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Development of Redox-Switchable Resorcin[4]arene Cavitands

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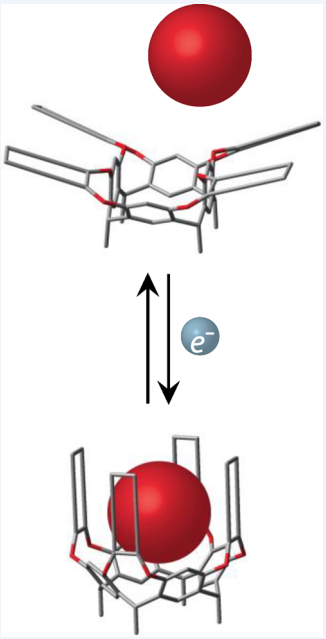
CONSPECTUS: Within the framework of miniaturization of electromechanical devices, the development of a redox-switchable molecular gripper as a tool for nanorobotics is appealing both from an academic and from a practical perspective. Such a tool should be able to controllably grab a molecular cargo, translocate it over considerable distances and time scales, and release it.

Resorcin[4]arene cavitands seem to be an ideal platform for the development of molecular grippers due to their ability to adopt two spatially well-defined conformations: an expanded kite and a contracted vase. Furthermore, they possess "legs" for functionalization and attachment to metal surfaces. While changes in temperature, pH, and metal-ion concentration were known to induce conformational switching, redox-switchable cavitands remained a challenge.

In this Account, we describe our efforts toward the development of a new class of resorcin[4]arene cavitands that are redox-switchable. First, we introduced the naphthoquinone moiety as a redox-active wall component and showed that cavitands containing four quinone walls strongly prefer the open kite conformation in both the quinone and hydroquinone redox states, while cavitands that contain two quinone and two quinoxaline walls can adopt both the vase and the kite conformations depending on solvent but not on redox state.

Next, in order to introduce a driving force for the conformational switching process in diquinone cavitands, we designed cavitands with hydrogen bond acceptor groups on the quinoxaline walls. These acceptors were sought to establish hydrogen bonds with the hydroquinone groups in the reduced redox state, thereby stabilizing the vase form. Oxidation to the quinone state would remove these interactions, switching the cavitand back to the kite form. Cavitands equipped with different hydrogen bond acceptor groups were synthesized and evaluated. We found that carboxamide moieties are best suited to assist redox-induced switching of conformational and binding properties.



With the goal of further increasing association constants and reducing guest-exchange rates via steric congestion, we exchanged the naphthoquinone with the triptycene-quinone moiety. The congesting influence of the triptycene-quinone moiety on the binding properties was quantified both in the presence and in the absence of additional hydrogen bond interactions that stabilize the vase form. X-ray crystallographic studies provided insights into the solid-state structures of the cavitands in different solvents and redox states. A significant enhancement of association constants and reduction in guest release rates was observed in the reduced redox state compared with the top-open system, yielding redox-switchable cavitand baskets.

These studies represent a step towards the development of redox-switchable molecular grippers on metal surfaces. Future challenges will consist in the development of cavitands that will no longer rely on an external proton source for the switching process, allowing redox-switching to be performed in purely aprotic media. Finally, suitable leg functionalization would enable the grippers to be interfaced with metal surfaces.

1. INTRODUCTION

The design, synthesis, and study of molecular systems whose conformational and binding properties can be predictively changed in response to external stimuli[1−3] are contributing to transforming supramolecular chemistry from a science field to an engineering field. While molecular analogues of various macroscopic objects[4−10] have been developed, molecules that could act as molecular grippers[11,12] remained underexplored. The requirement for a molecule to act as a gripper is the ability to close and open upon external stimulation and, in doing so, to grab and release molecular objects. Such an element could be applied to a wide range of areas, including nanorobotics,[13] drug delivery, and fundamental physical organic chemistry studies.[14−16]

Resorcin[4]arene cavitands are molecules that can adopt two spatially well-defined conformations: an expanded kite and a contracted vase (Figure 1A).[12] Because the conformational change that resorcin[4]arene cavitands undergo resembles the movement of a gripper, systems of this type present an ideal platform for the development of molecular grippers. The first resorcin[4]arene cavitand was reported by Cram and co-

