Drug delivery by controlling a supramolecular host-guest assembly with a reversible photoswitch

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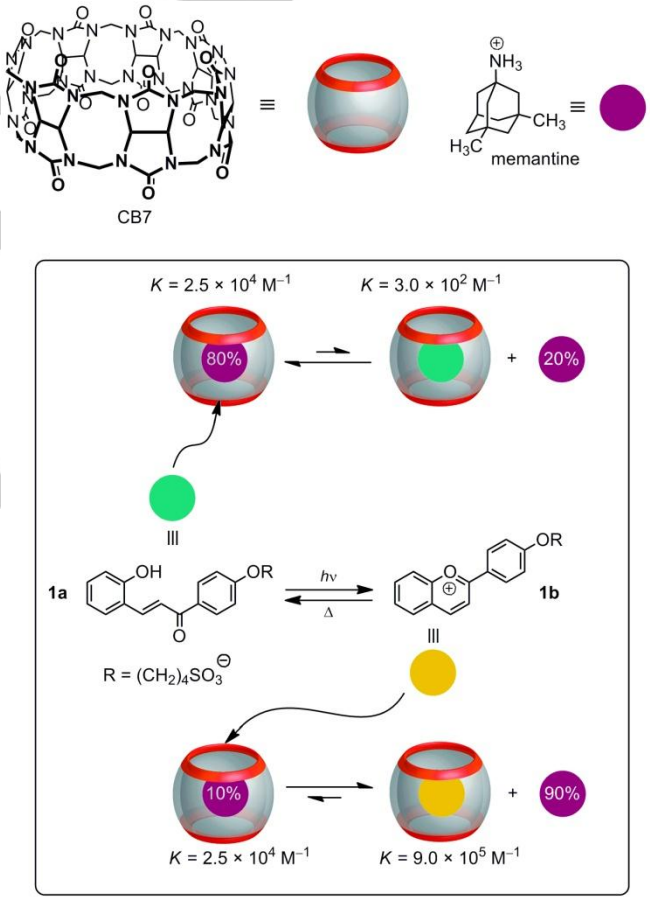
Abstract: The reversibly switchable *trans*-chalcone/flavylium photochromic system was successfully coupled to the complexation equilibrium of a drug-cucurbit[7]uril host-guest assembly. Hence, the phototriggered release of memantine under illumination at 366 nm was observed. The process can be partially reverted through a thermally activated back reaction.

The assembly and disassembly of host-guest complexes by means of the application of external stimuli is an elegant exercise of functional supramolecular chemistry that builds on the reversibility of non-covalent interactions.[1–5] This has led to viable approaches towards intelligent supramolecular materials, molecular information processing, the release/capture of compounds in bio-inspired applications, and drug delivery systems.[6–11] Among other stimuli, such as chemical and electrochemical signals, the use of light has been a preferred choice due to the possibility of conducting spatiotemporally and remotely controlled experiments.[1,12–16] Our own efforts in this field have focused on supramolecular complexes with cucurbituril hosts and their manipulation by means of photoinduced pH jumps.[17,18] The choice of cucurbiturils as host macrocycles for these applications is motivated by their unique supramolecular chemistry, including extraordinary high binding constants of a variety of organic guests in water.[3,19–22] As a consequence, the nanotechnological application potential of cucurbiturils at the intersection of analytical chemistry, catalysis, materials science, and bio-inspired research is continuing to unfold.[6,23–29] Special interest was awaken by the possibility to use cucurbiturils as vehicles in drug delivery and other pharmacological contexts.[30–36] Herein we exploited a strategy for the phototriggered release of a model guest drug from cucurbit[7]uril (CB7) by means of controlling host-guest equilibria with a photoswitch. The *cis-trans* photoisomerization of azobenzene motifs is a frequently used relay mechanism for controlling supramolecular assemblies, including cucurbituril complexes.[7,37–40] In this work we build on a chalcone-flavylium system, which enabled the photoinduced switching between a non-charged (chalcone) and a charged guest species (flavylium ion), with the latter binding about three orders of magnitude stronger to CB7 than the former (see below). Hence, upon irradiation a competitive guest is formed, able to displace an initially complexed drug (3,5-dimethyl-1-aminoadamantane, also known as memantine, a widely prescribed Alzheimer drug) from the macrocycle (see Scheme 1). The only precondition for the model drug is that its binding constant with CB7 should be ideally situated in the window defined by the ones for the chalcone and the flavylium ion.



