

Capsule Molecolari

Unione di due cavitandi

Connessione covalente

Legame idrogeno

Legame di coordinazione

Pre-organizzazione

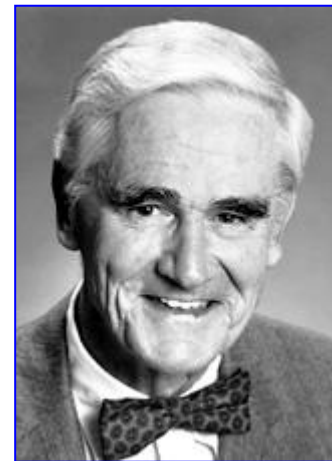
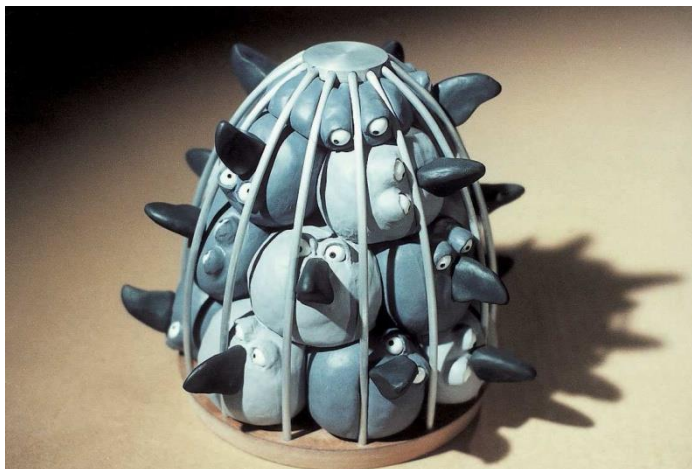
Protezione dal solvente esterno

Rallentamento delle cinetiche di scambio

Stabilizzazione di specie reattive

Reazioni catalitiche

Drug delivery

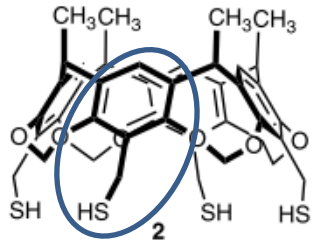


Carcerando:

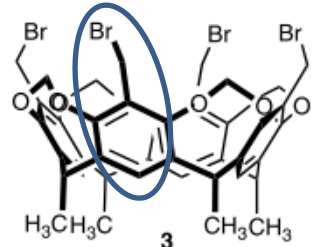
Contenitore molecolare chiuso (capsula) che definisce cavità sferica, i guest sono intrappolati (all'atto della sintesi) entrata e uscita solo per rottura di legame covalente, i.e. velocità di scambio virtualmente nulla

Carcerandi

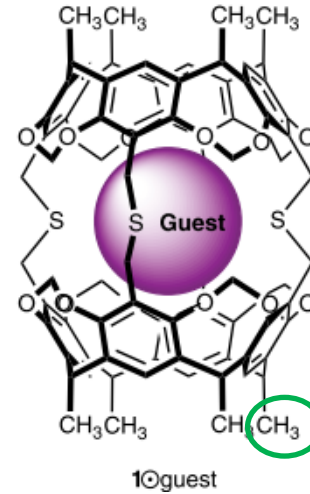
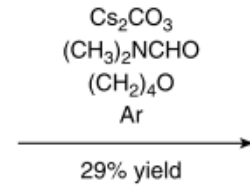
Benzil-tiolo



benzil cloruro
(o bromuro)

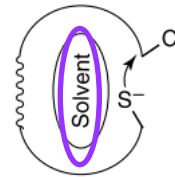
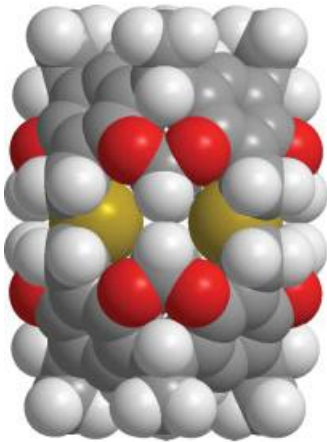


Alta dliuz



Guest: Cs^+ ; $(\text{CH}_3)_2\text{NCHO}$;
 $(\text{CH}_2)_4\text{O}$; Ar

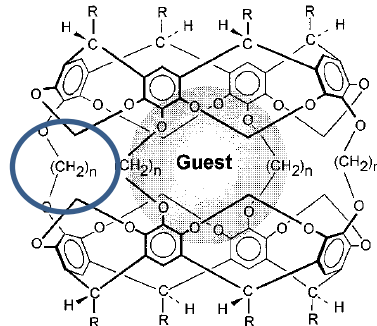
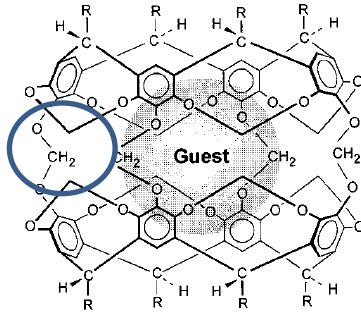
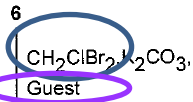
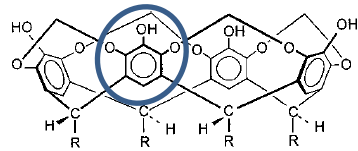
Insolubilità = caratterizz via IR, FAB-MS, analisi elementare, test chimici
FAB-MS dei carciplessi



Carcerandi

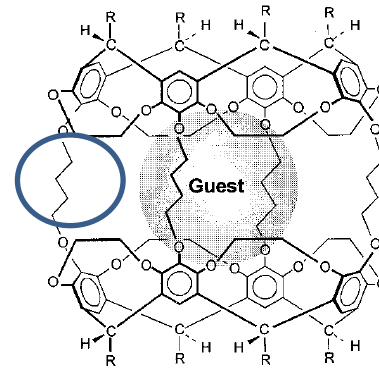
fenolo

bromo-clorometano

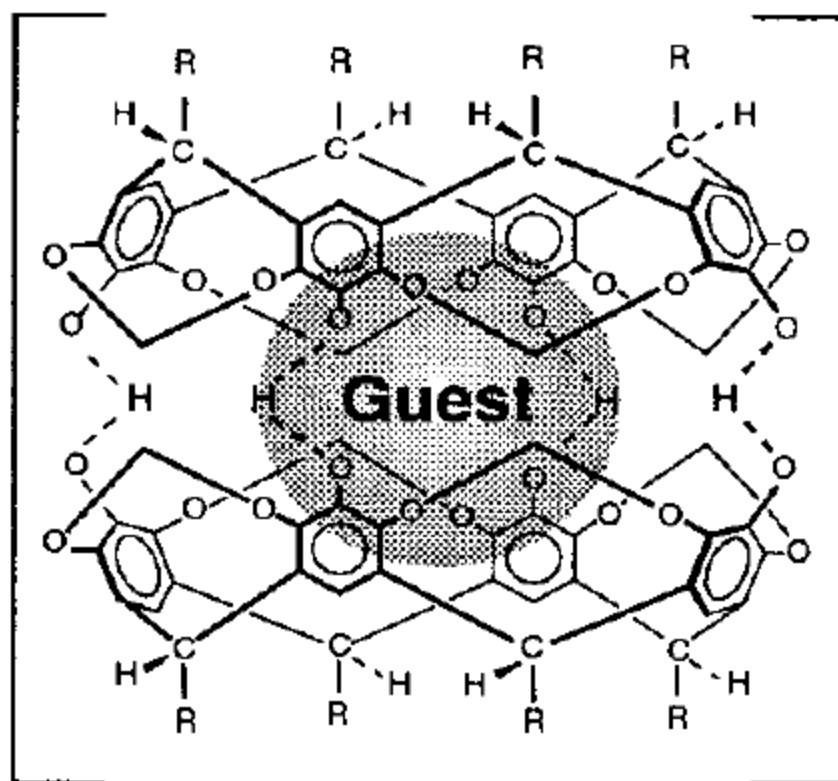


11•Guest $n = 2$ $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$

12•Guest $n = 3$ or $\text{C}_{11}\text{H}_{23}$

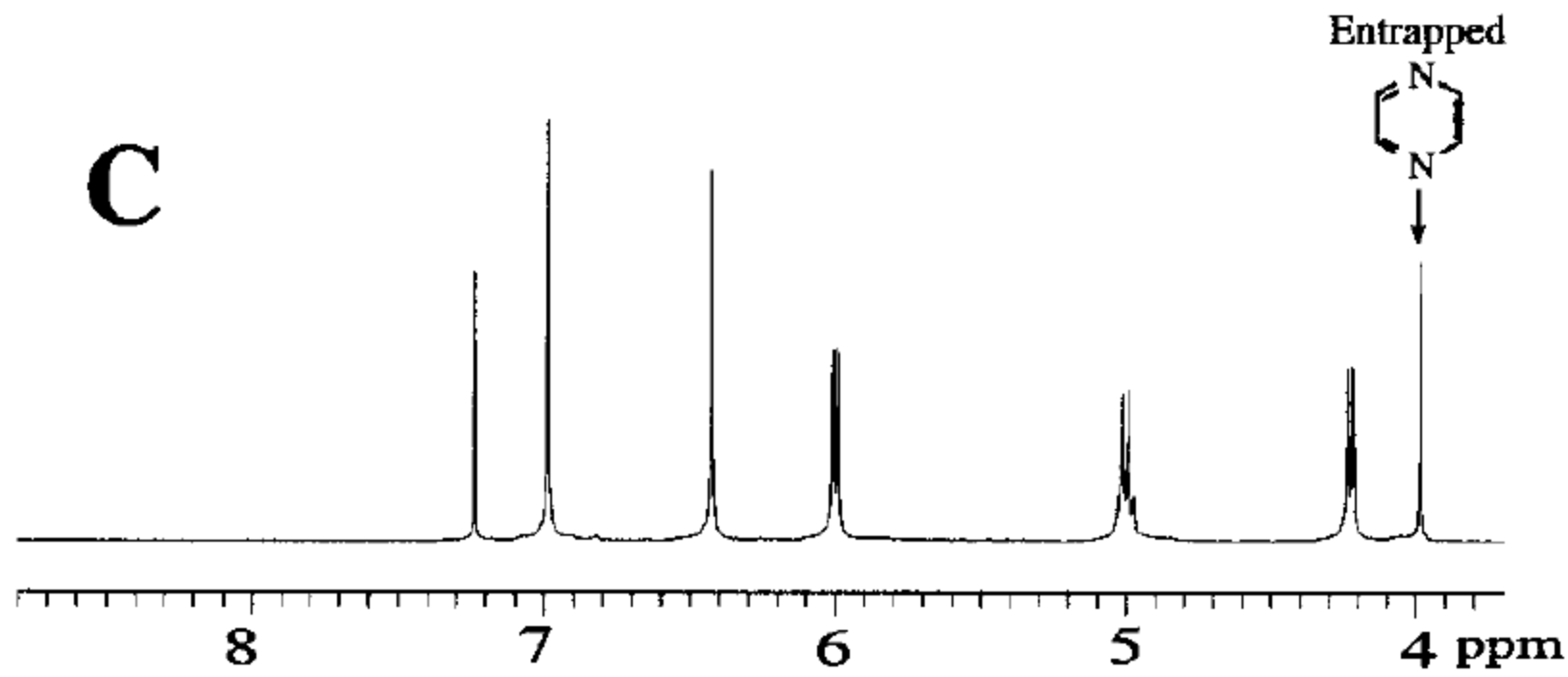


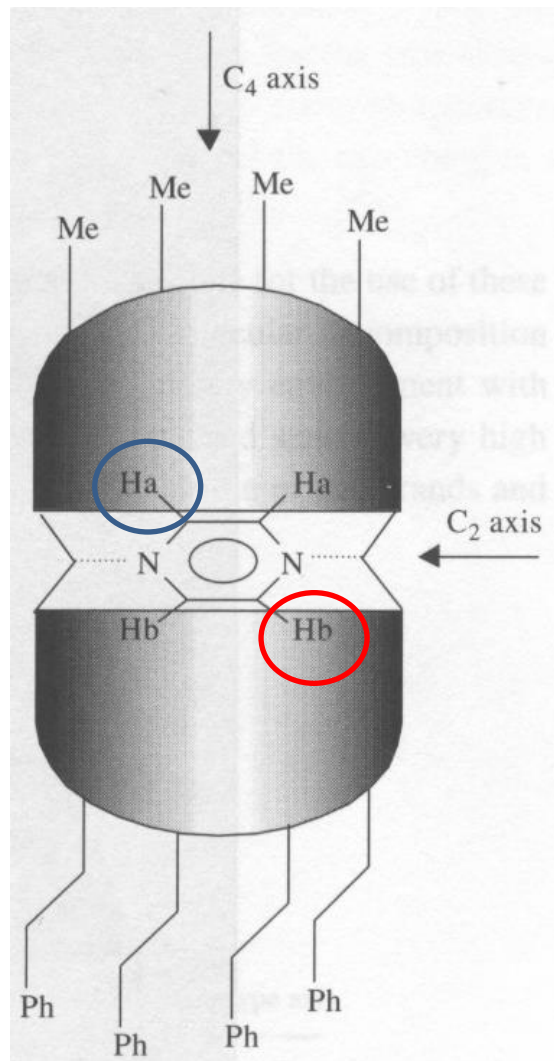
13•Guest $\text{R} = (\text{CH}_2)_4\text{CH}_3$