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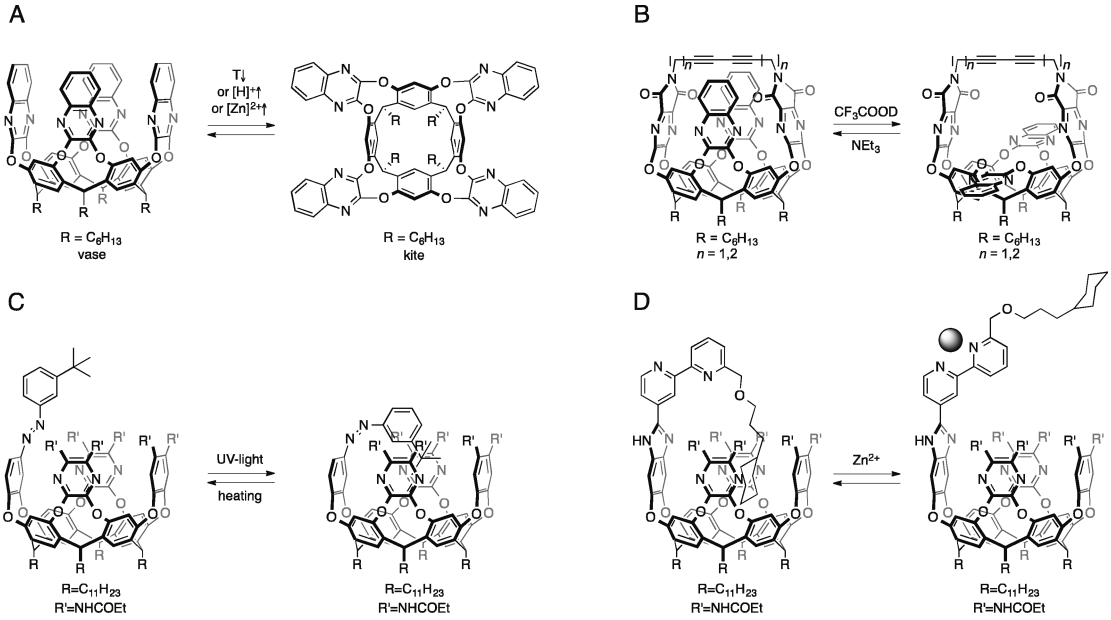

Figure 1. A) Parent quinoxaline-based cavitand that is switchable by changing temperature,[17−20] pH,[14−16,21] and Zn^{2+} ion concentration.[22] Cavitands, whose binding properties can be modulated by changes in pH (B),[23,24] by light (C),[25,26] and by metal-ion complexation (D).[27]

workers in 1982 and contained four quinoxaline units as cavitand wall components (Figure 1A).[17] Various stimuli have been discovered to induce a conformational switch in this type of cavitand, including changes in temperature,[17−20] pH,[14−16,21] and Zn^{2+} ion concentration.[22] Because cavitand molecules possess an interior cavity, they can take up guest molecules. The binding properties of cavitands have been modulated by changes in pH (Figure 1B),[23,24] by light (Figure 1C),[25,26] and by metal-ion complexation (Figure 1D).[27] The ability to modulate redox properties for tuning both the conformational and binding properties of cavitands, however, remained a highly desired but unreached goal.[28] Redox-switchable cavitands could be employed in electronic devices because they offer the potential to be interfaced and addressed on electroactive metal surfaces. This Account focuses on our work on the development of redox-switchable cavitands.

2. CHARACTERIZATION OF CONFORMATIONAL PROPERTIES OF CAVITANDS BY ^{1}H NMR SPECTROSCOPY

We will start our discussion with a description of how information about the conformational properties of cavitands can be deduced by ^{1}H NMR spectroscopy (Figure 2).[17−19,29] Cavitands can be present either in the vase or in the kite conformation. In addition, because the kite form is C_{2v} symmetric, there is interconversion between the two degenerate kite forms (kite1−kite2 interconversion). An important indicator for the adopted conformation is the ^{1}H NMR chemical shift of the methine proton, which is located directly below the wall and is therefore sensitive to the wall orientation. If the vase conformation is exclusively present, the methine proton (●) shift is observed at ca. 5.6 ppm. Because the vase form is C_{4v} symmetric, only one peak is observed for the upper rim (▲) and lower rim (▼) protons. On the other hand, if the kite conformation is exclusively present, the methine proton (●) shift is observed at ca. 4 ppm. The number of observed signals for the upper rim (▲) and lower rim (▼) protons then depends on the rate of the kite1−kite2

