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Molecular Switching in Confined Spaces: Effects of Encapsulating the DHA/VHF Photo-Switch in Cucurbiturils

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Abstract: Confinement of reactive chemical species uniquely affects chemical reactivity by restricting the physical space available and by restricting access to interactions with the solvent. In Nature, for example, confined protein binding pockets govern processes following photoisomerization reactions and the isomerizations themselves. Here we describe the first example of a dihydroazulene/vinylheptafulvene (DHA/VHF) photo-switch functioning in water, and we show how its switching behavior is strongly influenced by supramolecular interactions with a series of cucurbit[*n*]uril (CB) host molecules. In CB7 inclusion complexes, the kinetics of the thermal VHF-to-DHA back-reaction is accelerated, while in CB8 inclusion complexes, the kinetics is slowed down as compared to the free photo-switch. The effect of the CB encapsulation of the photo-switch can be effectively canceled by introducing a guest that binds the CB more strongly. According to DFT calculations, a stabilization of the reactive s-*cis* VHF conformer relative to the s-*trans* VHF appears to be a contributing factor responsible for the accelerated back-reaction when encapsulated in CB7.

Introduction

The ability to effectively harness the power of non-covalent interactions is essential for the function of sophisticated naturally occurring functional systems.[1] Both the catalytic properties of enzymes and the energy harvesting ability of photosynthetic systems are reliant upon specific supramolecular interactions.[2–4] In biological systems, the encapsulation of functional molecules in confined spaces may be used to modify the properties and functional output of those trapped molecules. For example, binding inside a hydrophobic pocket in a protein can influence the optical properties of a chromophore and photoisomerizations can induce conformational changes of the protein, which subsequently can trigger signal transductions of relevance for various biological functions. The retinal Schiff base chromophore is a naturally occurring photo-switch, the absorbance spectrum of which is highly sensitive to subtle variation in the binding pockets of Opsin proteins in which it is bound—a property that enables the human eye to differentiate between colors.[5,6] Conformational changes in the protein following the *cis–trans* photoisomerization of the retinal Schiff-base initiates the pathway leading to a nerve signal to the brain.[7–9] This adaptability of protein structures to accommodate chromophore molecules in their different states represents a level of sophistication that is difficult to achieve with artificial systems.[10–17]

An attractive strategy to modulate the behavior of reactive intermediates in water is to confine the physical space available to them by encapsulation inside an inflexible cavity.[18–19] Herein we describe the discovery that the dihydroazulene/vinylheptafulvene (DHA/VHF) photo-/thermo-switch[20] (Figure 1 a) works as a reversible switch in water and that its switching properties can be significantly modulated by a space-confinement by forming inclusion complexes with differently sized cucurbit[*n*]uril (CB) macrocycles.

While several previous studies have focused on the encapsulation of in particular azobenzene photo-switches in cyclodextrin and CB cavities,[21] this is the first example of how the DHA/VHF couple can be modulated by encapsulation, and by introducing the couple to water as the medium, it brings the photo-switch to the realm of bio-applications.[22]

Results and Discussion

A large bathochromic shift (often more than 150 nm) is observed upon converting DHA into VHF by irradiation, and a large change in physical and geometrical properties results from this photoisomerization.[23] The *meta*-stable VHF in time undergoes a ring-closure reaction, hence returning to the original DHA isomer. We designed the DHA/VHF system (Design shown in Figure 1 a; Synthesis in Scheme 1) to be water soluble yet capable of interaction with CBs. The photo-switch,