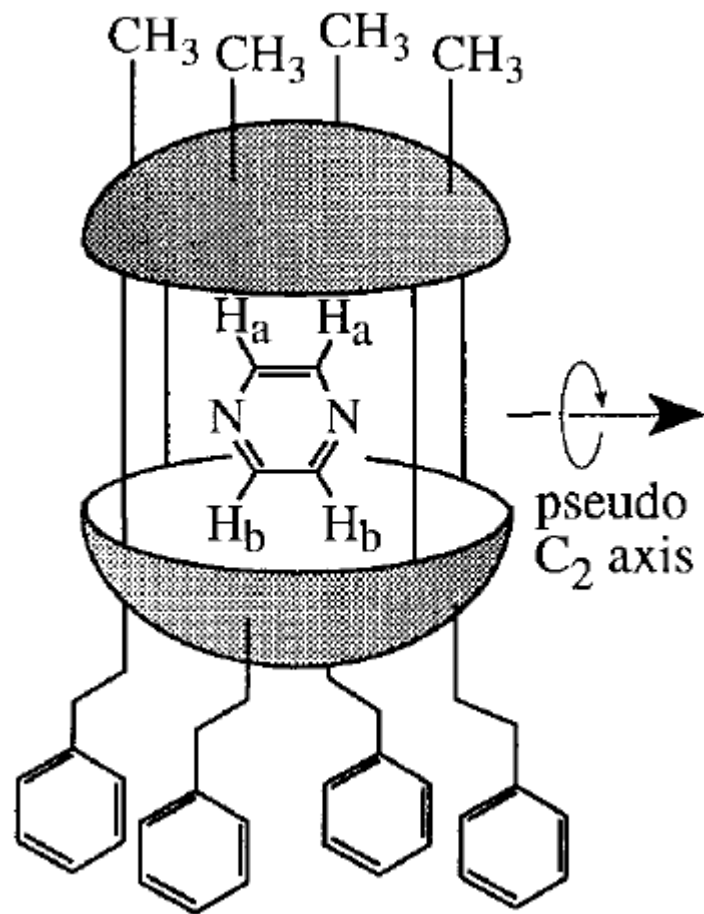


Complex 3-Guest

C

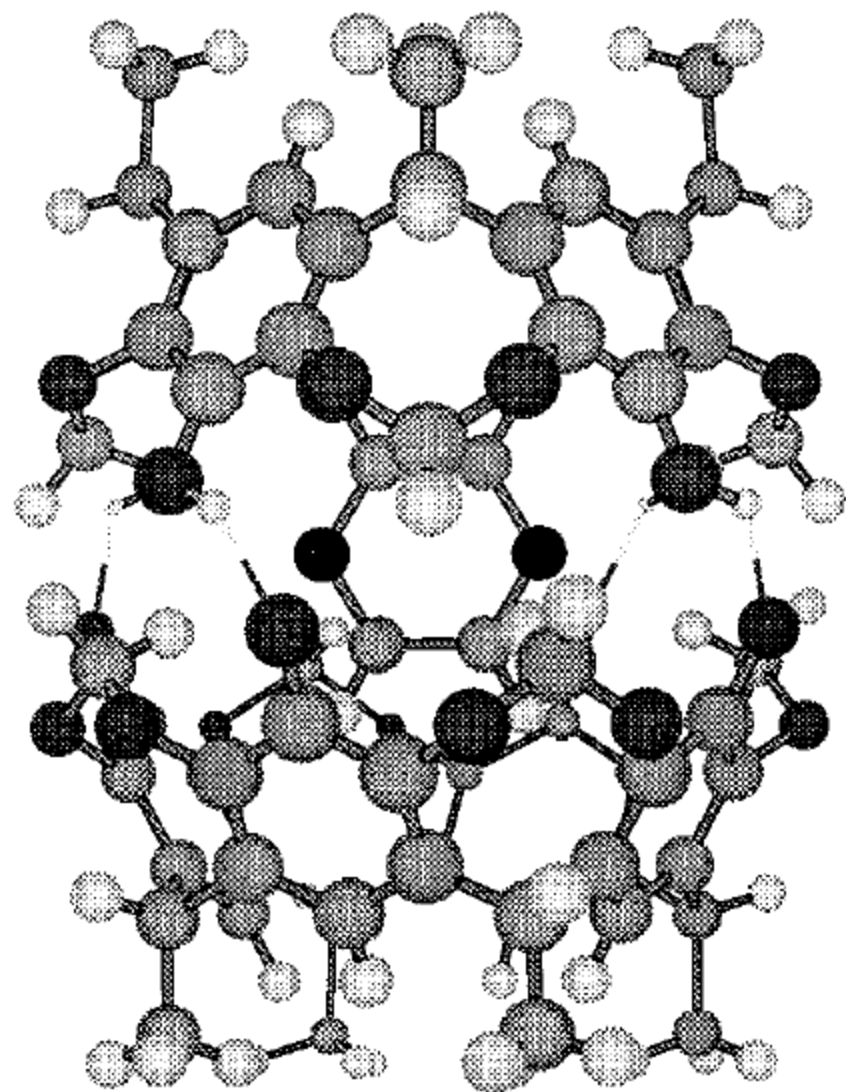






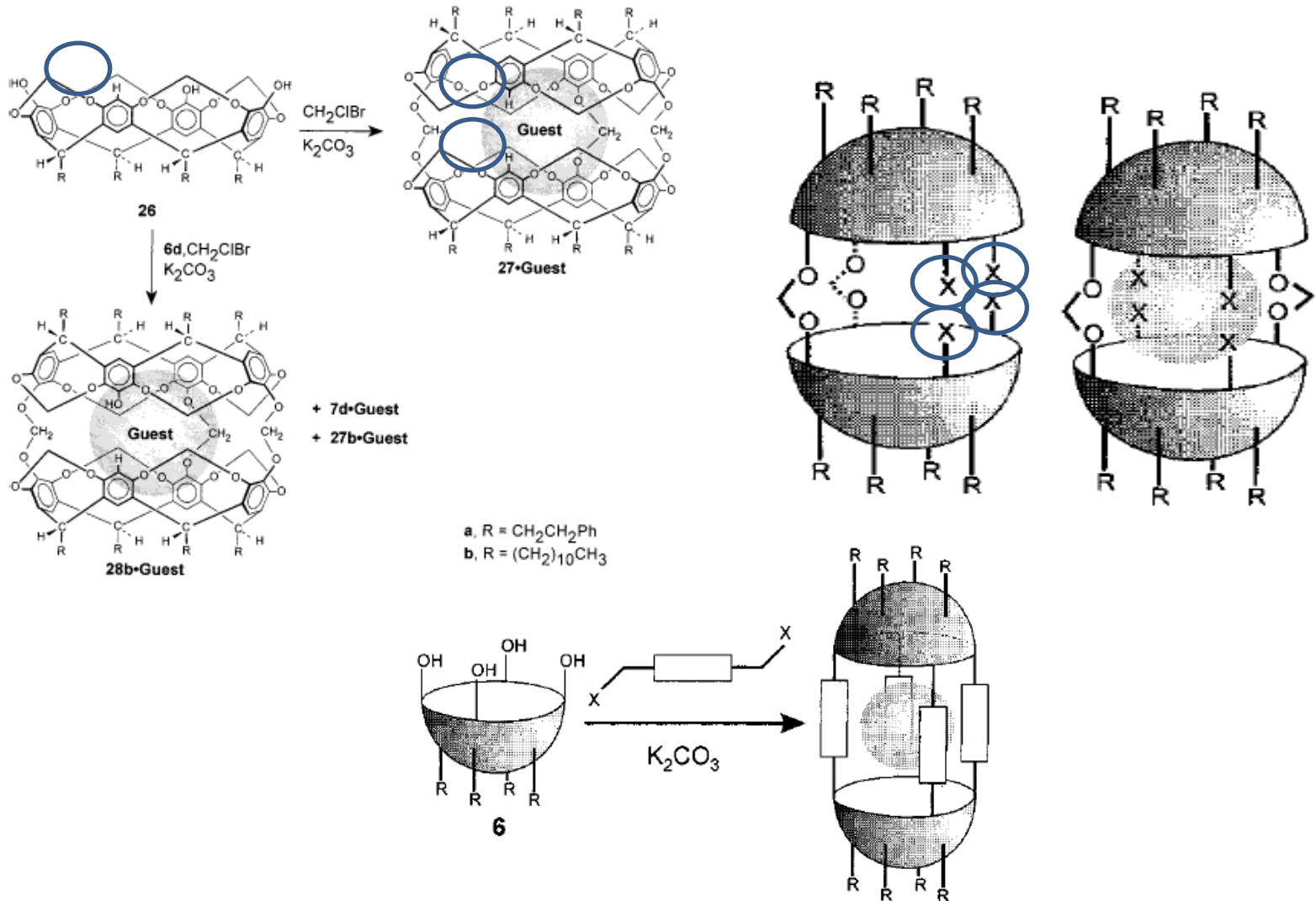
tively. The signals for pyrazine in asymmetric complex **3c**•pyrazine consisted of two *meta*-split doublets at 4.31 ($J = 1$ Hz) and 4.35 ppm ($J = 1$ Hz).¹⁶ This confirms that pyrazine is oriented in complex **3b**•pyrazine with its nitrogens at the equator and its hydrogens extending into the bowls (structure **A**, Figure 3). The activation energy for rotation of pyrazine about the pseudo- C_2 axes in asymmetric complex **3c**•pyrazine was measured by variable-temperature ^1H NMR spectroscopy to be 18 kcal/mol,¹⁷ which agrees well with the 19 kcal/mol activation

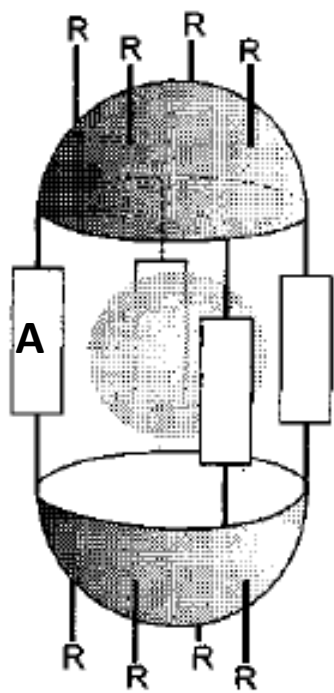
(17) The activation barrier for rotation of pyrazine about the pseudo- C_2 axes of asymmetric complex **3c**•pyrazine was calculated to be 18.3 kcal/mol based on a coalescence temperature (T_c) of 353 K and separation of the signals ($\Delta\delta_{\text{Hz}}$) of 14.3 Hz using the following equation: $\Delta G_c^\ddagger = RT_c - [22.96 + \ln(T_c/\Delta\delta_{\text{Hz}})]$ where ΔG_c^\ddagger is the activation barrier in kcal/mol; T_c is the temperature of coalescence, and $\Delta\delta_{\text{Hz}}$ is the separation of the signals in Hz. See: Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*; Wiley: New York, 1990; pp 194–197.



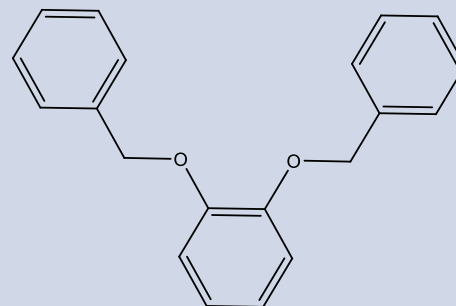
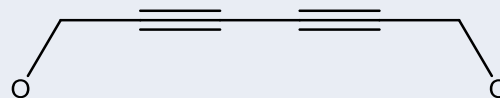
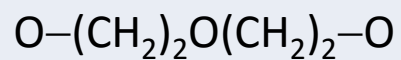
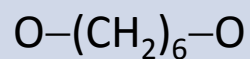
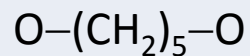
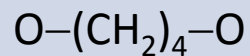
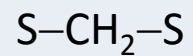
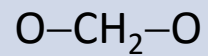
Emicarcerando:

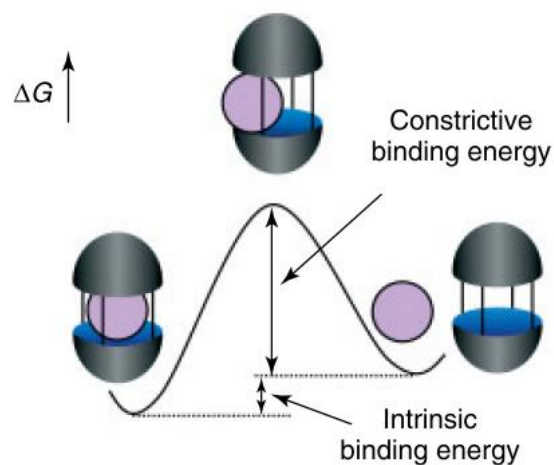
Contenitore molecolare chiuso (capsula) che definisce cavità sferica, i guest sono intrappolati (all'atto della sintesi) - entrata e uscita senza rottura di legame covalente, i.e. velocità di scambio misurabile





A





guests. In host–guest systems, there are two energetic quantities associated with guest binding—constrictive and intrinsic binding. The constrictive binding^{11,12} is the activation energy required for a guest to enter the host, while intrinsic binding is the change in energy upon formation of the host–guest complex from free host and guest. Intrinsic binding energy determines the equilibrium constant for binding; the intrinsic binding energy plus the constrictive binding energy determines the kinetic barrier to decomplexation.¹²

Intrinsic binding, the free energy of complexation, depends on the magnitude of the noncovalent interactions between the guest and the host’s inner surface.

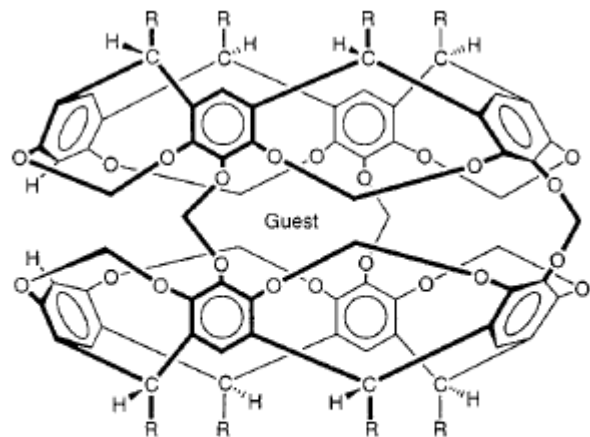
Constrictive binding, activation energy required for a guest to enter OR exit the inner cavity of a hemicarcerand through a size restricting portal in the host’s skin.

Constrictive binding: aumenta con le dimensioni del guest, diminuisce con le dimensioni dei portali, e con l’aumento della flessibilità dei linker (T).

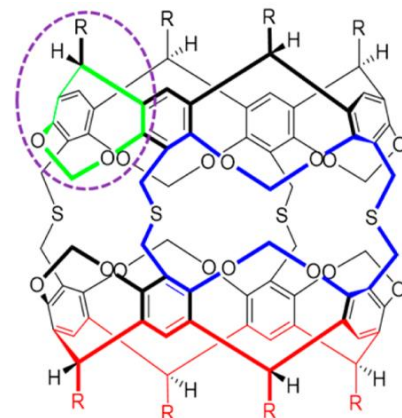
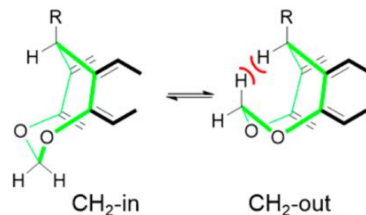
Gating: Gating in host-guest chemistry refers to conformational changes that occur in response to some stimulus, resulting in opening or closing of a physical barrier that controls access to the host.

- **Thermal Gating**
- **Stimulated Gating**

Gate mechanisms (molecular mechanics calculations) – **French door**
 chair-to-boat transition of the methylene bridges, calculated barrier 22 kcal/mol.

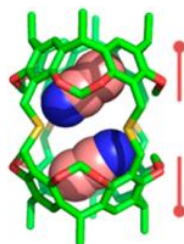
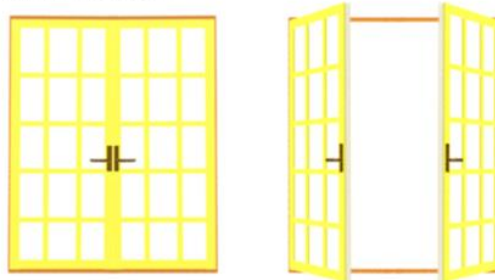


12 ⊕ Guest
 R = CH₂CH₂Ph

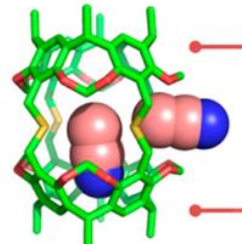


1a. R = (CH₂)₂Ph
 1b. R = Me

a. French door

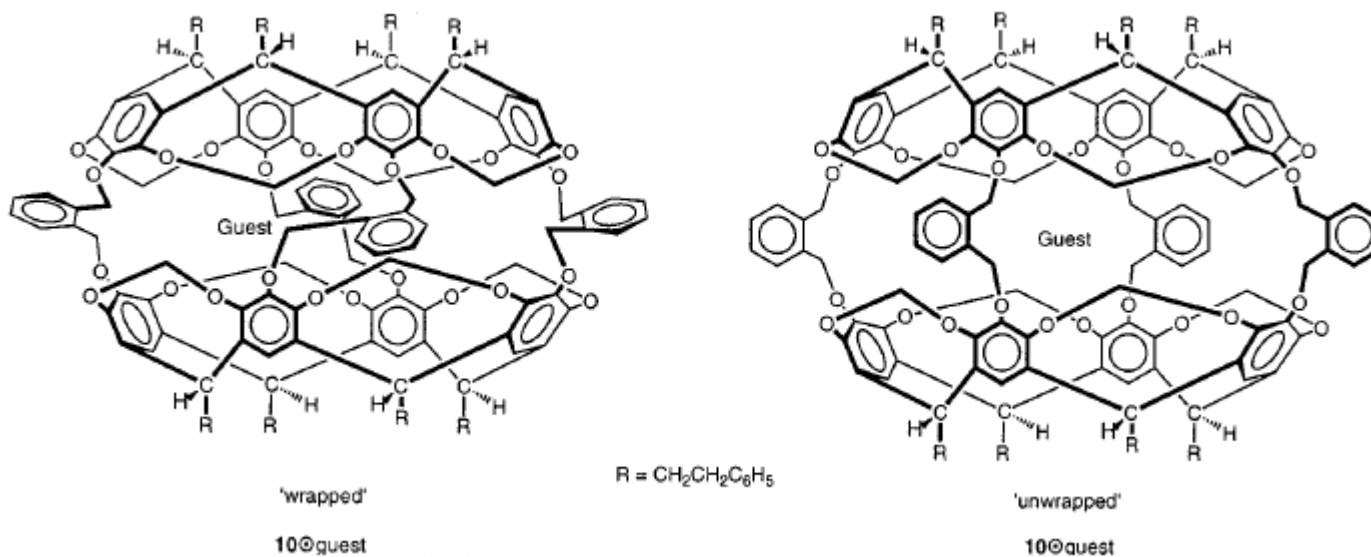


closed

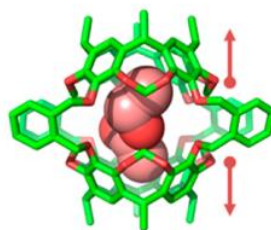
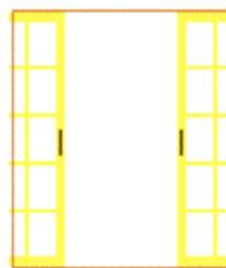
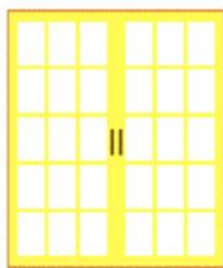