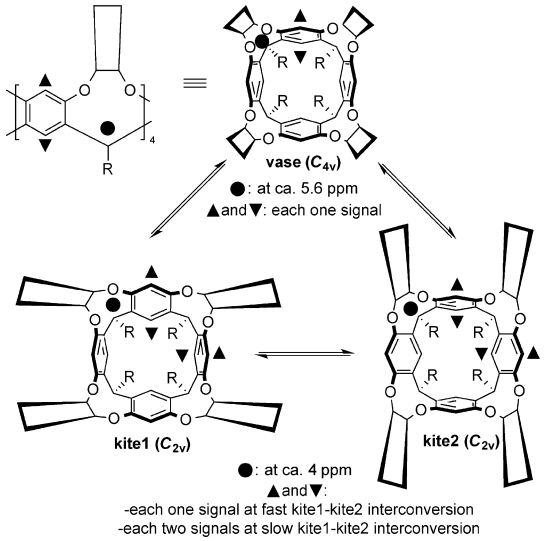

Figure 2. Conformational interconversion of a generic cavitand and summary of characteristic ^{1}H NMR features of the three situations: vase, kite with slow kite1−kite2 interconversion, and kite with fast kite1−kite2 interconversion.

interconversion. If this rate is fast on the NMR time scale, an averaged signal for each ▲ and ▼ proton is observed. If the rate is slow, however, two signals for each ▲ and ▼ proton are observed.

3. INTRODUCTION OF THE QUINONE UNIT AS A REDOX-ACTIVE CAVITAND WALL COMPONENT

The first step toward the development of redox-switchable cavitands was to identify a redox-active moiety that could be incorporated into a cavitand and would influence its conformational properties upon redox interconversion. From a synthetic perspective, at the beginning of the project in 2010, only three structurally different wall precursors had been frequently employed in cavitand chemistry, namely, 2,3-dichloroquinoxa-

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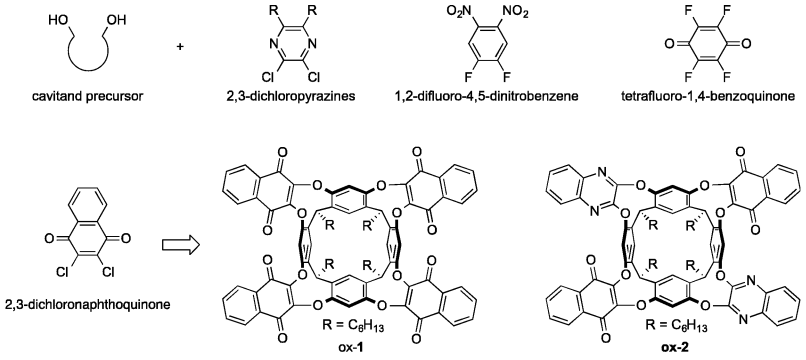

Figure 3. (top) Compounds that have been employed as reaction partners with cavitand precursors. (bottom) Idea of introducing the quinone moiety as a redox-active cavitand wall component to yield tetraquinone cavitand ox-**1** and diquinone cavitand ox-**2**.