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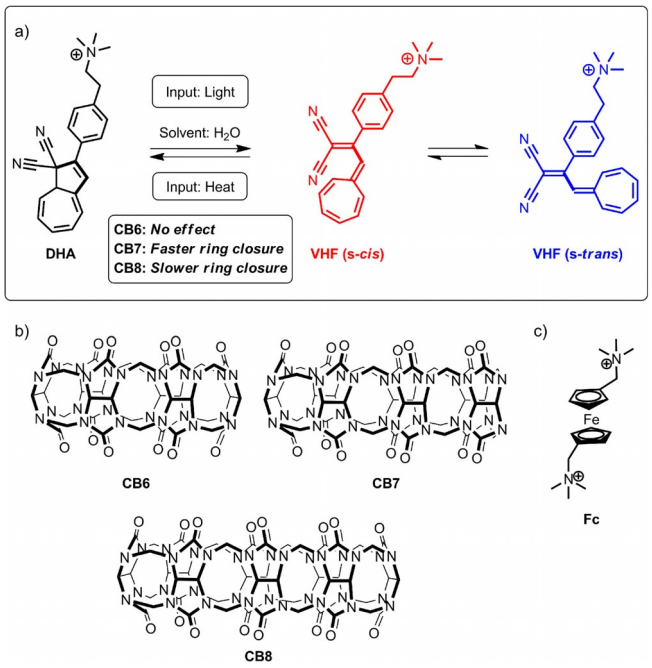
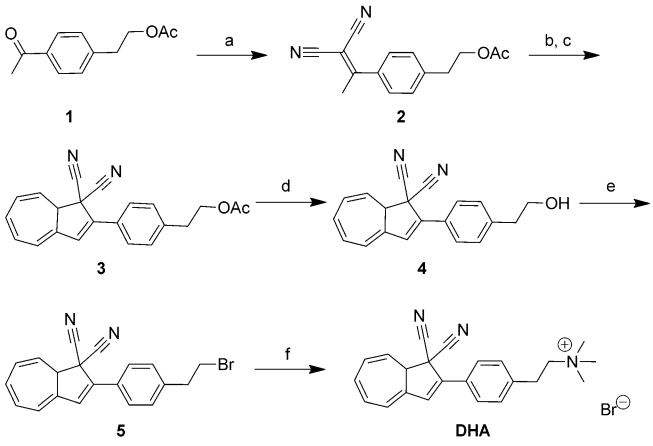


Figure 1. a) The DHA–VHF photo-thermo-switch. Only the *s-cis* conformer of the VHF can thermally switch back to the DHA form. The effect of CBs on the thermal back-reaction from VHF-to-DHA by adding cucurbit[*n*]urils CB6, CB7 and CB8 is indicated. b) Structure of the cucurbit[*n*]urils CB6, CB7 and CB8. c) Structure of a ferrocene based $10^{15}\,M^{-1}$ binder of CB7.



Scheme 1. Synthesis of water soluble DHA photo-switch (**DHA**): a) $CH_2(CN)_2$, $AcONH_4$/AcOH, toluene, reflux, 2 hours, 75%, b) tropylium tetrafluoroborate, CH_2Cl_2, Et_3N, −78 °C, 1 hour, 73%, then c) Ph_3CBF_4, CH_2ClCH_2Cl, 80 °C, 1.5 hours, 70%, d) $TsOH{\cdot}H_2O$, MeOH, 60 °C, 2 days, 96%, e) CBr_4, PPh_3, CH_2Cl_2, room temperature, 1.5 hours, 93%, f) $N(CH_3)_3$, THF, 50 °C, overnight, 59%.

which is largely hydrophobic, was equipped with a permanent positive charge in the form of a tertiary ammonium ion, which was intended to enhance water solubility and promote a favorable interaction with the CB host. Ammonium ions are known to be able to interact via ion–dipole interactions with the carbonyl moieties at the portals of CBs, while hydrophobic moieties of appropriate size can fit inside the hydrophobic cavities of the CBs.[24] In the case of amphiphilic molecules the hydrophobic effect has been found to be an important driving force for host–guest complexation with CBs.[25]

Synthesis

The synthesis of the ammonium-ion substituted water soluble photo-switch (**DHA**) is shown in Scheme 1. The substituted acetophenone **1** was condensed with malononitrile to yield the dicyanoethene compound **2**. Treatment of this intermediate with tropylium tetrafluoroborate followed by hydride abstraction using Ph_3CBF_4 gave the DHA-structure **3** via the corresponding VHF-structure in a ring closing reaction. Hydolysis of the acetate ester gave the alcohol **4** which was converted to the corresponding bromide (**5**) using Appel conditions. Conversion of the bromide to the final ammonium-ion DHA structure (**DHA**) was achieved by treatment with Me_3N in THF. High chemical yields were achieved through the synthetic protocol.

