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Light-Regulated Molecular Trafficking in a Synthetic Water-Soluble Host

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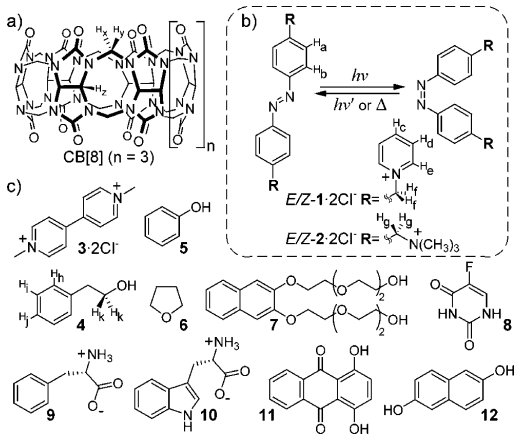
Supporting Information

ABSTRACT: Cucurbit[8]uril (CB[8])-mediated complexation of a dicationic azobenzene in water allows for the light-controlled encapsulation of a variety of second guest compounds, including amino acids, dyes, and fragrance molecules. Such controlled guest sequestration inside the cavity of CB[8] enables the regulation of the thermally induced phase transition of poly(*N*-isopropylacrylamide)—which is not photosensitive—thus demonstrating the robustness and relevancy of the light-regulated CB[8] complexation.

Light energy transduction is a fundamental phenomenon in the biosphere, where living organisms are able to exploit sophisticated noncovalent constructs to transform light into kinetic and potential energy. For instance, visual transduction is initiated by the photoisomerization of retinal in the integral membrane protein Bacteriorhodopsin (BR) and results in the release of a proton to the extracellular environment.[1] It is widely accepted that the exquisite control over the light-induced proton transfer is largely imparted by the delicate organization of the protein binding site. At a lower level of complexity, synthetic chemistry has enabled the production of artificial systems that, similarly to BR, can also bind and release protons and larger species through a diversity of light-controlled processes.[2] A variety of examples exist, including molecular tweezers, foldamers, cages, and macrocycles.[3] However, the design and synthesis of light-regulated containers that can operate in water remains a challenge, with only a few examples related to modified cyclodextrins.[4] Such materials, provided they show reversible and tight binding to both neutral and charged species, could have significant impact in a variety of areas, including photopharmacotherapy, drug delivery, and encapsulation technologies.

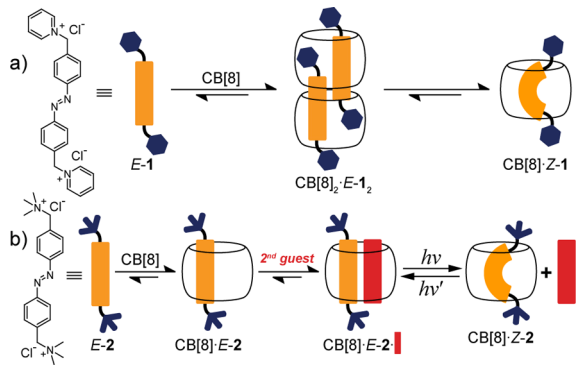
Here we describe a supramolecular container system exhibiting light-controlled encapsulation properties in water. Our multicomponent approach toward photoresponsive binding relies on an optimized design of its individual constituents and comprises the barrel-shaped molecule cucurbit[8]uril (CB[8])[5] and a photoresponsive ancillary guest (Chart 1). Recently, we reported the controlled complexation of neutral guests in CB[8] aided by a series of aromatic bis(imidazolium) derivatives.[6] Depending on their size, these salts can act as first guests for CB[8], enabling the encapsulation of relatively small second guests, including acetone, acetonitrile, and diethyl ether. The *E* isomers of azobenzenes **1** and **2** are also extended organic structures flanked by positively charged groups (Chart 1b and Scheme 1). We thus examine these molecules as responsive first guests that can potentially allow for the photochemical manipulation of the binding properties of CB[8] complexes.