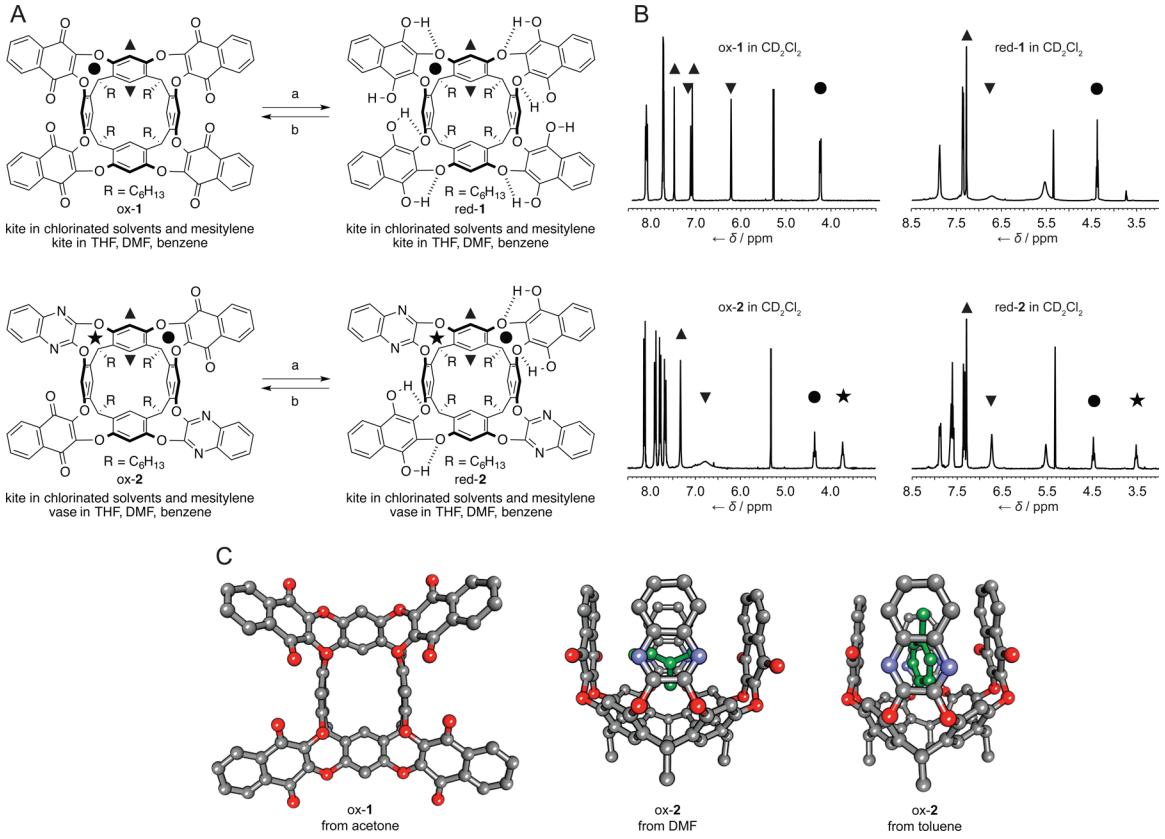

Figure 4. (A) Redox interconversion and summary of conformational properties of cavitands ox/red-**1** and ox/red-**2** in various solvents: (a) $Na_2S_2O_4$, $CDCl_3/H_2O$ (degassed), 60 °C, 3 h, quantitative; (b) air, quantitative. (B) ^1H NMR spectra of cavitands ox-**1** and red-**1** (298 K, 500 MHz) and ox-**2** and red-**2** (298 K, 300 MHz) in CD_2Cl_2. (C) Crystal structures of cavitands ox-**1** crystallized from acetone (kite form) and ox-**2** crystallized from DMF (vase form) and from toluene (vase form) at 100 K. The cavity-bound solvent molecules are shown in green. Exterior solvent molecules in the crystal lattice, *n*-hexyl chains, and hydrogen atoms are omitted for clarity.

lines (as in Figure 1A), 2,3-dichloropyrazines, and 1,2-difluoro-4,5-dinitrobenzene (Figure 3). The requirement for suitable wall precursors is the presence of two *ortho*-positioned leaving groups that are activated enough to undergo a 2-fold nucleophilic substitution reaction with the phenolic OH groups of the cavitand precursor, a nonbridged resorcin[4]arene also known as octol.[30] Thus, the leaving groups need to be positioned on an electron-withdrawing ring system, which is fulfilled by both the dinitrobenzene and the pyrazine core. Unfortunately, 2,3-dichloroquinoxalines, 2,3-dichloropyrazines, and 1,2-difluoro-4,5-dinitrobenzene do not yield redox-active cavitand walls. A fourth class of compounds that fulfill the requirements described above are dihalogenoquinones. Indeed, in one report by Cram and co-workers, tetrafluoro-1,4-benzoquinone had been employed as a cavitand wall component to bridge two cavitand precursors in a C-shaped fashion.[31] Although in this report tetrafluoro-1,4-benzoquinone has only been used as a structural element, we became interested in investigating the properties of the quinone moiety as a redox-active cavitand wall component. Literature reports suggested that the more easily accessible dichloroquinones should also be reactive enough to undergo substitution reactions with phenolic OH groups.[32] Thus, we sought to employ 2,3-dichloronaphthoquinone to yield tetraquinone cavitand ox-**1** and diquinone cavitand ox-**2** and to study their

