Host–Guest Chemistry

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Reversible Photochemically Gated Transformation of a Hemicarcerand to a Carcerand**

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In the 1980s, Cram pioneered the synthesis of container molecules, hemicarcerands and carcerands, the latter able to imprison guest molecules.[1] Hemicarcerands are selective host molecules whose binding affinity mainly depends on the size of the guest molecule. Hemicarcerands are important host molecules in research fields such as drug delivery, phase-transfer catalysis, and molecular recognition.[2] Calculations led to an understanding of how guests enter and escape from the container molecules by means of a thermal gating mechanism.[3] Gating converts hemicarcerands (open gate) into carcerands (closed gate) (Figure 1). Gating has been

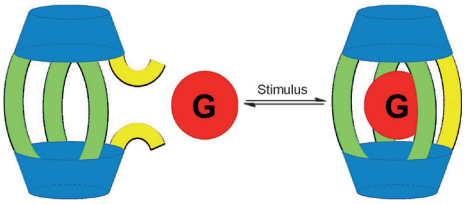

Figure 1. Gating in container molecules converts a hemicarcerand (left) into a carcerand (right).

achieved previously with stimuli such as heat[4] and redox[5] or acid/base chemistry.[6] Photochemical processes can serve as switching mechanisms in appropriately constructed container molecules;[7] Rebek used the *cis–trans* photoisomerization of azobenzene,[8] and Mattay used the photoreactivities of anthracene.[9] However, the use of photoswitchable gates to interconvert hemicarcerands and carcerands has not been demonstrated.[10] We report herein the synthesis of a reversible photoswitchable gated hemicarcerand based on the photochemical properties of anthracene. The reversible photochemical gating is demonstrated to control the stability of the host–guest complex, which could be important for delivery systems engineered to encapsulate and release guest molecules upon irradiation.

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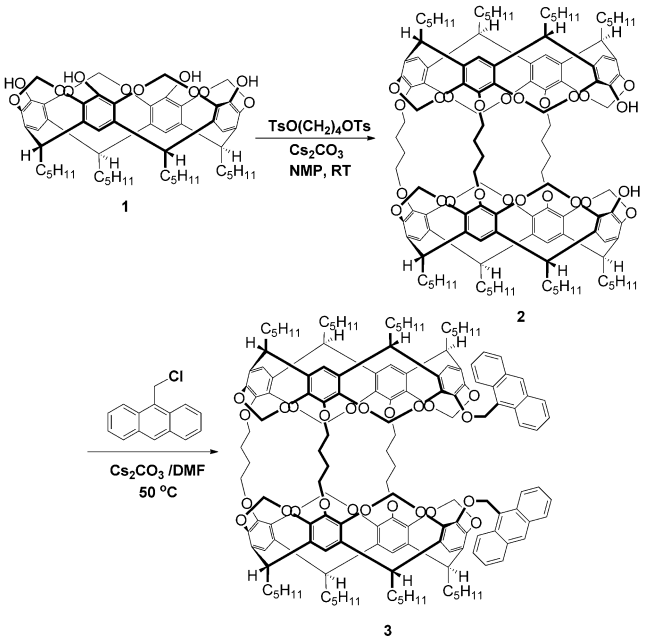
The synthesis of the new hemicarcerand is outlined in Scheme 1. Diol **2** can be prepared from precursor **1** in about 30% yield according to the procedure described by Cram et al.[11] Treating the diol **2** with 9-chloromethylanthracene



Scheme 1. Synthesis of the dianthracene hemicarcerand **3**. Ts = *p*-toluenesulfonyl.

using cesium carbonate as the base produces the hemicarcerand **3** as a yellow solid. The structure of **3** was confirmed by its ^{1}H NMR and ^{13}C NMR spectra, which both show the typical signals for the anthracene moieties (see Figure S1 in the Supporting Information).

The photochemical properties of this system were explored to determine if the hemicarcerand could be converted to a carcerand that traps guest molecules. We investigated the photochemical cycle between the open-state host **3** and closed-state host **4** (Figure 2) using ^{1}H NMR spectroscopy.

