Switchable Supramolecular Systems

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Container Molecules with Portals: Reversibly Switchable Cycloalkane Complexation**

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Supramolecular systems that can be reversibly switched in a controlled manner between stable states of distinct geometries and properties have enormous potential for innovative applications such as in energy harvesting and storage, or in the development of nanoscale optical and molecular electronics devices.[1] Among switchable molecular receptors,[1,2] the quinoxaline-bridged resorcin[4]arene cavitands introduced by Cram and co-workers in 1982[3] have attracted much attention. The geometry can be reversibly changed from a concave vase to a flat kite form upon a decrease in temperature[3,4] or upon addition of acid or metal ions.[4b]

Although molecular switches based on bridged resorcin[4]arene scaffolds that undergo multiple nanometer expansion–contraction movements have been constructed,[5] the reversible switching of the guest-hosting properties of these cavitands has not yet attracted much attention. In the absence of additional rim functionalization,[6] complexation in the vase bowls is rather weak[3,7] and the introduction of a room-temperature switching mechanism was not of much interest because of the rapid complexation–decomplexation rates as a result of their open-top geometries.

A plethora of closed-shell host molecules with fascinating inner-phase binding and reactivity properties have been prepared. These include covalently constructed molecular containers such as the carcerands, which encapsulate their guests irreversibly, and the hemicarcerands, which have shell holes large enough to permit the exchange of guest molecules.[3b,8] Supramolecular capsules elegantly formed by self-assembly through H-bonding[9,10] or metal-ion complexation[11,12] have also appeared, some of which can be dissociated by protonation of the host building blocks.[10f] Shape-selective guest encapsulation is observed in this case that is thermodynamically as well as kinetically stable on the time scale of NMR measurements or longer.

What has barely been addressed in the construction of container molecules is the introduction of a portal that allows controlled uptake and release of a guest molecule at ambient temperature. Herein we present two switchable container molecules, basket **1** and tube **2**. Both compounds are highly selective hosts for the complexation of suitable cycloalkanes in their closed conformation. The addition of acid[13] converts these molecules into open-portal conformers that are unable to complex guest molecules, whereas neutralization with base induces re-uptake of the guests. We also present a detailed thermodynamic and kinetic analysis of the complexation processes.

The synthesis of **1** and **2** by oxidative acetylenic coupling of **3** is shown in Scheme 1. The two containers form in a ratio of **1**/**2** ≈ 10:1, independent of the concentration of starting material **3** (0.5 to 14 mM). The two products could be conveniently separated by high-performance gel-permeation chromatography and fully characterized (see the Supporting Information).

At room temperature in solvents such as [D_6]acetone, $CDCl_3$, or [D_{12}]mesitylene, the container molecules are exclusively present in closed forms, as indicated by the highly characteristic chemical shift of their methine protons in the resorcin[4]arene core (5.5–5.7 ppm) in the ^{1}H NMR spectrum.[3,4] Molecular modeling studies (AM1 within Spartan '04[14]) show that the closed form of container **1** (excluding the hexyl chains on the lower rim) is a roughly spherical basket ($10 \times 8 \times 10$ Å^3), whereas **2** is a cylindrical tube ($26 \times 8 \times 10$ Å^3) (Figure 1).

Both **1** and **2** undergo pH-dependent switching: Addition of deuterated trifluoroacetic acid (CF_3COOD) to a solution of **1** in $CDCl_3$ or [D_{12}]mesitylene induced characteristic changes in the ^{1}H NMR spectrum (see the Supporting Information). Whereas the resonance of the methine protons $H^{a'}$ (Scheme 1) underneath the rigid bridged imide walls was shifted only marginally upon addition of acid, the signal for methine protons H^a underneath the flexible quinoxaline flaps experienced a diamagnetic shift of around 1 ppm. Owing to the rigidity of container **1**, the shift is less pronounced than for open-top quinoxaline-bridged resorcin[4]arene cavitands, which usually feature an upfield shift from $\delta \approx 5.6$ to 3.6 ppm upon acid-triggered conversion from the vase into the kite form.[3,4,13] Nevertheless, this shift is a characteristic probe that reveals a significant geometric change: the N atoms of the quinoxalines are protonated, and Coulombic repulsion forces these flaps outside; this movement is followed to some extent by the bowl (see the molecular model in Figure 1).