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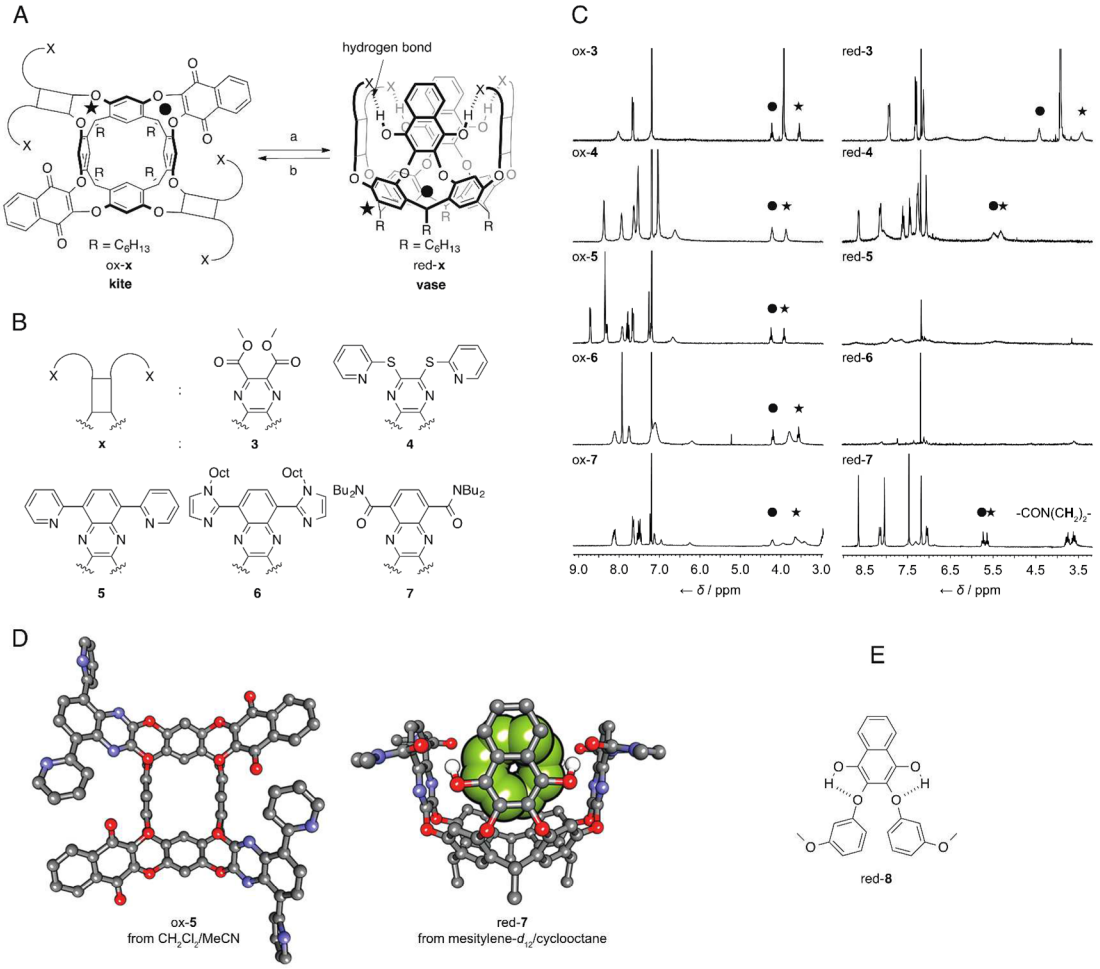

