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Photocaged Competitor Guests: A General Approach Toward Light-Activated Cargo Release From Cucurbiturils

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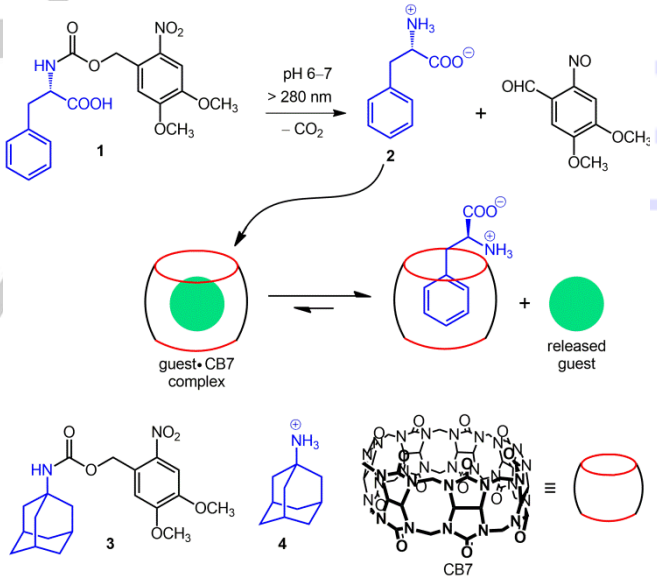
Abstract: A general approach toward the light-induced guest release from cucurbit[7]uril by means of a photoactivatable competitor was devised. An *o*-nitrobenzyl-caged competitor is photolyzed to generate a competitive guest that can displace cargo from the host macrocycle solely based on considerations of chemical equilibrium. With this tool the release of terpene guests from inclusion complexes with cucurbit[7]uril was demonstrated. The binding of the herein investigated terpenes, all being lead fragrant components in essential oils, has been characterized for the first time. They feature binding constants of up to 10^8 M^{-1} and high differential binding selectivity (spanning four orders of magnitude for the binding constants for the particular set of terpenes). By fine-tuning of the photoactivatable competitor guest the selective and also sequential release of the terpenes was achieved.

Introduction

The release of functional molecules by means of photoactivation is an attractive tool in processes where spatiotemporal control is an advantage.[1, 2] Often so-called caged compounds, where the active component is released by the removal of a light-sensitive protection group, have been exploited for these purposes. Examples for the light-induced release of signalling molecules,[3] drugs,[4] biomolecules,[5] fluorescent dyes,[6, 7] or natural products,[8, 9] are known. However, the covalent nature of these constructs requires elevated synthetic efforts, especially when combinatorial libraries of caged functional molecules are pretended.

The non-covalent nature of supramolecular interactions provides an interesting feature for combinatorial assembly, being an added value especially when light can be used to achieve the release of guests. Selectivity in photorelease is an important attribute that could be potentially achieved by exploiting the differential supramolecular binding of guests by a certain host type and their competitive displacement by a photogenerated molecular entity, being only dependent on considerations of chemical equilibria. In this context cucurbit[n]urils (CBn) are an emerging family of all-organic macrocyclic hosts[10, 11] that feature high guest affinities (generally in the range of 10^5–10^{10} M^{-1}; exceptionally up to 10^{17} M^{-1}) and selective binding of structurally diverse molecules in aqueous solution.[11-14] They are exploited for example for drug delivery,[15-17] monitoring/control of biological processes (e.g., enzymatic catalysis),[18-21] and biomolecule modification,[22-25] but also for the design of sensors and switches.[26-34]



Scheme 1. Schematic representation of the release principle, employing the phototrigger **1**. On irradiation the competitor **2** is formed, which in contrast to **1** is able to displace a guest from CB7. Further, the structures of the alternative phototrigger **3**, the competitor guest **4**, and CB7 are shown.

As part of our own research program we demonstrated recently the photorelease of guests from CB7 complexes by light-induced pH-jump or by coupling of a (pH-dependent) flavylium photoswitch to the host-guest equilibrium of a cucurbituril complex.[35, 36] However, these approaches required the implication and strict control of pH conditions and are therefore limited in their experimental design. This is not ideal for applications in more realistic contexts.

