Host–Guest Chemistry

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Photochemical Control of Reversible Encapsulation**

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The *cis–trans* photoisomerization of azobenzenes is a well-known phenomenon that is the basis of many molecular devices;[1,2] it is also probably one of the earliest switching mechanisms in supramolecular chemistry, with applications in crown ethers[3–5] and cyclodextrins.[6,7] The changes in molecular shape on isomerization are large and predictable, a feature that has also made them useful in biological applications.[8,9] We show herein that the photoisomerization can be indirectly used as a method to control encapsulation phenomena. This remote control is a consequence of the snug fit of *trans*-4,4′-dimethylazobenzene (*trans*-**1**) in the capsule **2·2**.[10] Photoisomerization causes *trans*-**1** to "break out" of the capsule, thus allowing the entry of other guest species. Occupancy of the extended assembly $\mathbf{2{\cdot}3_4{\cdot}2}$ can be controlled using the longer *trans*-4-methyl-4′-hexylazobenzene[11] (*trans*-**4**), and it is possible to switch between assemblies **2·2** and $\mathbf{2{\cdot}5_4{\cdot}2}$ by using photoisomerization.

The cylindrical capsule **2·2** recognizes guests that are congruent in shape and complementary in chemical surface.[12] The host may be filled with several small guests, or a suitable single guest, including benzanilides,[13] *n*-alkanes,[14] and stilbenes.[15] The latter guest showed unexpected photophysical properties when complexed: unlike the enhanced fluorescence seen when complexed with snugly-fitting antibodies,[16] the stilbene fluorescence is quenched when encapsulated by **2·2**, a result that is attributed to the gently twisted (nonplanar) conformation that it assumes in the capsule.[17] Given the parallels in behavior of stilbenes and azobenzenes, particularly with respect to *cis–trans* isomerism in a photostationary state, we undertook the examination of encapsulated azobenzene under the effects of irradiation.

The arrangement is shown in Figure 1 a; *trans*-**1** in capsule **2·2** was treated with an equimolar amount of *n*-tridecane in $[D_{12}]$mesitylene. The azobenzene is much more strongly bound and no *n*-tridecane was observed inside the capsule by ^{1}H NMR spectroscopy (Figure 1 b). The solution was then irradiated with 365 nm light and the encapsulated **1** was completely replaced by the encapsulated alkane within 50 minutes (Figure 1 b), that is, the irradiation forces the azobenzene out of the capsule. This effect apparently occurs by photoexcitation of *trans*-**1** to its *cis*-conformation, which no longer fits within **2·2**. Simultaneously, signals of *cis*-**1** in solution appeared at $\delta = 6.59$ ppm and 6.67 ppm in the ^{1}H NMR spectrum. On heating the sample to 160 °C for 2 minutes, *cis*-**1** reverted to its *trans* conformation and rapidly replaced *n*-tridecane in the capsule. This cycle was repeated many times without deteriorating the integrity of the system (four cycles are shown in Figure S4 in the Supporting Information).

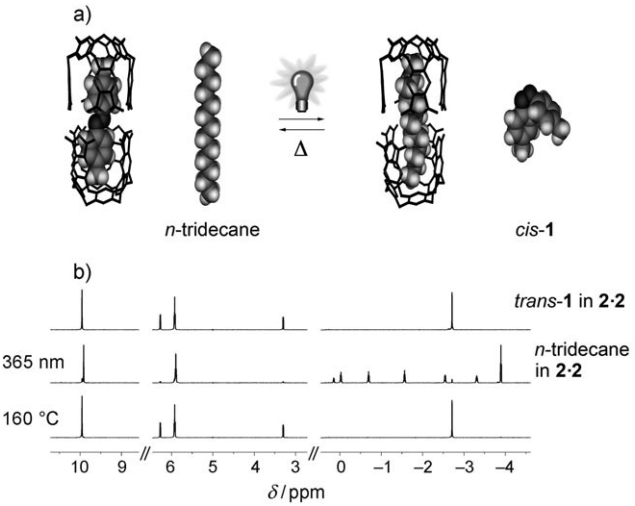

Figure 1. a) Light-induced guest exchange of *trans*-**1** by *n*-tridecane in **2·2**. b) Indicative regions of the ^{1}H NMR spectra ($[D_{12}]$mesitylene, 20 °C) are shown before irradiation (*trans*-**1** is the only guest) and after irradiation at 365 nm wavelength for 50 min at 20 °C (*n*-tridecane is the only guest). After heating the sample to 160 °C for 2 min, the initial state was completely restored.