Chart 1. (a) Structures of CB[8], (b) Photoresponsive First Guest Molecules 1 and 2, and (c) Selected Guests 3−12



The binding of azobenzene *E*-**1** to CB[8] was initially investigated by electronic absorbance spectroscopy (Figure

Scheme 1. (a) Formation of Host−Guest Complexes of CB[8] with 1, and (b) Stepwise Formation of 1:1:1 Ternary Complex of CB[8] with *E*-2 and Second Guest Molecule, Followed by Light-Induced Release



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S1). The main absorption band of *E*-**1** shifts to shorter wavelengths when the azobenzene guest is added to an aqueous solution of CB[8], whereas the n−π^* band redshifts and its intensity increases compared to free *E*-**1**. The structure of the complex prepared from equimolar amounts of *E*-**1** and CB[8] was further investigated by NMR spectroscopy. The ^{1}H NMR spectrum of *E*-**1** showed five distinct aromatic proton signals in the 7.60−9.10 ppm region (Figure 1a). However, in the presence

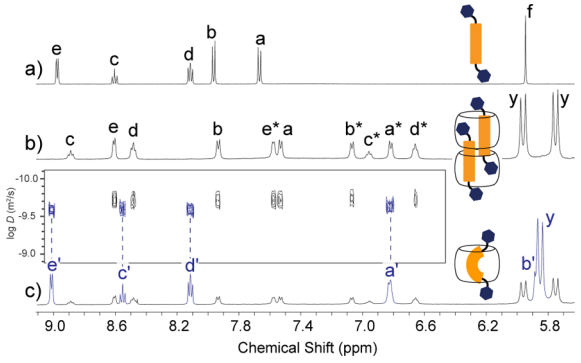

Figure 1. Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of *E*-**1** (a), a freshly prepared solution of an equimolar mixture of CB[8] and *E*-**1** (b), and the mixture after storage in the dark at 298 K for ∼3 months (c), with the corresponding ^{1}H DOSY plots. Signals corresponding to *Z*-**1** protons in (c) are indicated with apostrophes. The two groups of ^{1}H NMR signals of the asymmetrically encapsulated *E*-**1** in (b) are denoted by H*a*−*e* and H*a**−*e**. See Chart 1 for proton labeling.

of CB[8], the symmetry of *E*-**1** is reduced, and the bound azobenzene exhibits up to 10 sharp, well-defined, and widely dispersed aromatic proton signals (Figure 1b). Compared to free *E*-**1**, the signals corresponding to the protons of one of the pyridinium groups of *E*-**1** (H*c**−*e** in Figure 1b) significantly shift upfield in the presence of CB[8], suggesting that this part of the molecule lies deep inside the cavity of the host. In contrast, the other pyridinium group is positioned at the ureidyl carbonyl portal area of CB[8] according to the characteristic downfield shift of some of its proton resonances (H*c* and H*d* in Figure 1b). A series of ^{1}H NMR diffusion-ordered spectroscopy (DOSY) experiments were performed to investigate the size of this complex (Figures 1 and S6). These experiments revealed that the diffusion coefficient (D) of the complex resulting from an equimolar mixture of *E*-**1** and CB[8] is ∼79% of that for the binary complex of the model guest methyl viologen (**3** in Chart 1) and CB[8] (Figure S5). This means that the CB[8] complex of *E*-**1** is approximately twice as large as CB[8]·**3** (Figure S6). Considering its size, its binding stoichiometry (Figure S2), and the fact that the cavity of CB[8] can accommodate up to two flat aromatic moieties, we formulate the structure resulting from a 1:1 mixture of CB[8] and *E*-**1** as a four-component CB[8]$_2$·*E*-**1**$_2$ complex (Scheme 1a and Figure S25).

