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Redox-Switchable Resorcin[4]arene Cavitands: Molecular Grippers

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Supporting Information

ABSTRACT: Diquinone-based resorcin[4]arene cavitands that open to a kite and close to a vase form upon changing their redox state, thereby releasing and binding guests, have been prepared and studied. The switching mechanism is based on intramolecular H-bonding interactions that stabilize the vase form and are only present in the reduced hydroquinone state. The intramolecular H-bonds were characterized using X-ray, IR, and NMR spectroscopies. Guests were bound in the closed, reduced state and fully released in the open, oxidized state.

Molecular machines[1] that imitate the functions of macroscopic objects are a fascinating research endeavor because they stimulate our imagination. While microscopic analogues of various macroscopic objects, such as rotors,[2] shuttles,[3] tweezers,[4] turnstiles,[5] ratchets,[6] motors,[7] muscles,[8] cars,[9] and balances[10] have been prepared and studied, an important tool for the microscopic world is undeveloped: a molecular gripper. Such element could be applied to a wide range of areas, including nanorobotics, drug delivery, and fundamental physical organic chemistry studies. The requirement for a molecule to act as a gripper is the ability to open and close upon external stimulation; in doing so, guest molecules would be released and grabbed (Figure 1, top). A promising scaffold for the construction of molecular grippers is the resorcin[4]arene cavitand system[11] due to its ability to adopt two spatially well-defined conformations: an expanded kite and a contracted vase. While the switching ability of cavitands has been explored using stimuli such as changes in pH, temperature, metal ion concentration, or light,[12] the development of redox-switchable variants would be desirable in order for cavitands to be addressable on electroactive metal interfaces. Here, we describe the synthesis and detailed investigation of cavitands that can be redox-switched in solution between their kite and vase forms, thereby releasing and binding guests.

Recently, we reported the synthesis of a family of resorcin[4]arene cavitands containing quinone moieties as redox-active wall components.[13] However, these systems did not undergo a conformational change induced by redox interconversion between their quinone and hydroquinone states because there was no driving force for the switching process. We therefore sought to introduce such a driving force by designing a cavitand that takes advantage of strong intramolecular H-bonding interactions to specifically stabilize

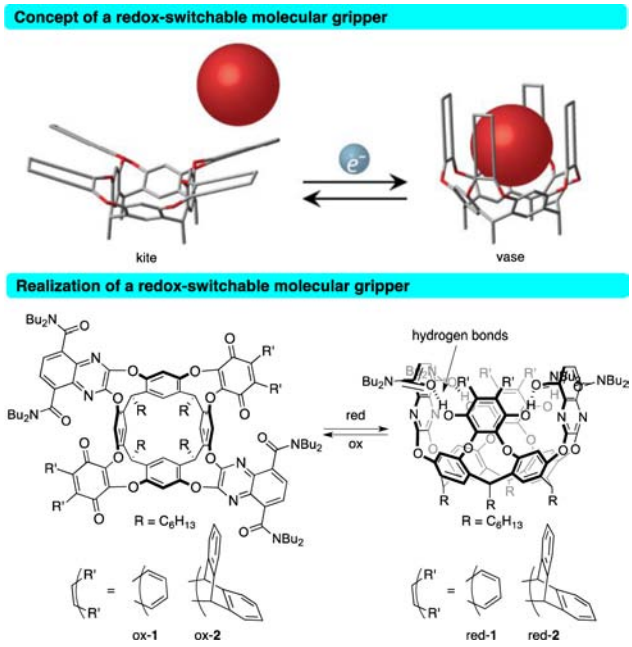

Figure 1. (Top) Schematic of a redox-switchable molecular gripper. (Bottom) Redox-switchable cavitand systems **1** and **2** with a vase conformation in the reduced state, stabilized by H-bonds.

the vase conformation in one redox state. This design was realized by placing *N*,*N*-di(*n*-butyl)carboxamides as H-bond accepting groups on the quinoxaline walls of diquinone-diquinoxaline cavitands ox-**1** and ox-**2** (Figure 1, bottom). Cavitands of this type are present in the kite form in chlorinated solvents, as we established in previous work.[13] Reduction would yield hydroquinone cavitands red-**1** and red-**2**, which would strongly prefer the vase conformation due to intramolecular H-bonds between the carboxamide and the hydroquinone moieties. Cavitand red-**1** would feature an open top, whereas the corresponding triptycene-based cavitand, red-**2**, would have a fully closed cavity.[13] Reoxidation to the quinone state would remove these interactions, thereby switching the cavitands back to the kite form.