To investigate the intramolecular anthracene photodimerization process of **3**, a dilute solution of **3** (10^{-4} M) in degassed $CDCl_3$ was irradiated with 350 nm UV light.[12,13] After irradiation for 1 h, the ^{1}H NMR spectrum of **3** in $CDCl_3$ showed the disappearance of the anthracene peaks from 7.20–8.20 ppm and the appearance of a new peak (singlet) around 4.40 ppm (Figure 3b). The aromatic signals of the anthracene dimer in **4** overlap with other aromatic signals of

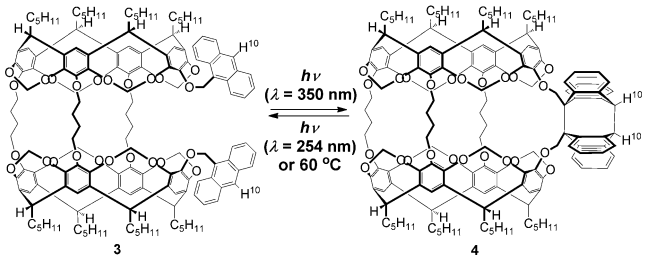


Figure 2. Photochemical reversible transformations between the open hemicarcerand **3** and closed carcerand **4**.

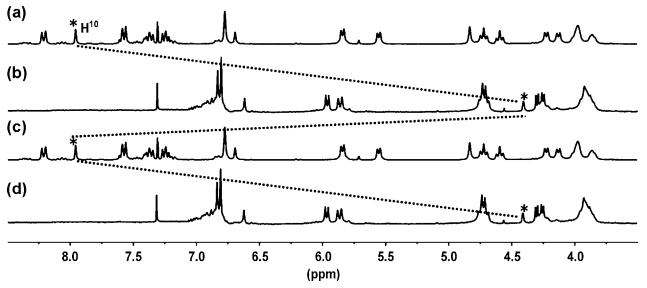


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) of a) host **3** b) irradiation of host **3** with light at 350 nm for 1 h, c) irradiation of b with light at 254 nm for 1 h or heating at 60 °C for 20 min, d) irradiation of c with light at 350 nm for 1 h.

the host molecule and appear as a large multiplet at 6.85 ppm (Figure 3b). Another indication of the formation of the intramolecular cyclodimer **4** is the characteristic chemical shift of the tertiary bridgehead protons H^{10} (Figure 2). In the open-state **3**, H^{10} corresponds to an aromatic signal that appears as a singlet at 7.91 ppm (Figure 3a). However, when the photodimerization process takes place, H^{10} is converted to an aliphatic proton in the closed-state **4**, changing its hybridization from sp^2 to sp^3. In the new ^{1}H NMR spectrum, this tertiary bridgehead proton H^{10} is identified as the new singlet at 4.40 ppm (marked with an asterisk in Figure 3b) due to two hydrogens. The chemical shift changes for the anthracene moieties and tertiary bridgehead protons H^{10} after the photodimerization in this system are consistent with literature examples.[13] The cycloreversion of the photodimer **4** back to open-state **3** could be achieved by short-wavelength UV irradiation. Upon irradiation of the same solution at 254 nm for 1 h, the starting state is restored, as evident from the reappearance of the anthracene peaks at 7.20–8.20 ppm in the ^{1}H NMR spectrum (Figure 3c). The reversible switching process could be repeated several times without noticeable degradation; two iterations are shown in Figure 3. The photodimer **4** could also be converted back to open-state **3** thermally. To open the cycloadduct **4**, the $CDCl_3$ solution of **4** (Figure 3b) was heated to 60 °C for about 20 min. The resulting solution gave a spectrum identical to that in Figure 3c.