DFT calculations (M062X/6-31G*) showed that *E*-**1** dimerization in CB[8]$_2$·*E*-**1**$_2$ is favorable compared to a purely bimolecular association of CB[8] and *E*-**1** (Figure S30). Further, the calculated structure of the quaternary complex is in full agreement with the asymmetrical encapsulation of *E*-**1**, as suggested by NMR data (*vide supra*), and shows that one pyridinium group of each *E*-**1** is accommodated inside the CB[8], while the other resides at the portal (Figure S25).

When an aqueous solution of CB[8]$_2$·*E*-**1**$_2$ is stored at 298 K in the absence of light, a new set of ^{1}H NMR signals—incompatible with the 2:2 complex—arises (Figures 1c and S15). Resonances corresponding to H*a* and H*b* of **1** show up as doublets at 5.90 and 6.82 ppm, indicating that the azobenzene is still encapsulated. In contrast, the pyridinium groups may reside at the ureidyl carbonyl portal area according to the shifting of their proton resonances (signals in the 8.10−9.05 ppm region, Figure 1c). The new species possesses a smaller size than CB[8]$_2$·*E*-**1**$_2$, as evidenced by its larger D value (Figures 1 and S7). Major changes were also observed in the electronic absorbance spectrum of CB[8]$_2$·*E*-**1**$_2$ simultaneously to the evolution of the ^{1}H NMR spectrum (*vide supra*). The intensity of the main electronic absorbance band decreased with time, which is typically ascribed to a decrease of the *E*:*Z* ratio.[7] In combination, these results suggest that CB[8] promotes the thermal *E*→*Z* isomerization of **1**, with tetramer CB[8]$_2$·*E*-**1**$_2$ as a metastable intermediate of the process (Scheme 1a). Formation of CB[8]·*Z*-**1** from an equimolar mixture of CB[8] and *E*-**1**, which can be accelerated by UV light irradiation (Figure S1), overcompensates the thermodynamic cost associated with the break-up of the CB[8]$_2$·*E*-**1**$_2$ homodimer and the thermal *E*→*Z* isomerization of **1**.

DFT calculations predicted that azobenzene *E*-**2** (Chart 1b) also binds to CB[8] in a 1:1 ratio and, in contrast to *E*-**1**, forms a binary CB[8]·*E*-**2** complex (Figure S27). This was confirmed by the downfield shift of the signals corresponding to H*a*, H*b*, and H*g* (Figure S17). Also, $D = (2.73 \pm 0.04) \times 10^{-10}$ m^2 s^{-1} was obtained by ^{1}H DOSY, which in combination with ITC results (Figure S2) suggests an absolute stoichiometry of 1:1 (Figure S8). A binding constant K_1 on the order of 10^6 M^{-1} was obtained by ITC (Figure S2). A series of ^{1}H NMR experiments confirmed, at least in the time frame of this study, that the *E* isomer of **2** is the most thermodynamically stable form in the presence of CB[8] (Figure S16), likely on account of its bulkier NMe_3^+ groups; thus, it can partake in stable heteroternary complexation (Scheme 1b).

To investigate the potential formation of ternary complexes, we selected 2-phenylethanol (**4** in Chart 1c), a naturally occurring fragrance molecule,[8] as a model second guest. The ^{1}H NMR spectrum of an equimolar mixture of CB[8], *E*-**2**, and **4** showed an upfield shift perturbation and substantial broadening of the aromatic signals of the alcohol upon binding to CB[8]·*E*-**2** (Figure 2). These changes are consistent with those previously observed for the CB[8]·**3** complexation of aromatic moieties such as 2,6-dihydroxynaphthalene (**12** in Chart 1c).[9] Formation of a CB[8]·*E*-**2**·**4** complex was further supported by ^{1}H DOSY