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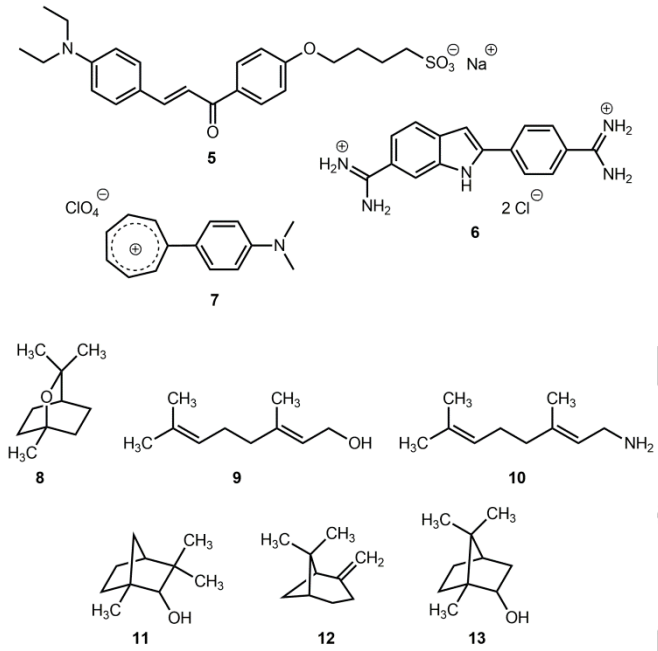
In this work we devise the light-activated photorelease from CB7 by using photoactivatable precursors that generate competitor guests, based on the photochemistry of the popular *o*-nitrobenzyl motif, that can be operated even under physiological conditions.[1, 2, 5, 37, 38] This was combined with the differential binding of guests, inherent to cucurbituril chemistry and leading to selective as well as sequential release. In addition, our approach does not require a photoactive host or guest.[27, 33, 39-48] Both can be photochemically silent, which expands the diversity spectrum enormously. The potential of this very flexible "plug-and-play" approach is showcased for the release of fragrant terpene guests, but could be easily expanded to other functional guests.



Scheme 2. Structures of the dyes **5**–**7** and the terpene guests **8**–**13**.

Results and Discussion

Design and Working Principle

Our strategy toward light-activated supramolecular release combines *o*-nitrobenzyl-caged compounds with the competitive displacement of a previously bound guest from its cucurbituril complex by a photogenerated competitor. This principle is illustrated in Scheme 1 for the example of phototrigger **1**, an NVOC-protected phenylalanine (NVOC: 6-nitroveratryloxycarbonyl). **1** itself does not bind to CB7. This was deduced experimentally at the micromolar concentration level by the failure to displace the chalcone charge-transfer dye **5** from its CB7 complex (K_{CB7} = 2.3 × 10^5 M^{-1})[49] by addition of **1**, monitored by UV/vis absorption spectroscopy (see Supporting Information). At millimolar concentration also no interaction between CB7 and **1** proceeded, as evidenced by the invariability of the ^{1}H-NMR signals on addition of CB7 (see Supporting Information). This very low supramolecular affinity is explained by (a) the repulsive electrostatic interaction between the negatively charged carboxylate group and the carbonyl-lined CB7 portal[20, 50] and (b) the inactivation of the amino group in the NVOC-protected compound **1**.[51] However, upon irradiation of **1** at >280 nm (the photoreaction can be performed at 365 nm but requires longer irradiation time) phenylalanine (**2**) is formed. The now available protonable amino group engages in ion-dipole interactions with the CB7 portal and offsets the effect of the carboxylate. This is translated into a more efficient supramolecular interaction with CB7 (K_{CB7} = 1.8 × 10^6 M^{-1})[13] and resulted in the release of dye **5** (see Figure 1), which was also independently confirmed by the corresponding competitive displacement titration with **2** (see Supporting Information). The absence of binding of **1** and its light-triggered conversion into an efficient CB7 binder constitute an ideal scenario with view on the release of a guest, such as dye **5**.