The photoresponsive properties of host **3** can also be followed by fluorescence spectroscopy. Photodimerization eliminates the characteristic fluorescence of anthracene in the closed state **4**. Experiments showed that when the solution of **3** was irradiated at 350 nm for 1 h, the typical emission band of anthracene with relative maxima at 420 nm decreased gradually in intensity (Figure 4a), implying that **3** was gradually converted into photodimer **4**, as reflected by the quenching of the fluorescence intensity. The photoreaction resulted in the stable photodimer **4**, as the fluorescence did not change after weeks. The fluorescence intensity of the system, however, recovered after irradiation of the same solution at 254 nm for

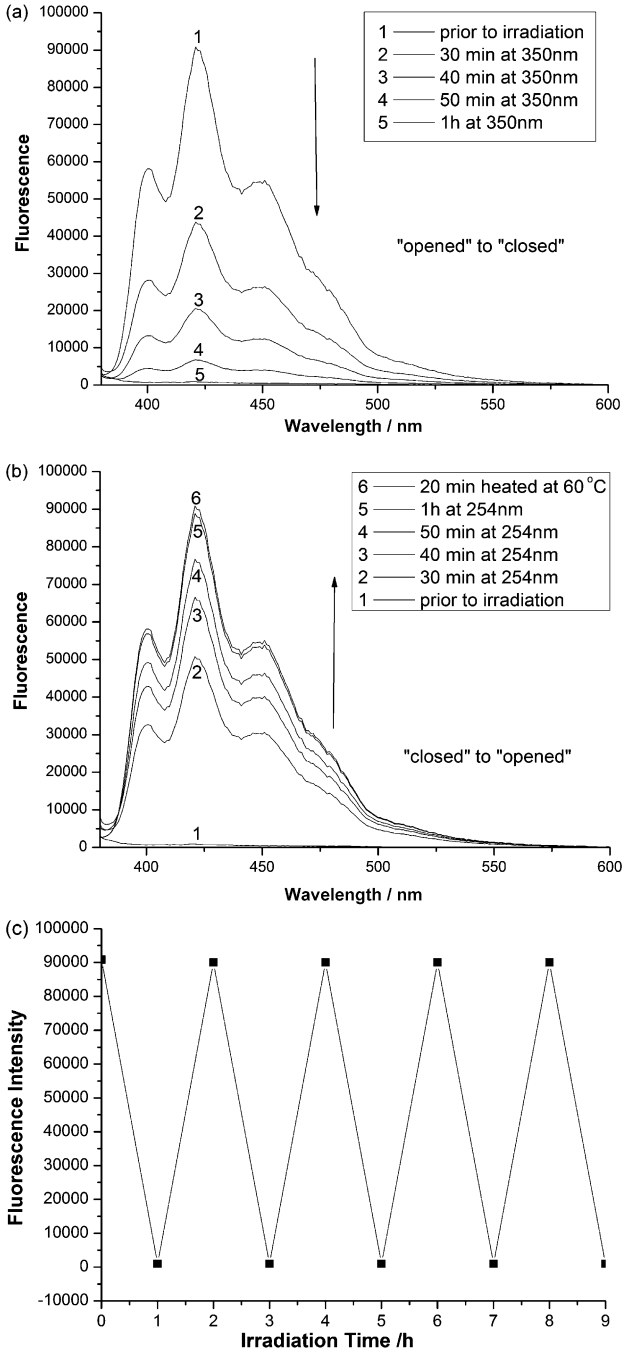


Figure 4. Fluorescence spectra of a) **3** upon irradiation at 350 nm for 1 h ($CHCl_3$, 10^{-4} M, RT). b) **4** upon irradiation at 254 nm for 1 h ($CHCl_3$, 10^{-4} M, RT). c) Changes in the fluorescence intensity at 420 nm upon alternating irradiation of 350 and 254 nm light.