Tube **2** is less rigid and therefore features a switching behavior very similar to that of open-top cavitands: methine proton resonances shift strongly from $\delta \approx 5.6$ to 3.7 ppm upon addition of CF_3COOD to a solution in $CDCl_3$ (see the Supporting Information). In this case, the resonance for the

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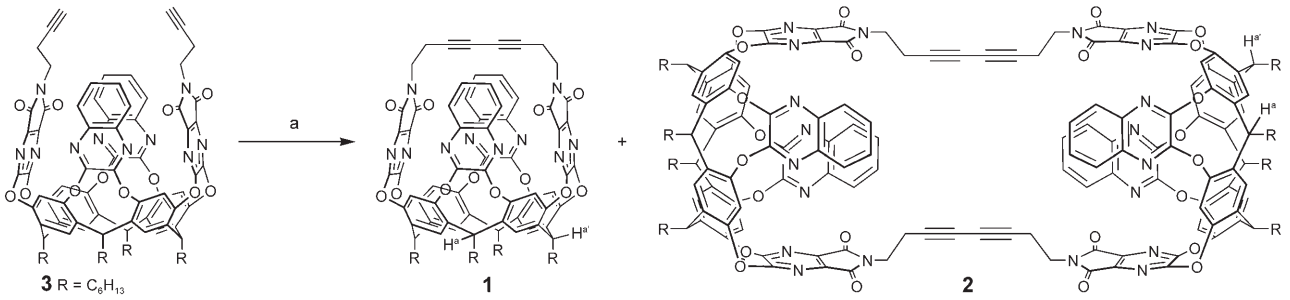
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Synthesis of the container molecules. a) CuCl, $CuCl_2$, air, *N*,*N*-dimethylformamide, 20 °C, 16 h. Yields: 31 % (**1**) and 6 % (**2**).

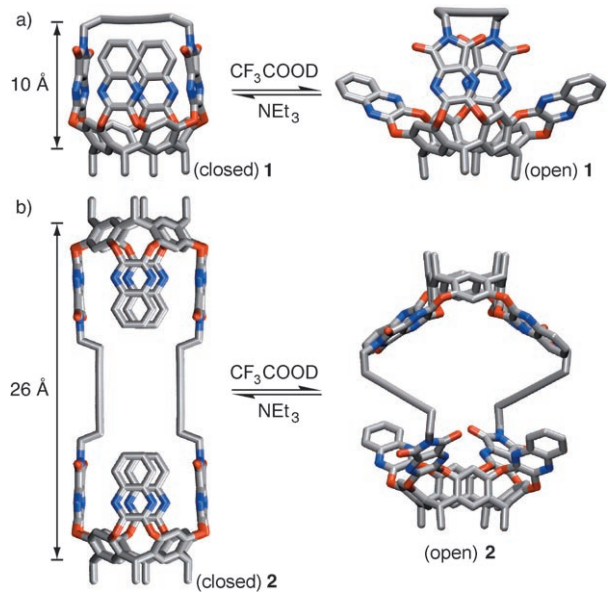


Figure 1. Molecular models (Spartan '04, AM1) of basket **1** (a) and tube **2** (b) in the closed and open forms. The hexyl chains on the lower rim as well as the hydrogen atoms are omitted for clarity.

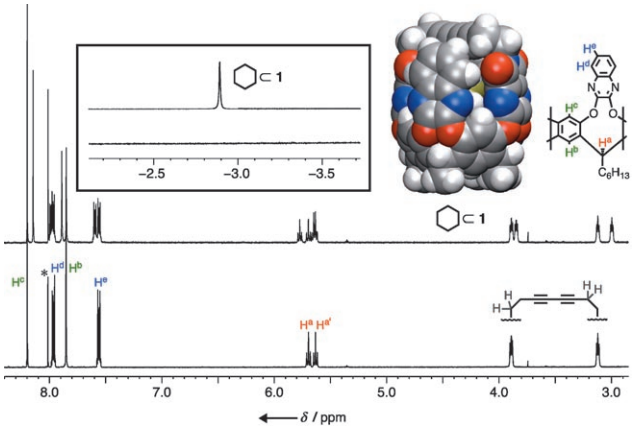


Figure 2. Portions of the ^{1}H NMR spectra (500 MHz, [D_6]acetone, 298 K) of pure **1** (c = 2.5 mM; bottom) and in the presence of cyclohexane (c = 75 mM, host occupation ca. 50 %; top). The inset shows the upfield-shifted signal of the bound guest. The methine protons underneath the quinoxaline walls are labeled as H^a; those underneath the imide walls as $H^{a'}$. The starred peak is residual $CHCl_3$ from the host crystals. Also shown is the space-filling representation for the complex cyclohexane⊂**1**, generated by MOLOC[15] with the MAB force field (hexyl residues omitted).

methine protons underneath the imide walls is also strongly affected. In protonated **2**, both cavitand moieties fully adopt a kite-like conformation as depicted in the computer-generated geometry in Figure 1 b.