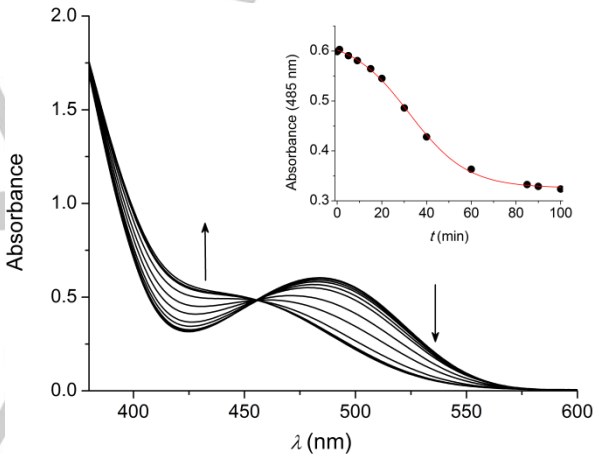


Figure 1. UV/vis-absorption spectral changes on irradiation (>280 nm) of a mixture of phototrigger **1** (500 μM), dye **5** (20 μM), and CB7 (50 μM); pH 7. The inset shows the temporal development of the photoreaction/displacement. No spectral changes were observed for the irradiation of a blank control where no phototrigger **1** was present.

The NVOC-protected competitor can be varied flexibly, thereby enabling the displacement of even stronger binding guests. For this purpose we designed 1-aminoadamantane-NVOC (**3**) which is expected to generate the strongly binding 1-aminoadamantane upon irradiation (**4**; K_{CB7} = 1.7 × 10^{14} M^{-1}).[52] Compound **3** binds to CB7 with a binding constant of K_{CB7} = 1.4 × 10^8 M^{-1} (measured by the displacement of 4',6-diamidino-2-phenylindole dihydrochloride **6** and monitored by fluorescence; K_{CB7} = 1.7 × 10^7 M^{-1}; this work).[53] Hence, **3** could be used to displace guests with affinities in the order of *ca*. 10^9–10^{13} M^{-1}. However, the insolubility of **3** (limited to *ca*. 10 μM in water/methanol 95/5) circumvents the premature release of even weaker binding guests in experiments that are conducted at the millimolar concentration level (see below).

Terpene Binding by CB7

As a title of example we have chosen to address the release of terpene guests from CB7 by means of the above described mechanism. Eucalyptol (**8**), geraniol (**9**), geranylamine (**10**), fenchyl alcohol (**11**), β-pinene (**12**), and borneol (**13**) were selected for being representative lead fragrant components of essential oils (see structures in Scheme 2). First, the binding of the guests **8**–**13** with CB7 was evaluated (see Table 1). Some of these compounds are highly hydrophobic, which turns this task into a real experimental challenge.[54] In the case of sufficiently water soluble guests (**8**, **10**, **11**, and **13**) isothermal titration calorimetry (ITC) was employed (see Figure 2(a)), albeit the binding constant of **13** turned out to be too large to be measured by direct titration (>5 × 10^7 M^{-1}). The data were contrasted with those obtained in dye displacement titrations (using the UV/vis-absorption changes of dye **5** or **6**) and were found to be in satisfactory agreement. For sparingly water-soluble terpenes (**9** and **12**) and very strong binders (**13**) dye displacement titrations were employed for the determination of the 1:1 binding constants; Figure 2(b). Interestingly, the set of terpenic guests spans an affinity range of four orders of magnitude (10^4–10^8 M^{-1}). Geraniol (**9**) is the weakest binder in the investigated series, while geranylamine (**10**) binds two orders of magnitude stronger, due to the presence of the protonable amino group. The bicyclic terpenes **12** and **13** are the strongest binders. Interestingly, small variations of the substituent positions on the bicyclo[2.2.1]heptane skeleton of the regioisomeric guests **11** and **13** result in rather pronounced differences of the binding strength. The observed variety of binding constants for the investigated series gives way to the prediction that the terpenic guests could be displaced selectively by the action of phototrigger **1**; see below.