In principle, the encapsulation of any other suitable guest could be initiated by light. For example, 4,4′-dimethylbenzil is a comparable guest for **2·2**. When ten equivalents of *trans*-**1** were also present in solution, only the azo compound was encapsulated by **2·2**. After irradiation, the ^{1}H NMR spectrum showed that benzil was the only encapsulated species. After heating the sample to 160 °C for 2 minutes, the guests completely exchanged their locations and the system reverted to its original state.

The photochemical manipulation extends to other encapsulation arrangements. Typically, a single guest is able to replace two occupants in an entropy-driven process[18] that increases the number of free molecules. For example, hydrogen-bonded homodimers of benzoic acid or benzamide are suitable guests for capsule **2·2**. Three equivalents of *trans*-**1** were sufficient to suppress binding of the acid or amide, but, after irradiation, the azo compound was replaced by the respective homodimers. After heating, the initial state was

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restored and the cycle can be repeated many times (see Figure S5 in the Supporting Information for ^{1}H NMR spectra recorded for substitution of *trans*-**1** by 4,4′-dimethylbenzil, benzoic acid, and benzamide).

The two possible mechanisms for light-induced guest switching are illustrated in Figure 2. In the first mechanism, in–out exchange of *trans*-**1** is faster than the light-induced conformational change and isomerization to the *cis*-form takes place outside **2**·**2**. Since *cis*-**1** is not encapsulated, any potential guest can then rush into the evacuated (solvent or solvent-impurity-filled) capsule. In the second mechanism, in–out exchange of *trans*-**1** is slow and the isomerization takes place inside of the capsule. The *cis*-geometry of the guest clashes with the capsule walls and forces them outward, thus breaking hydrogen bonds and facilitating exchange, that is, a "breakout" mechanism.

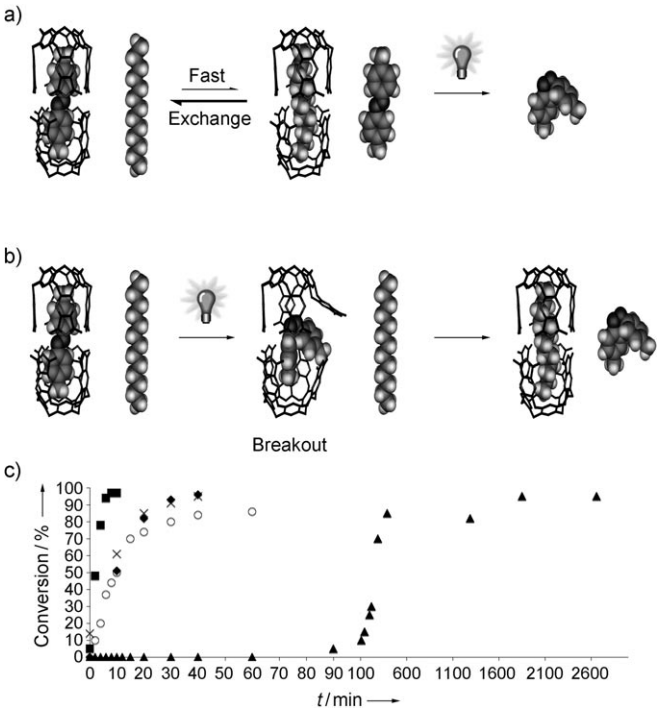

Figure 2. Two possible mechanisms for light-induced guest exchange: a) Fast exchange of the more strongly bound *trans*-**1** by *n*-tridecane is required for light-induced *cis–trans* isomerization outside the capsule. b) *cis–trans* isomerization takes place inside the capsule, thus leading to steric clashes with the walls that promote the "breakout" of **1** and occupancy by *n*-tridecane. c) Kinetic data for light-induced *cis–trans* isomerization of **1** (1.2 mM in [D_{12}]mesitylene) and correlated guest exchange. All data points were obtained by integration of appropriate ^{1}H NMR signals after the irradiation time corresponding to the *x*-axis values or after the corresponding waiting time in case the sample was not irradiated. ■: conversion of *trans*-**1** to *cis*-**1** in [D_{12}]mesitylene. ○: conversion of encapsulated *trans*-**1** to free *cis*-**1**. ×: conversion of encapsulated *trans*-**1** to free *cis*-**1** on irradiation in the presence of 30 equivalents of *n*-tridecane; ◆: percentage of encapsulated *n*-tridecane under these conditions. ▲: percentage of encapsulated *n*-tridecane without irradiation of encapsulated *trans*-**1** in the presence of 30 equivalents of *n*-tridecane (two different time scales are used).

