaged to form inclusion complexes with cucurbit[7]uril (CB7) in aqueous solution based on the well documented high binding affinity and selectivity of these macrocyclic nanocontainers for organic cations.^{34–36}



UV-Vis titration of **1** with CB7 afforded a binding constant of $K_{11} = 9.8 \times 10^5 \text{ M}^{-1}$ (in H₂O at 25 °C, see SI, Fig. S10) comparable

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 $[\]mbox{Scheme 1. Structures of trans-chalcone 1, flavylium cation 2 and CB7 molecules studied in this work.$

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with the value reported for tetraethylammonium cation $(1.0 \times 10^6 \text{ M}^{-1} \text{ in } D_2 \text{O} \text{ at } 25 \text{ °C}).^{37}$ The proximity of the *K* values suggests a similar binding mode for both guests, i.e., encapsulation of the triethylammonium group of **1** inside the cavity of CB7 which was confirmed by the observation of upfield complexation-induced ¹H NMR chemical shifts for the triethylammonium and propyl spacer protons after addition of 1 equivalent of CB7 (see SI, Fig. S11). Noteworthy, the aromatic ¹H NMR signals, that hardly change with 1 equiv. of CB7, undergo considerable broadening and shifts in the presence of excess of host suggesting the inclusion of the phenol group inside the cavity of a second CB7 molecule (probably due to hydrophobic effects) to form 2:1 host-guest complexes

 $(K_{21} = 2.0 \times 10^{2} \text{ M}^{-1} \text{ in } D_2 \text{O} \text{ at } 25 \text{ °C})$ under these conditions (SI, Fig. S12-S14).³⁸

The interaction of CB7 with flavylium species 2 (generated photochemically upon irradiation of 1) was also investigated by UV-Vis (Supporting Information, Fig. S15) and fluorescence (Fig. 1) titrations at pH = 2 (acidic conditions are required to avoid the thermal back reaction to form 1 during the titration experiment). As can be observed in Fig. 1., the changes in the emission spectrum of 2 upon addition of CB7 can be used to monitor pseudorotaxane formation. The emission intensity increases from free 2 to the 1:1 2:CB7 host-guest complex. Upon further addition of CB7 the emission intensity decreases again due to the formation of a 2:1 host-guest complex with lower fluorescence emission quantum yield. Fitting the variations observed for the emission intensity at 490 nm with the CB7 concentration to a 2:1 binding model affords the binding constants $K_{11} = 1 \times 10^7 \text{ M}^{-1}$ and $K_{21} = 1.2 \times 10^4 \text{ M}^{-1}$ (in H₂O, pH = 2, at 25 °C) in excellent agreement with UV-Vis absorption experiments. The higher CB7 affinity observed for 2 in comparison with 1 was expected on the basis of previous studies regarding the complexation of flavylium multistate systems with CB7.^{39–42} The determined fluorescence quantum yield for the free flavylium dye **2** ($\phi \approx 1\%$) and for the 1:1 host guest complex **2:CB7** (ϕ =24%) provide quantitative basis for the observed variations on the fluorescence properties.



Fig. 1. Emission spectra of flavylium **2** (2.2 μ M, λ_{ex} = 445 nm) at pH = 2 (HCl = 0.01 M) registered with increasing amounts of CB7. The black full lines correspond to the spectra of free dye and 1:1 complex while the dotted line was obtained for 300 μ M of CB7. For clarity, the spectra registered for intermediate concentrations of CB7 between 2.2 and 300 μ M are not shown. The inset shows the fluorescent intensity (490 nm) plotted against the CB7 concentration (from 0 to 300 μ M of CB7).



Scheme 2. Illustration showing the reversible displacement of the CB7 wheel after photoinduced interconversion of 1:CB7 into 2:CB7 complexes and thermal back reaction.

The ¹H NMR spectra in the absence and in the presence of 1 equivalent of CB7 (see Supporting Information, Fig. S16) show slight downfield complexation induced chemical shifts for the signals of the ethyl ammonium protons (a and b) and considerable upfield shifts for the signals of the phenyl group (f and g) along with proton e indicating that in the case of **2** the CB7 ring is located around the 2-phenyl group between the two positive charges (see Scheme 2). In the presence of excess of CB7 (10 equiv.) the signals of the triethylammonium group are displaced upfield and the f and g signals of the phenyl group return to lower field. These observations suggest that the first CB7 molecule, sitting around the phenyl, is pushed to the pyrylium moiety to allow the accommodation of the second host on the ammonium group.

Focusing on the 1:1 host-guest complexes, which can be obtained with equimolar concentrations of host and guest, the results suggest that the position of the CB7 wheel can be switched from the quaternary ammonium group in the case of 1 to the phenyl group for 2 upon irradiation with UV light (Scheme 2). Previous works documented on the construction of stimuli-responsive CBn-based pseudorotaxanes but the majority relies on pH and redox responsive assemblies.^{43,44} The fact that only a small number of light-responsive CBn pseudorotaxanes/rotaxanes were reported is a consequence of the challenges associated with such systems.^{39,45–53}

