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Reversibly controllable guest binding in precisely defined cavities: selectivity, induced fit, and switching in novel resorcin[4]arene-based container molecules

Thomas Gottschalk, Peter D. Jarowski, François Diederich *

Laboratorium für Organische Chemie, ETH Zürich, Hönggerberg, HCI, CH-8093 Zürich, Switzerland

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ABSTRACT

Two molecular baskets are presented, which were constructed based on a resorcin[4]arene platform. The molecules completely surround suitable guests, such as cyclo- or oxacycloalkanes, and bind them with high strength. The thermodynamic parameters for inclusion complexation were determined as well as the influence of encapsulation on the ring inversion barrier of bound cyclohexane. Two-dimensional NMR spectroscopy clearly shows the existence of a directed attractive interaction between oxacyclohexane and one of the hosts, which constrains the rotation of the bound molecule. Both containers exhibit remarkable binding selectivity as a consequence of their precisely defined structures. They both differentiate between homologous cycloalkanes, and whereas cyclohexane binds best within the larger of the two interior cavities, cyclopentane fits best in the smaller one. The selectivity is governed by ideal filling of space. We have conducted molecular dynamics experiments to understand the thermal fluctuations in the cavity sizes when a guest is bound. The simulations show that within a very narrow range the hosts adapt their binding site to different guests in order to optimize the fraction of occupied space. Once a binding geometry is established, it is characterized by a very low degree of flexibility. The guest-hosting properties of both molecules can be suspended by an external stimulus: addition of acid induces an opening of portals in the structures and immediately releases all bound cargo. Neutralization of the solution completely restores the initial state.

1. Introduction

Molecular-scale functional systems[1] have emerged in eclectic variety since Feynman's fundamental reflections on such machinery.[2] They are targeted at an enormous number of innovative applications in fields such as materials and catalysis, energy harvesting, information storage and processing, or targeted delivery and transport. Molecular switches are one such type of device:[3] external stimuli can be used to toggle between distinct stable states with different properties.

A particularly effective strategy in the construction of molecular switches for exerting dynamic control over physical properties is to provoke changes in molecular geometry:[4] to just name examples, motion in interlocked molecules can modify their fluorescence or conductivity and allow for the construction of macroscopic Boolean logic gates[4r] or nanoelectromechanical memory devices,[4l,v] whereas light can be used to induce unidirectional rotation in three-state chiroptical switches,[4h,k] which then directs the twist sense of helical polymers.[4u] Provoking a geometry change in rotaxanes or diarylethene molecular switches[4j] can control, among other materials properties, the water repellency of surfaces.[4s,t]

Controlled mechanical motion has also been exploited to modulate the guest-hosting properties of molecular (nano)systems, whereby allosteric[4a] and photoresponsive[4b,c] crown ethers represent classical examples. Most recently, (pseudo)rotaxane molecules attached to the surface of mesoporous silica have been reported. The molecular switches act as gatekeepers and allow encapsulation of guest molecules within the pores of nanoparticles; stimulation results in controlled release.[5]

Among switchable receptors are also the resorcin[4]arene cavitands, introduced by Cram et al. in 1982 (Scheme 1).[6] At room temperature and in organic solvents, the cavitands are exclusively present in the *vase* conformation, whereas lowering the temperature[7] or adding metal ions[8] or acid[9] converts the molecules to the open, flat *kite* form. This controllable transformation has recently been applied in the construction of molecular switches that undergo precisely defined multi-nanometer expansion/contraction movements.[10]

In their pristine quinoxaline-bridged guise, the cavitands are in principle capable of accepting guest molecules within their concave

* Corresponding author. Tel.: +41 44 632 2992; fax: +41 44 632 1109.
E-mail address: diederich@org.chem.ethz.ch (F. Diederich).

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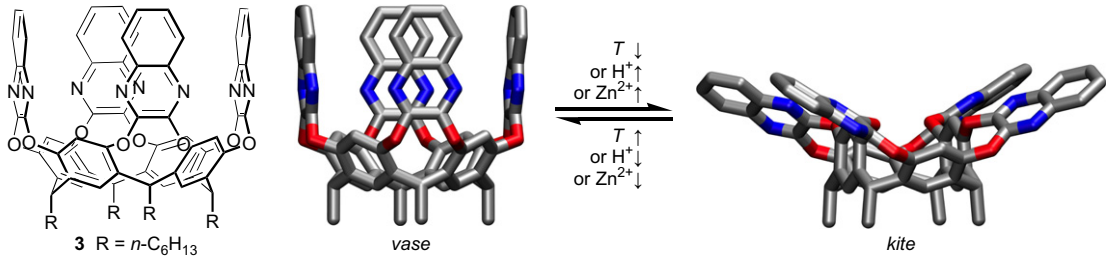


Scheme 1. Structural representation for the tetraquinoxaline-bridged cavitand **3** and molecular models (MOPAC2007, PM6), illustrating the *vase–kite* equilibrium. The cavitand can be switched to the *kite* conformation by lowering the temperature or by the addition of acid or metal ions.