The syntheses of ox-**1** and ox-**2** commenced with the preparation of wall precursor **3**, which was accessed from the commercially available 4,7-dibromobenzo[*c*][1,2,5]thiadiazole

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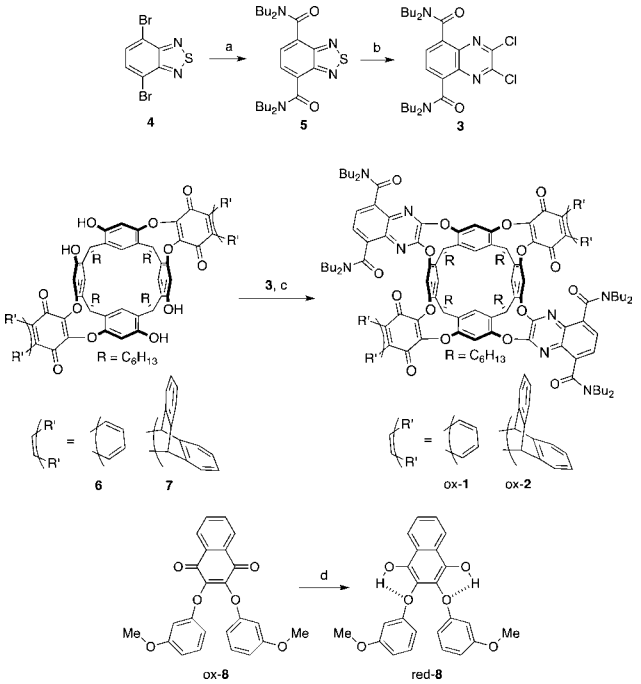
(**4**) (Scheme 1). Aminocarbonylation[14] of **4** with di(*n*-butyl)amine afforded compound **5**. Reductive sulfur extrusion,[15] condensation of the resulting diamine with oxalic acid,[16] and chlorination of the resulting diol with thionyl chloride[16] yielded wall precursor **3**. Reaction with tetrols **6** and **7** provided cavitands ox-**1** and ox-**2**. We also prepared hydroquinone red-**8** from ox-**8**[13] as a reference compound.

Scheme 1. Syntheses of Redox-Switchable Cavitands Ox-1 and Ox-2[a]



[a](a) *n*-Bu_2NH, CO (balloon), $Pd(OAc)_2$, Xantphos, K_3PO_4, toluene, reflux, 20 h, 99%. (b) (1) $NaBH_4$, $CoCl_2(H_2O)_6$, EtOH, reflux, 2 h; (2) oxalic acid, EtOH/HCl, reflux, 16 h; (3) $SOCl_2$, DMF, $(CH_2Cl)_2$, reflux, 3 h, 57% over 3 steps. (c) Cs_2CO_3, THF, reflux, 24 h, 85% (ox-**1**); 47% (ox-**2**). (d) $Na_2S_2O_4$, $CDCl_3/H_2O$, 60 °C, 3 h, quantitative. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

The conformational properties of the new cavitands in various solvents were characterized by ^{1}H NMR spectroscopy. Cavitands ox-**1** and ox-**2** are present in the kite form in chlorinated solvents, THF-d_8, and mesitylene-d_{12} (see Figure 2 left for ^{1}H NMR spectra of ox-**1**), as evidenced by the ^{1}H NMR resonance of the methine protons between 4.0 and 4.5 ppm. The NMR spectra are complex due to dynamic behavior on the NMR time scale, resulting from slow rotation of the amide moieties around the C_{Naph}–$CONBu_2$ bond[17] and slow kite1–kite2 interconversion.[13,18] An averaged C_{2v} symmetry becomes apparent for ox-**1** only above 130 °C.[19] Thus, the vase form and the vase-like transition state for kite1–kite2 interconversion are strongly destabilized, presumably due to steric repulsion between the amide and the quinone moieties.

We proceeded to test our switching concept, which is based on the stabilization of the vase form by H-bonds in the reduced hydroquinone state. Reduction of ox-**1** to red-**1** was performed in a biphasic mixture of $CDCl_3/H_2O$ using $Na_2S_2O_4$,[20] while ox-**2** was reduced to red-**2** using H_2, Pd/C in THF.[21] To our delight, both reduced species adopted the vase form in $CDCl_3$, as confirmed by characteristic ^{1}H NMR signals of the methine protons between 5.7 and 6.0 ppm. Figure 2 (bottom) shows ^{1}H NMR spectra of red-**1** in various solvents. A rigid vase form was observed not only in $CDCl_3$ and THF-d_8, but also in mesitylene-d_{12}. Remarkably, only the vase form is present even at −80 °C in CD_2Cl_2 and THF-d_8. Both cavitands revert to their oxidized states, ox-**1** and ox-**2**, upon exposing their solutions to air for 2–4 days.[22]