1 h. As shown in Figure 4b, irradiation of the solution of **4** at 254 nm for 30 min leads to an increase of the fluorescence of the system to more than 50% of the original intensity (line 2), and after 1 h, the intensity recovered to 99% of the original level (line 5). This indicates that the reverse reaction takes place, transforming **4** to **3** with photoinduced cleavage of the anthracene dimer and recovery of the anthracene emission. The fluorescence of the system could also be recovered thermally, as indicated by line 6 in Figure 4b, which is the fluorescence of the system after 20 min of heating at 60°C. Several cycles of alternate irradiation at 350 and 254 nm indicated good reversibility without detectable degradation of the system (Figure 4c).

The progress of the photodimerization was also monitored by thin-layer chromatography (hexane/EtOAc 8:1), which showed only one band with $R_f = 0.64$ after completion of the photodimerization. Photodimer **4** was purified after photolysis at 350 nm. In the high-resolution mass spectrum the molecular ion of photoproduct **4** has the same mass as the parent open-state host **3**. This confirms the [4+4] photodimerization of anthracene as the major process taking place photochemically, and excludes the possibility of a photoreaction between **3** and other impurities in solutions. All these spectroscopic results strongly suggest that **3** is able to form a stable intramolecular photodimer **4** through an intramolecular [4+4] cycloaddition of the two anthracene units.

The structures of different states of the host modeled with OPLS in Macromodel are shown in Figure 5. In Figure 5a, the two anthracene moieties are nearly parallel to each other on account of intramolecular π–π stacking interactions. The two anthracenes are separated by proper distances; they are able to form an intramolecular photodimer without introducing much strain to the host system as shown in Figure 5b.

The hemicarcerand was then used to complex various guest molecules such as *para*-dimethoxybenzene, 1,4-$(MeO)_2C_6H_4$. At first, the complexation of **3** with 1,4-$(MeO)_2C_6H_4$ was studied by ^{1}H NMR spectroscopy. As shown in Figure 6b, when 1.0 equivalent of 1,4-$(MeO)_2C_6H_4$ was added to a $CDCl_3$ solution of **3**, the proton signals of the guest showed no chemical shift change. Solvent deuterochloroform is the predominant guest here. So even if a hemicarceplex was formed between **3** and 1,4-$(MeO)_2C_6H_4$, its concentration is so low to be observed. When diphenyl ether[14] was used as the solvent, NMR spectra indicate that a hemcarceplex is formed: to a 10^{-4} M solution of **3** in 5 mL degassed Ph_2O was added 1.4 g 1,4-$(MeO)_2C_6H_4$, and the ^{1}H NMR spectrum of the mixture was measured. Owing to the large peaks of the solvent Ph_2O, the resolution of the spectrum was low, but a singlet at −0.32 ppm was observed. This indicates that **3** forms a hemicarceplex with 1,4-$(MeO)_2C_6H_4$: the upfield signal is due to the methyl protons of the guest in the hemicarceplex **3** ⊙ 1,4-$(MeO)_2C_6H_4$.

The Ph_2O mixture was irradiated at 350 nm for 1 h and then poured into 10 mL of methanol. The precipitate was dissolved in $CDCl_3$ and the ^{1}H NMR spectrum was recorded (Figure 6c). The methyl signal of the guest showed a dramatic upfield shift from 3.78 to −0.37 ppm ($\Delta\delta = 4.15$ ppm), and the anthracene peaks of the host **3** disappeared (Figure 6c). This indicates that after the gate of **3** is closed, a carceplex is formed between the carcerand **4** and the guest. MALDI mass spectra indicate formation of this carceplex. The carceplex **4** ⊙ 1,4-$(MeO)_2C_6H_4$ can stay in the dark at ambient temperature more than 4 weeks without detectable release of the guest molecule (Figure 6d).[15] This indicates that after the