Rates were measured to resolve the mechanistic choices (Figure 2c). Firstly, the light-induced isomerization of *trans*-**1** was investigated. After 8 minutes, 97% of *trans*-**1** isomerized into the *cis*-form in solution. When *trans*-**1** was encapsulated in the absence of a competitive guest, the end point of isomerization was reached after 40 minutes of irradiation and only 84% of free *cis*-**1** was obtained (the remaining *trans*-**1** stayed inside the capsule). Light-induced isomerization of encapsulated *trans*-**1** did not proceed faster in the presence of 30 equivalents of *n*-tridecane as an additional guest: again the end point was reached after 40 minutes, however 95% of *cis*-**1** was obtained in solution outside the capsule. The percentage of *n*-tridecane inside the capsule at each measurement matches the percentage of *cis*-**1** outside the capsule.

The rate of exchange of encapsulated *trans*-**1** with *n*-tridecane as an incoming guest was determined under conditions where no irradiation was applied: 30 equivalents of *n*-tridecane were required in order to partially displace encapsulated *trans*-**1**, although only 19% of *trans*-**1** was ultimately replaced at equilibrium. Thus, 19% exchange corresponds to 95% (within the experimental error) of conversion in this system. In Figure 2c, the 19% exchange is normalized to 95% to facilitate visualization. The end point was reached after about 1600 min; that is, the displacement of azobenzene by another guest is very slow. This finding was confirmed by ROESY NMR spectroscopy, which showed no exchange peaks between *trans*-**1** inside and outside of the capsule at 300 K or 335 K (Figures S6 and S7 in the Supporting Information). The exchange rates of similar shaped guests and capsule halves determined by fluorescence methods at much lower concentrations are also fully consistent with these findings.[19]

These experiments rule out the possibility that *cis–trans* isomerization of **1** takes place outside the capsule; instead, the light-induced guest switching proceeds by a "breakout" mechanism. The folding of the excited azobenzene forces the walls outward and facilitates guest exchange. Such wall motions are involved in vase-to-kite conformational changes of cavitands;[20] Diederich and co-workers have shown that the mobility of only two such walls is enough to enable guest exchange in related cases.[21]

The slow isomerization of encapsulated *trans*-**1** compared to that of free guest in solution is also consistent with this interpretation. The encapsulated excited state may transfer energy to the capsule walls either electronically or mechanically by forcing the walls outward and breaking some of the hydrogen bonds. In either case, the partitioning of the excited state is affected, thus leading to a decrease in the rate of isomerization.

Parallel experiments were applied to guest occupation of the extended capsule **2**·$\mathbf{3}_4$·**2**. Four molecules of a glycoluril such as dibutylaniline derivative **3** are incorporated into the capsule in order to form an extended assembly when suitable guests are present.[22] For example, when the longer *trans*-**4** is deployed as light-responsive guest, the mono-extended assembly **2**·$\mathbf{3}_4$·**2** is formed, as revealed by ^{1}H NMR spectroscopy (Figure S8 in the Supporting Information). Because **4** bears different substituents at the 4 and 4′ positions, and is too long to tumble inside, the assembly is desymmetrized: the two

cavitand ends show separate sets of ^{1}H NMR signals as do the hydrogen atoms on the two edges of the glycoluril units. Binding of the homodimer of 4-ethylbenzamide into **2·3$_4$·2** is suppressed in a solution containing 10 equivalents of *trans*-**4** and 2 equivalents of 4-ethylbenzamide. However, after irradiation with 365 nm light, the encapsulated homodimer of 4-ethylbenzamide is the only "social isomer"[23] present. This hydrogen-bonded dimer is symmetric and its ^{1}H NMR spectrum is simplified accordingly. Heating the sample to 160 °C for 2 min restored the initial state and the cycle could be repeated many times (Figure 3 and Figure S9 in the Supporting Information). Similarly, encapsulation of two molecules of *p*-cymene can be controlled in this way (Figure S10 in the Supporting Information); 4 equivalents of *trans*-**4** and 16 equivalents of *p*-cymene were optimal for this series of reversible changes in occupancy. There are three social isomers of *p*-cymene possible in **2·3$_4$·2**, but only two were observed, as previously described.[22]

