Invited Paper

Molecular Switching in Nanospaces

Henry Dube,[a] Fabien Durola,[b] Dariush Ajami[a] and Julius Rebek, Jr.[a]*
[a]*The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA*
[b]*Centre de Recherche Paul Pascal, CNRS - UPR 8641, 115 Avenue Schweitzer, 33600 Pessac, France*

Switching devices that operate on the molecular level lie at the heart of nanomachinery. The energies involved range from scores of kcal/mol during cleavage or formation of covalent bonds to a few kcal/mol when the signals are changes in conformation. Here we examine three systems that use light, metal/ligand binding, and acid/base chemistry as switching devices to transfer molecules in and out of the confined environments of encapsulation complexes or cavitands. The events are reversible and the original states can be recovered by treatment with brief heating, conventional chelating agents, or changes in protonation states, respectively. The control over these spaces augurs well for applications in drug delivery and sensors for small molecules.

Keywords: Azobenzene; Signaling; Cavitand; Reversible encapsulation; Photoisomerism.

LIGHT AND THE PHOTOISOMERIZATION OF AZOBENZENES

One of the earliest switching mechanisms applied in supramolecular chemistry is the *cis-trans* photoisomerization of azobenzenes. This isomerization changes the shape of the overall structure and atoms attached to the *p*- and *p*′-positions of the azobenzene move in a predictable way. This feature makes isomerism useful in many molecular devices[1,2] and azobenzenes have been attached to crown ethers,[3-5] cyclodextrins[6,7] and even proteins.[8,9] We used azobenzene photoisomerization in an indirect sense to control reversible encapsulation.

The cylindrical capsule **2**·**2** (Fig. 1) can bind several small guests[10] or a single longer guest including benzanilides,[11] *n*-alkanes[12] and stilbenes.[13] The encapsulation complex of 4,4′-dimethyl-*trans*-azobenzene (*trans*-**1**) with **2**·**2** involves a nearly ideal fit of the guest in the host.[14] Direct competition experiments in deuterated mesitylene show that *trans*-**1** is a much better guest than *n*-tridecane for the capsule: the upfield shift of the methyl singlet in the ^{1}H NMR spectrum confirms that only *trans*-**1** is bound and no *n*-tridecane is observed inside (Fig. 1b). Irradiation at a wavelength of 365 nm causes the folding to *cis*-**1** that no longer fits in the capsule. Accordingly, it "breaks out" of the capsule by forcing one or more walls outward and disrupting hydrogen bonds.[15] This facilitates the entry of other guest species, specifically *n*-tridecane, which is apparent from its characteristic widely-separated ^{1}H NMR signals when encapsulated (Fig. 1b). The NMR signals corresponding to the *cis*-**1** in solution appear at 6.59 ppm and 6.67 ppm. On heating this sample to 160 °C for 2 minutes, *cis*-**1** reverts to its *trans* conformation and rapidly replaces *n*-tridecane in the capsule. The irradiation/heating cycle can be repeated many times.

The ready replacement of *trans*-**1** on irradiation suggests that the encapsulation of any other potential guest can, in principle, be initiated by light. For example, a single guest often replaces two occupants in an entropy-driven process.[16] We used the photoisomerization to reverse these preferences. The hydrogen-bonded homodimers of benzoic acid or benzamide are good guests for **2**·**2** but when 3 equiv. of *trans*-**1** are present, only the azo compound is encapsulated. On irradiation the azo compound is quickly replaced by the respective dimers. Again, the initial state is restored after brief heating. This cycle can also be repeated many times without consequence. The ^{1}H NMR spectra recorded for substitution of azobenzene by benzamide are shown in Fig. 1b.

Kinetic studies confirmed that the isomerization of *trans*-**1** takes place inside of the capsule. The *cis* geometry

* Corresponding author. Tel: +858-784-2250; Fax: +858-784-287; E-mail: jrebek@scripps.edu

forces the capsule walls outward, and the "breakout" mechanism leads to guest exchange. The vase-to-kite conformational changes of cavitands[17] involve related outward wall motions and the mobility of only 2 walls is enough to enable guest exchange in these cases.[18] The rate of exchange of encapsulated azobenzene with *n*-tridecane as an incoming guest without irradiation was also determined. When 30 equiv. of *n*-tridecane compete with *trans*-**1** as a guest for the capsule, only 19% of *trans*-azobenzene is ultimately replaced at equilibrium. This endpoint is reached only after about 1,600 min, showing that the exchange is very slow. The slow exchange rates of similar shaped guests as determined by fluorescence methods are also fully consistent with these findings.[19]

The extended capsule **2**·$\mathbf{3}_4$·**2** (Fig. 2) was subjected to parallel experiments. Earlier, we showed that 4 molecules of highly soluble glycolurils such as dibutylaniline derivative **3** are incorporated into a new, extended capsule assembly when suitable guests are present.[20] We used a longer azobenzene *trans*-4-methyl-4′-hexyl-azobenzene[21] (*trans*-

