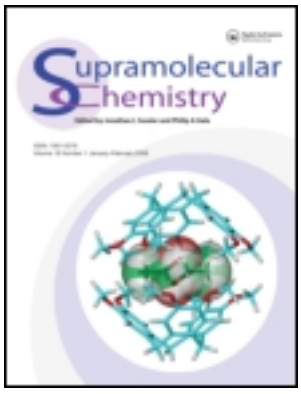

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Control of nanospaces with molecular devices

Fabien Durola [a] , Henry Dube [b] , Dariush Ajami [b] & Julius Rebek Jr [b]

[a] Centre de Recherche Paul Pascal, CNRS, UPR 8641, 115 Avenue Schweitzer, 33600, Pessac, France

[b] The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037, USA

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Control of nanospaces with molecular devices

Fabien Durola[a], Henry Dube[b], Dariush Ajami[b] and Julius Rebek Jr[b]*

[a]*Centre de Recherche Paul Pascal, CNRS, UPR 8641, 115 Avenue Schweitzer, 33600 Pessac, France;* [b]*The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*

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Cavitands and capsules define nanolitre spaces for recognition, isolation and reactions of small molecules. These systems are usually self-assembled and factors such as solvent size, stoichiometry and packing factors determine what goes into the spaces. Here, we examine two switching devices to control what and when guests get in and out of these hosts: bipyridyl-metal chelation and azobenzene photoisomerisation. The effects are reversible by treatment with conventional chelating agents and brief heating, respectively. Accordingly, it is possible to trigger reactions that take place within a cylindrical capsule by light, even though the reaction process is not photochemical by nature. Likewise, the presence of metals can regulate reactions without acting as direct catalysts.

Keywords: cavitand; molecular switch; photoisomerism; capsules

1. Bipyridyl rotors and metals

Molecular devices reproduce on the nanoscale level motions and even real machines familiar on the macroscale (*1*). Some time ago, we introduced bipyridyl rotors as chemical models for the allosteric effects in proteins (*2*), and even today biaryl rotors appear in many nanomachines (*3*). Metal chelation of bipyridyls is accompanied by predictable changes in conformation, and in supramolecular systems, this reliability has led to flapping motions (*4*) and controlled convergence of host on a guest (*5*). In molecular machinery, this rotor system is frequently used (*6*) as a switching device (*7*). We describe here its application in the context of cavitand complexation (*8*).

We outfitted a deep cavitand bearing a bipyridyl function and covalently tethered to it a cyclohexyl group (*9*) that allowed an intramolecular host–guest complex to form (Figure 1). Although cyclohexanes are generally poor guests for this cavitand, the case at hand enjoys a huge entropic advantage and it prevents the entry of external guests. It may rightly be regarded as an introverted function (*10*) but we called it a tail-eating arrangement – an 'Ouroborand' – as suggested by the armadillo lizard and Ouroboros, an ancient symbol that represents a serpent swallowing its own tail.

An ouroboros famously inspired Kekule's formulation of benzene and was recently used to describe self-threading molecules (*11*). In the resting state of the cavitand, the cyclohexyl tail can reach the cavernous mouth (Figure 2, config. A) because the configuration of the bipyridine is *anti*. When a metal ion is chelated and forces a *syn* bipyridine conformation, the guest is jerked out of the host (config. B). This allows access of an external guest, in this case, an adamantane derivative (config. C). Removal of the metal ion restores the initial configuration after adamantane is released (config. D).

As a reflection of the entropic advantage enjoyed by the intramolecular host–guest complex, attempts to completely replace the tethered guest with various solvents, as external guests, were unsuccessful. Specifically, acetone showed no displacement of the cyclohexyl, dichloromethane displaced some 20% and tetrahydrofuran forced out only 80%, even though these solvents are present at ~10 M concentration. The reversible cycle of events was realised in a solvent mixture that dissolved the metal complexes: 80% mesitylene-d_{12} and 20% acetonitrile-d_3. The ^{1}H NMR spectra are shown during the switching cycle. They comprise the resting state with internalised cyclohexyl (Figure 3(a)); the addition of excess AdCN shows no changes (Figure 3(b)); but then the addition of excess $ZnBr_2$ pulls the cyclohexyl tail out of the cavity with AdCN now inside almost half of the free cavities (Figure 3(c)); washing the NMR sample with water to remove the zinc ions returns the system to that seen after the addition of AdCN (Figure 3(d)).