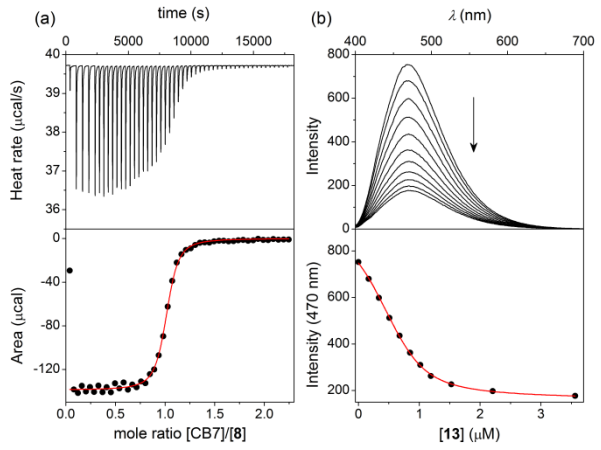


Figure 2. (a) Isothermal titration calorimetry (ITC) data for the binding of **8** by CB7 in water; titration of CB7 into 0.4 mM **8**. (b) Competitive displacement of **6** ([**6**] = [CB7] = 1 μM; K_{CB7}(**6**) = 1.7 × 10^7 M^{-1}, this work) by **13**, monitored by fluorescence spectroscopy (λ_{exc} = 362 nm; isosbestic point in UV/vis absorption spectra).

^{1}H-NMR spectroscopy confirmed the notion that the terpene guests are bound by the CB7 cavity. Gratifyingly, all investigated guests have various methyl groups and their proton signals are ideal indicators for gaining information about the binding situation of the terpenes. Especially the exchange kinetics for the bicyclic terpenes is slow on the NMR time scale, enabling the concomitant observation of the free and bound guest. On addition of CB7 to terpene solutions significant upfield chemical shift changes apply (Δδ *ca.* 0.5–1.0 ppm; see ^{1}H-NMR spectra in Supporting Information). This is indicative of a deep immersion of the guests into the macrocycle cavity.

Table 1. Binding affinities of the guests **8**–**13** with CB7.

	K (10^6 M^{-1})[a]	ΔH (kJmol^{-1})	$-T\Delta S$ (kJmol^{-1})
8	0.85[b] [0.34][c]	–37.4[b]	3.6[b]
9	0.046[c]		
10	3.2[b] [1.9][d]	–39.7[b]	2.5[b]
11	4.8[b] [8.6][c]	–42.3[b]	4.1[b]
12	≥10[e]		
13	260[d]	–61.7[b,f]	13.7[g]

[a] In square brackets data obtained by alternative methods are shown. [b] Measured by ITC in water at 25 ºC. [c] Measured by displacement of **5** in water (pH 9). [d] Measured by fluorescence monitoring of the displacement of **6** in water (pH 7). [e] Estimated by displacement of **7** in 10 mM acetate buffer (pH 4). Only a lower limit is given due to a higher uncertainty caused by the low solubility of **12**. [f] Binding constants larger than 5 × 10^7 M^{-1} are hard to measure by direct ITC titration. However, the ΔH value can be measured reliably by ITC. [g] The value for $-T\Delta S$ was calculated from ΔG (via K) and ΔH.

The ITC data for the terpenes **8**, **10**, **11**, and **13** reveal that their complexation is enthalpically driven; see Figure 2(a).[55] This is a typical situation found for the binding of hydrophobic guests by CB7 and interpreted as the benefit that results from the release of high-energy water molecules from the macrocyclic host cavity to the surrounding bulk water.[55] At the same time there is no entropic gain associated to the guest binding, pointing to a much less significant, if existent, contribution of a classical hydrophobic effect.