In their closed forms, molecular basket **1** and tube **2** complex cycloalkanes, in particular cyclohexane; the host–guest exchange in this case is slow on the ^{1}H NMR time scale. Figure 2 shows the 500-MHz ^{1}H NMR spectrum of pure **1** (c = 2.5 mM) in [D_6]acetone at 298 K (bottom) and after addition of cyclohexane (c = 75 mM, top). The resonance for complexed cyclohexane is shifted strongly upfield and appears as a singlet at $\delta = -2.9$ ppm. Also, the resonances of the host undergo specific complexation-induced shifts. A space-filling representation of the complex (Figure 2) shows that the container completely surrounds its encapsulated guest: the cyclohexane chair is preferentially sandwiched between the two quinoxaline flaps (see the Supporting Information), thereby undergoing favorable C–H···π interactions. The observation of 1 singlet for all 12 guest protons indicates that chair–chair interconversion and rotation within the cavity still occurs at 298 K.

The strong influence of solvent on complexation is shown by the thermodynamic parameters in Table 1. In [D_6]acetone, binding is weak because the solvent molecules efficiently compete for the inner space of the container. In [D_{12}]mesitylene, however, the association constants are enhanced nearly 1000-fold. Mesitylene is too large to solvate the cavity and does not compete for the binding site.[4a,16] The 55 % rule established by Mecozzi and Rebek says that an inclusion complex is favored when a guest fills about 55 % of the cavity volume.[17] This rule is nicely held in this case and explains the observed guest selectivities. The available

Table 1: Association constants (K_a) for the formation of 1:1 complexes of molecular basket **1** with cycloalkanes at 298 K.

Solvent	K_a [M^{-1}][a]		
	Cyclohexane	Cyclopentane	Cycloheptane
[D_6]acetone	5.6 ± 0.6	3.2 ± 0.3	(6.5 ± 0.6) × 10^{-1}
[D_{12}]mesitylene	(3.6 ± 0.8) × 10^3	(1.2 ± 0.2) × 10^3	(1.8 ± 0.2) × 10^2

[a] Determined by integration of the ^{1}H NMR resonances at slow host–guest exchange.

volume within **1** was determined by the cavity-filling method to be 200 Å^3. When this value was compared with the volumes of cycloalkane guest molecules, it turned out that cyclohexane occupies approximately 56% of the available space, whereas neither cyclopentane (47%) nor cycloheptane (65%) have the ideal volume for encapsulation. In a solution of **1** ($c = 0.84$ mM) in [D$_{12}$]mesitylene containing 1 equivalent each of the three cycloalkanes, the ratio of the formed complexes was 1:0.36:0.06 (cyclohexane/cyclopentane/cycloheptane), which is in excellent agreement with the relative ratios calculated from the association constants (1:0.33:0.05) (see the Supporting Information).

Tube **2** contains two initially identical binding sites. Accordingly, upon addition of cyclohexane ($c =$ 14 mM) to **2** ($c = 0.79$ mM in [D$_{12}$]mesitylene), we observed two singlets at $\delta = -2.86$ and -2.97 ppm in the ^{1}H NMR spectrum for the strongly shielded protons of cyclohexane. When the host is saturated with guest, only the more upfield shifted resonance for bound cyclohexane remains, which indicates that the signal at $\delta = -2.86$ ppm corresponds to the 1:1 complex and the signal at $\delta = -2.97$ ppm to the 1:2 host–guest complex. The concentrations of all species involved in the two sequential binding equilibria could be determined by integration of the NMR signals. This afforded $K_{a1} = 24\,\text{M}^{-1}$ for the formation of the 1:1 complex and $K_a = 1.4 \times 10^3\,\text{M}^{-2}$ for the overall 1:2 host–guest complexation (see the Supporting Information).