2. Photoisomerisation of azobenzenes

Shinkai and co-workers introduced the photoisomerisation of azobenzenes to supramolecular chemistry in 1979 (*12*), and it continues to be applied in many of today's molecular devices (*13*, *14*). The isomerisation of the long and narrow *trans*-**1** (Figure 1) causes its predictable folding to the shorter and wider *cis*-**1**. For the cylindrical capsule **2**·**2**

*Corresponding author. Email: jrebek@scripps.edu

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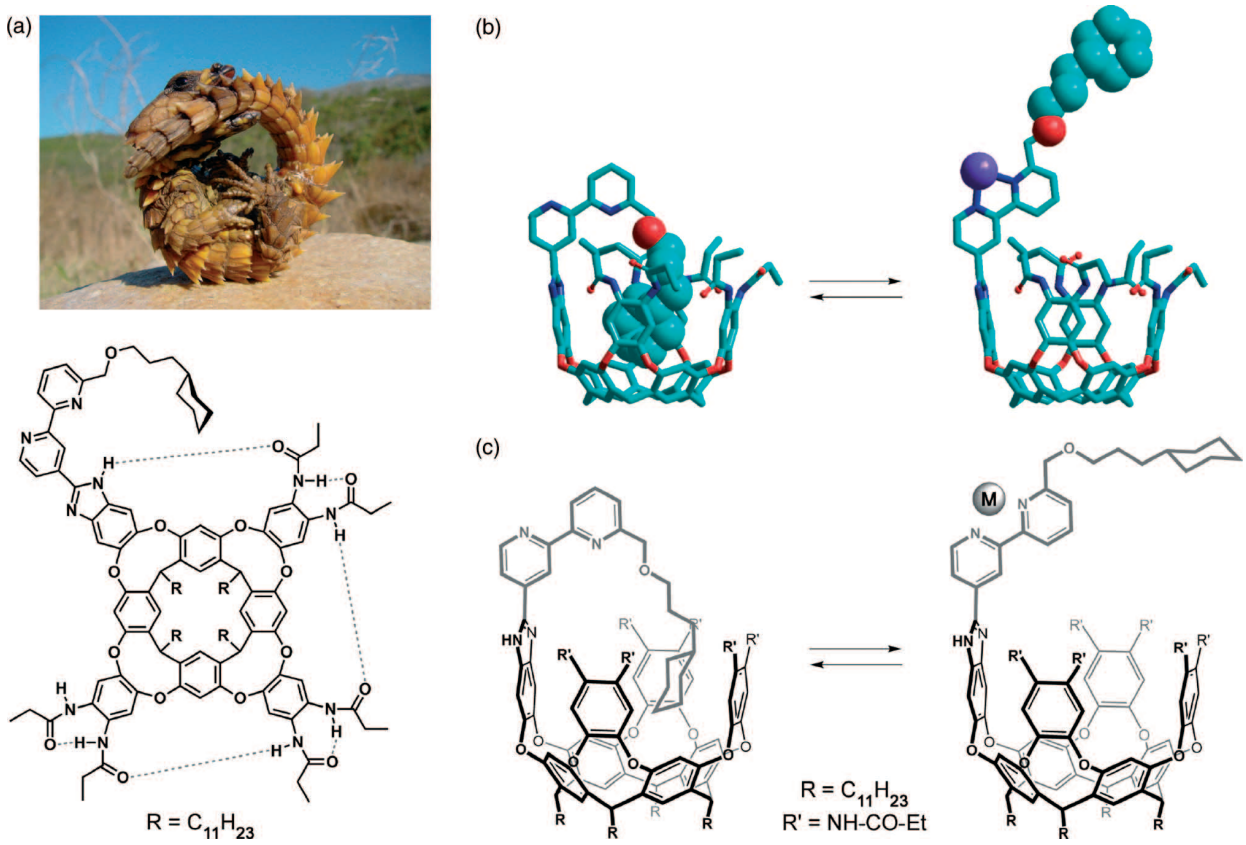

Figure 1. An armadillo lizard and the ouroborand in various depictions: (a) planar formula and (b) energy-minimised structures with the bipyridine ligand free or chelating a metal centre and (c) perspective views.