A different facet of the binding of terpenes by CB7 is the capacity of the macrocycle to retain the fragrant guest from passing to the gas phase. As a title of example we performed solid-phase microextraction (SPME) experiments[56] at constant temperature (24 ºC) with an aqueous eucalyptol solution ([**8**] = 50 μM) in the absence or presence of CB7 (120 μM; corresponding to 98% complexation degree of **8**), using a polyacrylate-coated fused-silica fiber (85 μm coating). The extracted terpene was subjected to gas chromatography coupled with mass spectrometric detection, providing relative concentrations of **8** in the headspace. Keeping the optimized experimental parameters constant (especially the times for extraction and

desorption), it was found that CB7 retained guest **8** to a large extent, characterized by a drop to 5% of the initially measured headspace concentration in the absence of the host macrocycle. Also the evaporation of the terpene from its water solution was slowed down by the macrocyclic host: a half-life of 229 minutes in the absence of CB7 is contrasted by 679 minutes in the presence of CB7 (see Figure 3).

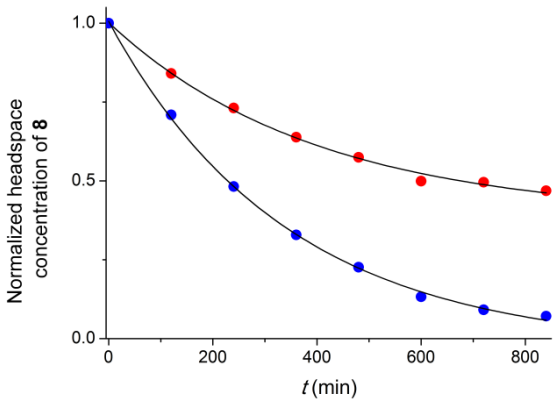


Figure 3. Transfer of **8** (50 μM) from aqueous solution (pH 7) to the gas phase, in the absence (blue data points) and presence of CB7 (120 μM, red data points); quantified by SPME. The normalized concentrations of **8** are expressed as chromatography peak areas divided by the initial zero-time peak area for each experiment (see text). The time corresponds to the duration of leaving the solution-containing vial open to the ambient atmosphere. Each point was measured after closing the container vial again and re-equilibrating the solution for 10 min.

Light-activated Guest Release

With the binding data at hand we proceeded to the photorelease of the terpene guests from their complexes at concentrations of hundreds of micromolar (100–400 μM) by irradiation in the presence of **1**. The release was monitored by ^{1}H-NMR spectroscopy; see Figure 4 for the example of eucalyptol (**8**) and the Supporting Information for the other terpenes. Under the specific experimental conditions (see caption of Figure 4) 87% of **8** was bound to CB7 before irradiation, while after two hours of irradiation (280 nm cut-off filter) 93% of all **8** was unbound. Hence, effectively 92% of all initially bound **8** was released. The experiment was repeated under comparable conditions for the other terpenes, employing optimized concentrations of CB7, terpene, and phototrigger. For geraniol (**9**), having the weakest CB7 affinity in the series, 100% release was obtained. The stronger binding geranylamine (**10**) and fenchyl alcohol (**11**) were less efficiently released; 45% and 54%, respectively. Finally, the strongly binding guests β-pinene (**12**) and borneol (**13**) are not displaced by the photogenerated phenylalanine (**2**). Hence, as anticipated, the variable binding affinity has direct impact on the efficiency of the photorelease experiment and thereby its selectivity. The release of guest **8** was also confirmed by determining the relative headspace concentrations before and after irradiation (6 hours with a TLC lamp at 365 nm) of an aqueous solution containing 50 μM **8**, 120 μM CB7, and 240 μM **1**. The corresponding SPME experiments indicated a 2.5-fold increase of the headspace concentration of **8** as the result of the photorelease.