Photo-switching behavior in confined space

The photo-driven conversion of DHA to VHF and the thermal-driven back-conversion can be conveniently monitored using UV/Vis absorption spectroscopy.[8] In Figure 2, the characteristic UV/Vis absorption spectra of the DHA/VHF system are shown, here observed for our new water soluble DHA.

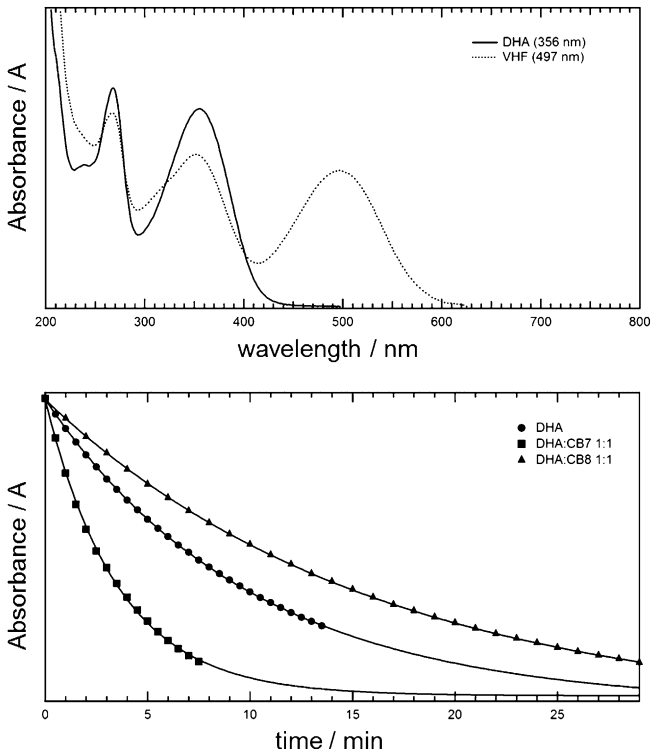


Figure 2. Top: UV/Vis absorption spectra of the DHA–VHF photo-switch in water. Full line: pure DHA. Dotted line: The solution of DHA after irradiation to form VHF. Bottom: Normalized plot of the exponential decay in absorbance at $\lambda = 497$ nm corresponding to the thermal back-reaction of the VHF in aqueous solution (2.5×10^{-5} M) and in the presence of 1 equivalent of CB7 and CB8.

The band in the spectrum at $\lambda_{max} \approx 500$ nm originates from the VHF structure and it arises when the dilute solution of DHA is irradiated with a blue laser (405 nm) for a few seconds. The exponential decay of this band is monitored with time and the data used to elucidate the kinetics for the thermal back-reaction (Figure 2, bottom).

The light induced ring-opening of the water soluble DHA to its corresponding VHF and its thermally induced back-reaction were monitored in pure water and a half-life of 6.9 minutes for the back-reaction was measured for a 2.4×10^{-5} M solution. It has previously been established that the rate of the thermal back-reaction increases with increasing polarity of the solvent. Related DHA–VHF photo-switches functioning in cyclohexane solvent and acetonitrile solvent (at room temperature) have half-lives of 2333 and 216 minutes, respectively, so our results are in keeping with this trend.[26] When the DHA-to-VHF and back cycle were repeated several times in water, we observed very little (< 5%) photo-bleaching of the system, which is encouraging for the future applications of this photoswitch.