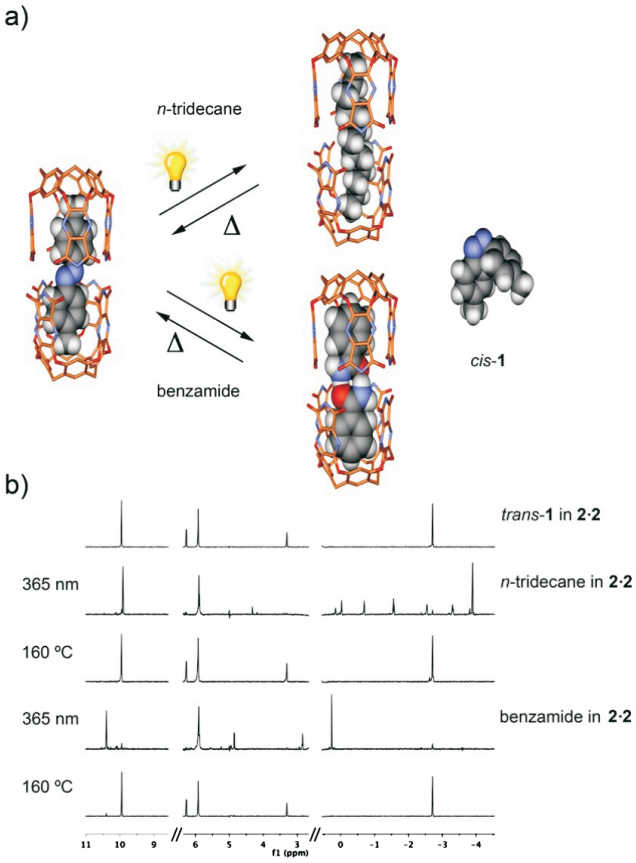

Fig. 1. (a) Light induced guest exchange of trans-**1** by n-tridecane or benzamide in **2**·**2**. Heating the sample restores the initial states. (b) Appropriate regions of the ^{1}H NMR spectra (mesitylene-d_{12}, 20 °C) are shown before irradiation (trans-**1** is the only guest) and after irradiation at 365 nm wavelength for 50 min at 20 °C (n-tridecane or benzamide is the only guest). After heating the sample to 160 °C for 2 min, the initial state is completely restored.

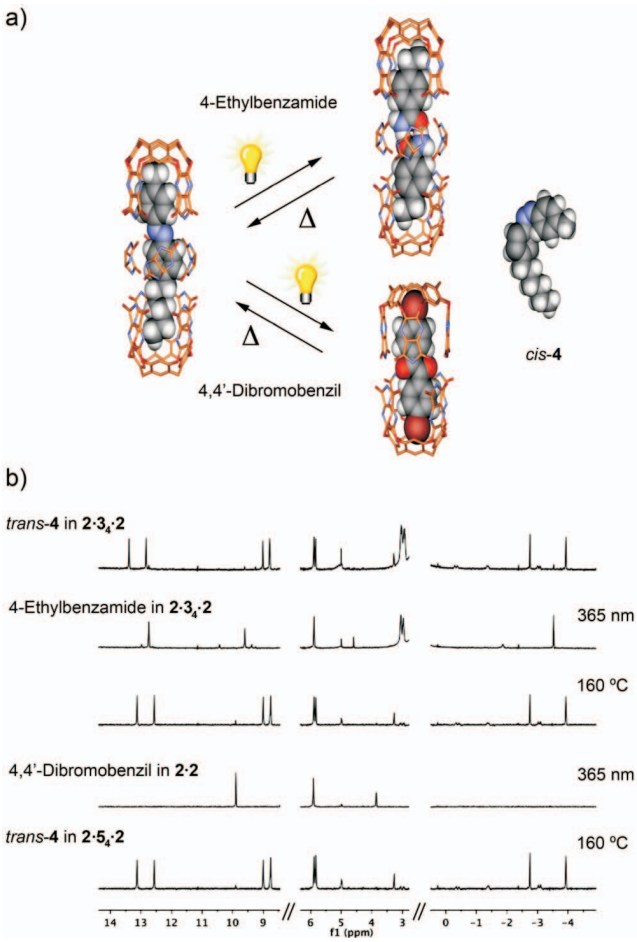

Fig. 2. (a) Light induced guest exchange of trans-**4** by 4-ethylbenzamide in the extended assembly **2**·$\mathbf{3}_4$·**2** and light induced guest exchange with concomitant change of assembly using trans-**4** as guest for **2**·$\mathbf{5}_4$·**2** and 4,4′-dibromobenzil as guest for **2**·**2**. b) Indicative regions of the ^{1}H NMR spectra (mesitylene-d_{12}, 20 °C) are shown before irradiation (trans-**4** is the only guest) and after irradiation at 365 nm wavelength for 50 min at 20 °C (the homodimer of 4-ethylbenzamide is the only guest in **2**·$\mathbf{3}_4$·**2** and 4,4′-dibromobenzil is the only guest in **2**·**2**). After heating the sample to 160 °C for 2 min, the initial state is completely restored.