Scheme 1. Coupling of a flavylium photoswitch with a memantine-CB7 host-guest equilibrium for the phototriggered release of the drug (memantine). The percentage numbers indicate the amounts of memantine in its complexed or free form under the chosen experimental conditions (see text).

In a first step we synthesized the water-soluble *trans*-chalcone **1a** shown in Scheme 1, containing a sulfonate group (see Experimental Section). This compound interconverts with other species by means of pH and light stimuli showing the same intriguing chemical-network features (see Appendix 1 in

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the Supporting Information) as known for other flavylium systems; such as the previously reported 4'-methoxyflavylium.[41,42] For the purpose of this work we focused on the photoinduced conversion between the *trans*-chalcone **1a** and the flavylium ion **1b**. Species **1a** is stable at pH 3.15 in the dark. However, on irradiation at 366 nm for *ca*. 50 min (light intensity 2.3 × 10^{-7} Einstein min^{-1}) the flavylium ion **1b** with its characteristic absorption band at 437 nm is formed quantitatively with a quantum yield of 0.08; see Figure 1. The identity of the flavylium ion **1b** as photoproduct was confirmed by monitoring the irradiation of **1a** by ^{1}H NMR spectroscopy (see Supporting Information). The system can be reverted to the *trans*-chalcone in a thermally activated process. Heating a solution of photogenerated **1b** for about three hours at 70 ºC yields back **1a** (k_{obs} = 4.0 × 10^{-4} s^{-1}) in 94% yield; see Supporting Information. As the speciation in flavylium systems is known to depend very much on the proton concentration, photoirradiation at varying pH values was performed. This enabled the determination of an apparent pK'_a of 4.2 at the photostationary state (see Supporting Information), thereby defining the requirement of pH ≤ 4 for our photoswitch. It is worth noting that the flavylium cation **1b** can also form as the thermodynamic stable species in the dark at very acidic pH values (pK'_a *ca*. 1). However, such thermal conversion of **1a** is very slow under our experimental conditions (half-life $t_{1/2}$ *ca*. 100 days, see Supporting Information). A large pK'_a shift (ca. 3.2) between the photostationary state and the dark equilibrated solutions is critical for near quantitative photoconversion of the *trans*-chalcone into the flavylium ion.

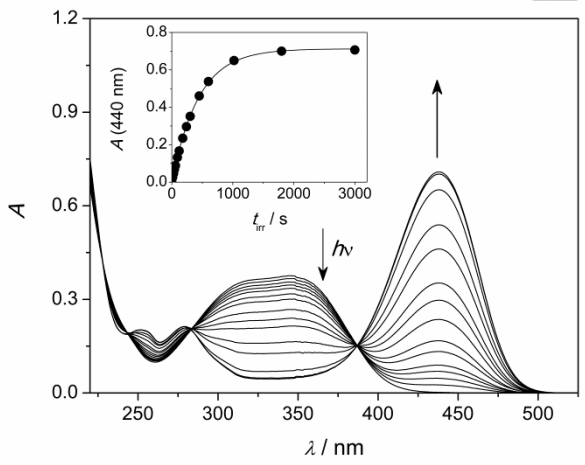

Figure 1. Spectral variations on irradiation (366 nm, I_0 = 2.3 × 10^{-7} Einstein min^{-1}) of the *trans*-chalcone **1a** (1.9 × 10^{-5} M) at pH 3.15 (see text and Supporting Information for the choice of the optimal pH condition). The inset shows the absorbance at 440 nm plotted against the irradiation time.