Next we investigated the ability of CB6, CB7 and CB8 to complex the photoswitch and modulate its switching properties. Firstly, the kinetics of the thermal back-reactions from VHF to DHA was studied on 2.5×10^{-5} M aqueous solutions of the photo-switch in the presence of various concentrations of each of the CBs. In each case the light induced conversion of DHA to VHF was possible in the presence of the CB and took place instantaneously upon irradiation with the blue laser. For CB6, the rate of thermal back-conversion of VHF to DHA was unaffected by the presence of the macrocycle. In the presence of 1 equivalent of CB7, the half-life of the thermal back-reaction (VHF-to-DHA) decreased from 6.9 minutes to 2.5 minutes while in the presence of 1 equivalent of CB8 the half-life increased to 11.2 minutes (Figure 2b).

In both cases, the decay in absorbance over time could be fitted perfectly with one exponential function and did not need a sum of two exponential functions with different time constants. This result signals that the exchange between the bound and unbound states of VHF is very fast and so the observed kinetics represents the weighted average of the two available reaction pathways-via a bound or unbound transition state.

The ability of CB7 to increase the rate of the back-reactions was examined in more detail by conducting the experiment at different photo-switch concentrations and in the presence of different concentrations of CB7. Figure 3a shows the kinetics monitoring by UV/Vis spectroscopy of back-conversion of VHF to DHA in the presence of various concentrations of CB7. The determined half-lives of the reactions are listed in Table 1 (entries 2 to 7). The half-life of the back-reaction changed from 2.5 minutes to 1.4 minutes upon increasing the quantity of CB7 from 1 equivalent to 10 equivalents. Following this inverse correlation, the addition of only 0.5 equivalents of CB7 had a reduced effect on the half-life of the reaction, decreasing it only to 3.5 minutes. However, when the concentration of CB7 was further increased up to 40 equivalents, while keeping the DHA concentration fixed at 2.5×10^{-5} M, the half-life of the back-reaction remained at 1.5 minutes, suggesting that the system had become saturated at this point, and that a strong binding interaction exists between CB7 and the photo-switch. Since the rate of the back-reaction increases in the presence CB7, it is reasonable to suggest that there must be a specific binding interaction between CB7 and VHF. Binding by CB7

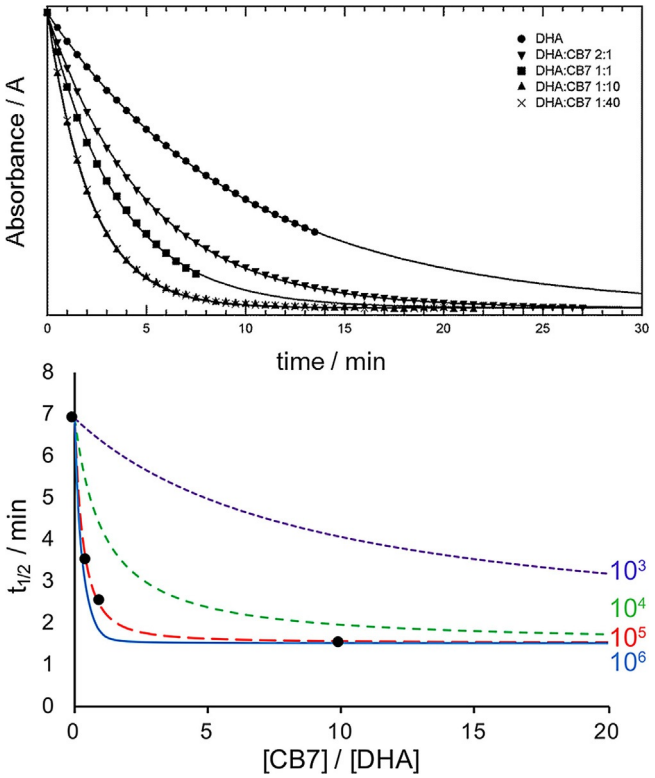


Figure 3. Top: Normalized plot of the kinetics (absorbance vs. time in minutes) of the thermal back-reaction of the DHA/VHF system in the presence of increasing concentration of CB7. Bottom: Plot of the change in $t_{1/2}$ relative to CB7 concentration. Predicted binding isotherms for the 1:1 interaction of CB7 with VHF are shown, with association constants of 10^3 (violet), 10^4 (green), 10^5 (red), and 10^6 M^{-1} (blue). From this we deduce that CB7 binds VHF with K_a of approximately 10^5 M^{-1}.