4) as the light-responsive guest in the extended assembly **2**·**3**$_4$·**2**. Characteristic proton signals in the ^{1}H NMR spectrum are shown in Fig. 3b. The assembly is desymmetrized: the two cavitand ends show separate sets of ^{1}H NMR signals as do hydrogens on the two edges of the glycolurils. In a solution containing 10 equiv. of *trans*-**4** and 2 equiv. 4-ethylbenzamide only the azo compound is encapsulated. But after irradiation at 365 nm, the encapsulated homodimer of 4-ethylbenzamide has replaced the azo compound. This new assembly is C_2 symmetric and its spectrum is simplified accordingly. Heating the sample to 160 °C for 2 minutes restores the initial guest and the cycle can be repeated many times (see Fig. 2).

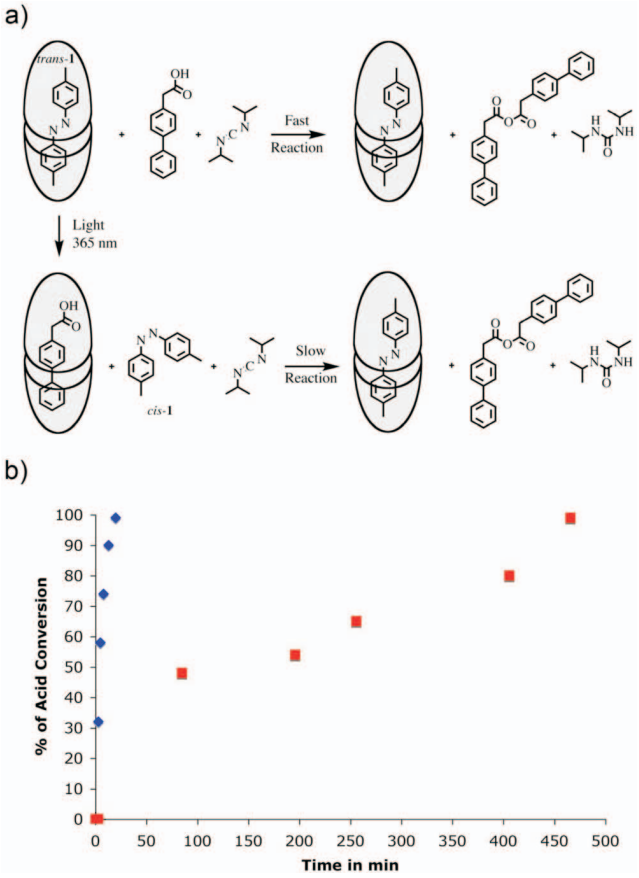

Fig. 3. (a) Light induced change of reaction kinetics of the dehydration of 4-biphenylacetic acid (0.8 mM) by DIC (14.4 mM) in the presence of trans-**1** encapsulated in **2**·**2** (1.2 mM) in mesitylene-d_{12} at 20 °C. (b) Diamonds show conversion when the sample is not irradiated. Squares show conversion after the sample was irradiated with 365 nm light for 50 min prior to addition of DIC. A 23-fold rate decrease was observed.

Finally, we could use photoisomerization as a remote control to switch between different assemblies **2**·**2** and **2**·**5**$_4$·**2**. The 4-dodecanephenyl glycoluril **5** has low solubility in deuterated mesitylene alone but is soluble when it is incorporated into a capsular assembly. Heating a mixture of **2**, glycoluril **5** and 3 equiv. of *trans*-**4** leads to formation of the extended assembly **2**·**5**$_4$·**2** with the azo compound as the only guest. The same assembly is also formed in the presence of additional 4,4′-dibromobenzil – a mediocre guest for **2**·**2**. After irradiation of the mixture for 50 min at 365 nm, only the capsule assembly **2**·**2** is obtained with 4,4′-dibromobenzil as guest. The precipitation of **5** from solution is observed and doubtless enhances the disproportionation process. The original extended assembly **2**·**5**$_4$·**2** is restored on heating the turbid solution for 2 min to 160 °C, with *trans*-**4** reappearing as the only encapsulated species (see Fig. 2). Again, this cycle can be repeated many times. Accordingly, the photochemical control can alter the nature of the capsule assemblies.