open

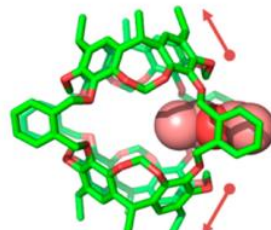
Gate mechanisms (molecular mechanics calculations) – **Sliding door**
twisting and untwisting of the two host cavitands – measured barrier (VT NMR) 12.6 kcal/mol



b. Sliding door

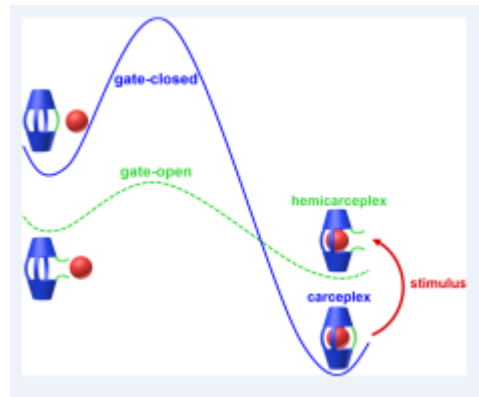
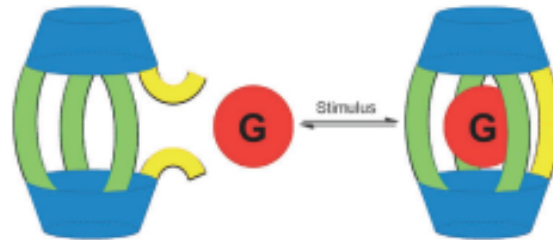


closed

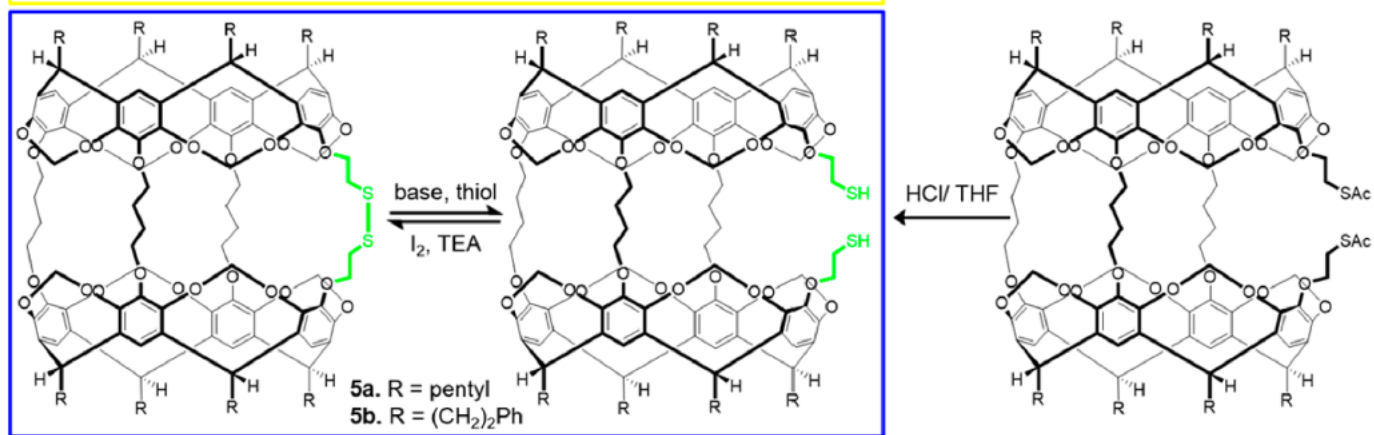


open

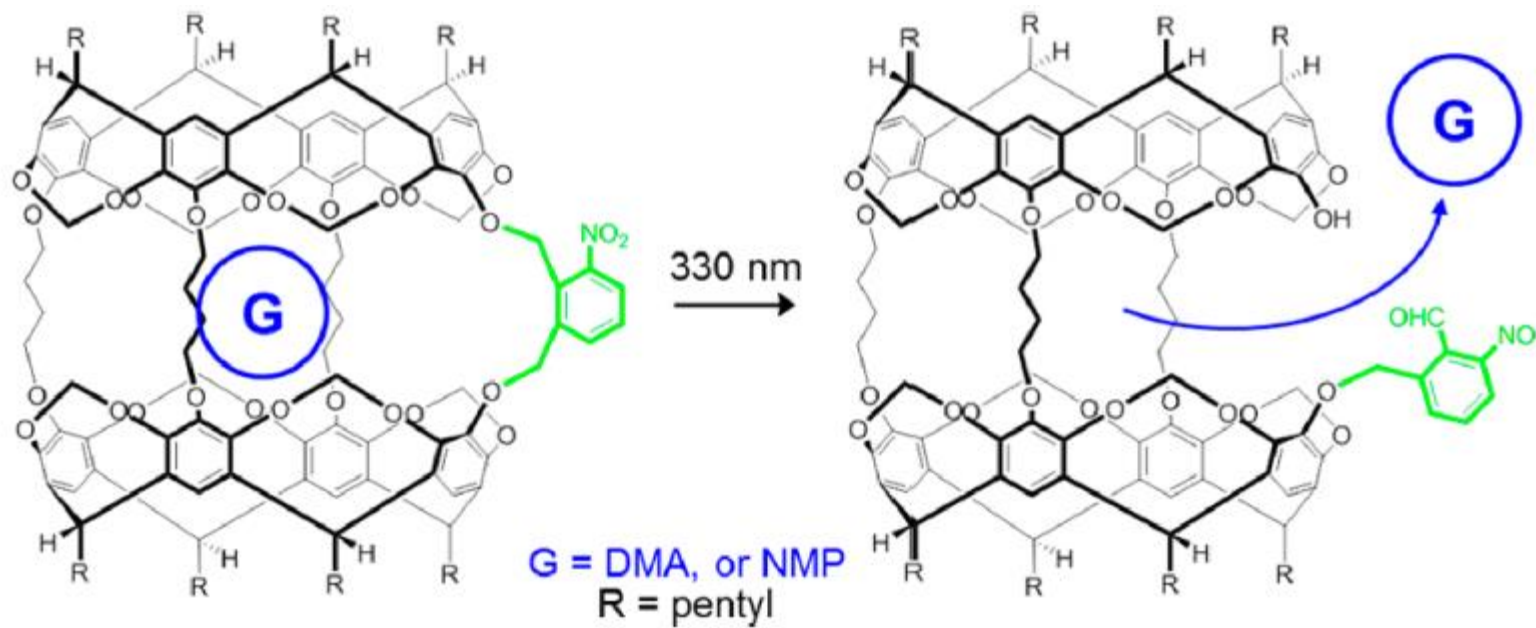
Stimulated Gating



Redox Gating



Photochemical Gating



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

Hao Wang, Fang Liu, Roger C. Helgeson, and Kendall N. Houk*

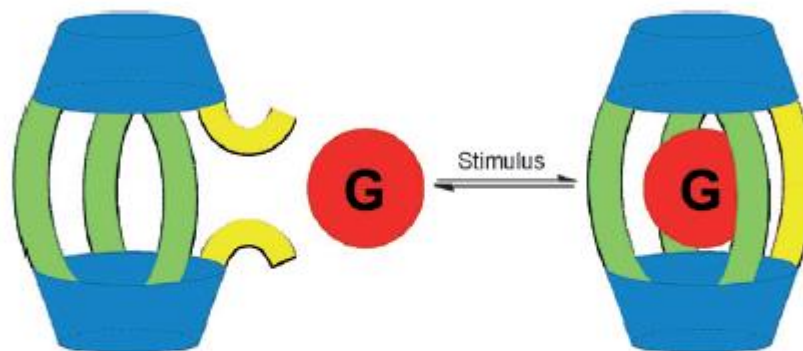
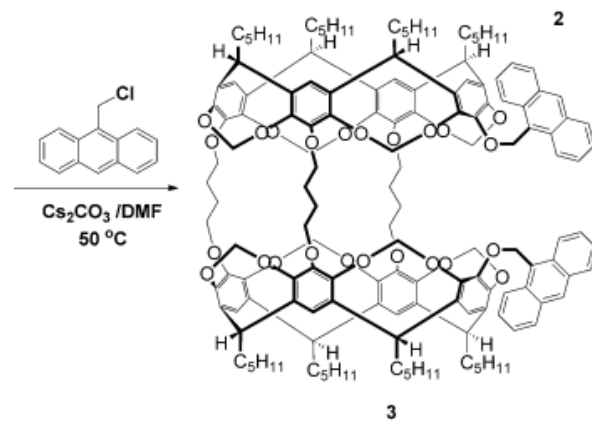
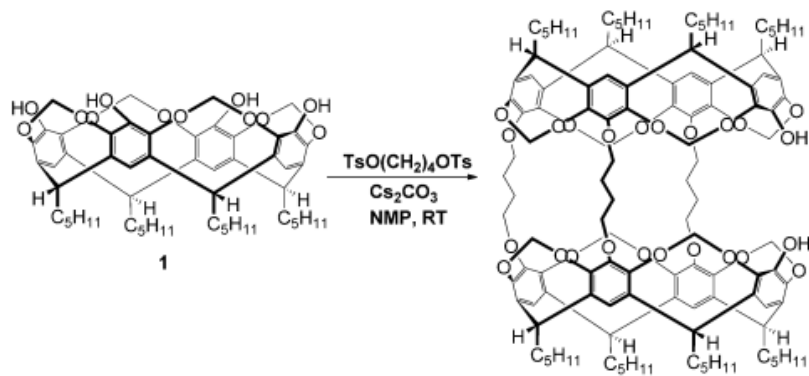
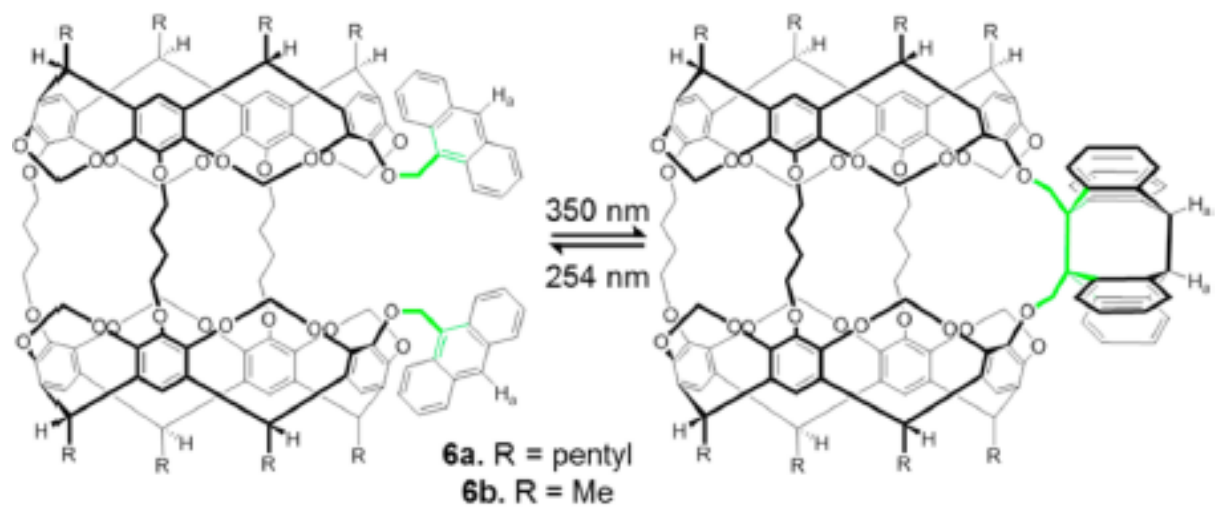


Figure 1. Gating in container molecules converts a hemicarcerand (left) into a carcerand (right).