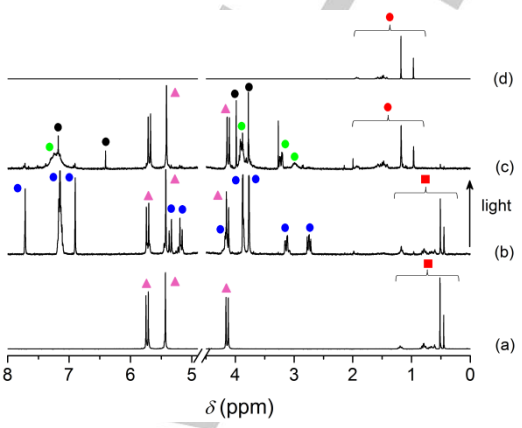


Figure 4. ^{1}H-NMR spectra of (a) **8**•CB7 host-guest complex (each component at 1 mM); (b) a mixture of **1** (1 mM), CB7 (125 μM), and **8** (100 μM) before irradiation; (c) after 120 min irradiation (>280 nm) of the same mixture as under (b); (d) only **8**; pD 6.5. The signals are assigned with color codes: **8** - red (complexed - squares, free - dots); **1** - blue dots; free excess **2** - green dots; NVOC-derived photoproduct - black dots; CB7 - magenta triangles. Note that **1** was used in large excess and that the exchange rate between free and complexed **2** is assumed to be intermediate. The ^{1}H-NMR signals of excess free **2** appear considerably broaden, while the signals of complexed **2** are not observed. The HOD signal is not shown for the sake of clarity (axis break).

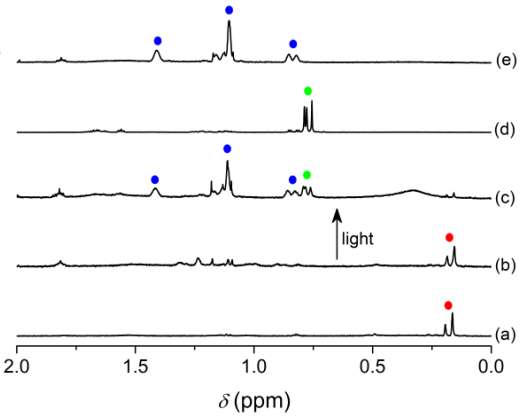


Figure 5. Photorelease of **13** from CB7 by light irradiation (>300 nm), monitored by ^{1}H-NMR spectroscopy. Conditions: 1-aminoadamantane-NVOC (**3**, 2 mM), CB7 (500 μM), and **13** (250 μM) in D_2O:CD_3OD 50:5; pD 6.8. The spectra were acquired after different irradiation times: 0 min (b) and 240 min (c). Additionally the spectra of (a) **13** (250 μM) in the presence of CB7 (500 μM), (d) only **13** (1 mM), and (e) **4** (1 mM) in the presence of CB7 (1 mM) are shown. Corresponding signals are color-coded: red - methyl signals of complexed borneol; green - methyl signals of free borneol (**13**); blue - signals of complexed 1-aminoadamantane (**4**).

As outlined above, the described approach is of general nature and the light-triggered formation of a stronger competitor should allow the delivery of **12** or **13**. This has been tested with

phototrigger **3**. The photoirradiation yields the competitor **4** which binds sufficiently strong to displace even borneol (**13**) quantitatively (see above and Figure 5) during 240 minutes of irradiation at >300 nm. The insolubility of the phototrigger in the millimolar concentration range eliminated the risk of a premature displacement before exposure to light, only forming water-soluble competitor during the photoreaction.

In a final experiment the selective and sequential displacement by photogenerated **2** was illustrated by irradiating a mixture of CB7 complexes of four terpenes (**8**, **9**, **11**, and **13**) and phototrigger **1** (see Figure 6). Under the chosen experimental conditions and in accordance with the differentiated terpene affinities for the host macrocycle (Table 1), geraniol (**9**) is practically quantitatively released after 10 minutes of irradiation. After 40 minutes also eucalyptol (**8**) is released in 75%. Fenchyl alcohol (**11**) is more resistant and after 120 minutes *ca*. 25% are non-complexed. Borneol (**13**) withstands the displacement by **2**, as already observed in the experiment with the individual terpene (see above). It should be stressed that this sequentiality would not be possible for other macrocyclic nanocontainers, lacking the high binding selectivity displayed by CB7.[30]