Having established the chemical and functional basis of the photoswitch, the differential binding properties of **1a** and **1b** with CB7 were studied. On the one hand, the ^{1}H NMR titration[43] of **1a** with CB7 confirmed the predicted weak 1:1 binding (apparent K = 3.0 × 10^2 M^{-1}). Noteworthy, Na^+ ions may be competitive CB7 binders at millimolar concentrations.[44] However, the accordingly corrected binding constant for **1a** is very similar, K = 4.0 × 10^2 M^{-1}; see Supporting Information. On the other hand, the UV/vis-absorption titration of the photogenerated ion **1b** (at pH 1) yielded a much larger 1:1 binding constant of K = 9.0 × 10^5 M^{-1}; see Figure 2. This is straightforward rationalized by the significant ion-dipole interaction between the positively charged guest and one of the carbonyl portals of CB7. Such feature is missing for **1a**. The recording of ^{1}H NMR spectra of **1b** in the presence of CB7 corroborated the notion of the formation of a stable inclusion complex, which was accompanied by pronounced upfield shifts of the protons 4, 5, and 8 that are immersed in the CB7 cavity (see Figure 3). Similar observations have been made for the CB7-complexation of related flavylium systems, thereby providing solid ground for our interpretations.[41,45–48]

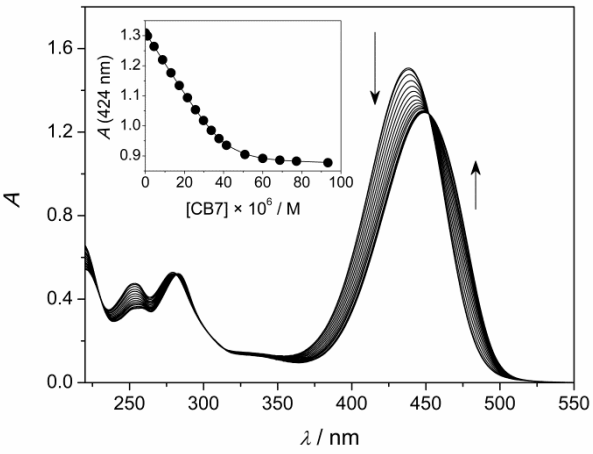

Figure 2. Spectral variations observed for **1b** (4.1 × 10^{-5} M) upon gradual addition of CB7 at pH 1 (to assure the sole presence of the under these conditions thermodynamically stable flavylium cation). The inset shows the absorbance variations registered at 424 nm plotted against the CB7 concentration. The fitting line corresponds to a 1:1 binding model.

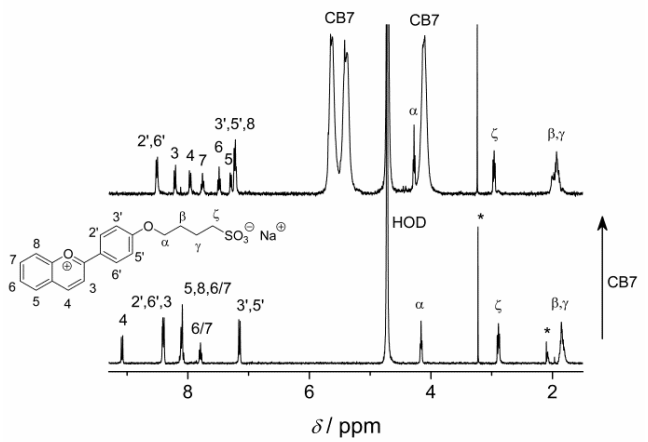

Figure 3. ^{1}H NMR spectra of **1b** (1 × 10^{-3} M) in the absence (bottom) and in presence of 1.5 equivalents of CB7 (top), obtained in D_2O with 0.1 M DCl. The asterisks denote unidentified solvent impurities (methanol, acetone).