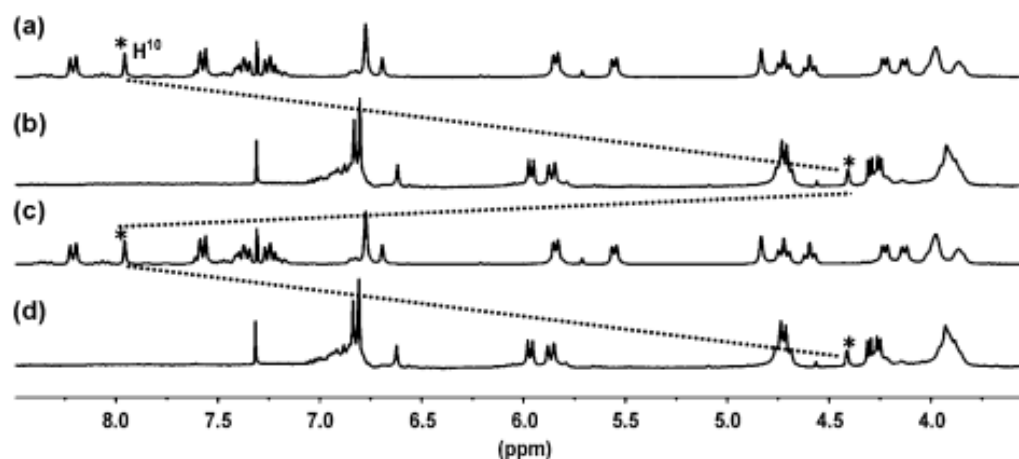
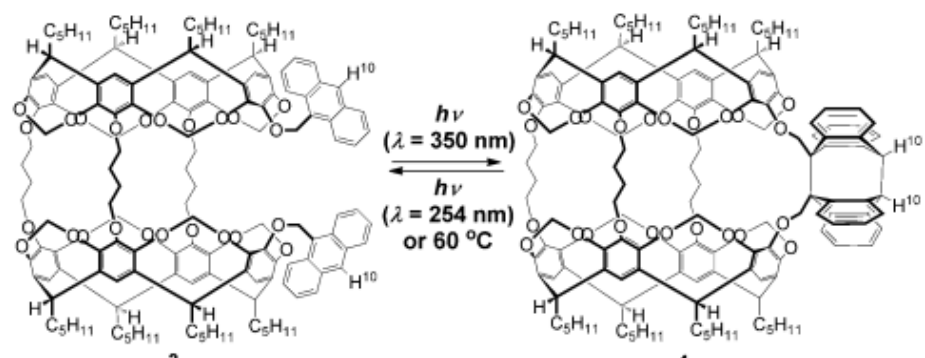
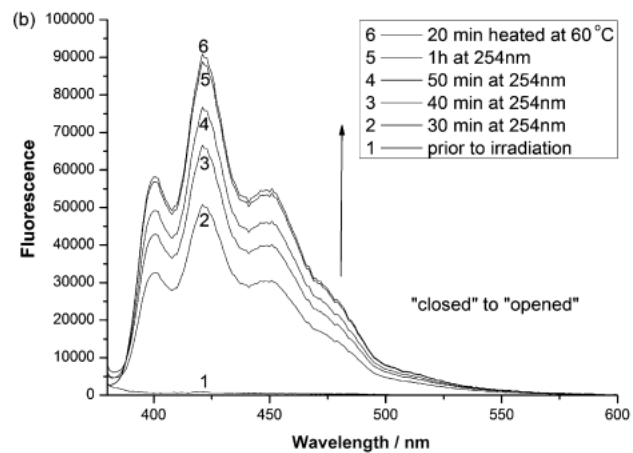
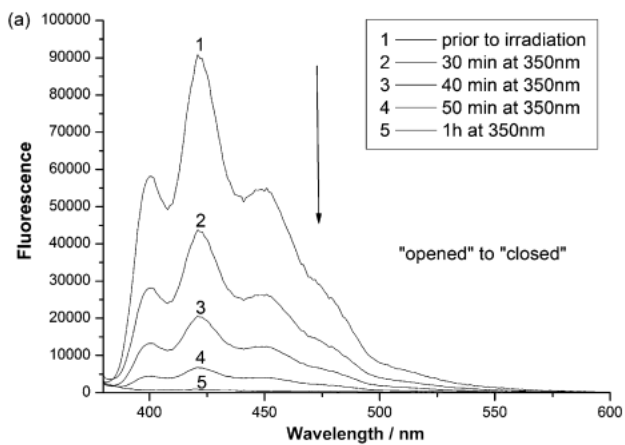
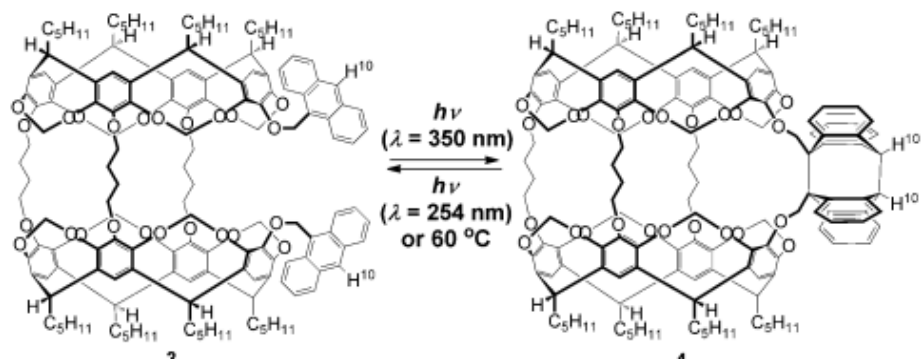
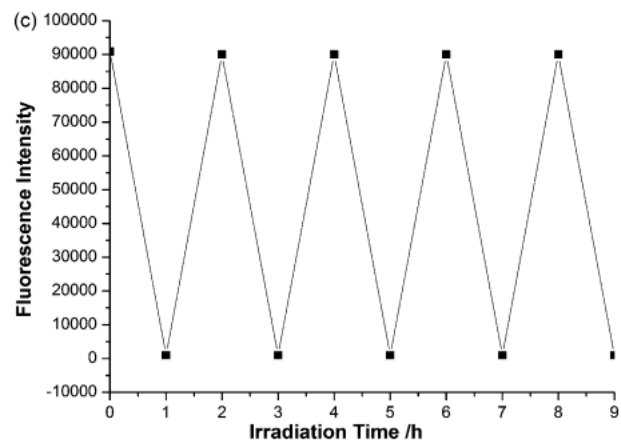
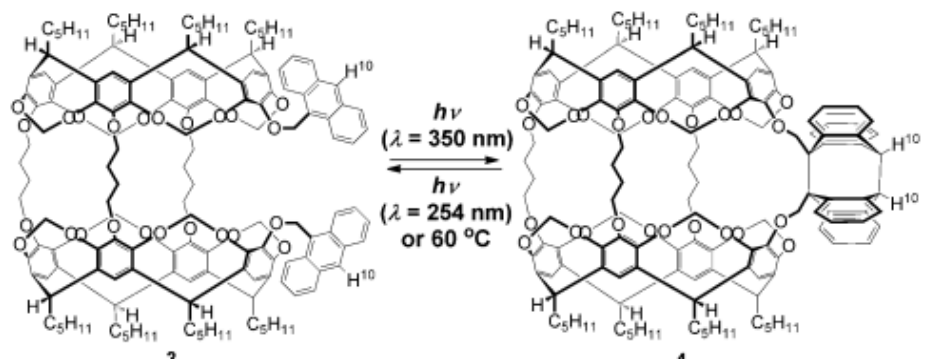
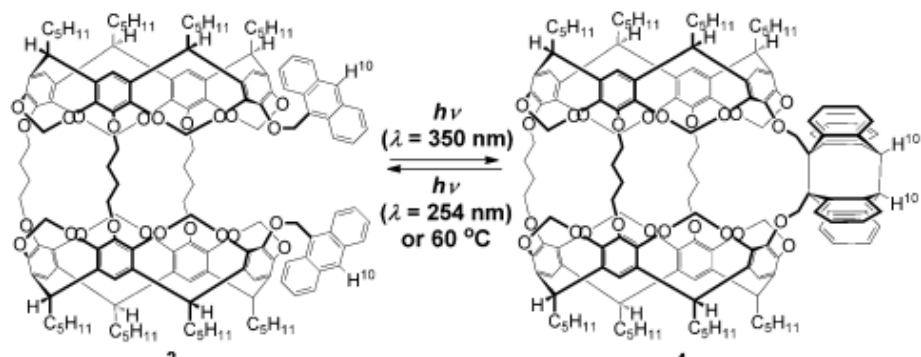


Figure 3. Partial ^1H NMR spectra (400 MHz, CDCl_3) of a) host **3**, b) irradiation of host **3** with light at 350 nm for 1 h, c) irradiation of **b** with light at 254 nm for 1 h or heating at 60 °C for 20 min, d) irradiation of **c** with light at 350 nm for 1 h.

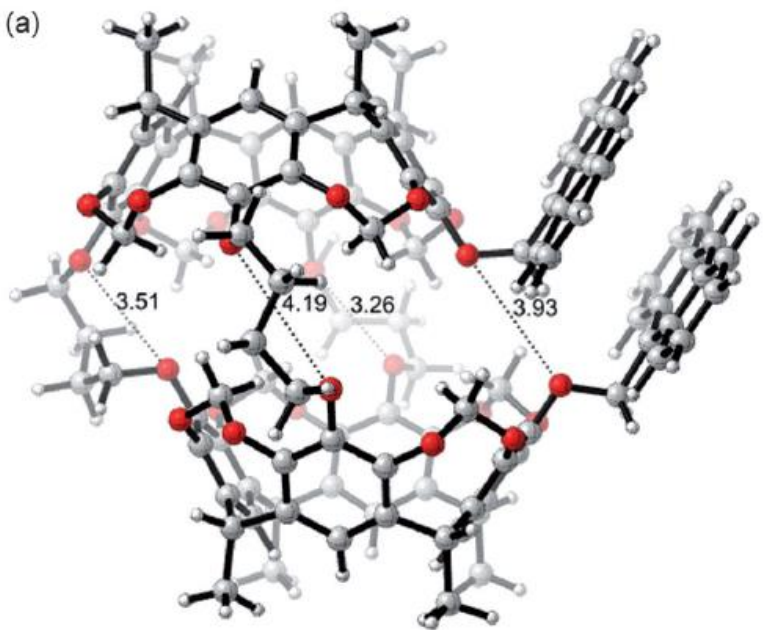




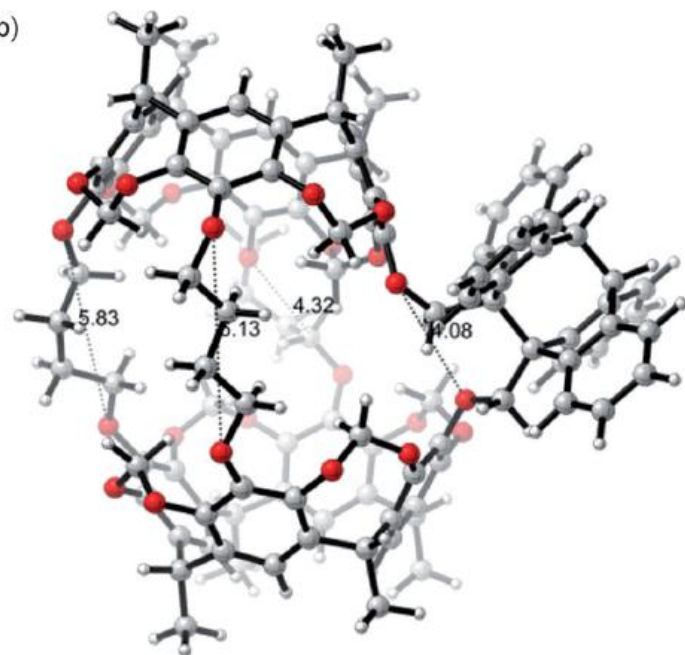


The progress of the photodimerization was also monitored by thin-layer chromatography, which showed only one band after completion of the photodimerization. Photodimer 4 was purified after photolysis at 350 nm. In the high-resolution mass spectrum the molecular ion of photoproduct 4 has the same mass as the parent open-state host 3.

(a)



(b)



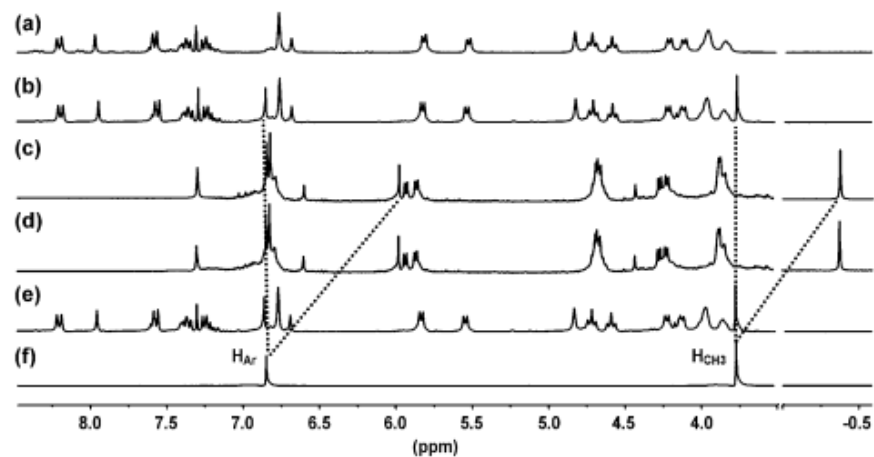
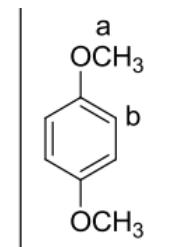
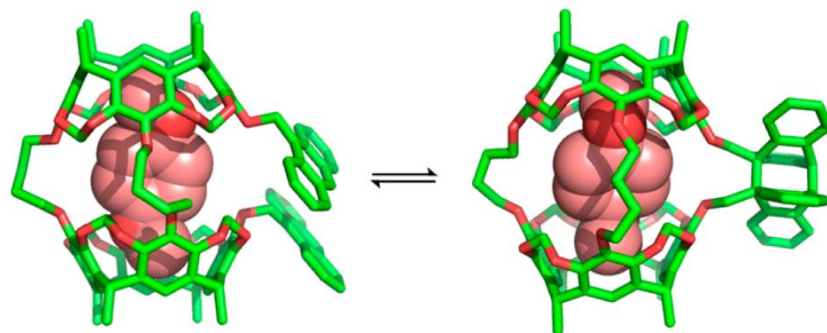
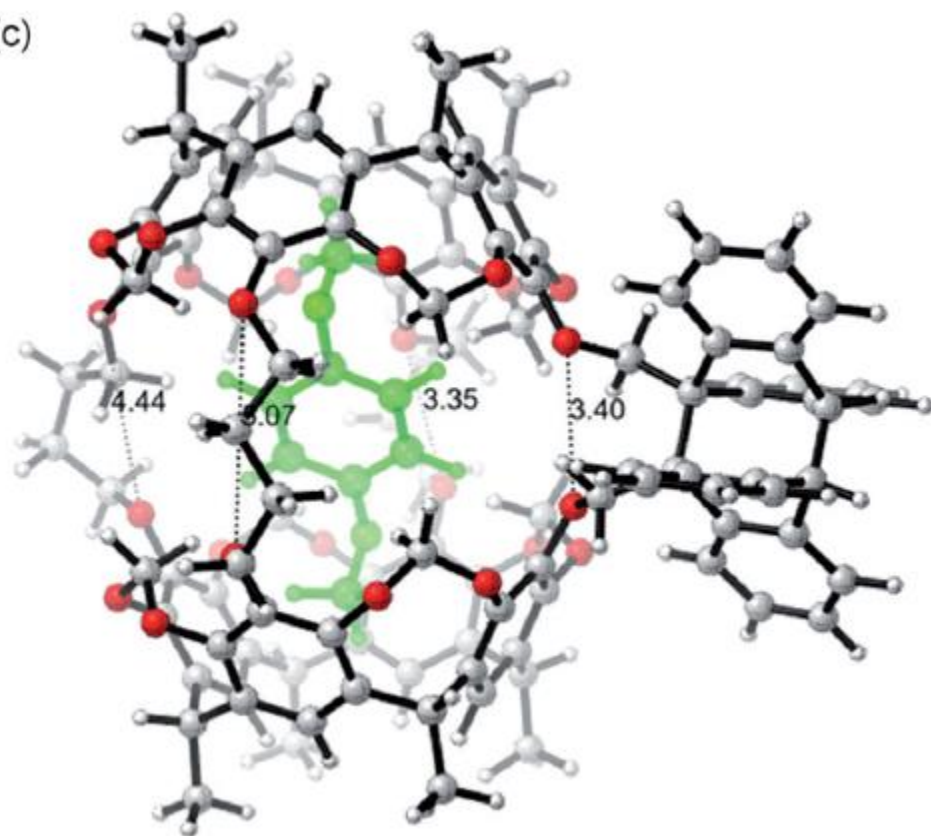


Figure 6. Partial ^1H NMR spectra (400 MHz, CDCl_3) of a) host **3** b) addition of 1 equiv of 1,4-(MeO) $_2\text{C}_6\text{H}_4$ into host **3** solution without irradiation, c) 4 \odot 1,4-(MeO) $_2\text{C}_6\text{H}_4$,^[16] d) c after 4 weeks in dark and RT, e) irradiation of c with light at 254 nm for 1 h or heating at 60°C for 20 min, f) guest 1,4-(MeO) $_2\text{C}_6\text{H}_4$.

(c)



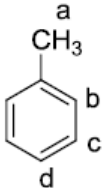
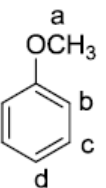
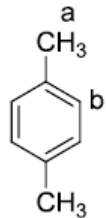
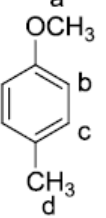
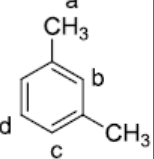
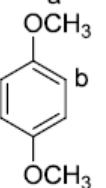
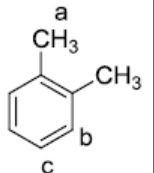
Guest	H	$\Delta\delta$ (ppm)	Guest	H	$\Delta\delta$ (ppm)
	H _a	3.96		H _a	3.87
	H _b	1.53		H _b	1.60
	H _c	1.85		H _c	1.95
	H _d	3.35		H _d	3.30
	H _a	4.17		H _a	4.01
	H _b	1.06		H _b	0.84
				H _c	0.98
				H _d	4.21
	H _a	3.17		H _a	4.15
	H _b	hidden		H _b	0.85
	H _c	1.86			
	H _d	hidden			
	H _a	2.34	CH ₂ Cl ₂ —CHCl ₂	H _a	0.95
	H _b	1.54	CH ₂ Br ₂ —CHBr ₂	H _a	1.02
H _c	1.95				

Table S1: Complexation of **4** with various guest molecules and the chemical shift changes of corresponding Hs (before and after complexations) on the guests.