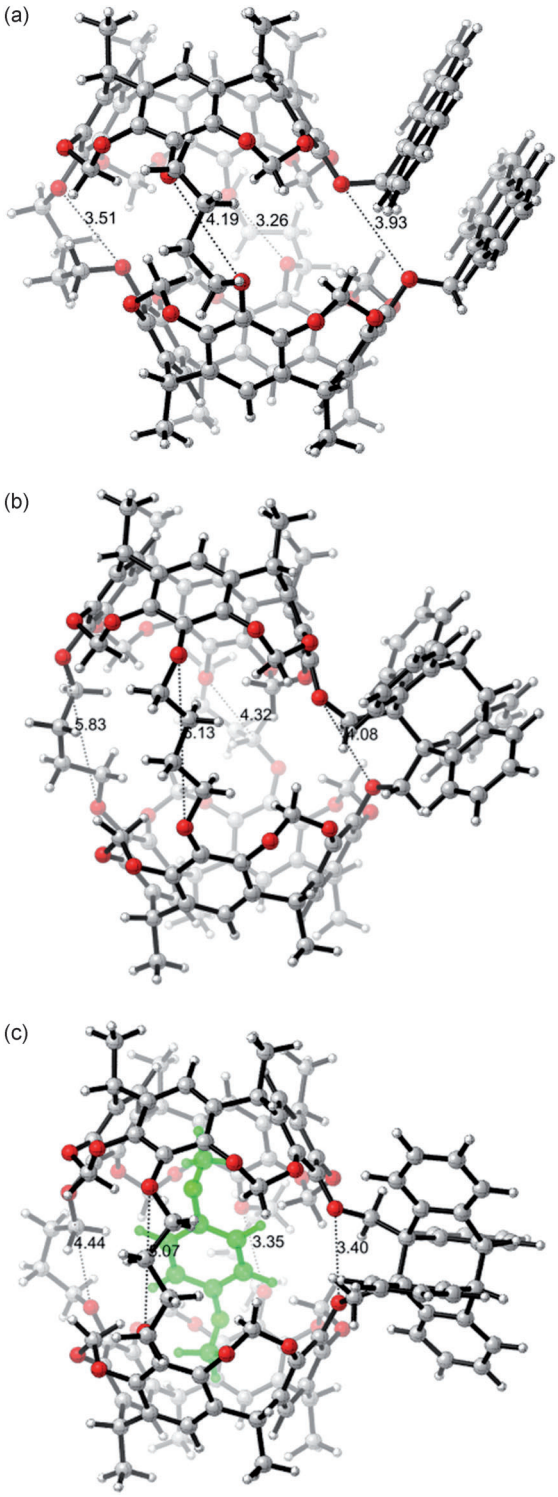


Figure 5. Energy-minimized structures of a) open state host **3** b) closed state host **4** c) carceplex **4** ⊙ 1,4-$(MeO)_2C_6H_4$ using Schrödinger Macromodel (OPLS_2005, GB/SA $CHCl_3$).

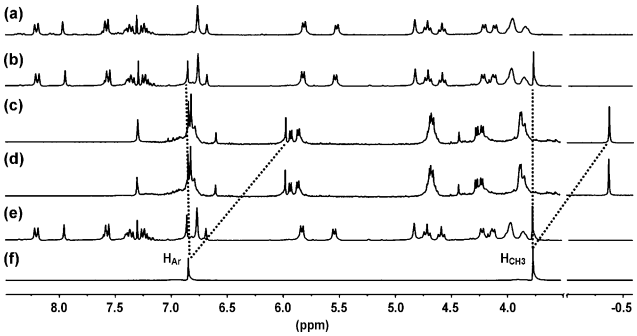


Figure 6. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) of a) host **3** b) addition of 1 equiv of 1,4-$(MeO)_2C_6H_4$ into host **3** solution without irradiation, c) **4**⊙1,4-$(MeO)_2C_6H_4$,[16] d) c after 4 weeks in dark and RT, e) irradiation of c with light at 254 nm for 1 h or heating at 60 °C for 20 min, f) guest 1,4-$(MeO)_2C_6H_4$.