Figure 5. (A) Design concept of redox-switchable cavitands: (a) $Na_2S_2O_4$, $CDCl_3/H_2O$ (degassed), 60 °C, 3 h, quantitative; (b) air, quantitative. (B) Investigated hydrogen bond acceptor groups attached to the walls of the cavitands. (C) Sections of the ^1H NMR spectra (298 K) of cavitands ox-**3**–**7** and red-**3**–**7** in $CDCl_3$ (300 MHz). The symbols ● and ★ represent methine protons. (D) Crystal structure of cavitand ox-**5** crystallized from CH_2Cl_2/MeCN (kite form) and cavitand red-**7** crystallized from mesitylene-d_{12}/cyclooctane (vase form) at 100 K. Exterior solvent molecules, *n*-hexyl, *n*-butyl chains, and hydrogen atoms are omitted for clarity. (E) Reference compound red-**8**.

conformational preferences in the oxidized and reduced redox states (Figure 3).[29]

Figure 4A summarizes the conformational properties of cavitands ox/red-**1** and ox/red-**2**. We found that cavitand ox-**1** strongly prefers the kite conformation in most organic solvents. Thus, the ^1H NMR spectrum of cavitand ox-**1** in CD_2Cl_2 (Figure 4B) exhibits methine protons (●) at 4.25 ppm. The presence of two sharp signals for each of the bowl protons, ▲ and ▼, indicates that the kite1−kite2 interconversion is slow on the NMR time scale. The preference of cavitand ox-**1** for the kite form was further confirmed by X-ray crystallography (crystals from acetone, Figure 4C). The reduced state, red-**1**, was accessed via reduction of ox-**1** with $Na_2S_2O_4$. Cavitand red-**1** is also present in the kite form in CD_2Cl_2, as revealed by a chemical shift of the methine protons (●) at 4.39 ppm. However, cavitand red-**1** exhibits a much faster kite1−kite2 interconversion than ox-**1**, which is indicated by the presence of only one signal for each aromatic proton, ▲ and ▼. This suggests that the transition state for the kite1−kite2 interconversion, which resembles the vase form,[19] is stabilized in the reduced form. However, this stabilization is not large enough to induce a switch to the vase form. Presumably, the adoption of the vase form in the cavitands ox/red-**1** is hindered by repulsive C═O···O═C or C−OH···HO−C interactions. Air oxidation fully regenerates ox-**1**.

Because these repulsive interactions are not present in the diquinone system ox-**2**, cavitand ox-**2** is structurally more flexible (Figure 4A); although ox-**2** also adopts the kite form in CD_2Cl_2 (Figure 4B, methine protons ● and ★ at 4.36 and 3.74 ppm), its kite1−kite2 interconversion rate is faster than that of ox-**1** (only one signal for each aromatic protons, ▲ and ▼). Furthermore, in the solvents DMF, THF, and benzene, which are better able to stabilize the vase conformation, cavitand ox-**2** adopts the vase form. The vase form is also preferred in the solid state, when the cavitand is crystallized from DMF or toluene (Figure 4C). In this case, solvent molecules fill the interior cavity. To test the switching ability of ox-**2**, we accessed its reduced state, red-**2**. However, we found that cavitand red-**2** exhibits the same solvent-dependent conformational preferences as ox-**2**, meaning that a conformational change in these systems cannot be induced by reduction. The inability of cavitand ox-**2** to switch upon reduction can be explained by the lack of a driving force that would render this process favorable.

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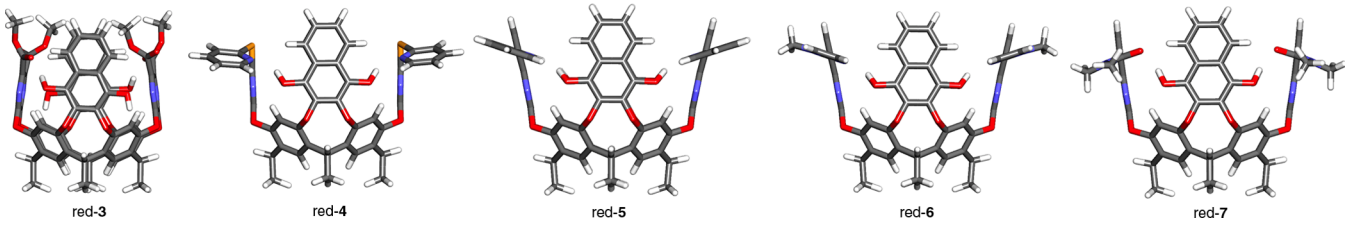

Figure 6. Structures of cavitands red-**3**−**7** optimized at the DFT B3LYP/6-31G(d) level of theory. Alkyl chains were exchanged with methyl groups.