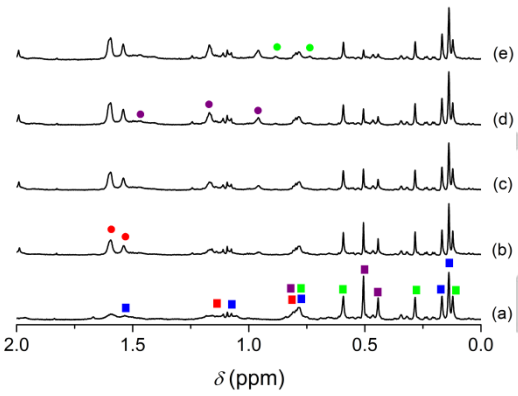


Figure 6. (a) Mixture of **8**, **9**, **11**, and **13** with CB7 (600 μM) and **1** (1 mM) in D_2O:CD_3OD 60:1; pD 6.5. Each terpene was used in a concentration of 150 μM. (b)-(e) The same mixture, as under (a), after 10 min, 20 min, 40 min, and 120 min irradiation time, respectively. Characteristic signals of complexed (marked with squares) and released terpenes (marked with dots) are color-coded: **8** - purple, **9** - red, **11** - green, **13** - blue. In the initial spectrum (a) the colored squares correspond to terpene-CB7 complexes. The colored dots in the spectra (b), (d), and (e) indicate the appearance of released terpenes. For the sake of clarity, they have been solely marked in the corresponding spectrum where their release arrived at the maximum level under the employed conditions (see text). Note that complexed borneol [**13**, blue squares in spectrum (a)] is not released at all.

Conclusions

A new approach for the light-induced release of guests from their cucurbituril complexes by means of the photodeprotection of *o*-nitrobenzyl-tagged competitor guests was developed. The experimental design is very flexible, allowing for the fine-tuning of the competitor binding strength and for the selective release of non-chromophoric guests. To showcase the potential of the design, terpene guests were employed. The chosen compounds are lead ingredients of essential oils and their binding to CB7 was quantified herein for the first time. The binding constants span a range of four orders of magnitude, reaching values as high as 10^8 M^{-1}. These features enabled the selective and also sequential light-induced release of the terpenes. Noteworthy, the described photofunctionality can be extended to a wide spectrum of competitors and guests.

Experimental Section

Materials and General Methods

Phenylalanine-NVOC (**1**) was synthesized as previously described and the identity of the sample was confirmed by ^{1}H-NMR spectroscopy.[57] 1-Aminoadamantane-NVOC (**3**) was prepared as described below. Phenylalanine (**2**), 1-aminoadamantane (**4**), 6-nitroveratryloxycarbonyl chloride, 4',6-diamidino-2-phenylindole dihydrochloride (**6**), and the terpenes **8**–**13** are commercially available from Aldrich in highest purity and were used as received. Cucurbit[7]uril, the *trans*-chalcone dye **5**, and *p*-*N*,*N*-dimethylaminophenyltropylium perchlorate (**7**) were available from previous studies.[35, 49]

The pH of the solutions was adjusted with HCl or NaOH and measured with a Crison basic 20+ pH meter. UV/vis absorption spectra were recorded using a Varian Cary 100 Bio or a Shimadzu UV-1603 spectrophotometer. Fluorescence spectra were measured with a Varian Eclipse fluorimeter. Indicator dye displacement assays were conducted with constant concentrations of dye and CB7. The solutions were allowed to equilibrate after addition of the terpene until no changes were observed in absorption or emission as a function of time. In the case of less water-soluble terpenes up to 0.4 vol% ethanol was employed as co-solvent.

Synthesis of 1-aminoadamantane-NVOC (3)

1-Aminoadamantane (100 mg, 0.66 mmol) and sodium carbonate (69.96 mg, 0.66 mmol) were dissolved in 2.2 mL water (milli-Q quality). 6-Nitroveratryloxycarbonyl chloride (NVOC-Cl, 182 mg, 0.66 mmol), dissolved in 2.2 mL 1,4-dioxane, was then added slowly under stirring to the aqueous solution. After stirring at room temperature for 2 hours, the reaction solution was diluted with 20 mL dichloromethane, followed by the addition of 20 mL 1 N aqueous sodium bisulfate solution. The organic phase was separated and the aqueous phase was extracted with fresh dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated *in vacuo* to give a yellow solid as crude. Purification by silica gel chromatography with *n*-hexane/*t*-butylmethylether (2:1) as the eluent provided 122 mg (47% yield) of **3** as a slightly yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.98 (s, 1H), 5.44 (s, 2H), 4.74 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.09 (s, 3H), 1.95 (d, J = 2.7 Hz, 6H), 1.67 (s, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.61, 148.08, 139.86, 128.88, 110.09, 108.26, 62.95, 56.55, 51.14, 41.94, 36.36, 29.54 ppm. Note: (NH)(O)C=O was not observed. HRMS (ESI) Calcd for $C_{20}H_{27}N_2O_6$ $[M + H]^+$ 391.1869. Found 391.1866.