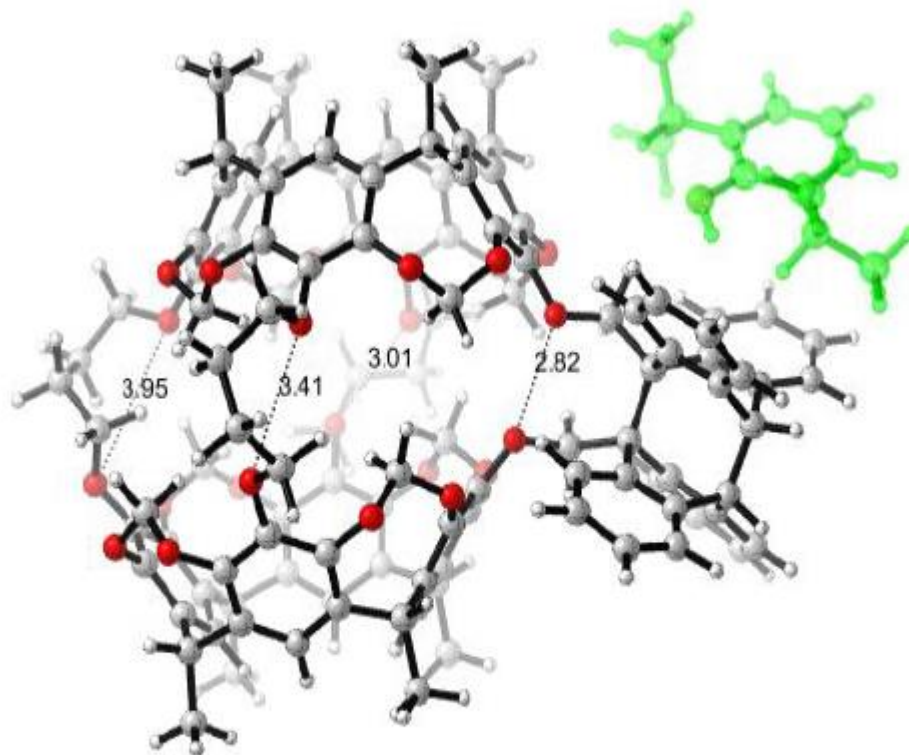
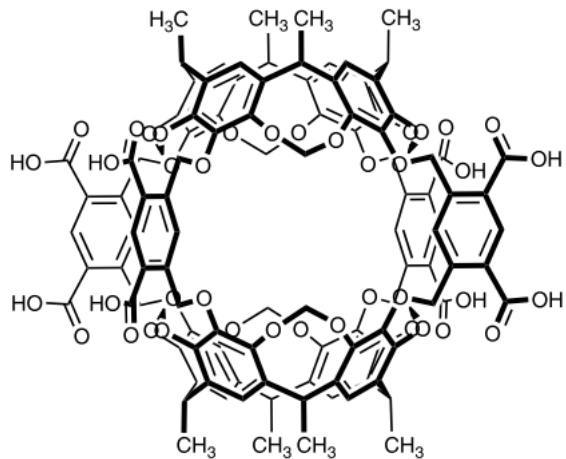


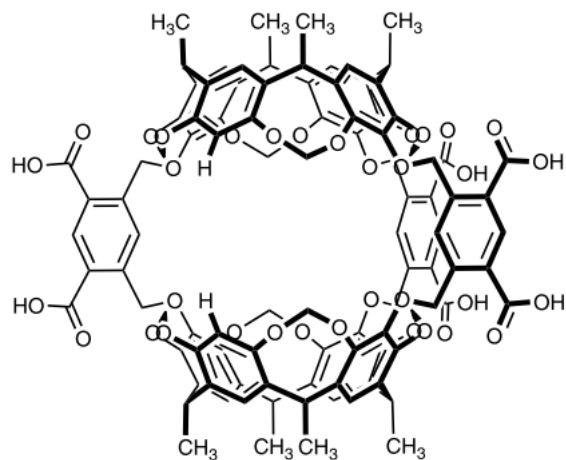
Figure S2: Molecular modelling of complexation of **4** with propofol (2,6-diisopropylphenol) using Schrödinger Macromodel (OPLS_2005, GB/SA CHCl₃). (The geometry began with the guest inside the host; the guest came out of the host after the minimization)

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 ^1H 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.



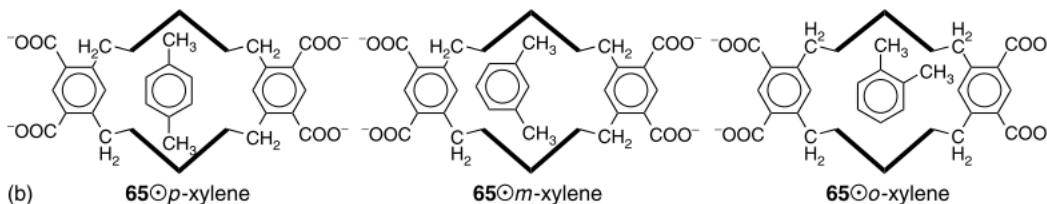
Water soluble octa-acid hemicarcerand:

Hydrophobic effect (higher than cyclodextrines)!

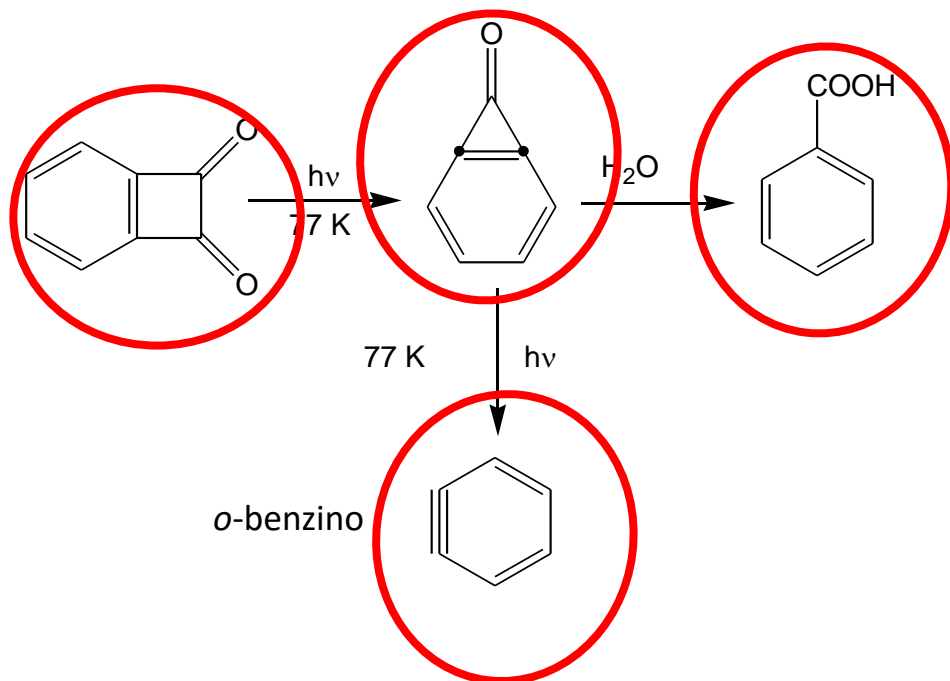


CH- π interactions for isomeric xylenes or dimethoxybenzenes direct the order of affinity:

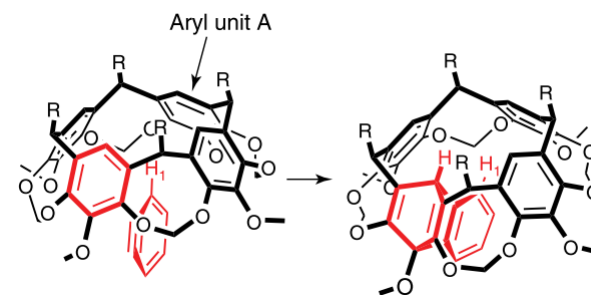
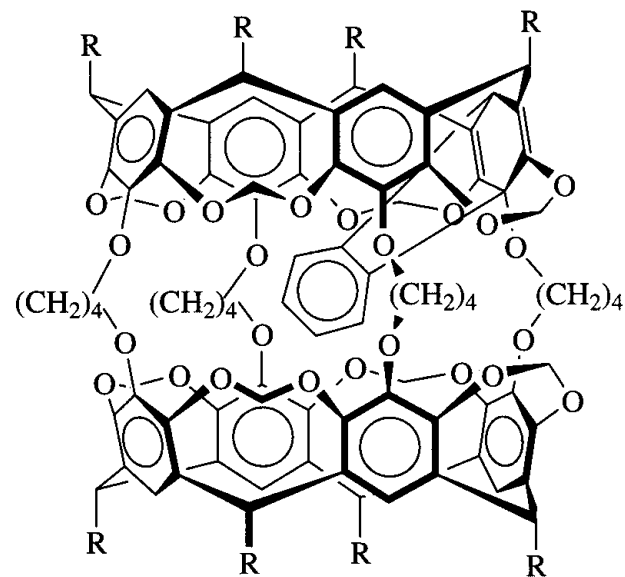
meta > para >> ortho

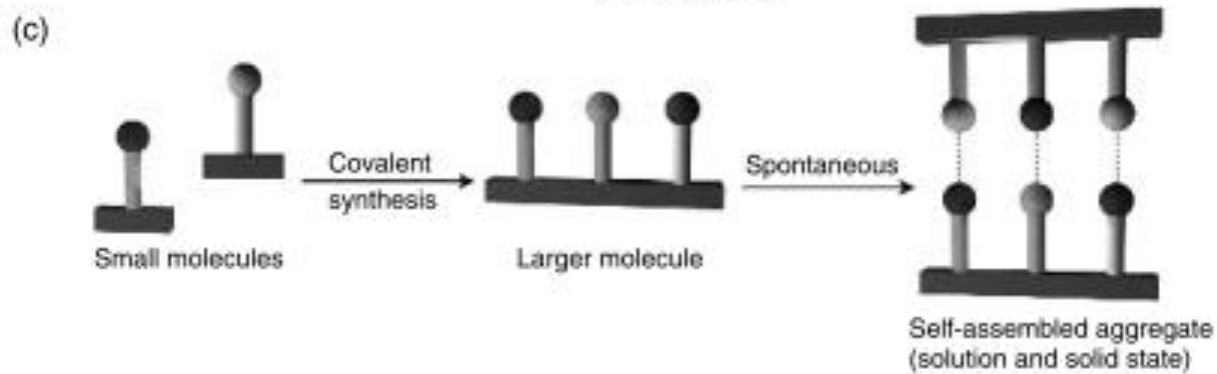
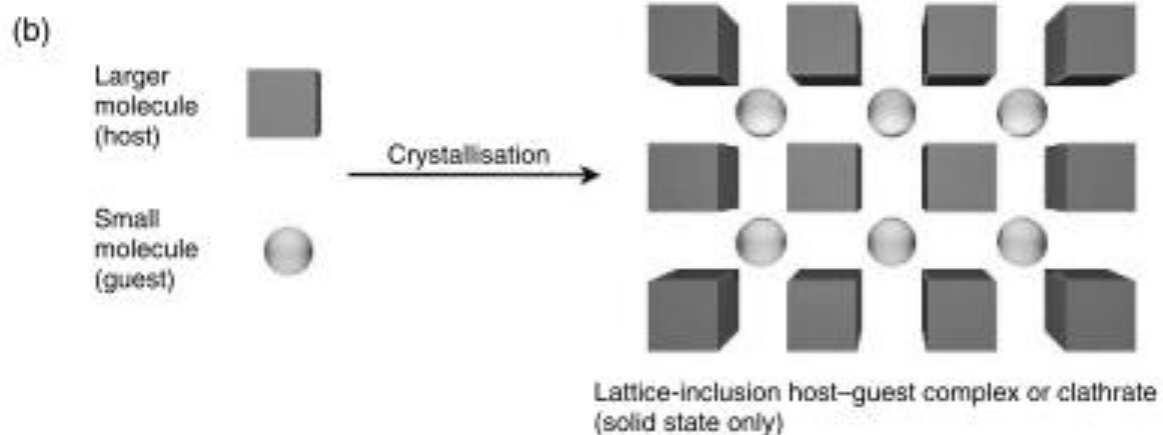
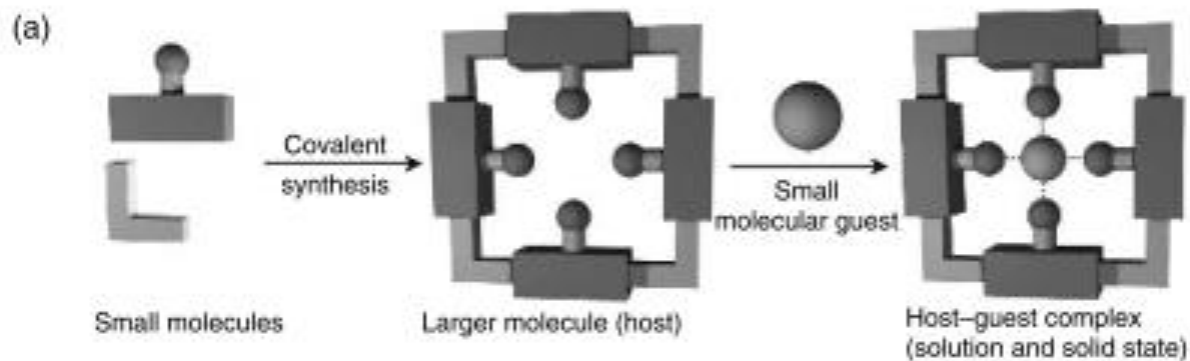


Benzociclobutendione Benzociclopropenone

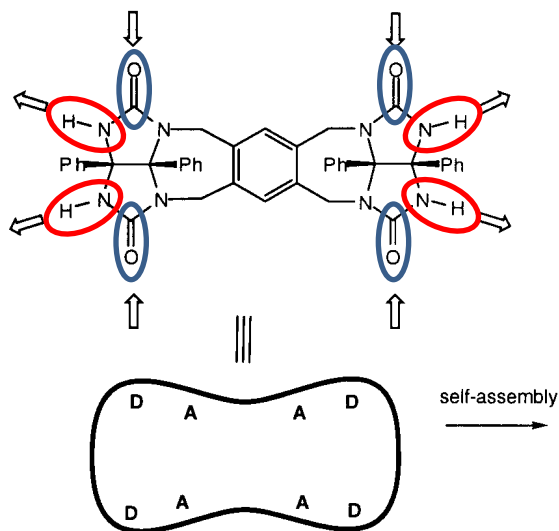


^1H e ^{13}C NMR a bassa T

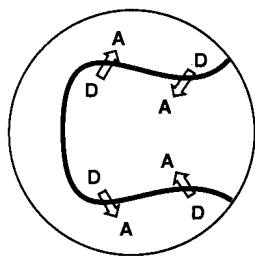




Tennis-ball

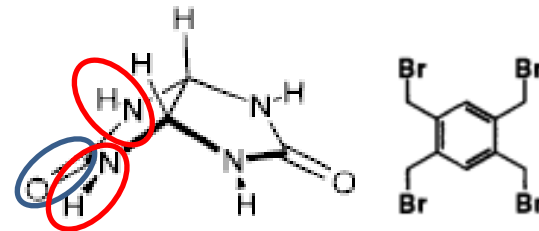


D = hydrogen bond donor
A = hydrogen bond acceptor

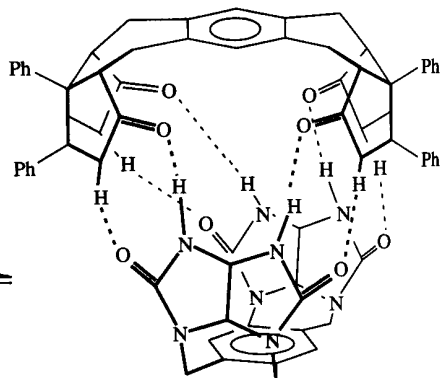
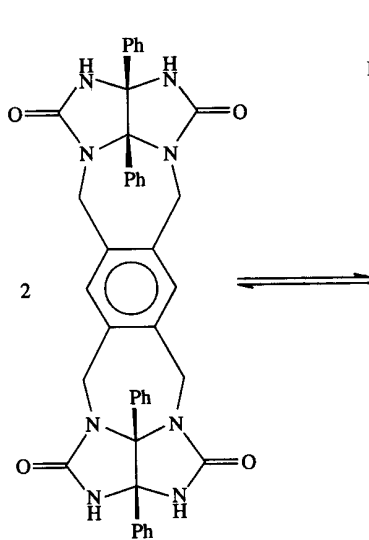


tennis ball

The formation of a molecular tennis ball

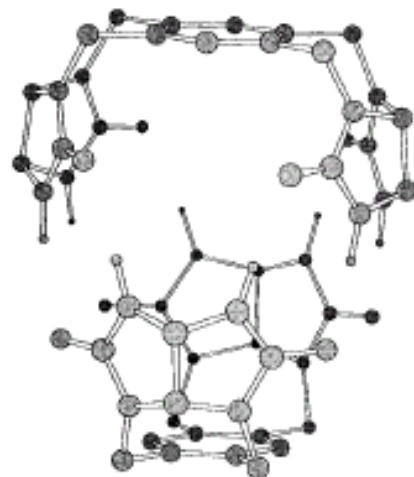


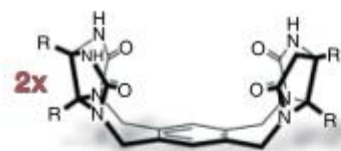
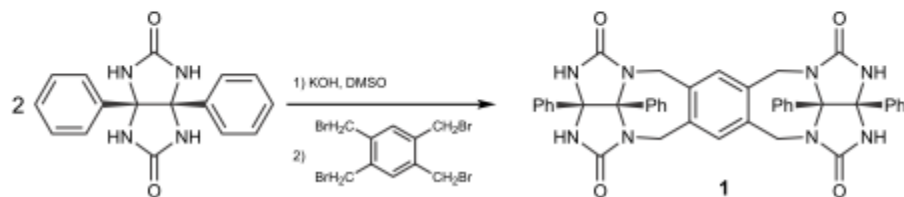
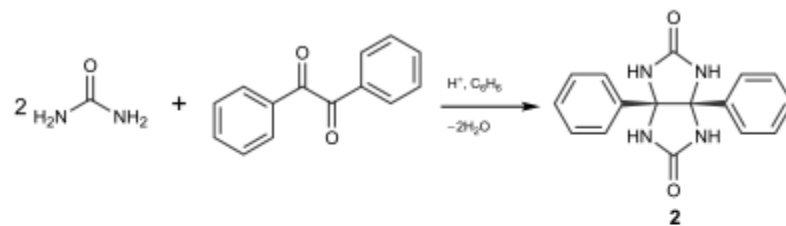
unità glicolurile