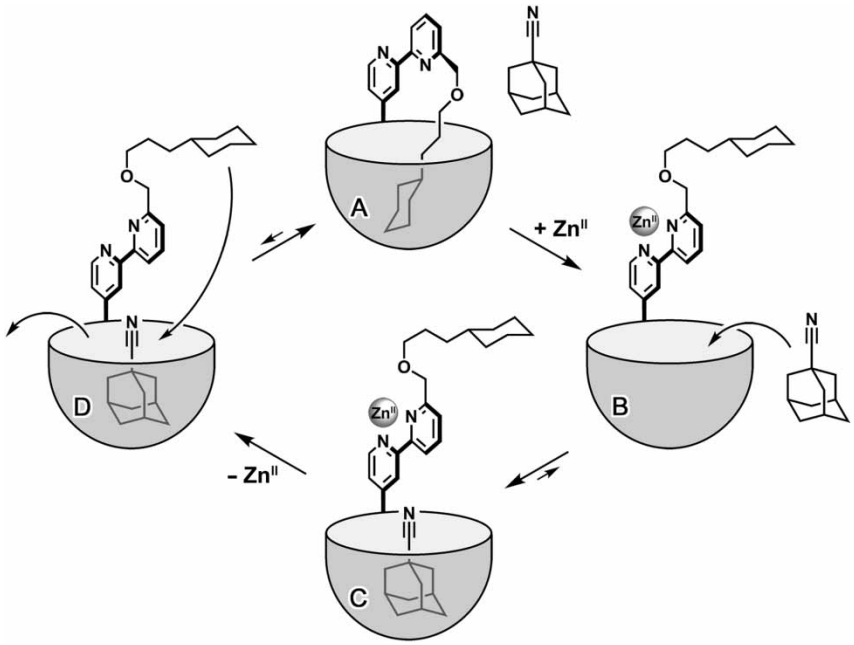

Figure 2. The reversible cycle of coordination-controlled guest exchange in the ouroborand's cavity.

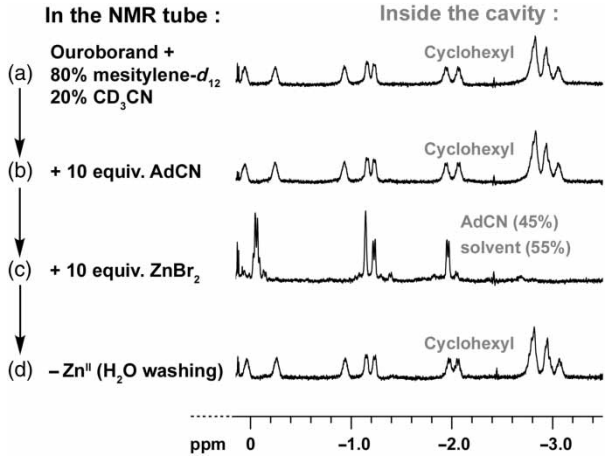

Figure 3. NMR spectra of the coordination-triggered guest-exchange of the ouroborand: (a) pure ouroborand in mesitylene-d_{12} (80%) and CD_3CN (20%); (b) 10 equiv. AdCN added in the NMR tube; (c) 10 equiv. $ZnBr_2$ added in the NMR tube and (d) water added to the NMR tube, then extraction and drying on Na_2SO_4.

(*15*), only the *trans* form can be accommodated and it provides a good fit of guest in the host, as might be expected from its affinity for the nearly isosteric benzanilides (*16*) and stilbenes (*17*). We arranged a competition between *trans*-**1** and *n*-tridecane in deuterated mesitylene. Although *n*-alkanes are good guests (*18*), only the azo compound is found inside the capsule, and a methyl singlet appears in the upfield region of the ^{1}H NMR spectrum (Figure 4(b)). However, when this solution is irradiated at 365 nm for 1 h, the *trans*-**1** is completely replaced by the encapsulated alkane (*19*). On heating this sample to 160°C for 2 min, the original complex reappears and the irradiation/heating cycle can be repeated many times.

Does the azobenzene 'break out' of the capsule? We believe so. The exchange rate of encapsulated *trans*-**1** with *n*-tridecane without irradiation is very slow: replacement of encapsulated *trans*-**1** by the added *n*-tridecane takes about 1 day to reach equilibrium. The isomerisation of *trans*-**1** inside of the capsule forces the capsule walls outwards, as it occurs in the vase-to-kite conformational changes of cavitands (*20*). This motion breaks some hydrogen bonds and facilitates guest exchange. For guest exchange in related cavitands, only two walls need to fold outwards (*21*). The capsule halves do not need to separate; this would require the rupture of all eight bifurcated hydrogen bonds and is a very slow process (*22*).