Interestingly, the two binding sites of tube **2** must be addressed individually. 1,4-Di(cyclohexylethynyl)benzene comprises two cyclohexane moieties that are appropriately spaced to be simultaneously bound by **2**. However, **2** does not bind this guest. In contrast, methylcyclohexane is bound reasonably well and forms a 1:2 complex ($K_a \approx 1.5 \times 10^2\,\text{M}^{-2}$); two cyclohexylacetylene molecules bind much more weakly ($K_a \approx 16\,\text{M}^{-2}$). Molecular modeling studies (Supporting Information) suggest that the alkyne moieties of the guests severely restrain the conformational flexibility of the two octa-3,5-diynediylene bridges of the host, which could be the reason why ditopic guests are not bound. Further structural investigations are required to clarify these findings.

The acid-induced conformational switching of **1** and **2** (Figure 1) turns off their hosting ability. The addition of increasing amounts of CF_3COOD to a solution of cyclohexane⊂**1** induced a rapid decline of the intensity of the ^{1}H NMR resonance for bound guest until complete release had occurred at $[CF_3COOD] = 1.4$ M (Figure 3). In contrast, CD_3COOD is not able to protonate the quinoxaline flaps and therefore can not switch the container.[18] In a control experiment (Figure 3), even 2.4 M CD_3COOD did not lead to significant release of guest from the cavity of **1**. This finding clearly demonstrates that decomplexation is indeed caused by the acid-induced conformational change of the host and does not originate from a nonspecific solvent polarity effect.

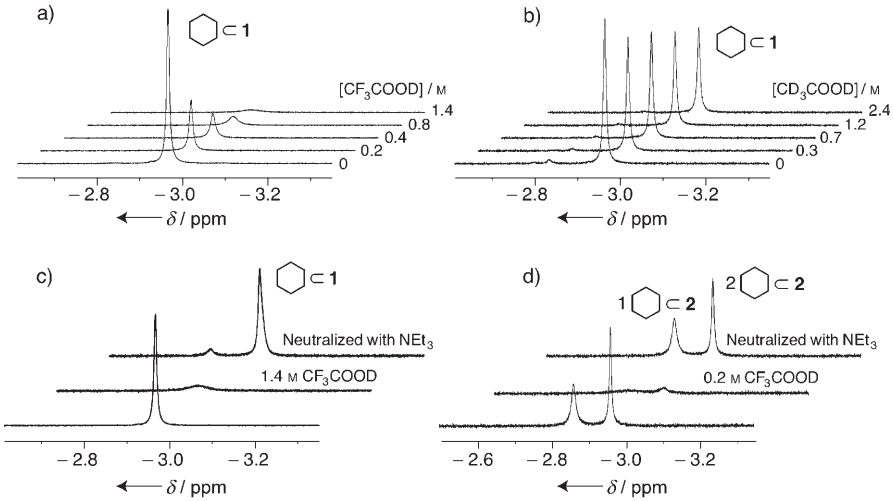


Figure 3. Portions of ^{1}H NMR spectra (500 MHz, 298 K, [D$_{12}$]mesitylene). a) Upon addition of CF_3COOD, container **1** ($c = 3.0$ mM) loses its ability to bind cyclohexane ($c = 1.5$ mM). b) A control experiment with CD_3COOD, which cannot protonate the quinoxaline flaps, confirms that guest release is not a nonspecific solvent-polarity effect. The slight decrease in peak intensity results mainly from dilution of the solution upon addition of the acid. c) The opened container can be switched back to the closed form with NEt_3 ($c \approx 1.4$ M) and binds the cyclohexane guest again at full strength. d) Reversible switching of guest complexation is possible also for tube **2**. Minor amounts of complex remain after addition of CF_3COOD, as not all the container molecules are completely protonated.

As discussed above, tube **2** is even more susceptible to pH-dependent switching because of the substantially larger conformational space it can occupy. Thus, a concentration of 0.2 M CF_3COOD (240 equiv) was sufficient to induce the disappearance of the signals for one and two bound cyclohexane molecules (Figure 3). It is remarkable that the binding capabilities of **1** and **2** are turned off immediately and completely by a mechanism that is founded solely on the protonation of the host and the conformational changes induced thereby. The switching mechanism is fully reversible. When we neutralized the acidic solutions with appropriate amounts of NEt_3, both container molecules **1** and **2** instantly returned to their fully closed conformations and guest binding was restored completely (Figure 3).