Table 1. Kinetics measurements of the thermal back-reaction from VHF to DHA (Figure 1a). Data obtained using UV/Vis absorption spectroscopy at room temperature.

No	Photo-switch	Solvent[a]	Stoic.	Conc.[a]	$t_{1/2}$[b]
1	DHA	H_2O		2.4×10^{-5}	6.9
2	DHA:CB7	H_2O	1:0.5	2.5×10^{-5}	3.5
3	DHA:CB7	H_2O	1:1	2.5×10^{-5}	2.5
4	DHA:CB7	H_2O	1:10	2.5×10^{-5}	1.5
5	DHA:CB7	H_2O	1:1	2.4×10^{-6}	3.0
6	DHA:CB7	H_2O	1:10	2.4×10^{-6}	1.4
7	DHA:CB7	H_2O	1:40	2.5×10^{-5}	1.5
8	DHA:CB8	H_2O	1:1	9.8×10^{-5}	11.9
9	DHA:CB8	H_2O	1:1	2.0×10^{-5}	11.2
10	DHA:CB8	H_2O	1:1	2.0×10^{-6}	8.7
11	DHA:CB8	H_2O	1:0.5	4.4×10^{-5}	11.1

[a] Concentration of DHA photo-switch in M. [b] $t_{1/2}$ is the half-life of the back-reaction (VHF-to-DHA). Half-lives are reported in minutes, uncertainties less than 10%.

must stabilize the transition state for the thermal back reaction thereby lowering the activation energy and increasing the rate of the back reaction.

If the half-life of the back-reaction of the photo-switch is modulated as a result of a specific binding interaction with CB7, the change in the half-life of the reaction will be related to the concentration of the complex between VHF s-*cis* and CB7 (see Supporting Information). This means the dependence of $t_{1/2}$ on CB7 concentration can provide a binding isotherm from which an association constant ($K_{a(VHF:CB7)}$) can be assessed. Figure 3b shows the obtained $\delta t_{1/2}$ values in the presence of an increasing concentration of CB7 (black dots). Due to the limited number of data points it was not possible to directly fit the data to a 1:1 binding model. Instead the predicted binding isotherms were plotted for a 1:1 binding in this system for $K_a =$ 10^3, 10^4, 10^5 and $10^6\,\text{M}^{-1}$. A binding constant $K_{a(VHF:CB7)}$ of approximately $10^5\,\text{M}^{-1}$ was therefore estimated from the graph. The kinetics of the thermal back-reaction was further monitored at a lower concentration of photo-switch (2.5×10^{-6} M) in the presence of varying concentrations of CB7. Here again a strong binding on the order of $10^6\,\text{M}^{-1}$ was estimated from the $t_{1/2}$ values (Supporting Information Figure S7).

In order to investigate the origin of this binding interaction we turned to NMR spectroscopy. As it was not possible to study the binding of CB7 to VHF, due to its short lifetime, we instead examined the interaction of CB7 with DHA. A Job Plot was made and indicated that a 1:2 binding interaction takes place with two CBs binding to one DHA molecule (Supporting Information Figure S1). DHA was then titrated with a solution of CB7. The ^{1}H residue that underwent the largest chemical shift change upon binding was the methyl group on the tertiary ammonium group, which is consistent with the expected interaction of these groups with the carbonyls at the rim of the CB. Small chemical shift changes were also observed for the phenyl protons and the proton on the 5-membered ring of the DHA ring, while the protons on the 7-membered ring of the azulene were unaffected by complexation with CB7. The chemical shift changes were fitted to a 1:2 binding isotherm and association constants K_1 and K_2 of approximately $>10^5\,\text{M}^{-1}$ and $\approx10^4\,\text{M}^{-1}$ were estimated (Supporting Information Figure S3). We suggest that the first strong binding encapsulates the DHA molecule while the second binding could be due to an additional interaction between the tertiary ammonium group and a second CB macrocycle. A similar binding interaction could be envisaged for VHF s-*cis* where the first stronger binding, would be primarily responsible for confining the space available to the photo-switch and influencing the half-life of the thermal back-reaction.