We performed parallel experiments on the extended capsule $\mathbf{2 \cdot 3_4 \cdot 2}$. This system is assembled when suitable guests are present (*23*) and excess glycolurils such as dibutylaniline derivative **3** are in the solution with the original capsule $\mathbf{2 \cdot 2}$. We prepared a longer azobenzene, *trans*-4-methyl-4′-hexyl-azobenzene (*24*) (*trans*-**4**) as the light-responsive guest (Figure 5(a)). In a solution containing 10 equiv. of *trans*-**4** and 2 equiv. of *p*-ethylbenzamide, only the azo compound is encapsulated. But after irradiation with 365 nm light, the encapsulated homodimer *p*-ethylbenzamide has replaced the azo compound. This

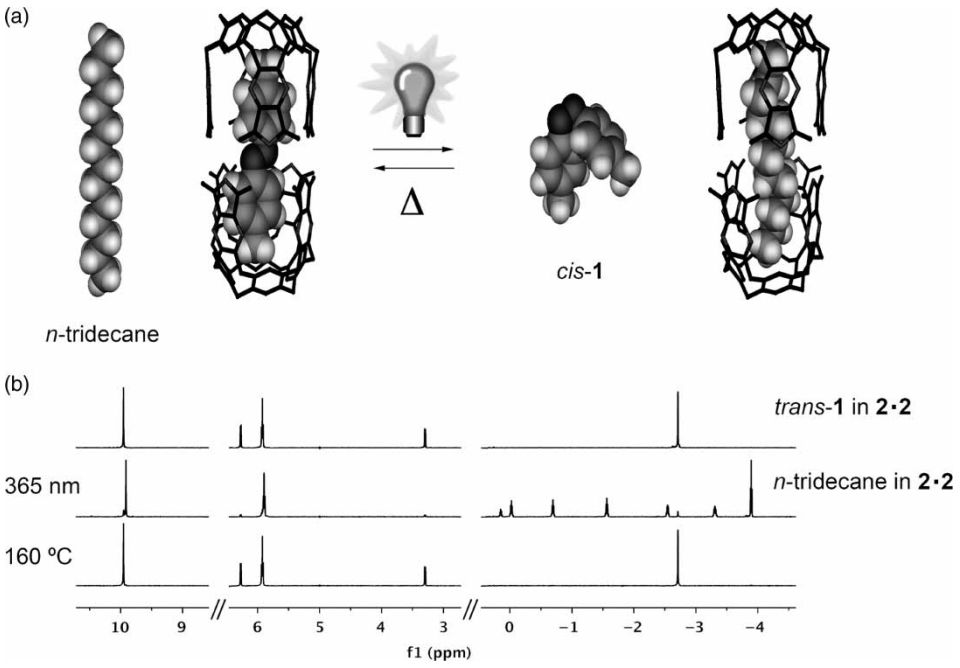

Figure 4. (a) Light-induced guest exchange of *trans*-**1** by *n*-tridecane in capsule $\mathbf{2 \cdot 2}$. (b) Indicative regions of the ^{1}H NMR spectra (mesitylene-d_{12}, 20°C) are shown before irradiation (*trans*-**1** is the only guest) and after irradiation at 365 nm wavelength for 50 min at 20°C (*n*-tridecane is the only guest). After heating the sample to 160°C for 2 min, the initial state is restored.