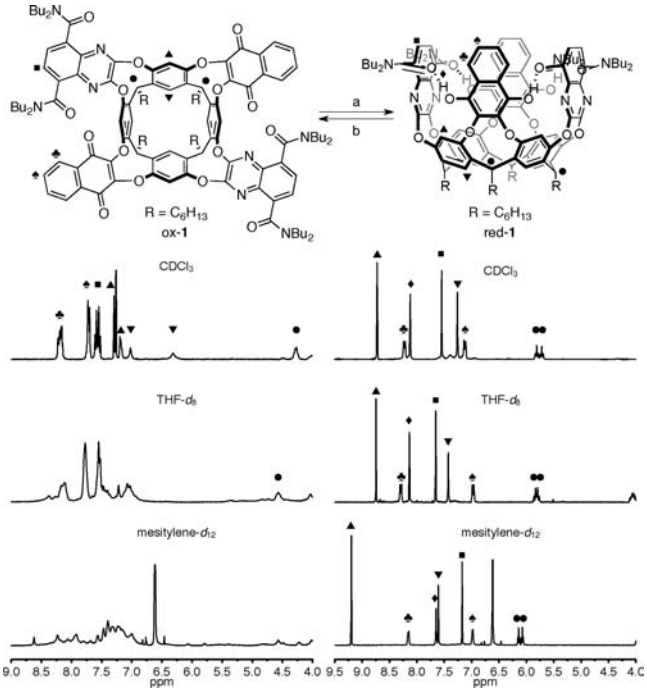


Figure 2. (Top) Redox interconversion between the quinone and hydroquinone states of cavitand **1**. (a) $Na_2S_2O_4$, $CDCl_3/H_2O$, 60 °C, 3 h, quantitative. (b) Air, quantitative. (Bottom) Sections of the ^{1}H NMR spectra (298 K) of cavitands ox-**1** and red-**1** in $CDCl_3$ (300 MHz), THF-d_8 (300 MHz), and mesitylene-d_{12} (500 MHz).

The H-bonds that hold the cavitands in the vase form were characterized using X-ray, IR, and NMR spectroscopies. We obtained a crystal structure of cavitand red-**2** with encapsulated $CDCl_3$ crystallized from mesitylene-d_{12} (Figure 3, bottom). Notably, this is the first crystal structure of a hydroquinone cavitand. The average O···O distances between the amide and the OH oxygen atoms are 2.73 Å. The OH hydrogen atoms are rotated out of the aryl plane toward the amide oxygen atoms with an average dihedral angle of 26.5°.[23] Formation of H-bonds in solution is indicated by a shift and broadening of the IR peak corresponding to the stretching frequency of the OH group (in $CDCl_3$ at ca. 1 mM concentration). The peak shifts from 3555 cm^{-1} in reference compound red-**8** (which lacks H-bonds to amide units) to 3324 cm^{-1} in red-**1** and 3313 cm^{-1} in red-**2**. The ^{1}H NMR signal of the OH group shifts from 5.60 ppm in red-**8** to 8.14 ppm in red-**1** and 8.54 ppm in red-**2**, respectively (in $CDCl_3$). Taken together, these parameters classify the intramolecular H-bonds as strong, neutral H-bonds.[24]

Having realized conformational switching upon changing the redox state of the cavitand, we probed the function of the gripper by assessing its ability to bind and release guests. Binding studies with cavitands are usually conducted in mesitylene-d_{12} due to its large size, which reduces competition with guest molecules for the binding site. To our surprise, the hydroquinone cavitand red-**2** was insoluble in mesitylene-d_{12}.[25] Cavitand **1**, on the other hand, was soluble in mesitylene-d_{12} in

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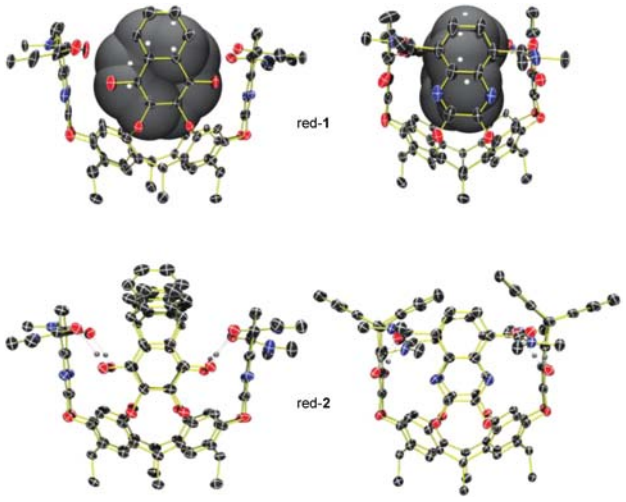