Fig. 2. (a) shows the spectral variations observed after irradiation of 1 with 365 nm light in the presence of 1 equivalent of CB7 at pH = 4.2. This experiment indicates that 1:CB7 complex (88% is formed under these conditions, see mathematical model in the SI) is quantitatively converted into 2:CB7 (> 93% of complex) with a quantum yield of 10%. However, above ca. pH = 5 the photoinduced conversion of 1:CB7 into 2:CB7 decreases. The absorption spectra observed at the photostationary state (maximum possible photoconversion) at different pH values (Fig. 2.(b)) allows the determination of an apparent $pK_a = 6.1$. The pH-coupled photochemical interconversion of 1:CB7 into 2:CB7 arises from the well-known chemical network of reversible reactions exhibited by flavylium systems.³⁰ The primary photochemical event is the trans to cis photoisomerization of the chalcone. Once formed, the cis species equilibrates fast with the hemiketal species through a ring-closure tautomerization. Finally, depending on the pH, this species dehydrates to give the flavylium cation. Conversely, at high pH values irradiation of the trans-chalcone leads to the formation of a mixture of

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cis-chalcone and hemiketal while under more acidic conditions this mixture is rapidly converted into flavylium cation.



Fig. 2. (a) UV-Vis spectral variations of *trans*-chalcone 1 (26 μ M) in the presence of 1 equivalent of CB7 at pH = 4.2 (10 mM of citrate buffer) after irradiation with a 365 nm UV-light source. (b) Spectra taken at the photostationary state at different pH values obtained after irradiation of 1 (26 μ M) with 1 equivalent of CB7 in 10 mM citrate buffer.

The net result is the observation of the photochemical conversion of trans-chalcone 1 into flavylium cation 2. Because shuttling of the CB7 ring is only observed when the flavylium cation is formed, the system behaves as an AND molecular logic gate that works with H^{+} and light inputs. Moreover, if the pH is low enough (pH \approx 2) the pseudorotaxane can be LOCKED in the aromatic station because the flavylium cation is the thermodynamically stable species under highly acidic conditions and does not return to the trans-chalcone state / quaternary ammonium station in the dark. This process is reversible and the pseudorotaxane can be UNLOCKED by neutralization with NaOH. It is worth noting that when the trans-chalcone solution is acidified in the dark the system will be out of the equilibrium and can, in principle, evolve to the flavylium cation. However, the kinetic barrier is high and this process can take several months to reach the equilibrium at room temperature (the $t_{1/2}$ is ca. 100 days at pH =2 for a similar flavylium derivative).⁵¹ The stimuli-responsive operation of this system is summarized in Scheme 3.

The pH-coupled photoresponsive shuttling was also tested by ¹H NMR experiments. At pD = 7.4, irradiation of **1:CB7** with a 365 nm light source leads to the disappearance of the signals corresponding to this species and the appearance of broad, poorly defined signals that can be assigned to an equilibrium mixture of complexed trans-chalcone, cis-chalcone, hemiketal and ca. 10% of **2:CB7** in agreement with an apparent $pK_a = 6.1$ (see SI, Fig. S17). The system is reversible and heating the sample for 2 hours in the dark at 80 °C leads to the recovery of the spectrum corresponding to 1:CB7. On the other hand, when the same experiment is conducted at pD = 4.96 (Fig. 3), it can be clearly observed that 1 CB7 is completely converted into 2:CB7 upon excitation with 365 nm light. As already demonstrated, 1:CB7 into 2:CB7 interconversion leads to displacement of the CB7 ring from the quaternary ammonium to the aromatic station. Again, heating the sample in the dark leads to the recovery of the spectrum corresponding to 1:CB7 confirming the reversibility of the system. However, at 25 °C the thermal recovery is much slower ($t_{1/2}$ = 151 hours at pH = 5, see Fig. S19 in the SI) which account for long-lived photostationary state. It is worth noting that at this pD value ca. 10% of 2:CB7 (estimated from the integration of the signals corresponding to protons a) was not reconverted into 1:CB7.

Complete recovery of **1:CB7** can be achieved at pD = 5.3 but at the cost of reducing the conversion yield (88%) of the **2:CB7** photoproduct (see Supporting Information, Fig. S18).



Scheme 3. Illustration showing the pH-coupled photoresponsive shuttling according to an AND molecular logic gate. At pH around 5 the system is reversible and returns to the trans-chalcone in the dark. However, the system can be LOCKED in the flavylium state by acdification (ca pH = 2) after irradiation and UNLOCKED by addition of base to pH > 5. Simplified representation of the potential energy of the system at selected pH values.



Fig. 3. ¹H NMR spectra of 1:CB7 in D₂O (0.4 mM) at pD = 4.96 (acetate buffer 10 mM) in the presence of 1 equivalent of CB7. Before (bottom), after irradiation with 365 nm light (middle) and upon standing overnight in dark at 60 °C. The signals marked with * are assigned to ca. 10% of 2:CB7 that equilibrates with 1:CB7 at this pD value.

In summary, we have devised a water-soluble bistable pseudorotaxane that shows pH-gated photoresponsive ring shuttling. The CB7 ring is only translocated after the application of pH and light stimuli (an AND molecular logic behavior). Noteworthy, the operating pH values fall within those that can be employed for biological systems. At neutral or slightly basic conditions no translocation occurs while at pH values around 5 near quantitative ring translocation can be observed. The system is reversible in the dark but can be made irreversible (locked) at more acidic pH values and unlocked by neutralization. In addition to these special stimuli responsive features, the present system also displays good fluorescent properties which further increase his potential for molecular machine-based applications.

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Conflicts of interest

There are no conflicts to declare.

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Phototriggered ring shuttling in a water-soluble fluorescent pseudorotaxane can enabled and disabled at different pH values.