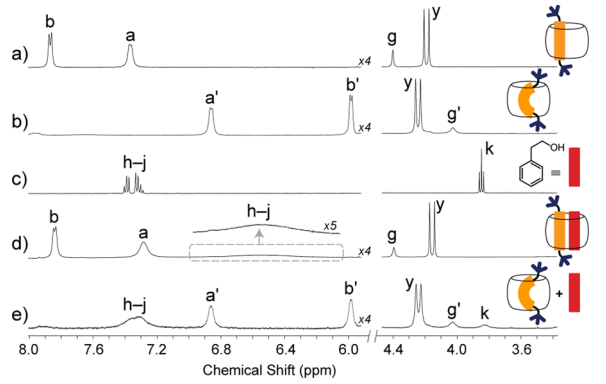

Figure 2. Selected regions of the ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of CB[8]·**2** before (a) and after (b) UV light irradiation, **4** (c), and CB[8]·*E*-**2**·**4** before (d) and after (e) UV light irradiation. See Chart 1 for proton labeling. Signals corresponding to protons of *Z*-**2** are indicated with apostrophes.

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(Figure S10) and *ab initio* calculations (Figures S29 and S31). While azobenzenes **1** and **2** share many similar structural and physical characteristics, none of the complexes comprising CB[8] and **1**, neither the transient CB[8]$_2$·*E*-**1**$_2$ nor the most stable CB[8]·*Z*-**1**, allowed for the encapsulation of **4**, as evidenced by ^{1}H NMR (Figure S18).

Binary complex CB[8]·*E*-**2** can bind a variety of neutral extended aromatic guests, as well as more chemically, and biologically relevant species including amphiphiles, dyes (quinizarin, **11** in Chart 1c, which is also a structural analogue to the antineoplastic agent mitoxantrone), the amino acids L-phenylalanine and L-tryptophan, and the antimetabolite 5-fluorouracil (guests **8**–**10** in Chart 1c). In addition to NMR (Figures S11–S13), we performed ITC experiments to obtain a full thermodynamic description of the binding of CB[8]·*E*-**2** to a library of second guests (Figure S3 and Table S1). The second guest association constants, K_2, were in the range of 10^3–10^5 M^{-1}. Association is governed by enthalpy, which is consistent with other CB[8] ternary complexes.[10] Further, aliphatic guests, e.g., tetrahydrofuran (**6** in Chart 1c), can also be encapsulated.

The photoisomerization properties of **2** in the presence and absence of CB[8] were initially investigated by electronic absorbance spectroscopy. The intensity of the π–π^* absorption band of *E*-**2** decreased upon UV light irradiation, and two new bands appeared at ∼305 and ∼425 nm (Figure S1). These bands were related to *Z*-**2** and the spectrum changes were ascribed to a decrease of the *E*:*Z* ratio upon UV light irradiation.[7] When an aqueous solution of CB[8]·*E*-**2** was exposed to UV light, the intensity of the main band also decreased, whereas the n–π^* became weaker and blue-shifted. These observations are comparable to those described for analogous cationic azobenzene guests in the presence of CB[8]; we were thus led to believe that the interaction of *Z*-**2** and CB[8] may be similar to that reported previously,[11] with *Z*-**2** included inside the cavity of the macrocycle (see Supporting Information). This was supported by the upfield shift of the signals of H*a*, H*b*, and H*g*, relative to those of free *Z*-**2** (Figure S17), and the fact that *Z*-**2** and CB[8] still share a single *D* value after UV light irradiation as measured by ^{1}H DOSY (Figure S9).

Exposure of an aqueous solution of the ternary complex, CB[8]·*E*-**2**·**4**, to UV light induces the *E*→*Z* isomerization of **2** and the release of **4** from the multicomponent container (Scheme 1b). This was revealed by the upfield shift of the signals of H*a*, H*b*, and H*g* of **2** and the downfield shift of the aromatic proton resonances of **4** (Figure 2). Also, ^{1}H DOSY analysis showed that CB[8]·*Z*-**2** and **4** diffuse as independent molecular species after UV light irradiation (Figure S14). Although quantitative conversion of *E*-**2** into *Z*-**2** and concomitant release of **4** cannot be attained after UV light irradiation, the system, at equilibrium, reaches a highly CB[8]·*Z*-**2** enriched state (*E*:*Z* ratio ∼1:5) with the bimolecular complex and free **4** as the major components. Irradiating the mixture with visible light (420 nm) reverts the system back to the CB[8]·*E*-**2**·**4** enriched state. The system can be reversibly cycled many times between the *E*-**2** and the *Z*-**2** enriched states by alternating exposure to UV and visible light (Figure S20). An analogous photoregulated phenomenon was also observed for the ternary complexes involving CB[8]·*E*-**2** and the previously mentioned library of second guest molecules.