A possible application for this system involves using the photoisomerism of an azo guest to manipulate chemical reactions not known to be photoresponsive. In order to test the influence of light on the kinetics of such a reaction, we chose the dehydration of carboxylic acids by carbodiimides. When a mixture of 4-biphenylacetic acid and the encapsulation complex of *trans*-**1** in **2**·**2** is treated with 18 equiv. of *N*,*N*′-diisopropylcarbodiimide (DIC) the reaction is complete after 20 min. If the mixture is irradiated for 50 min at 365 nm prior to addition of DIC the reaction rate decreases significantly (23-fold). Irradiation leads to encapsulation of the acid and the reaction kinetics are limited by the slow release of the acid from the capsule as shown in Fig. 3.

In summary, the cis/trans photoisomerization of azobenzenes continues to be a reliable switching mechanism in supramolecular chemistry. The azo compounds are spectators that indirectly control encapsulation of alkanes, dimeric amides and an long acid.

METAL CHELATION AND BIPYRIDYL ROTORS

Molecular devices are notional versions of macroscopic objects that reproduce on the nanoscale functions that are familiar on the macroscale:[22] self-assembled capsules act as reaction flasks;[23] catenanes and rotaxanes are shuttle-like machines;[24] encapsulation complexes can be spring-loaded[25] and many nanomachines are biaryl rotors.[26] On/off switches involving extension/contraction

motions are among the oldest[27] molecular devices[28] and machinery[29] and they continually appear in the recent literature.[30] Earlier we introduced bipyridyl rotors as chemical expressions of the Pauling principle for enzyme catalysis[31] – with maximum binding at the transition state – and models for the allosteric behaviour of proteins: how binding information at a remote site can alter the behaviour of an active site (Fig. 4).[32]

Since then, biaryl rotors have become much-admired as nano devices,[33] particularly in the context of forced unidirectional rotation.[34-36] In supramolecular chemistry there are delightful examples by Lehn involving metal chelation that result in changes resembling flapping motions,[37] and Lützen[38] who controlled the chelation of guests with two cavitands attached to a bipyridyl. The reliability of the bipyridyl rotor system made it irresistible for us to combine it with the synthetic receptors currently pursued in the laboratory. We prepared a resorcinarene-based deep cavitand with one wall functionalized[39] as a bipyridyl linked to a cyclohexyl group.[40] When the linker is long enough and flexible, an intramolecular host/guest complex results (Fig. 5). The appropriate filling of space is one of the key determinants for the binding of guests in these cavitands. Cyclohexane is ordinarily a modest guest but it enjoys an entropic advantage by being covalently bound and it prevents entry of external guests.

We called this deep cavitand an "Ouroborand" as

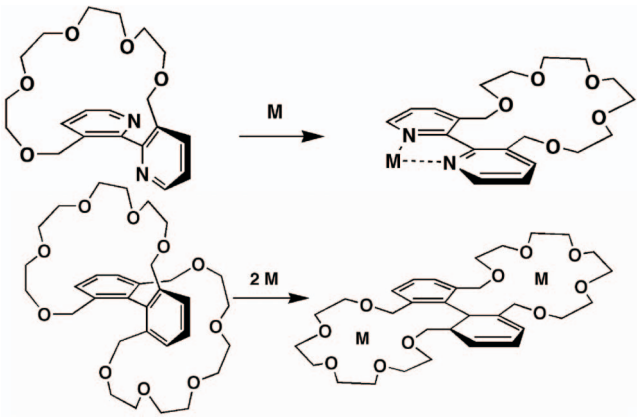

Fig. 4. Molecular rotors as allosteric effectors in chemistry. Top: Binding of transition metals at the bipyridine restricts the conformation of the crown ether and alters the ether's transport selectivity for alkali ions. Bottom: Binding of an ion at one site fixes the biaryl dihedral angle and organizes the second site for enhanced binding.

Ouroboros ("tail-eater" in Greek) is an ancient symbol representing a serpent swallowing its own tail. Ouroboros was