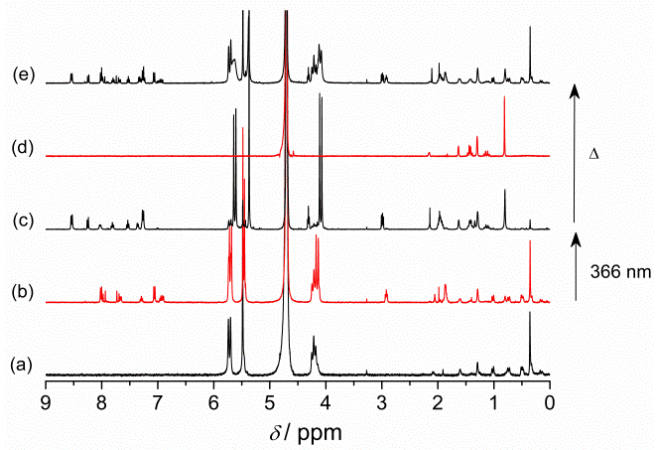

Figure 4. ^{1}H NMR spectra of (a) the memantine-CB7 complex, (b) **1a** (1×10^{-3} M), CB7 (1×10^{-3} M) and memantine (5×10^{-4} M) before irradiation, (c) the same after one hour of irradiation at 366 nm, (d) free memantine, and (e) the same as in (c) after standing overnight in the dark at 70 ºC. The spectra (a) and (d) were acquired in non-buffered D_2O and are shown for the sake of comparison. The remaining experiments were performed in 0.01 M acetate-buffered D_2O solution (pD = 4.4). The pH (pD) condition of these experiments was chosen to guarantee optimized photochromic transformation and thermal recovery in the presence of CB7. The somewhat higher pH (4 *versus* 3.2 in the absence of CB7) was adjusted due to the known pK_a shift of guests upon CB7 complexation.[47]

According to the idea expressed in Scheme 1 we proceeded to the key experiment, testing the release of memantine from CB7 on transformation of the *trans*-chalcone **1a** into the competitive binder **1b**. For this purpose an acetate-buffered D_2O solution (pD = 4.4) containing optimized concentrations of CB7 (1×10^{-3} M), **1a** (1×10^{-3} M), and memantine (5×10^{-4} M) was irradiated at 366 nm. The drug model memantine was chosen in a lower concentration in order to allow an efficient competition of the photogenerated flavylium ion **1b**. The binding constant of memantine is known as $K = 2.5 \times 10^{4}$ M^{-1} and, hence, it was expected that the flavylium ion ($K = 9.0 \times 10^{5}$ M^{-1}) would displace the drug efficiently.[49] Indeed, in the ^{1}H NMR spectrum the signals of the CB7-complexed memantine vanished on irradiation (one hour at 366 nm) and the resonance signals assigned to the free drug appeared (Figure 4). Under the chosen experimental conditions the initial solution contains *ca*. 80% complexed memantine, while after irradiation only *ca*. 10% of the drug are complexed by CB7. This corresponds to an effective release of 90% of the initially complexed memantine. On standing overnight in the dark at 70 ºC the situation was partially inverted due to the thermally activated **1b**-to-**1a** conversion, yielding back an amount of *ca*. 60% complexed memantine (Figure 4). The less than quantitative reversal of the situation is explained with a higher stabilization of the flavylium ion **1b** in the CB7 complex as compared to the free ion (see above). Under the chosen experimental conditions the equilibrium between **1b** and **1a** is characterized by *ca*. 50% flavylium ion, translating into the described only partial memantine re-complexation. The reversible interconversion, if required by an application, can be achieved by optimizing the experimental conditions, e.g., by using more diluted solutions. As a title of example, the mole fraction of the flavylium cation at the equilibrium is estimated to be 14% for a 1.9×10^{-5} M solution of **1a** in the presence of 5.0×10^{-4} M of CB7 at pH = 3.9 (see Supporting Information). Noteworthy, the design of reversibly addressable multicomponent systems consisting of CB host-guest complexes and photoresponsive switches is not a trivial task, as the presence of the host macrocycle often leads to a stabilization of the photoproduct.[50,51] However, it is also important to note that for the feature of drug delivery, reversibility is not a pre-requirement at all.

In conclusion, we devised a method for the photocontrolled release of the memantine model drug from the cucurbit[7]uril macrocycle in water. The release is mediated by the formation of a strongly binding flavylium cation as competitor by irradiation of a weakly binding *trans*-chalcone as precursor. The herein demonstrated proof-of-principle could be expanded to other photoswitchable systems and different chemical environments.