The underlying basis for the photocontrolled "catch-and-release" process is that *Z*-**2** fully occupies the cavity of CB[8] with a binding constant much higher than that of the second guests. A series of ITC experiments allowed us to confirm our hypothesis. The *E* isomer of **2** exhibits a binding constant on the order of 10^6 M^{-1}. After UV light irradiation, the decrease of the *E*:*Z* ratio is accompanied by an increase of 1 order of magnitude in K_a. In comparison, second guest molecules partake in heteroternary CB[8] complex formation with much lower K_2, typically on the order of 10^3–10^5 M^{-1}.[5] The high affinity of *Z*-**2** toward CB[8] is likely on account of the increased volume the molecule occupies (Table S2), in contrast to the more extended *E*-**2**, and its ability to fully occupy the cavity of CB[8]. Further, ion–dipole interactions between the electron-poor NMe_3^+ groups and the electron-rich ureidyl carbonyl portals of CB[8] are favored in CB[8]·*Z*-**2**, as the distance between the NMe_3^+ groups decreases from ∼13 Å in *E*-**2** to ∼7 Å in *Z*-**2**.

The ability of CB[8]·*E*-**2** to catch and release guests in a remote fashion led us to consider whether light-controlled complexation could also govern transformations that are not known to be photoresponsive.[12] We anticipated that it could serve as an external handle on the thermally induced phase transition of poly(*N*-isopropylacrylamide) (PNIPAM). To evaluate this idea, the random terpolymer **P1** (M_n = 55 kDa, PDI = 1.25, Figure 3) was prepared by copolymerization of *N*-isopropylacrylamide and *N*-(2-hydroxyethyl)acrylamide and subsequent modification of a fraction of the hydroxyl groups with 2-(4-biphenyl)ethyl isocyanate (Scheme S2).[13]

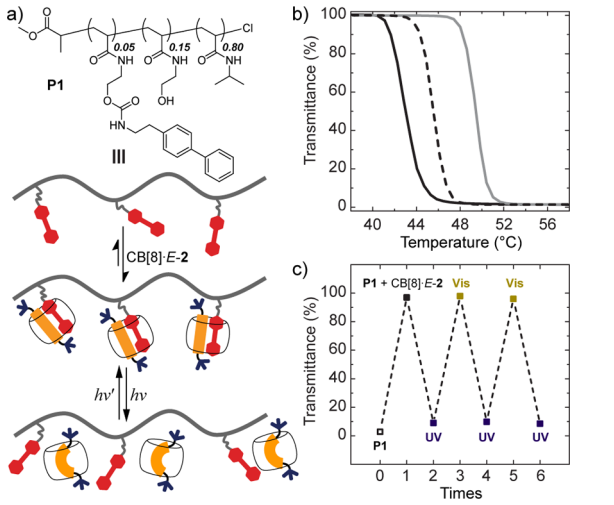

Figure 3. (a) Structure of **P1** and schematic of the light-controlled complexation of the biphenyl moieties of **P1**. (b) Transmittance (recorded at 600 nm and at a heating rate of 1 °C/min) of **P1** (0.1 mM in H_2O) as a function of temperature in the absence (full black line) and presence (full gray line) of CB[8]·*E*-**2**, and after UV light irradiation (dashed line). (c) Changes in the transmittance of **P1** (0.1 mM in H_2O) at 47 °C by alternating irradiation with UV and visible light in the presence of CB[8] and **2**.