Eight linear H-bonds

V ca. 60 \AA^3



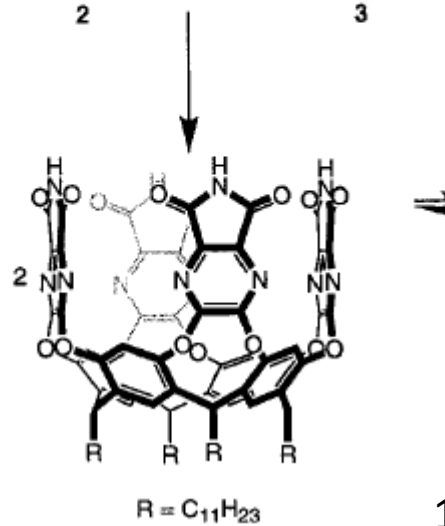
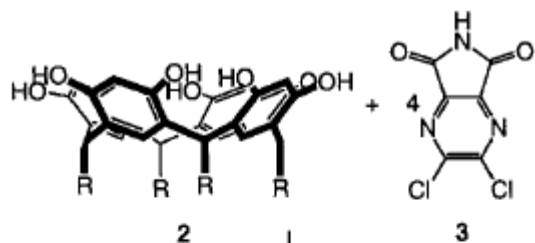


$\text{R} = \text{C}_6\text{H}_5$



$V \text{ ca. } 60 \text{ \AA}^3$

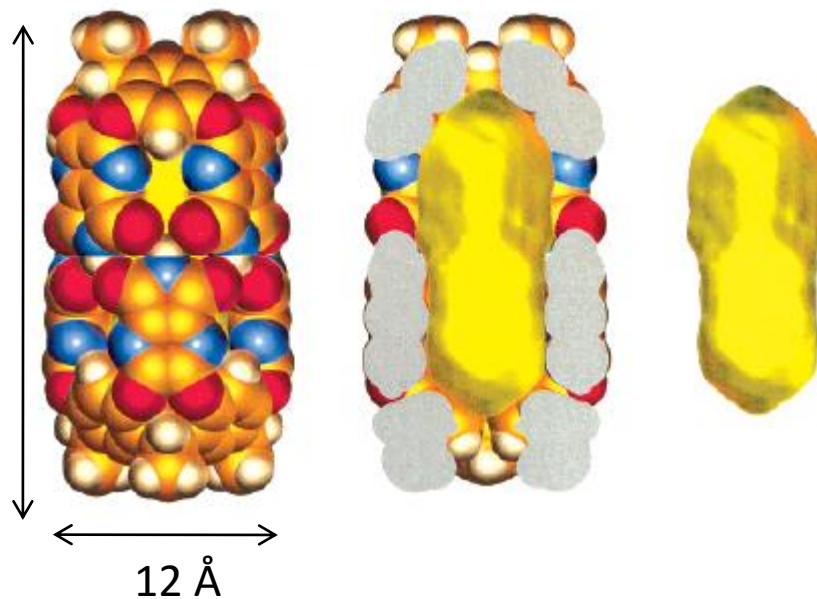
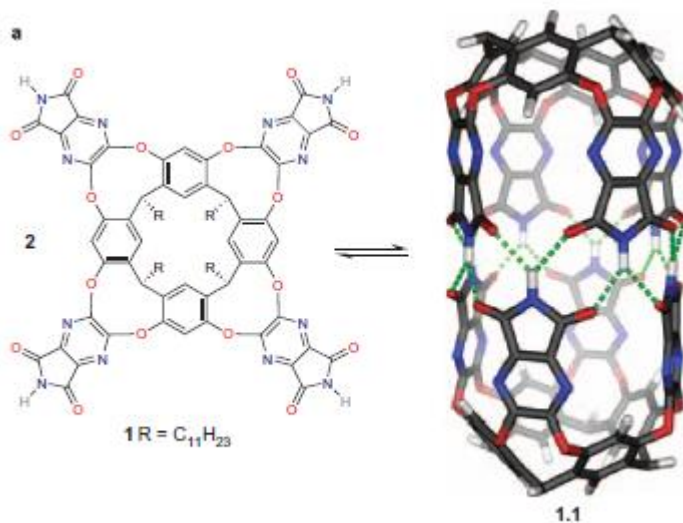
Molecular Cylinder



16 Å

Eight bifurcated H-bonds

$V \text{ ca. } 420 \text{ \AA}^3$



From molecular mechanics calculations:

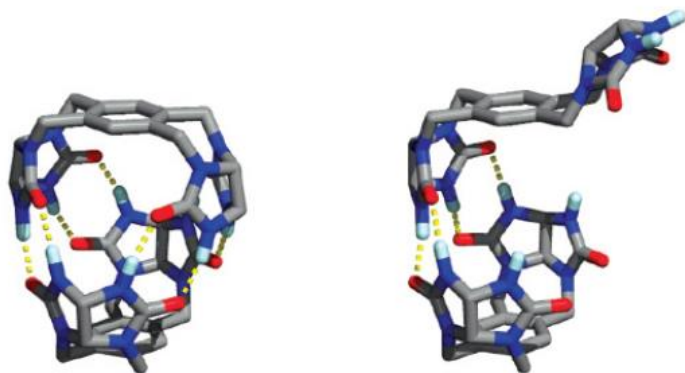
the encapsulated guest(s) occupy approximately 55% of the available space (same occupancy inside most weakly interacting organic solvents).

Stability decreases at higher or lower space occupancy.

The ins and outs of molecular encapsulation

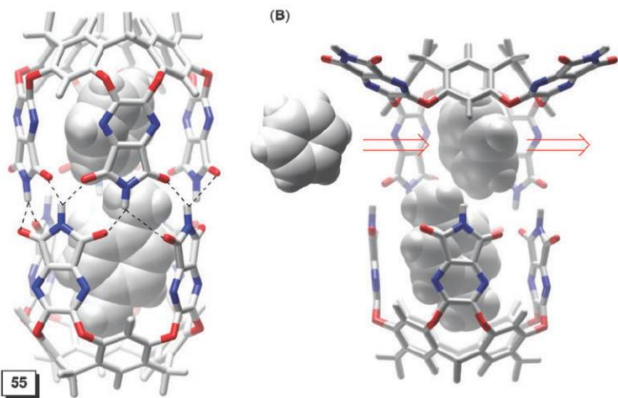
Liam C. Palmer and Julius Rebek, Jr.*

Org. Biomol. Chem., 2004, 2, 3051–3059



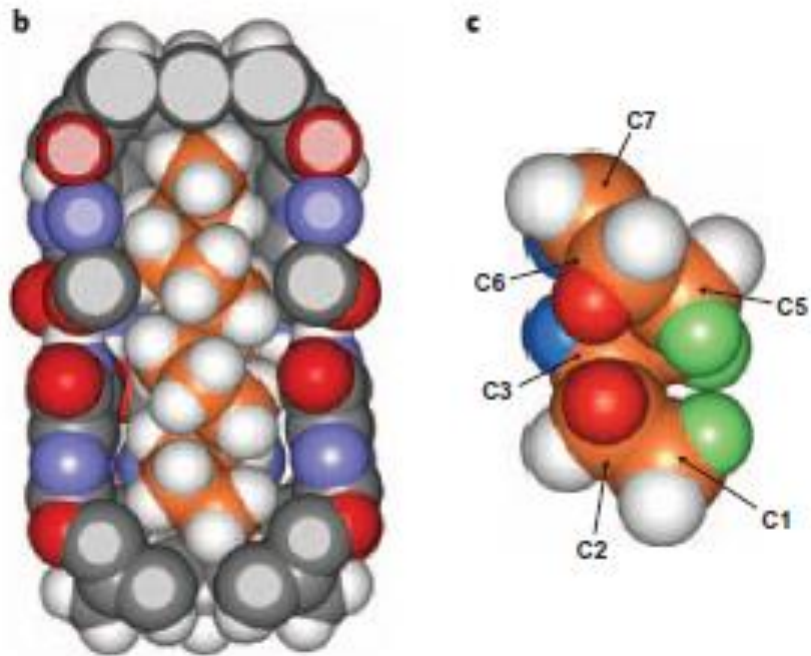
A priori, two plausible exchange mechanisms can be imagined: (1) a dissociative mechanism in which the two capsule subunits completely separate, or (2) a gating mechanism²² whereby one “flap” of the tennis ball opens by ring inversion of the seven-membered ring (as shown in Fig. 5).

Fig. 5 The intact tennis ball, left, and the conformation with an open flap, right. The structure on the right represents intermediate of a possible “gating” mechanism.

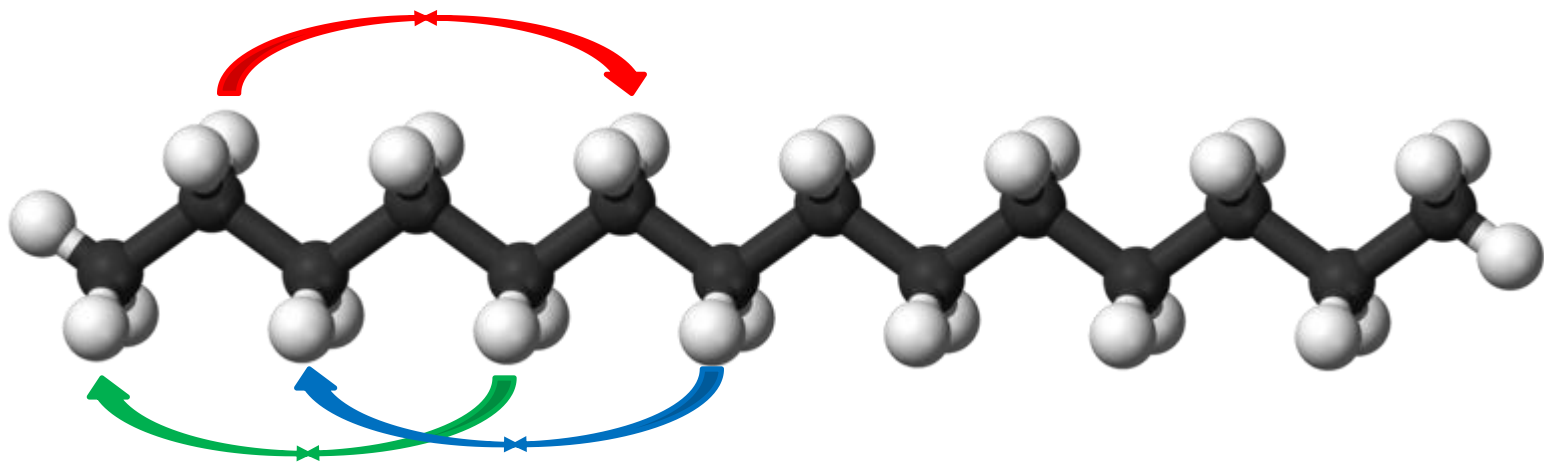


Small guests like toluene can escape by opening of a single flap, left. Larger guests like dimethylbiphenyl require opening of two or more flaps, right.

Contrasting the mechanism in apolar media, the presence of methanol seems to cause large guest exchange by complete dissociation of the capsule subunits. Complexes of small guests are not stable under these conditions.



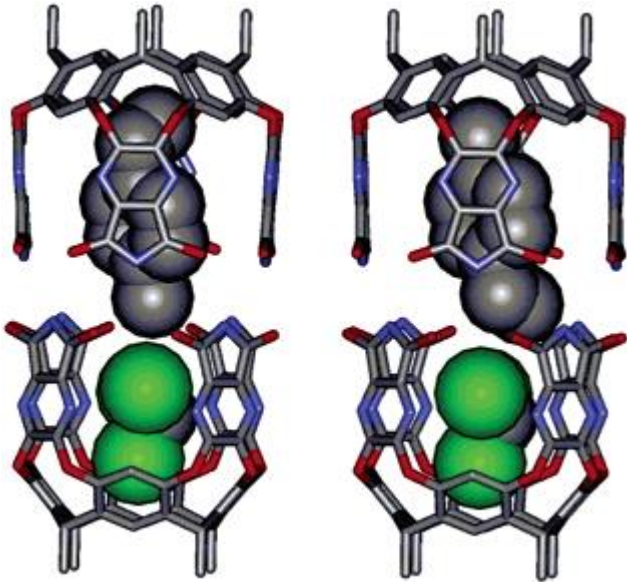
Model structure: incapsulation of coiled alkanes - tetradecane



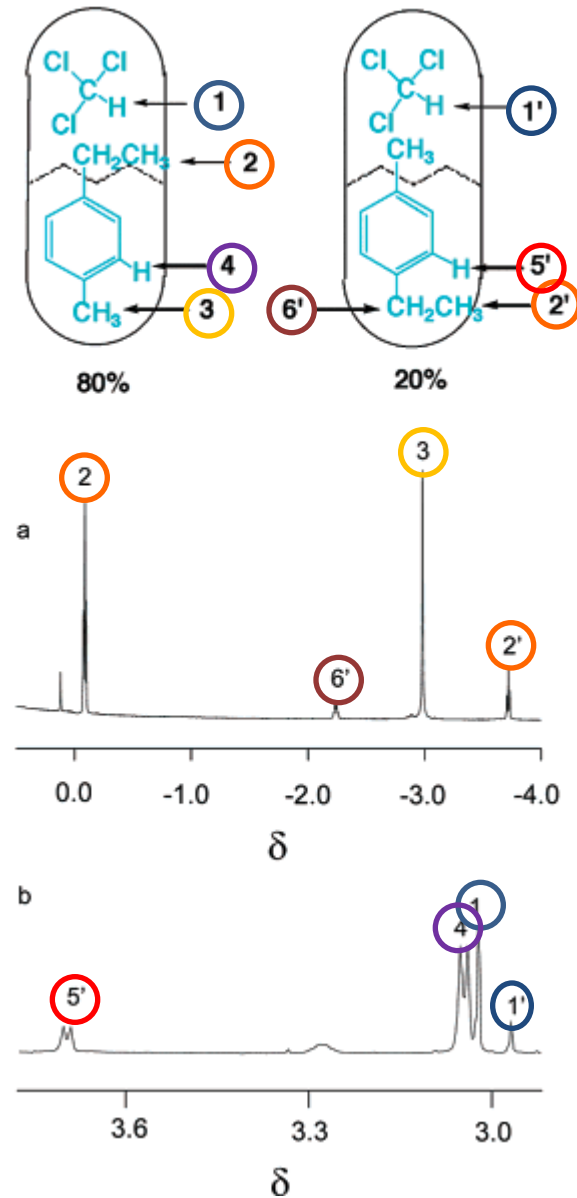
Social Isomers:

A new form of isomerism arises when two different guests are confined to a cylindrical, self-assembled host capsule. The shape and dimensions of the capsule prevent the guests from exchanging positions or tumbling on the NMR time scale. The phenomenon depends on matching guest size and shape with that of the host and on the interaction of the two guest molecules. The orientation of one guest depends on the presence and nature of the other.