The determination of large ($>10^5\,\text{M}^{-1}$) binding constants using NMR spectroscopy-based titrations is associated with very large uncertainties. To verify the conclusions based on the NMR spectroscopy-based titrations we therefore determined the binding constant using isothermal calorimetry titration experiments (Figure 4). This did indeed confirm a large first and a somewhat smaller second binding constant (K_1 and K_2 of approximately $10^6\,\text{M}^{-1}$ and $10^5\,\text{M}^{-1}$).

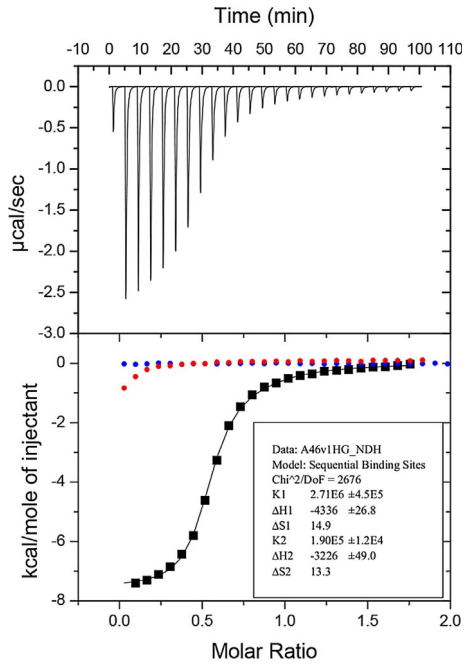


Figure 4. Data for the titration of CB7 with DHA in H_2O. Data with dilution references subtracted (black squares), fitted curve (black line), and dilution references of CB7 (blue circles) and photoswitch (red circles).

The binding of DHA to CB8 was also determined using ITC, and binding affinities of $10^5\,\text{M}^{-1}$ and $10^3\,\text{M}^{-1}$ were found (see ESI). To obtain reliable data the ITC for the CB8 complex were collected at 45 °C.

In contrast to CB7, the addition of CB8 to a solution of the photo-switch increased the half-life of the reaction (Table 1, entries 8–11). Thus, in the concentration range $2.0–9.8\times10^{-5}$ M for DHA:CB8 in a 1:1 ratio, the half-life spans 11.2–11.9 min, while it was only 6.9 and 2.5 min for the neat DHA and DHA:CB7 (1:1 ratio), respectively, at DHA concentrations within the concentration range provided above (2.4×10^{-5} M). We therefore suspect that this phenomenon must again be the consequence of interactions with the cucurbituril and in this case an interaction that destabilized the transition state for the back reaction. Notably, upon decreasing the concentration of the photo-switch and CB8 (1:1 ratio) from 10^{-5} M to 10^{-6} M the effect of CB8 is strongly reduced. Presumably the molar fraction of the complex at this low concentration is too low to significantly influence the kinetics of the thermal back-reaction, which indicates that the binding interaction between VHF s-*cis* and CB8 is somewhat weaker than was observed with CB7. NMR titrations were hampered by the low solubility of CB8 in pure H_2O.

Computational investigations

In an attempt to better understand how complexation with CB7 or CB8 can modulate the photo-switching properties of DHA/VHF we examined the host–guest complexes between DHA and VHF with CB7 and CB8 using density functional theory (DFT) calculations. At the B3LYP/6-31G(d) level of theory

the potential energy surfaces for both VHF and DHA in their unbound and in their CB7- and CB8-bound states were probed for different conformational minima.[27] The structures of the different conformations found for each of the three situations are illustrated in Figure 5.