gate is closed and **3** is transformed to **4** upon irradiation at 350 nm, the portal size of the host is reduced, which increases the activation energy for the decomplexation. As a result, a carceplex was formed and was stable at room temperature. The release of the guest molecules, however, could be accomplished readily photochemically or thermally, when the gate is opened. Upon irradiation at 254 nm or heating at 60 °C of the previously generated carceplex **4**⊙1,4-$(MeO)_2C_6H_4$ in solution, the methyl signals of 1,4-$(MeO)_2C_6H_4$ exhibited a downfield shift along with the reappearance of the anthracene peaks in the ^{1}H NMR spectrum (Figure 6e). This indicates that the reopening of the dianthracence gate converted **4**⊙1,4-$(MeO)_2C_6H_4$ carceplex to hemicarceplex **3**⊙1,4-$(MeO)_2C_6H_4$ and increased the size of the host's portal. As a result, the activation energy for decomplexation in the open state **3**⊙1,4-$(MeO)_2C_6H_4$ is decreased and the incarcerated guest 1,4-$(MeO)_2C_6H_4$ can egress easily. The gate-opened hemicarcerand is then almost exclusively filled with the solvent $CDCl_3$.

In Cram's studies, the decomplexation of a hemicarceplex with a tetramethylene bridge can also be achieved thermally, but it often requires high temperature and long time.[11] We have identified that this thermal decomplexation occurs through a conformational change in the host molecule.[3] By contrast, the thermal gating mechanism for our system is the transformation of the anthracene dimer to monomer, which creates a large portal in the host through which the guest is able to exit.

Molecular modeling was used to study the carceplex further. The energy-minimized structure of **4**⊙1,4-$(MeO)_2C_6H_4$ shows a compact host–guest system. The cavity of **4** is spacious enough and complementary for the inclusion of 1,4-$(MeO)_2C_6H_4$ (Figure 5c). The two OMe groups of the guest nicely fit into the two hemispheres of the host, achieving stabilizing van der Waals interactions with the aromatic rings of the host. This is also consistent with the ^{1}H NMR observations that the methyl protons undergo dramatic upshifts due to the shielding effects of the aromatic rings.

A variety of small aromatic and aliphatic molecules were able to serve as guest in carceplexes analoguous to **4**⊙1,4-$(MeO)_2C_6H_4$. These include toluene, *o*-xylene, *m*-xylene, *p*-xylene, anisole, 4-methylanisole, 1,1,2,2-tetrachloroethane, and 1,1,2,2-tetrabromoethane (Table S1 in the Supporting Information). Larger compounds were also explored as guests, including *tert*-butylbenzene, 4-methyl-5-(2-hydroxyethyl)thiazole,[17] and 2,6-diisopropylphenol (Propofol), which is an intravenously administered hypnotic agent. However, no complexes were formed when the host was subjected to similar conditions for host–guest complexation. For 2,6-diisopropylphenol, molecular models show that the two isopropyl groups are so large that the compound does not fit into the cavity of **4** (Figure S2 in the Supporting Information).

In summary, a new reversible photoswitchable gated hemicarcerand containing two anthracene groups was designed and synthesized. The photochemical properties of this system were studied by ^{1}H NMR and fluorescence spectroscopy. The photoswitchable cycle between the open (hemicarcerand) and closed (carcerand) states of the host is well controlled by radiation of different wavelengths, and controlled encapsulation and release of the guest molecules such as 1,4-dimethoxybenzene was observed. We are currently working on enlarging the cavity size of the host as well as increasing the water solubility of the host.

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[14] Our calculations indicate that two chloroform molecules readily occupy the open hemicarcerand, but that the diphenyl ether can only partially enter the cavity. Also mentioned in Ref. [11], Ph_2O was used as the solvent because its molecular volume is too large to occupy the interiors of hosts that have tetramethylene bridges.
[15] Previous similar examples by Cram in Ref. [11] show that the tetramethyelene bridge hemicarceplex has a half-life longer than 336 h.
[16] The preparation and characterization of carceplex **4**⊙1,4-$(MeO)_2C_6H_4$ is described in the Supporting Information.
[17] This guest was able to form a hemicarceplex with a host with larger cavity. See, J. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 497 – 498.