Figure 3. Crystal structures of cavitands red-**1** (guest: cyclooctane) and red-**2** (guest: $CDCl_3$, disordered, not shown) at 100 K, both crystallized from mesitylene-d_{12}. Mesitylene-d_{12} solvent molecules residing outside the cavities, *n*-hexyl, *n*-butyl groups, and hydrogen atoms (except on the OH-group of red-**2**) are omitted for clarity. Thermal ellipsoids are shown at the 30% probability level for red-**1** and 50% for red-**2**.

both redox states, allowing binding studies to be performed. As expected, ox-**1**, which is present in the open kite form, showed no binding of small molecules. In contrast, the reduced vase cavitand, red-**1**, readily bound various guests, as shown by characteristic upfield shifts of the guest ^{1}H NMR signals.[26] Red-**1** complexed a variety of hydrocarbons, including adamantane, *cis*-1,2-dimethylcyclohexane, and *trans*-1,2-dimethylcyclohexane, with slow guest exchange on the NMR time scale. The highest binding constant measured within the cycloalkane series was for cyclooctane (K_a = 83 M^{-1}), which is an unusually large guest for resorcin[4]arene cavitands. Insights into this selectivity were gained from a crystal structure of red-**1** with encapsulated cyclooctane crystallized from mesitylene-d_{12} (Figure 3, bottom). The quinoxaline walls have an opening angle of 7.3°, which results in a rather large cavity among resorcin[4]arene cavitands.[27] This observation explains why red-**1** is present as a rigid vase in mesitylene-d_{12} (Figure 2, bottom): red-**1** probably also complexes this large solvent molecule. In contrast, cavitands with smaller cavities that cannot accommodate mesitylene-d_{12} show dynamic exchange in their ^{1}H NMR spectra.[18,28]

Alicyclic guests containing H-bond-accepting carbonyl groups give, in most cases, even higher association constants, compared to pure hydrocarbon guests (Table 1). The highest binding constant measured within the cycloalkanone series was for cycloheptanone (K_a = 224 M^{-1}), and a binding constant of similar magnitude was measured for ε-caprolactam. A remarkably high association constant for the binding of top-open cavitands to neutral guests was measured for 1,4-cyclohexanedione (K_a = 1080 M^{-1}). This guest has the ideal size for fitting into the cavitand.[29] The first-order rate constant for the decomplexation of 1,4-cyclohexanedione from red-**1** in mesitylene-d_{12} at 298 K was determined using an inversion-transfer NMR experiment to be k_{-1} = (10.5 ± 0.2) s^{-1}.[30] The measured rate constant corresponds to an activation free enthalpy of $\Delta G^{\ddagger}$ = (16.1 ± 0.1) kcal mol^{-1}, which is comparable to other rigid, top-open cavitand systems.[31]

Table 1. Association Constants K_a at 298 K for the Binding of Small Molecule Guests to Cavitand Red-1[a]

Guest	K_a (red-**1**⊂guest) / M^{-1}
	13
	99
	29
	3
	23
	83
	47
	224
	157
	42
	1080

[a] K_a values were determined by integration of the ^{1}H NMR resonances of the relevant species, relative to 1,3,5-trimethoxybenzene as an internal standard. Errors in K_a values are estimated to be roughly 20%.

Oxidation of the sample in air allowed the cavitand to revert to its open kite form (ox-**1**), resulting in guest release.

In summary, we have successfully developed cavitands that possess all the necessary features of a redox-switchable molecular gripper: redox-addressable conformational and binding properties. This work has broad implications for the design of switchable molecular systems whose functionality can be predicted, and moves the field of cavitand chemistry closer to molecular engineering. Our redox-switchable cavitand system is now ready to be tested as a molecular gripper by chemically attaching it to a suitable surface,[32] and further investigating its application in nanorobotics.[33]

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data, kinetic data, variable-temperature NMR studies, and electrochemistry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) In $(CDCl_2)_2$, see Section 4.1 in the Supporting Information.
(20) Cyclic voltammetry (CV) and rotating-disk voltammetry (RDV) data on ox-**1**, red-**1**, and red-**8** are presented in Section 8 of the Supporting Information.
(21) We found that the use of $Na_2S_2O_4$ for the reduction of the triptycene-quinone moiety leads to side products, while H_2, Pd/C resulted in a clean conversion to the hydroquinone product.
(22) Solid samples of red-**2** were stable in air for at least two months.
(23) The OH hydrogen atom position was refined as the maximum of the electron density on a conus around the oxygen atom with a fixed radius and opening angle.
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(26) Details on binding studies together with a list of guests that showed no binding, very weak binding, or binding with fast guest exchange are presented in Section 6 of the Supporting Information.
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(30) For the determination of decomplexation kinetics, see Section 7 of the Supporting Information.
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NOTE ADDED AFTER ASAP PUBLICATION

Figure 2 was incorrect in the version published ASAP August 27, 2012. The corrected version reposted August 28, 2012.