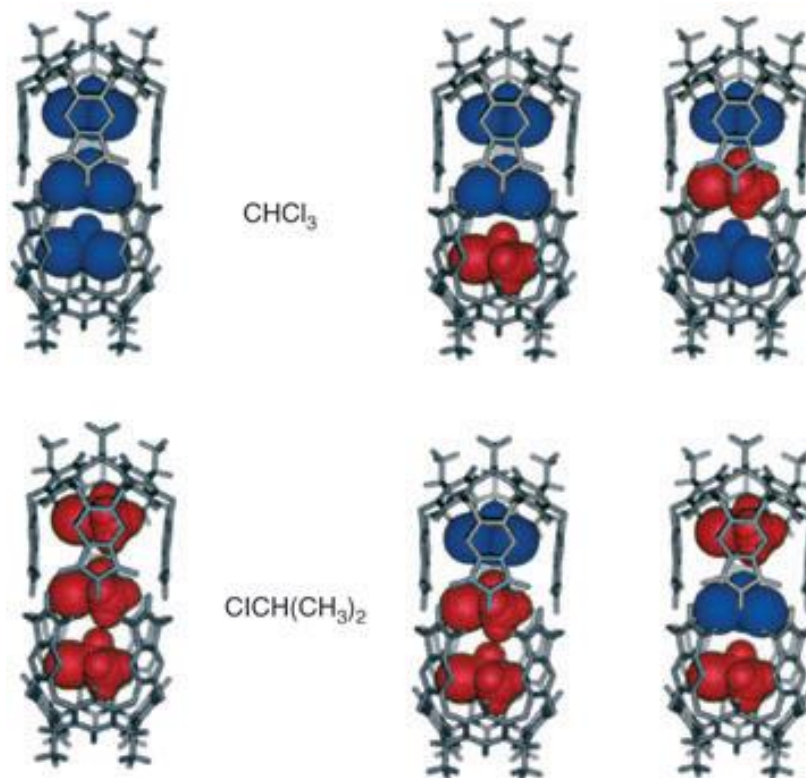
Social Isomers



MM optimized structures:
cloroformio e *para*-etiltoluene



Constellation Isomers

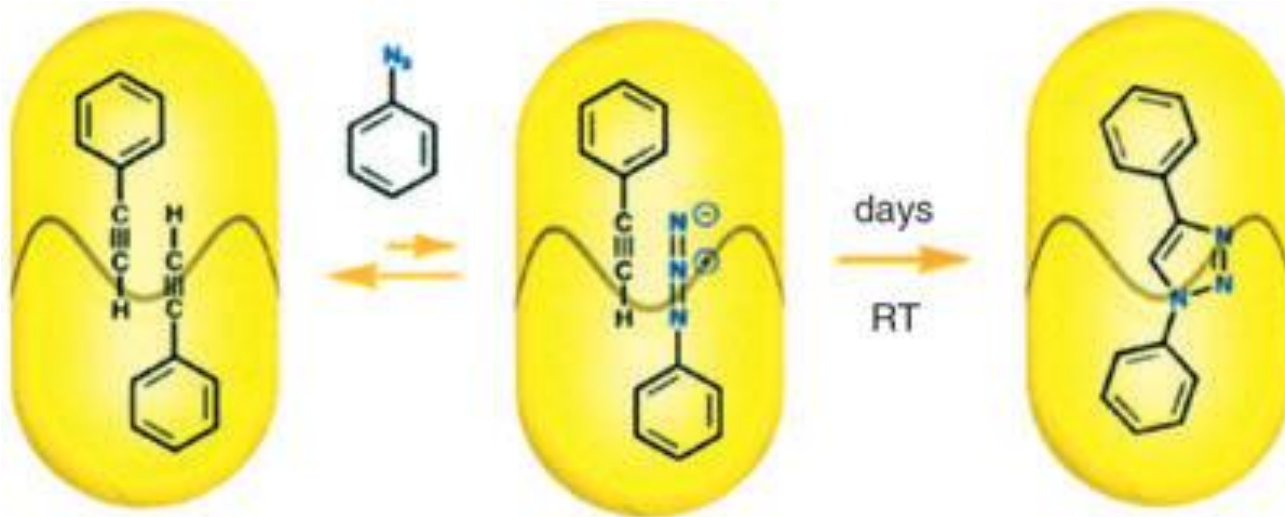


MM optimized structures:
cloroformio e *iso*-propilcloruro

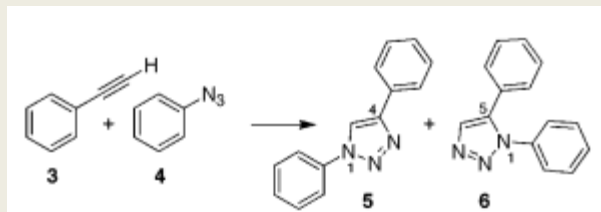
In addition to being able to preserve highly labile species, they may serve as catalysts and accelerate reactions inside their inner cavity by either concentrating the reactants leading to higher effective concentrations or TS stabilization or by preorganising them inside the capsule.

They may create a micro-environment in which two encapsulated reactants are held together in a orientation that differs from their most reactive arrangement in solution (or gas phase) leading to products that are disfavoured in equivalent solution phase reactions.

Reattività nelle capsule molecolari



Cicloaddizione 1,3 regioselettiva di fenilacetilene e fenilazide:



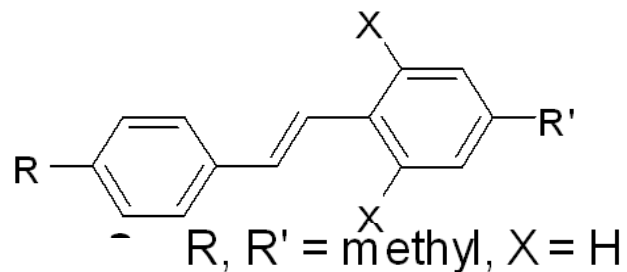
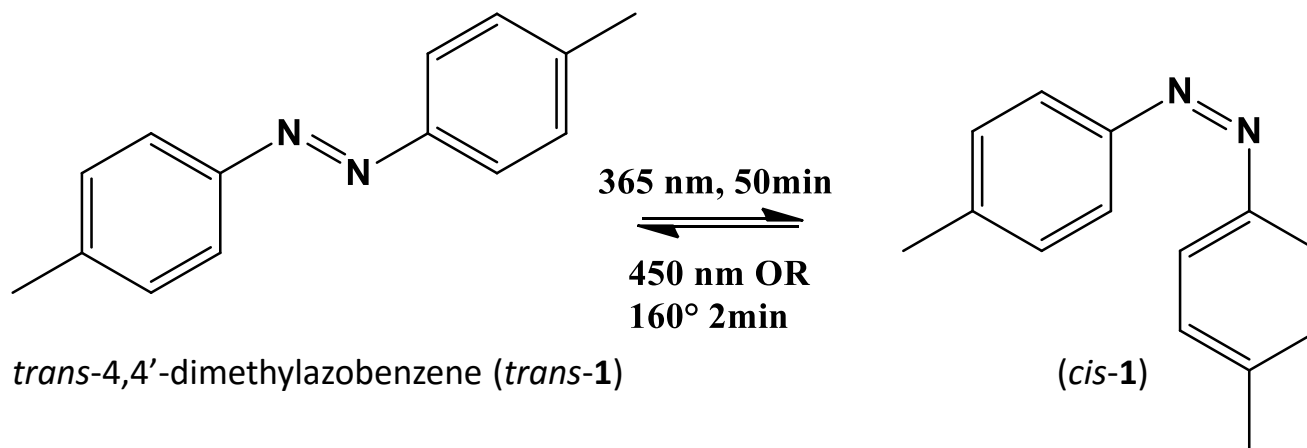
Volume definito = [] 4M vs mM

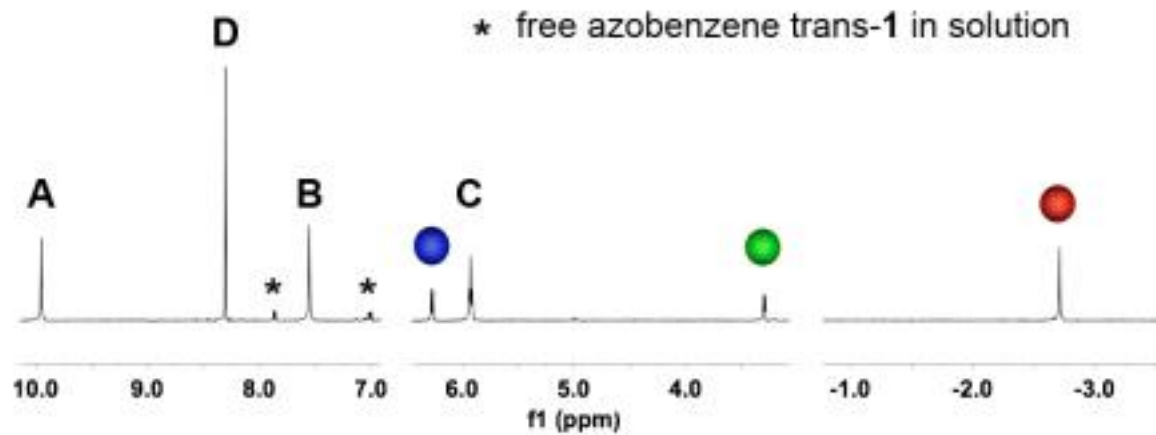
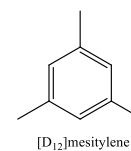
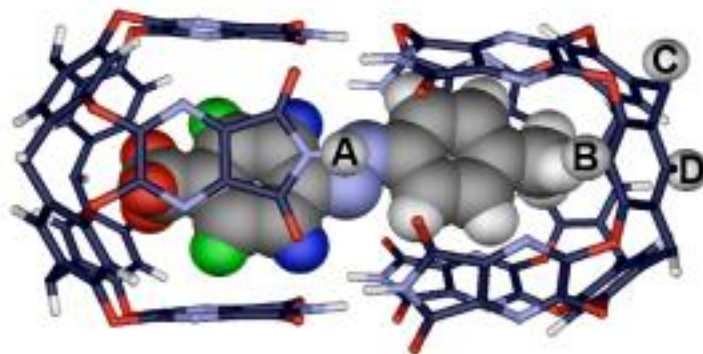
Tempo di contatto = 1 s vs 1 ns

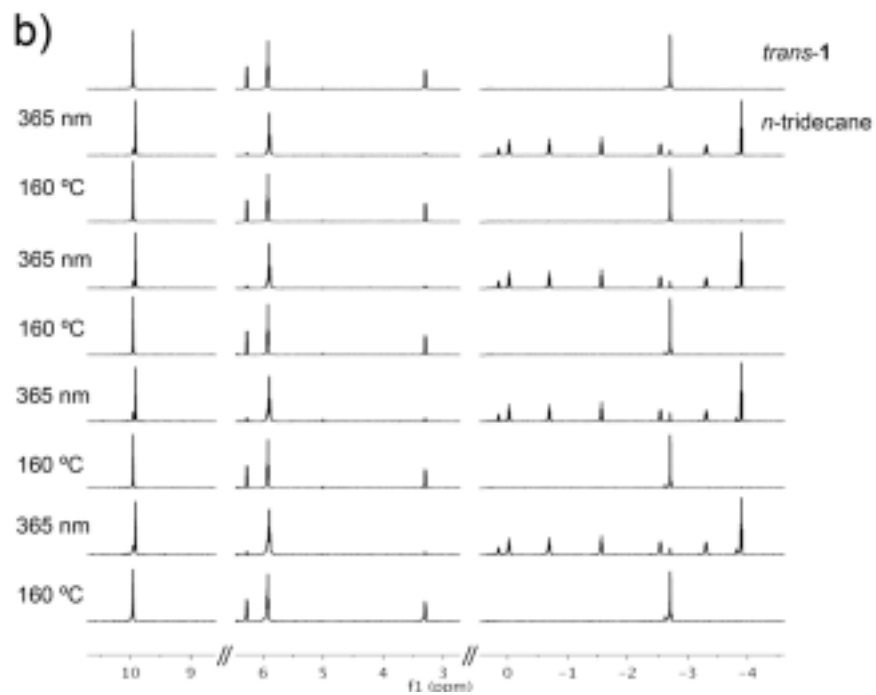
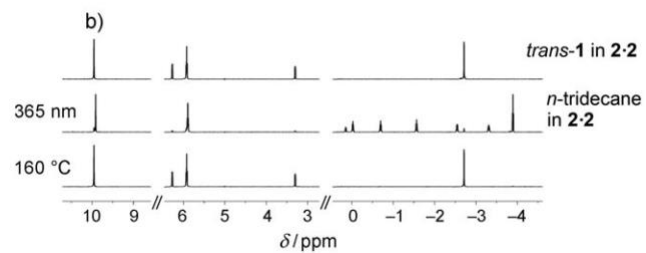
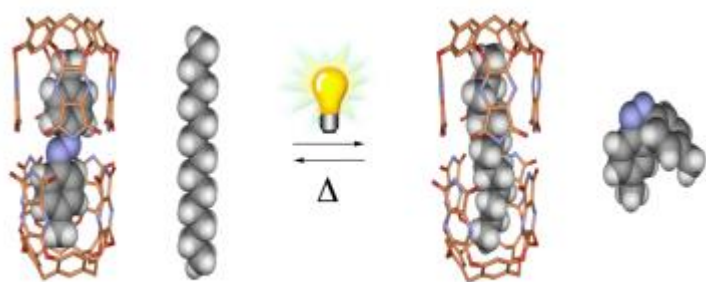
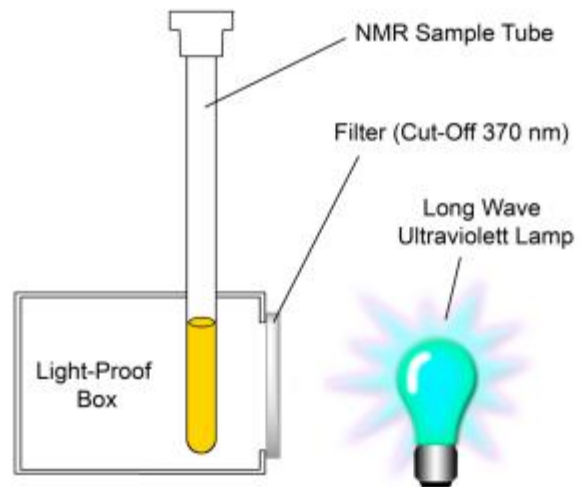
Solvatazione fissa

Photochemical Control of Reversible Encapsulation

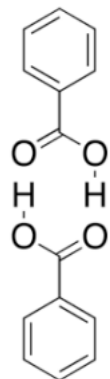
Henry Dube, Dariush Ajami, and Julius Rebek, Jr.*



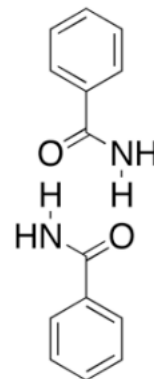




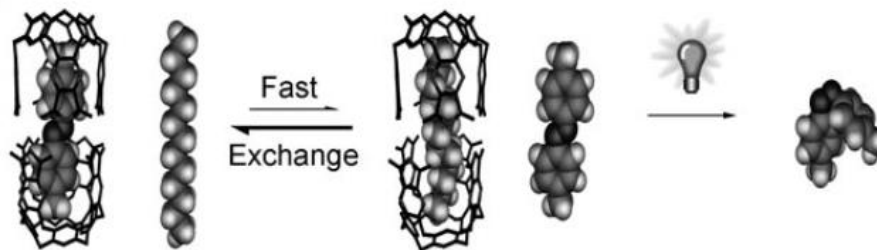
Guest =



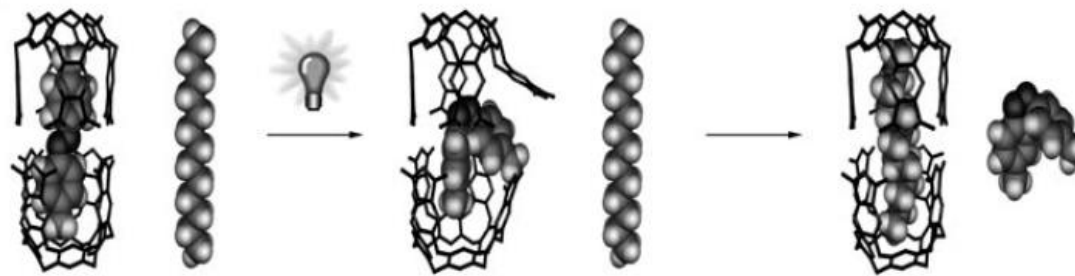
Guest =



a)



b)