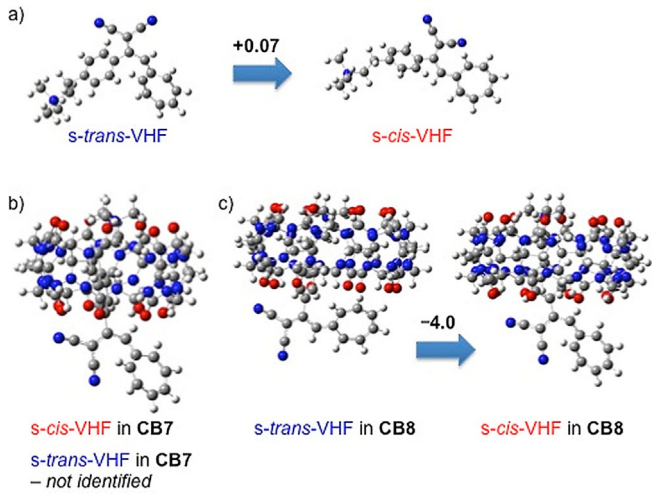


Figure 5. a) Structures of the identified conformational minima for VHF conformers in the unbound state, b) structure of the single identified minimum for VHF in CB7 (only s-*cis* conformer), c) structures of the identified minima for VHF conformers in CB8. Relative energies (in kJ mol^{-1}) based on DFT calculations are shown.

We have limited the calculations to the 1:1 complexes with CB7 and CB8. As will become evident below, the results of this analysis can only partly explain the experimental results. For the CB7 complex with VHF, we were only able to identify a mimimum with VHF in the reactive s-*cis* conformation, while for unbound VHF the s-*trans* conformation is the favored one (by 0.07 kJ mol^{-1}). This enhancement of the s-*cis* conformation is noteworthy as for both complexes, the trimethylammonium appendage is inside the CB, while most of the VHF moiety is outside. In order for the back-reaction to take place a conformation closely related to the s-*cis* form is required, so any s-*trans* conformers must first undergo an endergonic conversion before ring closing can take place. The lack of an s-*trans* conformational minimum for VHF in the presence of CB7 could, therefore, be a contributing factor for the faster back-reaction in the presence of CB7. Indeed, previous studies have shown that when locked in the s-*cis* conformation, the VHF ring closure reaction occurs almost instantenously.[28,29] For encapsulation of VHF in CB8, we find energy mimima for both s-*cis* and s-*trans* conformers, but of lowest energy for the s-*cis* conformer (more stable by 4.0 kJ mol^{-1}). As the back-reaction is slower for this complex than for unbound VHF, existing mainly as the s-*trans* conformer, it is clear that other effects come into play than the position of the s-*cis*/s-*trans* equilibrium. For CB7 we found that two association events take place, and this is also the case for CB8. Most likely, the second encapsulation of the VHF guest molecule will occur at the VHF moiety itself (basically the only part of the molecule still available, cf. Figure 5). This association is therefore likely to influence strongly the activation energy of the ring-closure reaction, and, apparently, encapsulation by CB8 increases the activation energy for the back-reaction to an extent that is not counterbalanced by its favoring of the s-*cis* conformation. While we are not able to reliably compute these effects, the calculations do support that the specific effects on the kinetics of the photo-switch are due to size selective binding by the cucurbiturils: CB6 is too small to bind the photo-switch and so has no effect, CB7 binds the reactive s-*cis* VHF, but not s-*trans* VHF, and CB8 binds both s-*cis* VHF and s-*trans* VHF.

Competition experiments

If the effect of CB7 and CB8 on the back-reaction is indeed due to encapsulation of the guest molecules, competitive binding of the CBs ought to diminish or even cancel out the effects (Table 2). KCl is known to increase the solubility of poorly soluble CB6 and CB8 by the binding of K^+ ions to the portals of the CB macrocycles. This increased solubility caused us to investigate the kinetics of the DHA/VHF system in concentrated KCl solutions (Table 2 entries 1–4). The presence of 0.2 M KCl did not have an effect on the half-life of the photo-switch on its own (Table 2, entry 1). However, the competitive binding of K^+ ions to the CBs almost cancelled the effect of the CBs on the kinetics of the VHF back-reaction. Only in the presence of 10 equivalents of CB7 was a small decrease in $t_{1/2}$ relative to the unbound photo-switch seen.