Experimental Section

General: All solvents and chemicals employed for synthesis and for preparation of samples were of reagent or spectrophotometric grade and used as received. Millipore grade water was used. Cucurbit[7]uril was available from previous studies.[47] The final pH of the solutions was measured with a Crison basic 20+ pH meter. UV/vis-absorption spectra were recorded with a Varian Cary 100 Bio or a Varian Cary 5000 spectrophotometer. NMR experiments were run on a Bruker AMX 400 instrument operating at 400 MHz (^{1}H) and 101 MHz (^{13}C).

Synthesis: 4'-Hydroxyacetophenone (1.0 g, 7.3 mmol) was treated with one equivalent of 1,4-butane sultone and one equivalent of sodium carbonate in 10 ml isopropanol and stirred under reflux overnight. After cooling to room temperature, the solution was filtered and the solid was carefully washed with methanol. The filtrate was concentrated by rotary evaporation and the product was precipitated by addition of diethyl ether. After filtration, further washing with diethyl ether, and drying in high-vacuum 1.3 g (60% yield) of an off-white solid were obtained. The identity of the desired 4'-(1-sulfo-4-butyloxy)acetophenone sodium salt was confirmed by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, D_2O): δ = 7.92 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 4.12 (t, J = 5.5 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.52 (s, 3H), 1.93 – 1.78 ppm (m, 4H).

4'-(1-Sulfo-4-butyloxy)acetophenone sodium salt (0.1 g, 0.34 mmol) and salicylaldehyde (0.04 g, 0.34 mmol) were dissolved in 0.4 ml methanol and the solution was cooled down to 0 ºC with an ice bath. After addition of 0.044 ml of 40% NaOH, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted in 5 ml of distilled water, neutralized with 1 M HCl and extracted with diethyl ether. The aqueous phase was concentrated by evaporation and the crude product was purified by reverse phase (C18) column flash chromatography with gradient elution from 100% H_2O to 70% H_2O/30% CH_3CN. After evaporation of the solvent and drying in high vacuum **1a** was obtained as a yellowish solid (0.1 g, 74% yield). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.03 – 7.92 (m, 3H), 7.73 (d, J = 15.8 Hz, 1H), 7.57 (dd, 1H), 7.19 – 7.09 (m, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.82 – 6.75 (m, 2H), 4.03 (t, J = 5.5 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 1.96 – 1.80 ppm (m, 4H); ^{13}C NMR (101 MHz, CD_3OD): δ = 190.25, 163.28, 157.38, 140.29, 131.40, 130.81, 130.59, 129.05, 121.89, 121.16, 119.44, 115.67, 114.10, 67.60, 50.85, 27.89, 21.51 ppm; HRMS (ESI) calcd for $C_{19}H_{20}NaO_6S$ [M+H$^+$]: 399.0873; found: 399.0867.

Photochemistry: Irradiation experiments were carried out with a spectrofluorimeter Spex Fluorolog 1681 at the wavelength of 366 nm (I_0 =

2.3×10^{-7} Einstein min^{-1}) or, in the case of reactions monitored by NMR spectroscopy, with a Xenon-Hg lamp using a bandpass filter for wavelength selection (366 nm, $I_0 = 1.9 \times 10^{-6}$ Einstein min^{-1}). The light intensity was measured by ferrioxalate actinometry.[52]

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Keywords: photochemistry • host-guest chemistry • drug delivery • flavylium • cucurbiturils

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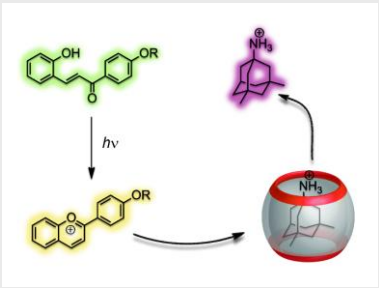
Entry for the Table of Contents

COMMUNICATION

Light on and action: Controlling a host-guest equilibrium with a flavylium-based photoswitch leads to the efficient light-triggered release of memantine, a widely prescribed Alzheimer drug. The supramolecular host system is constituted by a cucurbituril macrocycle, that binds preferably to a flavylium ion that is formed from a *trans*-chalcone in a phototriggered reaction. Thereby the initially complexed memantine guest is competitively displaced.



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