Breakout

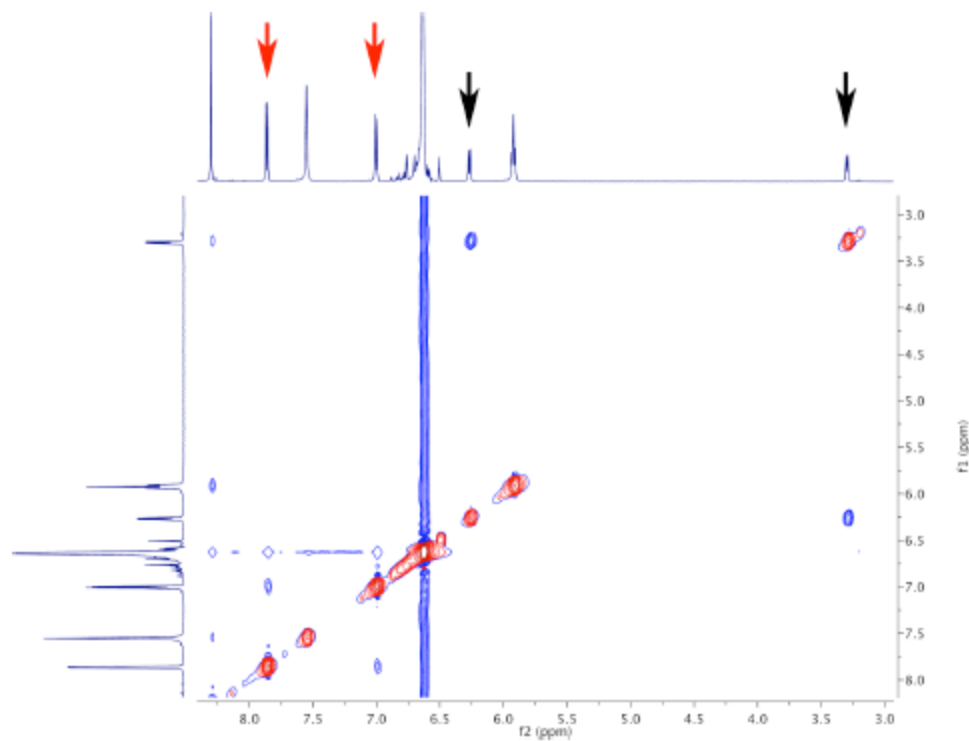
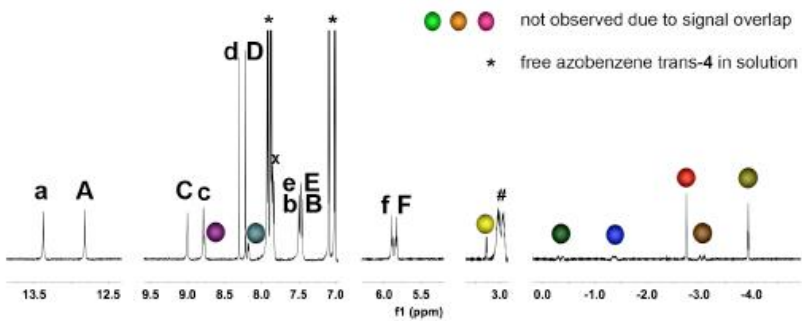
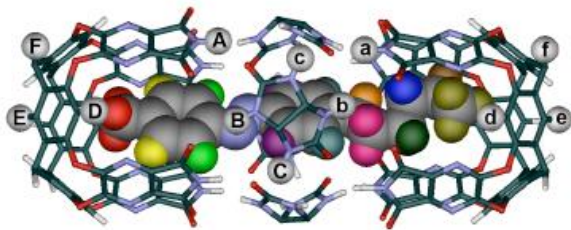
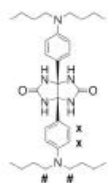
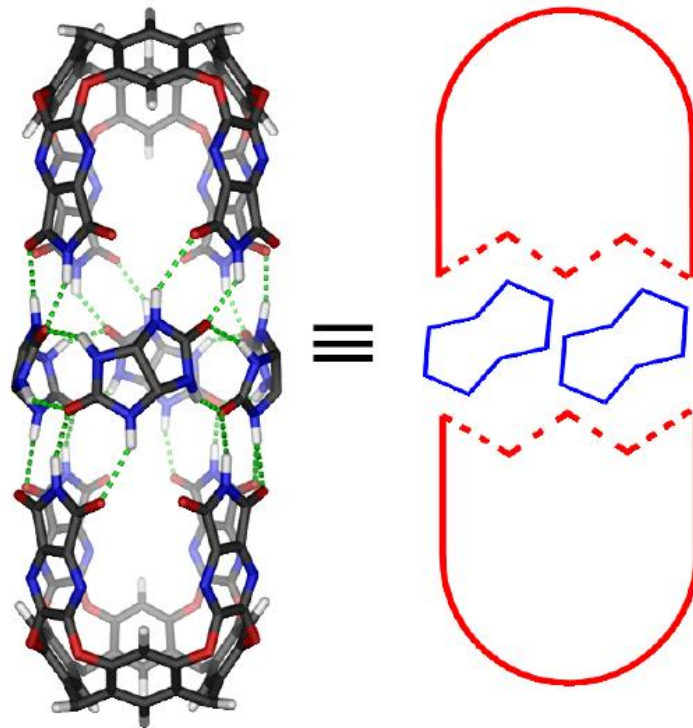
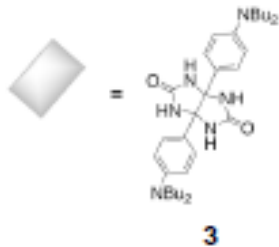
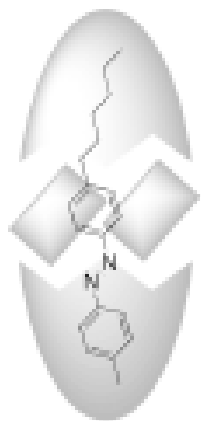
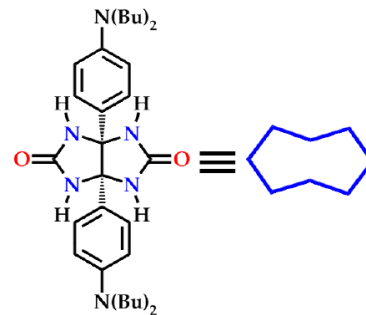


Figure 6SI: Partial ¹H NMR ROESY spectrum (mesitylene-*d*₁₂, 300 K, mixing time = 0.3 s, D1 = 1.5 s) of the host guest complex of *trans*-1 and 2·2 in the presence of 1.5 equiv. *trans*-1 free in solution. Red arrows assign the aromatic signals of free *trans*-1 whereas black arrows assign the aromatic signals of encapsulated *trans*-1. No exchange signals between these signals can be observed as the guest exchange is slow.

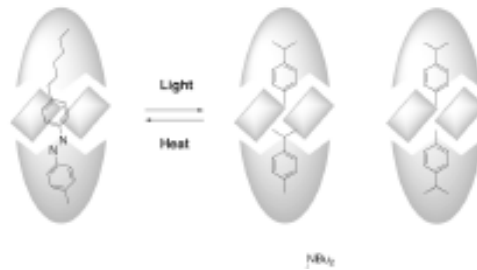
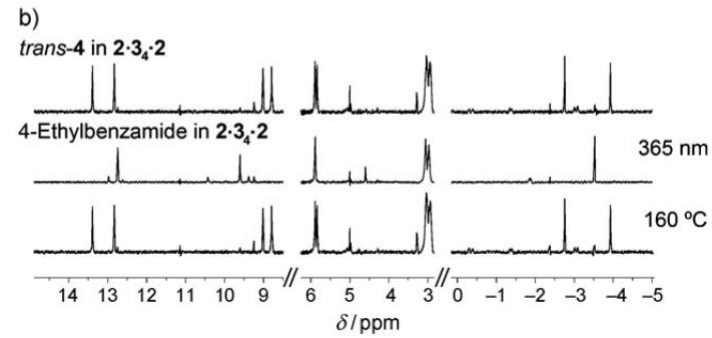
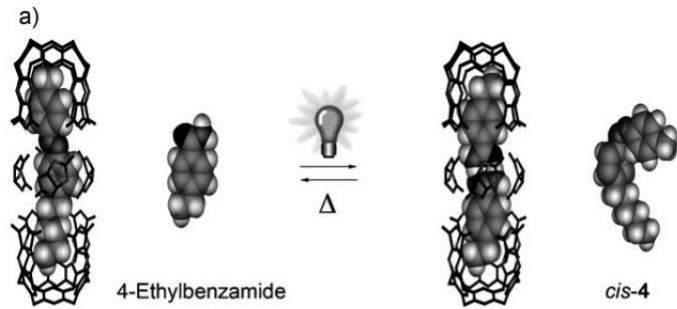
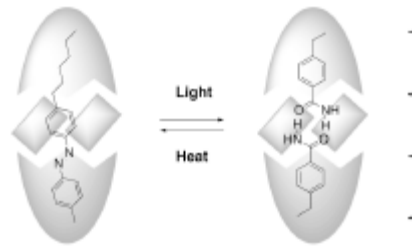


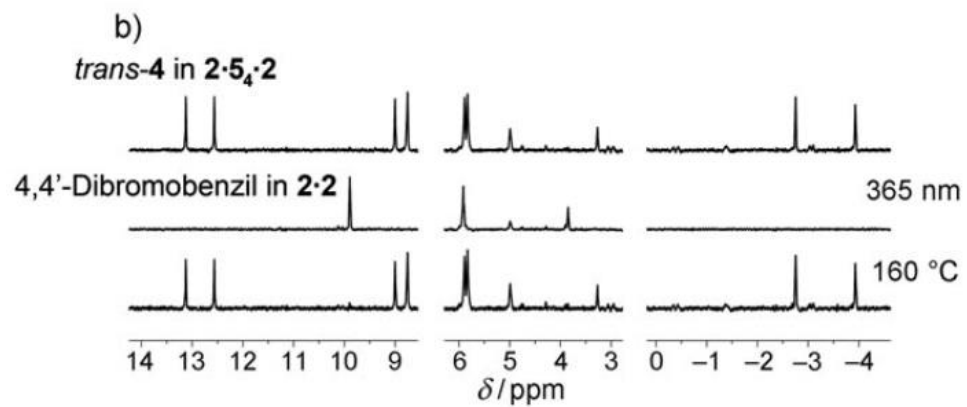
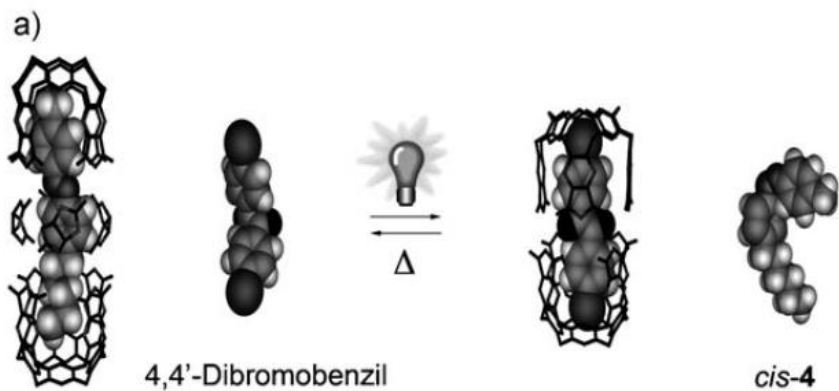
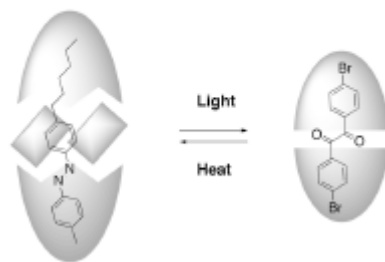
620 Å³

24 Å

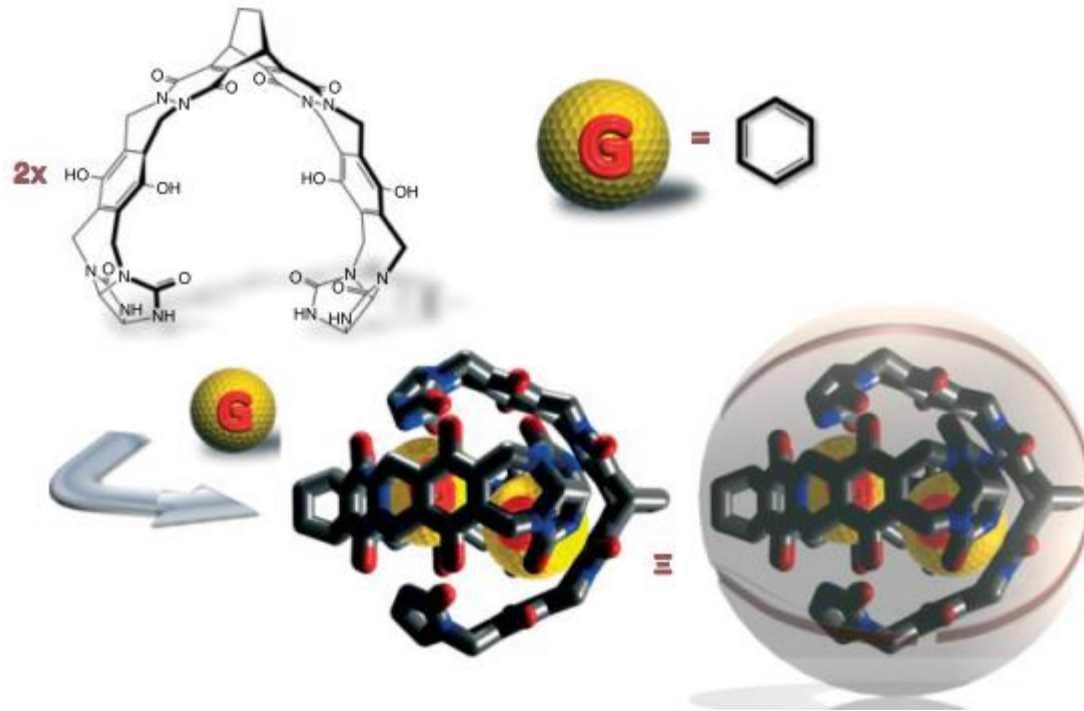


(B)



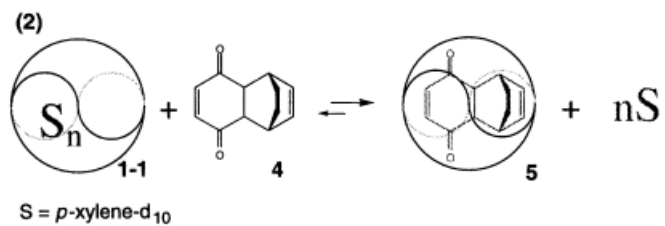
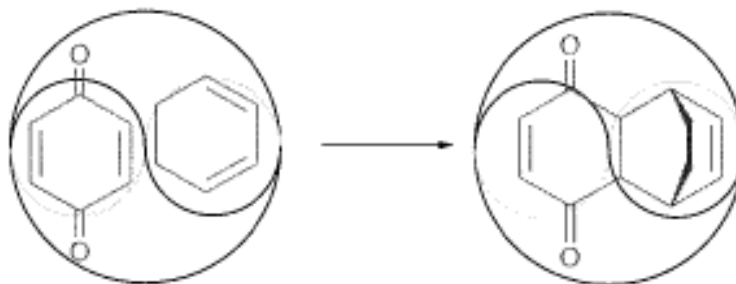
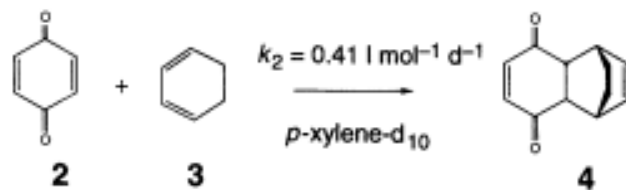


Soft Ball



V ca. 400 Å³

Reattività nelle capsule molecolari



Reattività nelle capsule molecolari

Cicloaddizione Diels-Alder acceleraz di ca. 200 volte

[] = 5M

Solvatazione

Tempo di contatto