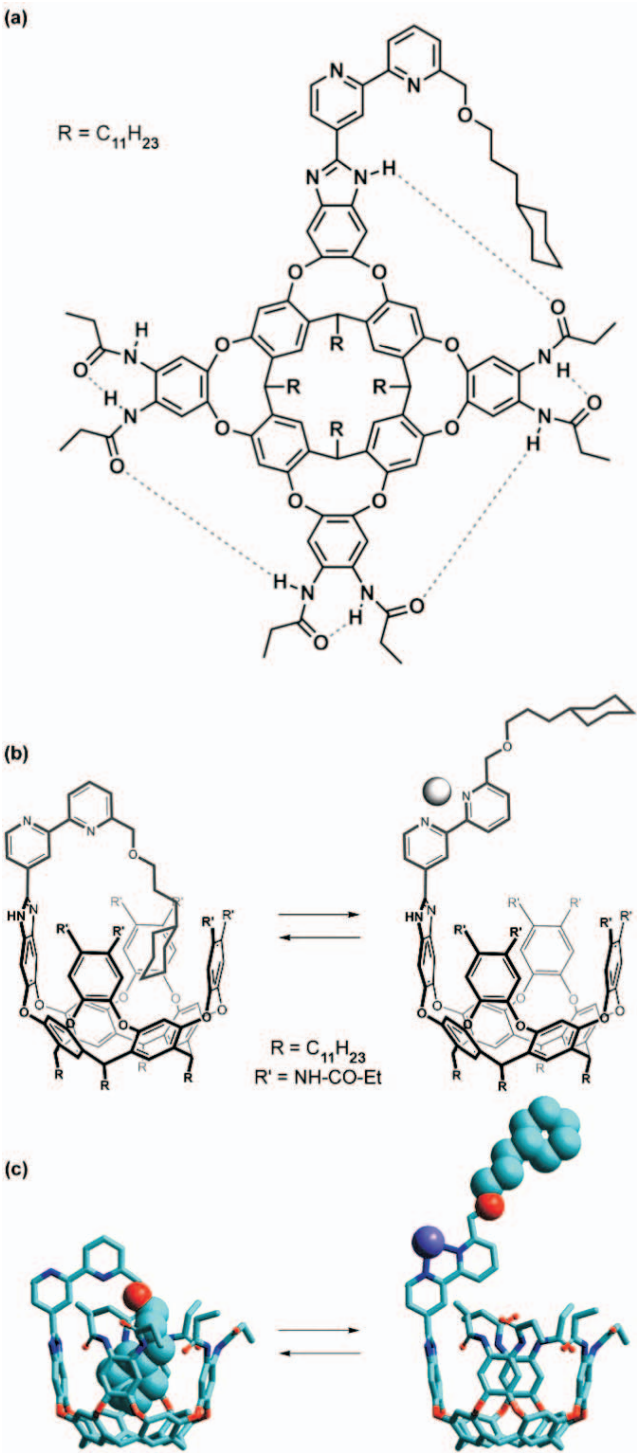

Fig. 5. Representations of the ouroborand; (a) planar formula and (b) perspective views with the bipyridine ligand free or chelating a metal center; (c) energy minimized structures.

used to describe self-threading molecules[41] and it is widely believed to have inspired Kekule's formulation of benzene, nearly 150 years ago.

The favored conformation of the free bipyridine of the cavitand, is *anti* and allows the cyclohexyl to reach the cavity (Fig. 6 config. A). When a metal ion is chelated by the bipyridine, a conformational change is forced that pulls the guest out the cavity (config. B). Now the cavity is open to an external guest such as an adamantane derivative (config. C). When the metal ion is removed, the adamantane is released (config. D) and the initial configuration is restored. Accordingly, metal coordination-driven switching opens or closes access of guests to the cavity.

The behavior of this molecule was monitored by ^{1}H NMR. Integration of the upfield NMR signals in mesitylene-d_{12} revealed that all cyclohexyl hydrogens of the ouroborand and even a part of the linker chain are located in the cavity (Fig. 8a). The head-to-tail arrangement of the secondary amides on the rim the cavitand is directional (clockwise or counterlockwise) and the cavitand exists as 2 cycloenantiomers. Interconversion of these cycloenantiomers (racemization) is slow on the NMR timescale, and the pattern of signals corresponding to the pyridine-CH_2-O protons shows them to be diastereotopic with a large coupling constant (Fig. 7a). The simplicity of the spectra excludes dimeric or oligomeric assemblies where a cyclohexyl of one ouroborand is the guest of another. Acetone-d_6 is also unable to displace the intramolecular guest (Fig. 7b). In the smaller dichloromethane-d_2 (at a concentration of ~10 M) the solvent molecule competes for the cavitand.

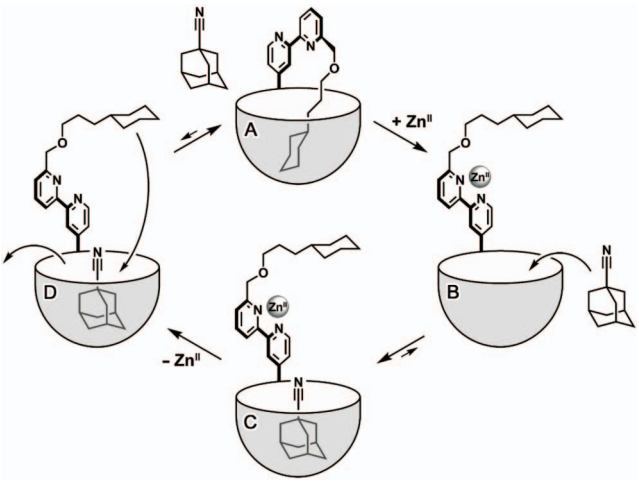

Fig. 6. Reversible mechanism of the coordination controlled guest exchange in the ouroborand's cavity.