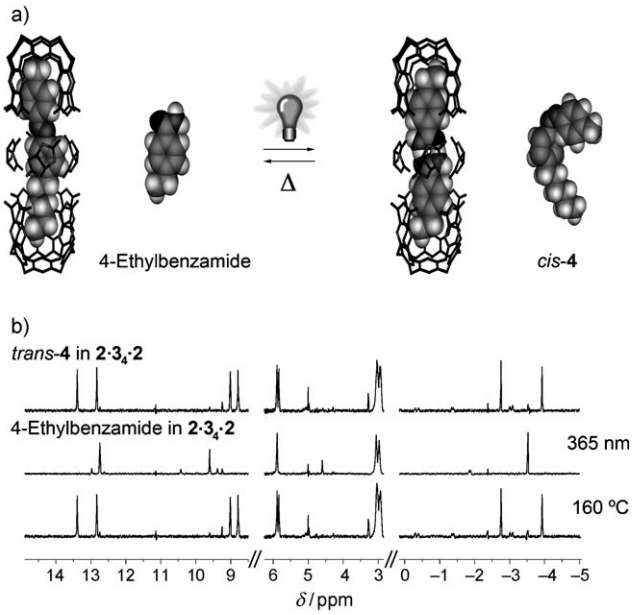

Figure 3. a) Light-induced guest exchange of *trans*-**4** by 4-ethylbenzamide in the extended assembly **2·3$_4$·2**. b) Indicative regions of the ^{1}H NMR spectra ([D$_{12}$]mesitylene, 20 °C) are shown before irradiation (*trans*-**4** is the only guest) and after irradiation at 365 nm for 50 min at 20 °C (the homodimer of 4-ethylbenzamide is the only guest). After heating the sample to 160 °C for 2 min, the initial state was completely restored. This cycle was repeated three times (see Figure S9 in the Supporting Information).

Finally, it was possible to switch between different capsule assemblies through photoisomerization. We used 4-dodecanephenyl glycoluril **5**, which has low solubility in [D$_{12}$]mesitylene until it is incorporated into an assembly; for example, the assembly **2·5$_4$·2** was formed when a mixture of capsule-half **2**, glycoluril **5**, and 3 equivalents of *trans*-**4** were heated. The same assembly was formed in the presence of additional 4,4′-dibromobenzil, which is a mediocre guest for **2·2**. After irradiation of the mixture for 50 minutes with 365 nm light, the capsule **2·2** with 4,4′-dibromobenzil as guest was obtained. The resulting solution is slightly turbid, which indicates that **5** precipitates from solution once it is freed from the assembly. On heating the solution at 160 °C for 2 minutes, the original extended assembly **2·5$_4$·2** was restored, with *trans*-**4** as the only encapsulated guest (Figure 4, see also Figure S11 in the Supporting Information). Accordingly, an external signal can reversibly switch not only encapsulated guests, but the very nature of the capsules that they occupy.

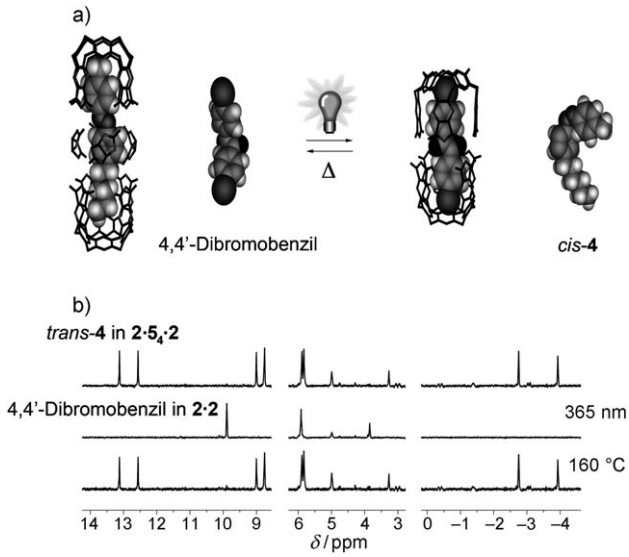

Figure 4. a) Light-induced guest exchange with concomitant change of assembly. b) ^{1}H NMR spectrum ([D$_{12}$]mesitylene, 20 °C) is shown before irradiation (*trans*-**4** is the guest in the extended assembly **2·5$_4$·2**) and after irradiation at 365 nm for 50 min at 20 °C (4,4′-dibromobenzil is the guest in the capsule **2·2**). After heating the sample to 160 °C for 2 min, the original state was completely restored.

It should be possible to bring this system to the next level of complexity where photoisomerization can be used to affect chemical reactions that are not known to be photosensitive; we are currently working toward this goal.

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