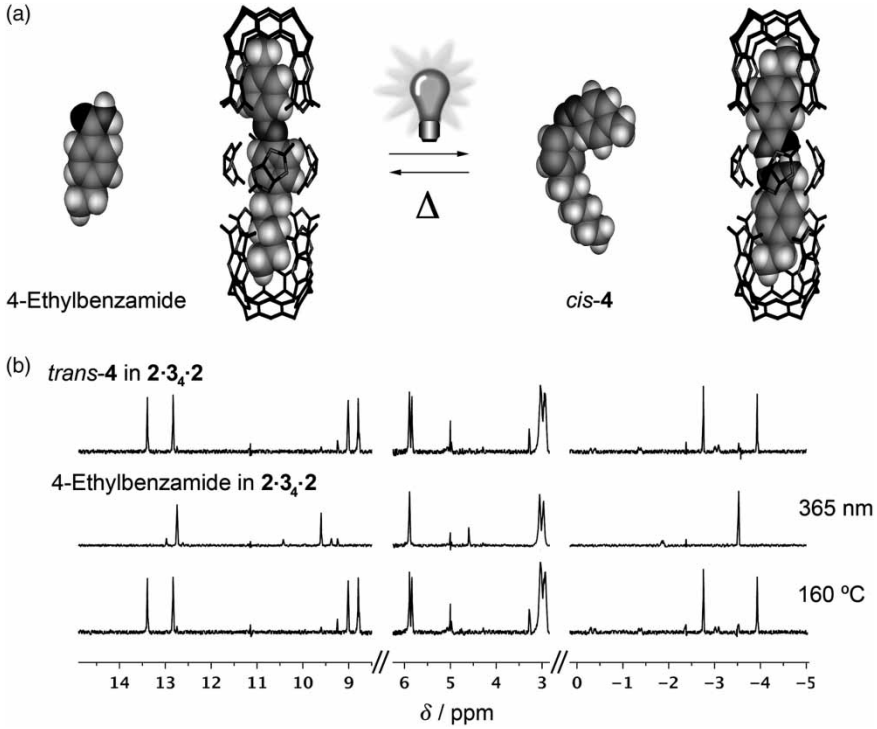

Figure 5. (a) Light-induced guest exchange of *trans*-**4** by the homodimer of 4-ethylbenzamide in the extended assembly $\mathbf{2 \cdot 3_4 \cdot 2}$. (b) Indicative regions of the ^{1}H NMR spectra (mesitylene-d_{12}, 20°C) are shown before irradiation (*trans*-**4** is the only guest) and after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

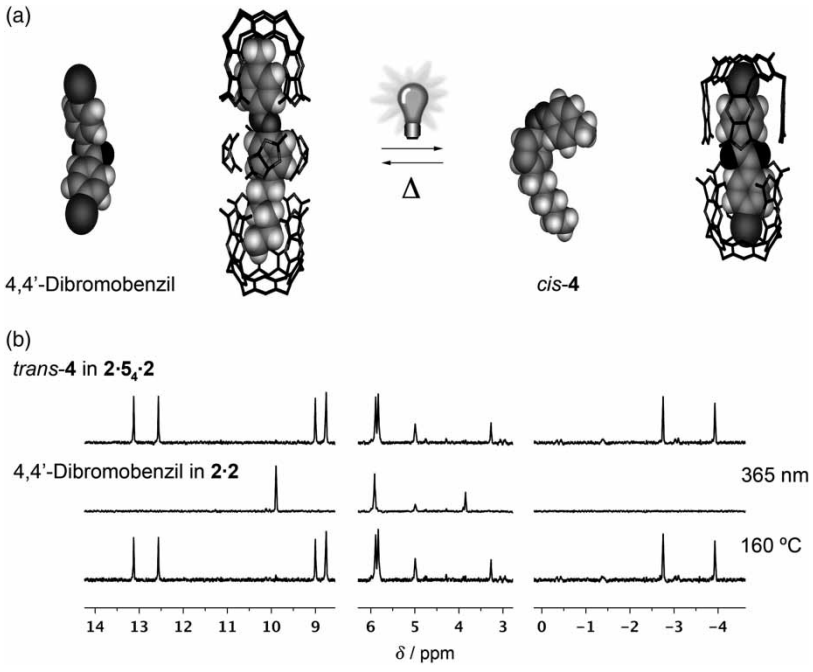

Figure 6. (a) Light-induced guest and capsule exchange. (b) The ^{1}H NMR spectrum (mesitylene-d_{12}, 20°C) is shown before irradiation (*trans*-**4** is the guest in the extended assembly $\mathbf{2 \cdot 5_4 \cdot 2}$) and after irradiation at 365 nm wavelength for 50 min at 20°C (4,4′-dibromobenzil is the guest in the capsule $\mathbf{2 \cdot 2}$). After heating the sample to 160°C for 2 min, the starting point is completely restored.

assembly is symmetric and the spectra are simplified accordingly. Heating the sample to 160°C for 2 min restores the initial guest occupation (see Figure 5(b)) and the cycle can be repeated many times.

The photoisomerisation was also used to switch between the assemblies **2·2** and **2·5$_4$·2**. This took advantage of the low solubility of 4-dodecanephenyl glycoluril **5** in deuterated mesitylene. It shows good solubility only when it is incorporated into the capsular assembly. A mixture of **2**, glycoluril **5** and 3 equiv. of *trans*-**4** and 4,4′-dibromobenzil **6** gives exclusively the extended assembly **2·5$_4$·2** with only the azo compound as the guest. On irradiation of the mixture, only the capsule assembly **2·2** is obtained with **6** as the guest. The precipitation of **5** from solution is observed. On heating the turbid solution for 2 min to 160°C, the original extended assembly **2·5$_4$·2** is restored with *trans*-**4** as the guest (Figure 6).

We are currently working to apply photoisomerism to control chemical reactions not known to be photosensitive. This could be done for the reaction of carboxylic acids with isonitriles that takes place under ambient conditions in the capsules (*25*), but requires microwave heating in free solution (*26*).

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