(Fig. 7c) and some cyclohexyl groups are forced out of the cavity: a broadened singlet appears for these pyridine-CH_2-O protons, as they are now remote from the asymmetric nanoenvironment. When the very good guest THF-d_8 is used as the solvent more than 80% of the cavitands contain THF molecules, but some 20% are still cling to the cyclohexyl "tail" (Fig. 7d).

We realized the reversible switching process in 80%

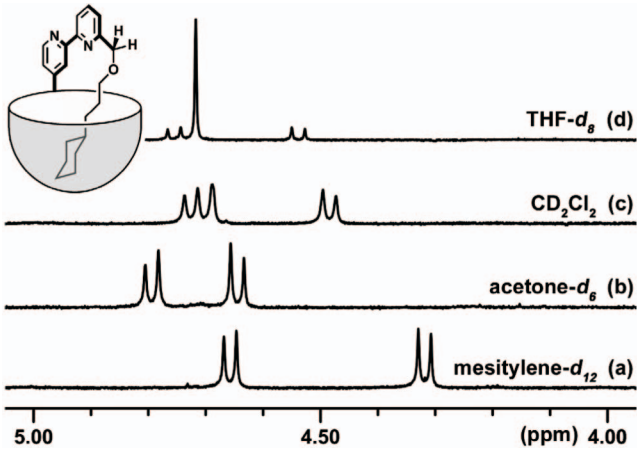

Fig. 7. NMR signals of the pyridine–CH_2–O protons when the ouroborand is solubilized in deuterated (a) mesitylene, (b) acetone, (c) dichloromethane or (d) THF. Doublets correspond to the cartoon shown whereas singlets correspond to solvent-occupied cavitands.

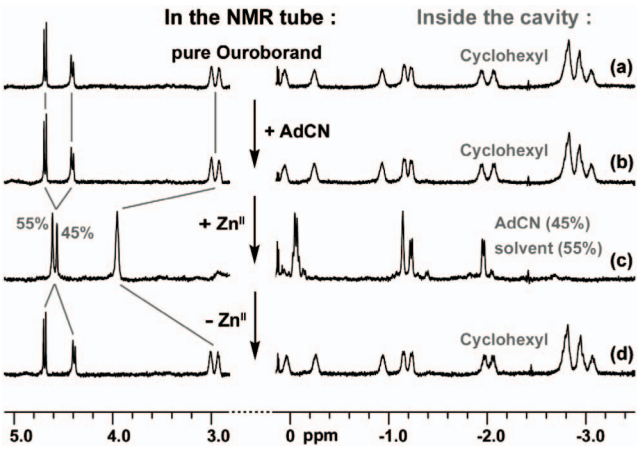

Fig. 8. NMR study of the coordination-triggered switch and guest-exchange of the ouroborand; (a) pure ouroborand in mesitylene-d_{12} (80%) and CD_3CN (20%); (b) 10 eq. AdCN added in the NMR tube; (c) 10 eq. $ZnBr_2$ added in the NMR tube; (d) water added to the NMR tube, then extraction and drying on Na_2SO_4.

mesitylene-d_{12} and 20% acetonitrile-d_3 (required to dissolve the metal complexes). Excess amounts of the free guest, 1-adamantane-carbonitrile (AdCN) and $ZnBr_2$ as the metal were necessary for observation of reversible switching between the two states. Fig. 8 shows the ^{1}H NMR spectra during the steps of the switching cycle: The resting state with internal cyclohexyl (Fig. 8a); Addition of 10 equiv. of AdCN to the NMR solution (no changes, Fig. 8b); Addition of 10 equiv. of $ZnBr_2$, the cyclohexyl tail is now outside the cavity, replaced in almost half of the molecules by an adamantane-based guest (Fig. 8c); Extraction of the NMR sample with water (Fig. 8d), the spectrum returns to the one after addition of AdCN (Fig. 8b). The zinc ions were washed out, and allowed the system to revert to the ouroborand state.

ACID/BASE CONTROL OF A SPRING-LOADED DEVICE

We recently engineered an alternative to the rotor using a system that involves linear motions of expansion and contraction. Above, we described the cylindrical capsule **2·2** and **2·3$_4$·2** (Figs. 1 and 2) and some of their encapsulation complexes in organic solvents. A number of studies with this capsule have defined its capacity[42] but the most peculiar guests encountered to date have been the normal alkanes,[43] guests that can adopt shapes complementary to their hosts. We took advantage of this conformational flexibility of normal alkanes and applied their extended and compressed shapes to create a "spring-loaded" device.