interior.[11] Still, as a consequence of their open-top geometry and conformational flexibility, binding is weak and guest exchange proceeds rapidly in the absence of additional rim functionalization.[12] Closed-shell structures enforcing an interior cavity do on the other hand allow for the formation of stable and inert encapsulation complexes. Uptake and release of smaller molecules into and from these containers are then, however, difficult to control dynamically because exchange kinetics are a function of host structure: covalently closed surfaces completely inhibit guest exchange, while the introduction of shell holes of appropriate size can allow for entrance and egress of smaller species.[13] Self-assembled capsules[14] and cages[15] do additionally impose their own association–dissociation dynamics on the exchange kinetics of their encapsulation complexes,[13j,k,16] and approaches to exert dynamic control over guest uptake and release properties of enforced inner phases have targeted influencing the self-assembly of supramolecular structures.[14b,j]

Herein, we report on the syntheses and on extensive binding, molecular dynamics, and switching studies of the switchable baskets **1** and **2** (Scheme 2), resorcin[4]arene-based container molecules that accommodate suitable guests within well-defined cavities and completely surround them. The molecules show remarkable binding selectivity as a consequence of their precisely defined geometry. Portals delimiting the cavity are opened upon the addition of acid and binding is suspended as a result of the induced change in structure. The process is fully reversible; neutralization of the solution completely recovers the initial state.[17]

2. Results and discussion

2.1. Container molecules with portals based on a resorcin[4]arene platform

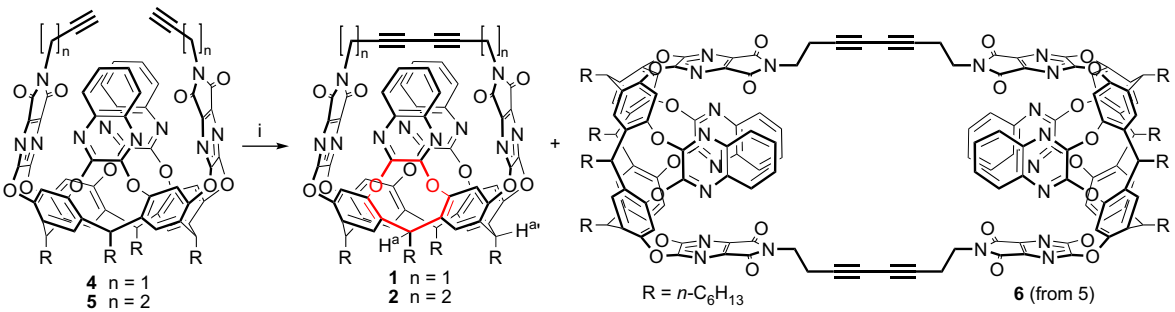
The switchable baskets **1** and **2** are constructed from a resorcin[4]arene bowl, to which two quinoxaline flaps are appended in *anti*-orientation (Scheme 2 and Fig. 1). Two diazaphthalimide walls are connected to each other by a rigid hexa-2,4-diyne-1,6-diyl bridge in the case of **1** and by an octa-3,5-diyne-1,8-diyl unit in **2**. The acetylenic connections cap-off the baskets and enforce precisely defined cavities within **1** and **2**.

Pairs of adjacent phenol ethers, by which the quinoxaline flaps are attached to the resorcin[4]arene bowl, act as hinges to open these portals in the switching process. However, the barrier for the required flip of the constrained nine-membered ring (Scheme 2, highlighted in red) is high[9b] and at room temperature in solvents such as acetone-d_6, $CDCl_3$, or mesitylene-d_{12}, the molecules are exclusively present in their *closed* conformations.[7,9b]

To assess the degree of rigidification caused by bridging the cavitand structure with alkyne bridges, we have performed molecular dynamics experiments (1000 ps simulation time with 1.0 fs time steps, MMFF94s force field, 300 K, GB/SA model for $CHCl_3$, MacroModel 9.5).[18] Figure 2 compares the local conformational space of *vase*-**3**, lacking any rim bridging, and the *closed* conformer of **1**. It is clear that the *vase* form of the tetraquinoxaline-bridged cavitand **3** is poorly defined because the walls are subjected to enormous fluctuation. In sharp contrast, *closed*-**1** exhibits a highly restricted local conformational space. The acetylenic bridge enforces the structure as a whole, including bowl and portals; a precisely defined cavity results.

2.2. Synthesis and purification

The key step in the synthesis of **1** and **2** is an oxidative acetylenic coupling reaction of open-top precursor cavitands **4** and **5** (Scheme 2). Intramolecular coupling of **5** affords the basket **2** along with a dimeric structure, the switchable tube **6**, in a ratio of **2**/**6** ≈ 10:1. The two products can be separated by preparative high-performance gel-permeation chromatography (GPC).[17] Precursor **4** does not give isolable quantities of a dimerization product under the coupling conditions, most probably because the resulting tube would be too strained. The open-top precursor molecules are formed by bridging the bis-*anti*-quinoxaline cavitand **7**[19] with the propynyl- or butynyl-substituted 2,3-dichlorodiazapthalimide **8** and **9**, respectively (Scheme 3). Synthesis of these wall units proceeds, in the case of **8**, via condensation of 2,3-dichloropyrazine-5,6-dicarboxylic acid anhydride[20] with propargylic amine **10**, or for



Scheme 2. Synthesis of switchable container molecules. (i) CuCl, $CuCl_2$, DMF, 17 h; 20% (**1**), 31% (**2**), 6% (**6**).