Isothermal Titration Calorimetry

Isothermal Titration Calorimetry (ITC) measurements were performed on a Nano ITC (TA Instruments) with standard volumes. The solutions were thoroughly degassed before use by stirring under vacuum. The sample cell was loaded with the terpene solution and a 250 µl autopipette was filled with the CB7 solution. The guests were titrated in a sequence of 50 injections of 5 µl after achievement of baseline stability.

Photorelease Experiments

The photorelease was followed in NMR experiments that were run on a Bruker AMX 400 or an Agilent 400 MR instrument, operating at 400 MHz (^{1}H) or 100 MHz (^{13}C). The solutions for NMR were prepared in D_2O (in some cases with CD_3OD as co-solvent) and the pD was adjusted with DCl or NaOD. Corrections due to isotope effects were applied using the equation pD = pH* + 0.4, where pH* is the reading taken from the pH meter.[58]

Light-irradiation experiments were conducted with a 200 W Hg-Xe lamp using a 280 nm cut-off filter or with a 150 W Xe lamp. Experiments with phototrigger **3** were done in a suspension, because of its insolubility in water. Compound **3** was pre-solubilized in CD_3OD and then diluted to the final concentration. This re-precipitation assured reproducible conditions and the irradiation time until the completion of the photoreaction, indicated by the solubilization of all photoproducts, was rather constant between different experiments. In a mixture of water/methanol (95/5) compound **3** has a maximum solubility of 200 µM. It is assumed that the photoreaction proceeds in the solution phase, accompanied by a progressive re-equilibration between solid and solubilized **3** until the photoreaction is complete.

The relative concentrations of phototrigger and terpene•CB7 complex were optimized for achieving the best release performance (see cases of **8** and **11** in Supporting Information). The same is true for the pD value. While the pD was *ca*. 6.5 for most terpenes, a slightly more acidic medium (pD 5.5) was employed for geranylamine (**10**), the only terpene with a protonable amino group. However, even under less acidic or slightly basic conditions (pD 6.5 or pD 8) the same performance as in acidic solution was observed for the photorelease of **10**, demonstrating the robustness of the proposed approach (see Supporting Information).

Solid-phase Microextraction

The solid-phase microextraction was done with a polyacrylate-coated (85 µm) fused silica fiber, analyzing the headspace of an equilibrated water solution of 50 µM **8** in the absence or in presence (120 µM) of CB7 at a constant temperature (24 ºC). The adsorption and desorption times were optimized to 10 min and 5 min, respectively. The relative eucalyptol (**8**) headspace concentration was determined by gas chromatography coupled to an ion-trap mass spectrometer [Varian 3800 with a Saturn 2200 mass detector and a HP-5MS column (Agilent Technologies)]. The temperature programme started at 60 ºC, was then raised to 250 ºC at a rate of 10 ºC/min and maintained for 5 min at the final temperature. Helium was used as carrier gas at a flow rate of 1 mL/min. The injector temperature was 250 ºC.

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Keywords: photochemistry • supramolecular chemistry • cucurbiturils • release • terpenes

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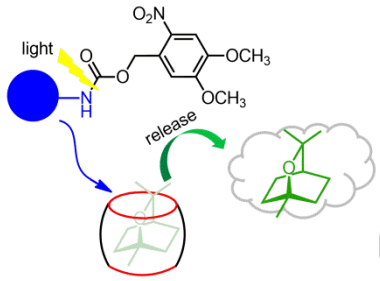

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