Alkanes as long as tetradecane (n-C_{14}) are encapsulated in **1** but longer alkanes, such as n-C_{15} are not accommodated at all – there is no way they can contort to fit inside. But even C_{14} cannot fit in an extended conformation; instead it must adopt a compressed one.[44] This reduces its length about 5 Å, just enough to be accommodated and the compression makes the guest molecule shorter and thicker. As a result, attractive CH-interactions are enhanced between hydrogens on the alkane's surface and the 16 aromatic panels that define the lining of the capsule (Fig. 9). This coiling is not without an energetic penalty because each *gauche* interaction (in the liquid phase)[45] destabilizes the structure by some 0.55 kcal/mol. Evidently this price is paid by the attractive forces and the release of solvent mol-

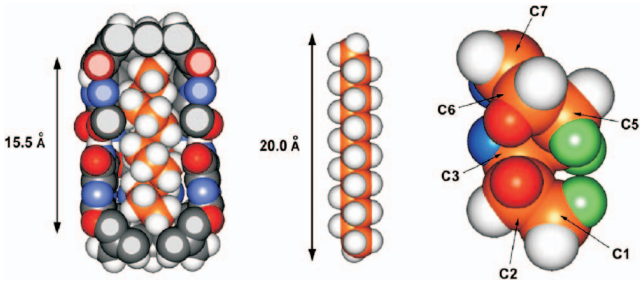

Fig. 9. Dimensions of n–C_{14} in extended (left) and encapsulated (center) conformations. The relevant crosspeaks of the 2D NMR spectra are color coded on the model of a helically coiled conformation (right).

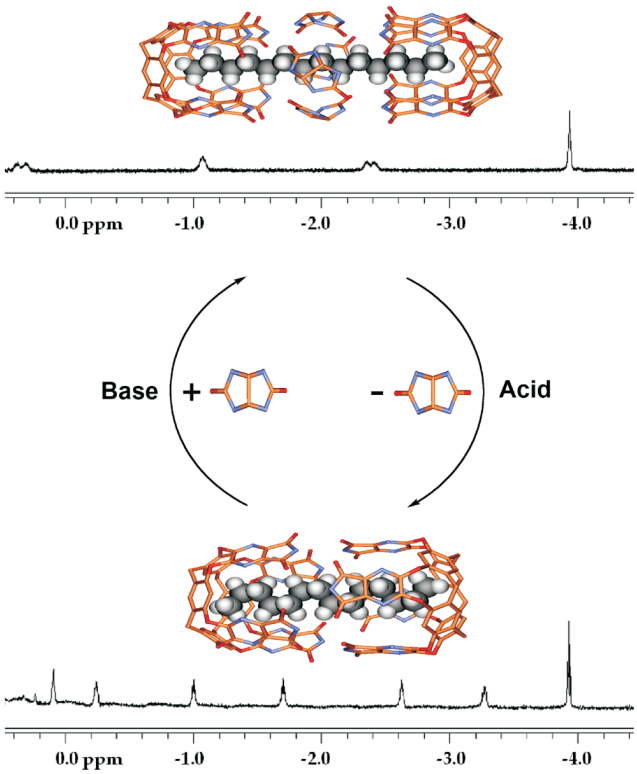

Fig. 10. The reversible compression and expansion of encapsulated n-tetradecane in the expanded capsule **2·3$_4$·2** (top) and the capsule **2·2**. The coiled and the extended conformations of tetradecane are evident from the upfield regions of the ^{1}H NMR spectra which are shown together with the respective host guest complexes. The signals move downfield as tetradecane is extended and the methylenes move away from the capsule's walls and toward its center. The chiral nature of the expanded assembly is reflected in the diastereotopic protons of the methylenes. The glycolurils insert under basic conditions and allow the guest to relax in **2·3$_4$·2**. Acid precipitates the glycouril and regenerates the capsule **2·2** with coiled tetradecane inside.

ecules during the encapsulation of the alkane. The specific conformation was deduced from two-dimensional NMR studies that show the close proximity of hydrogens on C_1 to C_5, C_2 to C_6, etc. *These indicated a coiled, helical conformation*.[46]

The glycolurils that insert into the capsule/tetradecane complex increase the length of the capsule **2**·$\mathbf{3_4}$·**2** by some 7 Å and the volume by nearly 50% and form a new belt of hydrogen bond donors and acceptors at the center of the assembly.[47] Accordingly, tetradecane relaxes into an extended conformation in the expanded capsule **2**·$\mathbf{3_4}$·**2** and this is evident by changes in the ^{1}H NMR spectrum. The methylenes of the alkane in the new capsule move away from the walls and toward the center of the structure. *Their NMR signals move downfield*. The tetradecane in the original vs the expanded capsule shows very different NMR spectra as featured in Fig. 10.

The insertion of four glycolurils constricts the center of the cavity in **2**·$\mathbf{3_4}$·**2** and creates a chiral space. This is reflected in the diastereotopic protons seen, for example, at C_2 of the alkane guest. The system reverts to the original capsule through addition of a guest such as benzanilide, which is nearly ideal in size for **2**·**2**. These changes take place on mixing at the millimolar concentrations used for the NMR studies. But the *gauche* interactions of the coiled alkane must exert some force on the capsule's interior as the alkane tries to extend to the lower energy conformation of antiperiplanar C-C bonds.