Table 2. Kinetics measurements of the thermal back-reaction from VHF to DHA in competition experiment. Data obtained using UV/Vis absorption spectroscopy at room temperature.

No	Photo-switch	Solvent[a]	Stoic.	Conc.[b]	$t_{1/2}$[c]
1	DHA	KCl/H_2O		4.5×10^{-5}	7.2
2	DHA:CB7	KCl/H_2O	1:1	4.5×10^{-5}	6.8
3	DHA:CB7	KCl/H_2O	1:10	4.5×10^{-5}	4.0
4	DHA:CB8	KCl/H_2O	1:1	2.4×10^{-5}	7.6
5	DHA:Fc	H_2O	1:1	2.2×10^{-5}	7.5
6	DHA:CB7:Fc	H_2O	1:1:1	2.2×10^{-5}	8.1
7	DHA:CB7:CB8	H_2O	1:1:1	4.4×10^{-5}	2.6
8	DHA:CB7:CB8	H_2O	2:1:1	4.4×10^{-5}	4.3

[a] Measured in either pure H_2O or in 0.2 M KCl in H_2O. [b] Concentration of DHA photo-switch in M. [c] $t_{1/2}$ is the half-life of the back reaction (VHF-to-DHA). Half-lives are reported in minutes, uncertainties less than 10%.

The next competition experiment involved the introduction of ferrocene-based guest (Fc, Figure 1c) that is known to bind extremely strongly to CB7 ($K_a \approx 10^{15}$ M^{-1}).[30] We first confirmed that the Fc molecule did not in itself influence the kinetics of the DHA/VHF photo-switch (Table 2, entry 5). Then the experiment was performed in the presence of one equivalent of each of CB7 and Fc. The previously observed effect of CB7 to decrease the half-life of the back-reaction was completely cancelled out (Table 2, entry 6). Evidentially the very strong binding of Fc to CB7 outcompetes the binding of DHA to CB7.

In a final competition experiment, the kinetics of the thermal back-reaction was studied in the presence of both CB7 and CB8 (Table 2 entries 7 and 8). Comparing entries 1 and 4 in Table 1 (DHA and DHA:CB7 1:1 in H_2O), with entries 7 and 8 in Table 2 it is clear that the presence of CB7 is the controlling factor. In fact, the experiments with 1 and 0.5 equivalent of the CB7 (Table 1, entries 2 and 3) compare well with the experiments conducted without the presence of CB8 (Table 2, entries 7 and 8). This experiment clearly demonstrates that the DHA/VHF system interacts more strongly with CB7 than with CB8.

Conclusion

To conclude, we have described the first example of the DHA/VHF photo-switch in water and have described how the switching behavior can be influenced by the formation of inclusion complexes with CBs. Experiments show that the DHA is encapsulated by two units of CB7 with high association constants, and most likely such 1:2 complexes should therefore also be formed with the larger CB8. Calculations reveal that encapsulation of the trimethylammonium appendage of the VHF enforces the reactive s-*cis* conformer. As the overall influence of CB7 and CB8 on the ring closure kinetics is opposite, CB7 enhancing it and CB8 retarding it, the second CB complexation must play an important role as well. This encirclement is likely to take place at the VHF moiety, and therefore it should influence strongly the relative energies of the s-*cis*-VHF and the transition state for its ring-closure reaction. Indeed, the overall rate of ring closure depends both on the position of the s-*trans*/s-*cis* pre-equilibrium and the actual activation energy for conversion of the s-*cis*-VHF. As CB8 retards the reaction, the increase of activation energy must be predominant over the s-*cis*-VHF stabilization. For CB7 the two effects may work in concert or the enforcement of the s-*cis* conformer may be so dominant that a potentially higher activation energy is out-balanced. Computationally it is not a trivial matter to settle these effects. This conceptual work illustrates how encapsulation within a specific confined space can modulate the properties of the DHA/VHF photo-/thermo-switch in a defined manner and paves the path for the use of this switch in more complex systems with biological applications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azulene · cucurbituril · host–guest interactions · macrocycles · molecular switches

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