In the presence of CB[8]·*E*-**2**, the structural design of **P1** allows for the formation of ternary complexes between the pendant biphenyl units of the polymer, *E*-**2**, and CB[8] (Figure 3a). This was shown through a combination of ^{1}H NMR spectroscopy and isothermal titration calorimetry (ITC) experiments (Figure S3). With regard to the thermoresponsive properties of **P1**, the presence of pendant biphenyl and hydroxyl groups has a large influence in the polymer cloud-point temperature (T_{cp}). An aqueous solution of **P1** (0.1 mM) exhibits T_{cp} = 43.0 °C (Figure 3b), higher than that of unmodified PNIPAM (32.6 °C). This difference in T_{cp} is a result of the larger content of hydrophilic *N*-(2-hydroxyethyl)acrylamide repeating units compared to the hydrophobic biphenyl group content.

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Upon addition of 1 equiv of CB[8]·*E*-**2**, the T_{cp} of the polymer system increases to 49.5 °C (Figure 3b). This change can be attributed to the effect of side-chain complexation, resulting in a switch from the hydrophobic biphenyl moieties to the hydrophilic doubly charged ternary complexes. After UV light irradiation, the T_{cp} of the polymer system drops to 45.4 °C as the CB[8]·*Z*-**2** complexes are released from **P1** and the hydrophobic biphenyl groups are unmasked (Figure 3b). The original T_{cp} of **P1** (43.0 °C) cannot be fully recovered due to the inherent *E*:*Z* composition of the photostationary state of CB[8]·**2** after UV light irradiation.

Light-controlled switching of the T_{cp} enabled us to reversibly transition between clear and turbid solutions of **P1**, **2**, and CB[8] at *a constant temperature*. At 47 °C, a mixture of **P1** and CB[8]·*E*-**2** (1 equiv of the binary complex per biphenyl group) in water is clear. After UV light irradiation at the same temperature, the solution turns turbid as a result of the decomplexation of the biphenyl groups of the polymer (the mixture of CB[8], **2**, and **P1** after UV light exposure has T_{cp} = 45.4 °C, which is lower than 47 °C). Irradiation with visible light induces an increase in the transmittance of the solution, from turbid back to clear again, and many cycles of alternating turbid/clear states can be carried out by using light of the appropriate frequency (Figure 3c).

In conclusion, we have shown that photochromic host−guest complexes, which quantitatively self-assemble from equimolar amounts of CB[8] and azobenzenes *E*-**1** and *E*-**2**, exhibit an absolute stoichiometry imposed by the positively charged groups of the guest. The asymmetrical encapsulation of *E*-**1** inside a 2:2 CB[8] complex exhibits a remarkable level of regioselectivity, considering the high symmetry of the reagents, and may enable the investigation of well-defined dye aggregates in solution.[14] Although the complete elucidation of the energy landscape associated with the CB[8] complexes of azobenzene **1** is still a matter of further research in our laboratories, it is evident that neither CB[8]$_2$·*E*-**1**$_2$ nor CB[8]·*Z*-**1** allow for the formation of heteroternary complexes. Conversely, azobenzene *E*-**2** binds to CB[8] in a 1:1 ratio to form a CB[8]·*E*-**2** complex, thus allowing for the photocontrolled catch and release of a variety of second guest molecules. Equipping CB[8] with a photoresponsive ancillary guest may be regarded as a supramolecular approach to imparting photoresponsive properties to an otherwise photoinactive host, such that the complicated synthetic, covalent modification of host systems may be avoided. Our CB[8] catch-and-release strategy is a general approach to regulate the encapsulation of biologically important molecules, which may find applications in the fragrance industry[15] and other fields, including photopharmacology[16] and optogenetics.[17] It may become useful for the development of artificial molecular devices that, in a fashion reminiscent to BR, can perform complex light-activated functions. Finally, we have demonstrated that it can be readily exploited in systems with higher levels of complexity to regulate phenomena that are not known to be photoresponsive, such as solution-phase transitions of thermoresponsive polymers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11642.

Experimental details, characterization data and spectra, and computational studies (PDF)

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Notes

The authors declare no competing financial interest.

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