We worked to control the coiling and extension of the alkane from the outside by addition of acid and bases. A glycoluril was prepared that had remote basic sites, a dibutylaniline derivative.[48] It showed excellent solubility in mesitylene-d_{12}, the solvent of choice for these NMR studies as it is the largest commercially available deuterated solvent. The coiled alkane in the original capsule is not unlike a compressed spring and addition of the glycoluril allows the guest to relax and extend in the longer capsule **2**·$\mathbf{3_4}$·**2**. However, HCl gas bubbled into the NMR solution protonates the basic sites of the glycoluril and causes it to precipitate. This treatment regenerates the original capsule **2**·**2** with the coiled alkane inside. Next, trimethylamine was introduced into the NMR sample. This base deprotonates the glycoluril, which re-enters the solution and expands the capsule to **2**·$\mathbf{3_4}$·**2**. Then acid is added to regenerate **2**·**2** (Fig. 10). Some six cycles of acid/base treatment were possible in a single NMR tube before the buildup of trimethylamine hydrochloride began to distort the ^{1}H NMR spectra. The acids and bases control the reversible compression and relaxation of *n*-tetradecane.

It came as no surprise that the expanded capsule could

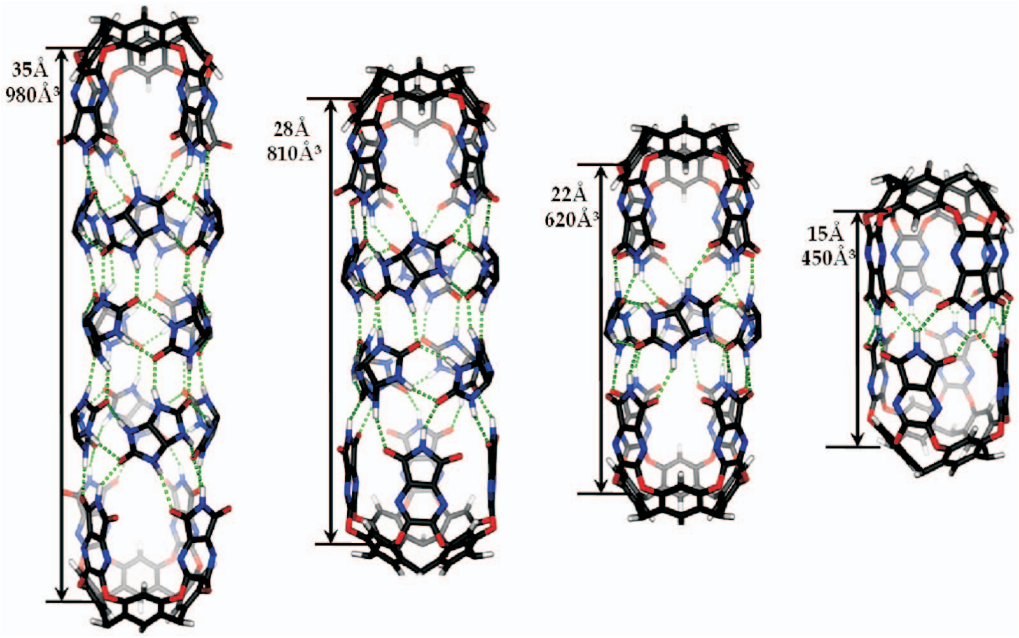

Fig. 11. Energy minimized structures and approximate dimensions of capsules extended by glycolurils. The length refers to the accessibility of methyl groups in the inner space as determined by semiempirical methods. Peripheral groups have been removed for viewing clarity.

accommodate normal C_{15}, C_{16}, C_{17}, C_{18} and C_{19}. What was unexpected was the emergence of yet another capsule in the presence of C_{19}. A new capsule was formed that involved *two* belts of glycolurils: a double expansion had taken place.[49] This new hyperextended capsule $\mathbf{2}\cdot\mathbf{3}_{\mathbf{8}}\cdot\mathbf{2}$ (Fig. 11) also accommodated some natural products such as capsaicin and anandamide. The latter is the endogenous ligand for the cannabanoid receptor of the brain.[50]

We tested even longer hydrocarbons such as C_{24} to C_{29} and found another encapsulation complex involving *three* glycoluril belts. The complete assembly comprises 15 molecules and there is evidence of coiling with the longer guests.

This behavior promises that spring-loaded capsules of additional complexity can be devised in the future. For the present, preliminary results reveal that even longer capsules can be made with the simple recipe of **2**, glycoluril **3** and ever longer alkanes. Is there a limit? We have reason to think there is not. The multitude of forces that drive such complex self-assembly are currently under investigation in our laboratories and will be reported in due course.

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