We determined the thermodynamic parameters for the complexation of cyclohexane by the molecular basket **1** by variable-temperature ^{1}H NMR spectroscopy and subsequent van't Hoff analysis (Table 2 and Supporting Information).

Table 2: Thermodynamic parameters for binding of cyclohexane with container **1**.

Solvent	$\Delta G^{293\,\text{K}}$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔS [cal mol^{-1} K]	$T\Delta S^{293\,\text{K}}$ [kcal mol^{-1}]
[D$_6$]acetone	-1.0 ± 0.8	-8.0 ± 0.4	-24 ± 1	-7.0 ± 0.4
[D$_{12}$]mesitylene	-4.8 ± 0.8	-6.3 ± 0.4	-5.2 ± 1	-1.5 ± 0.4

Although the free enthalpy of binding is much larger in [D_{12}]mesitylene ($\Delta\Delta G^{293\,K} = 3.8$ kcal mol^{-1}), the enthalpic driving force is more favorable in [D_6]acetone ($\Delta\Delta H =$ 1.7 kcal mol^{-1}). Thus, the difference in binding affinity in the two solvents originates from a remarkable difference in the complexation entropy ($\Delta(T\Delta S^{293\,K}) = 5.5$ kcal mol^{-1}). In both solvents, similar entropic costs are presumably involved for the transfer of the guest into the cavity and the loss of its translational (and parts of its rotational) degrees of freedom. Therefore, we propose that the dramatically different changes in solvation entropy originate from the differences in solvation of the host cavity. One molecule of acetone presumably solvates the interior of the container rather loosely (volume occupancy: 36 %) and, upon displacement by the guest, is transferred back into the bulk, where solvent cohesive interactions (C–H···O hydrogen-bonding and dipole–dipole interactions) enforce stronger ordering. This supposition is supported by the favorable enthalpic term measured in acetone.[19] Furthermore, mesitylene, because of its size, does not solvate the interior of the cavity. When cyclohexane is added to the solution, a dramatic concentration gradient arises: the concentration of cyclohexane is finite on the outside of the container and zero inside. Equilibration of this gradient occurs, driven by entropy of mixing, which contributes to compensating for the entropic costs of entrapping the guest inside the cavity.

Finally, we investigated the kinetics of the constrictive binding of cyclohexane by the closed form of **1** in [D_{12}]mesitylene by a variable-temperature DPFGSE (double-pulsed field-gradient spin-echo) magnetization-inversion-transfer experiment.[20] Quantitative evaluation of the spectral evolution after selective inversion of the signal for bound cyclohexane allowed he determination of equilibrium rate constants, and their temperature dependence unveiled the activation parameters for guest binding and release. (Supporting Information). At 308 K, the pseudo-first-order rate constant for complexation k'_{in} is 1.7 s^{-1}, whereas the first-order rate constant for decomplexation k_{out} is 2.5×10^{-3} s^{-1}. The activation parameters for decomplexation were determined from an Eyring plot to be $\Delta H^{\neq} = (17 \pm 1)$ kcal mol^{-1}, $\Delta S^{\neq} = (-16 \pm 2)$ cal mol^{-1} K^{-1}, and $T\Delta S^{\neq 293K} = (-5 \pm 1)$ kcal mol^{-1}. Thus, both enthalpic and entropic contributions obstruct the decomplexation process and give an activation free enthalpy at 293 K of $\Delta G^{\neq 293K} = (22 \pm 2)$ kcal mol^{-1}. The unfavorable enthalpic term results from the disruption of attractive host–guest interactions as well as from a massive reorganization of the container to a more strained, open conformation that can release the guest molecule. The unfavorable entropic term presumably also results from the generation of empty space inside the container during the first-order decomplexation step, which, in turn, generates a dramatic concentration gradient of cyclohexane between the inside and outside of **1**. Clearly, decomplexation by a squeezing out of the guest is much slower than acid-triggered release.

In summary, we synthesized two novel container molecules—a molecular basket and a molecular tube—that form stable 1:1 and 1:2 host–guest complexes, respectively, with suitably sized cycloalkanes, such as cyclohexane. Most importantly, we showed that both structures can be converted into open conformations upon acidification and that this switching completely turns off the host properties without breaking any bonds. Guest uptake is immediately and completely reestablished upon neutralization. We foresee the introduction of switchable portals as a future way to facilitate product release in catalytic processes inside container molecules.

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