4. DEVELOPMENT OF REDOX-SWITCHABLE CAVITANDS

We reasoned that in order to achieve conformational switching in diquinone cavitands, the vase form would need to be stabilized by interactions that would be present only in the reduced hydroquinone state.[33] From a structural perspective, the only change that occurs upon quinone reduction is the transformation of C═O to C−OH groups. Thereby, a weak hydrogen bond acceptor is converted into a strong hydrogen bond donor. Our idea was therefore to exploit hydrogen bonds, which are among the strongest noncovalent interactions,[34−37] as a driving force for the conformational switching process. This could be accomplished by placing suitable hydrogen bond acceptor groups on the quinoxaline walls of a diquinone cavitand (Figure 5A). Reduction of quinone to hydroquinone units would then enable the formation of intramolecular hydrogen bonds, thereby switching the cavitand to the vase form. Reoxidation to the quinone state would remove these interactions and switch the cavitand back to the kite conformation. The hydrogen bond acceptor groups that we investigated were the ester (**3**), pyridine (**4**, **5**), imidazole (**6**), and *N*,*N*-dialkylcarboxamide groups (**7**) (Figure 5B). The cavitands were prepared, and their redox state-dependent conformational properties were investigated.[33,38]

The ^{1}H NMR spectra of cavitands ox-**3**−**7** and red-**3**−**7** are presented in Figure 5C. The methine protons, ● and ★, of the oxidized states ox-**3**−**7** are located between 3.6 and 4.4 ppm in $CDCl_3$, indicating that these cavitands are present in the kite form. This observation is in line with the behavior of the parent diquinone cavitand ox-**2**. The preference for the kite form was further confirmed by an X-ray structure of cavitand ox-**5** (crystallized from CH_2Cl_2/MeCN, Figure 5D), which portrayed the cavitand in the kite conformation.

The reduced cavitands, red-**3**−**7**, on the other hand, exhibit more diverse behavior (Figure 5C). While the ester-substituted cavitand red-**3** is present in the kite form, meaning that redox-switching does not take place in that system, the *S*-pyridine-substituted cavitand red-**4** adopts a dynamic vase form. The ^{1}H NMR spectra of pyridine- and imidazole-substituted cavitands red-**5** and red-**6** display broad peaks, hinting at either dynamic behavior or intramolecular aggregation of the cavitands. To rule out decomposition as a potential explanation for the complex spectra, we exposed the solutions of red-**5** and red-**6** to air for 1−3 d, thereby fully restoring the oxidized states ox-**5** and ox-**6**. In contrast to these systems, the ^{1}H NMR spectrum of cavitand red-7 exhibits sharp triplets corresponding to the methine protons, ● and ★, revealing that the cavitand adopts a rigid vase conformation.

The intramolecular hydrogen bonds between the hydroquinone OH groups and the carboxamide C═O groups of red-**7** were characterized by IR spectroscopy, NMR spectroscopy, and X-ray crystallography.[38] Compared with reference compound red-**8** (Figure 5E), which lacks H-bonds to amide units, the IR absorption band of the OH group of cavitand red-7 is broader and shifted from 3555 to 3324 cm^{-1} in $CDCl_3$ solution. The ^{1}H NMR signal of the OH group shifts from 5.60 ppm in red-**8** to 8.14 ppm in red-7 in $CDCl_3$ at 298 K. Crystals of red-7 were grown from a mesitylene-d_{12} solution containing cyclooctane. The X-ray structure of red-7 shows the cavitand in the vase form with encapsulated cyclooctane (Figure 5D). The average O···O distance between the carboxamide and the OH oxygen atoms is 2.68 Å. The torsion angle between the C═O moiety and the quinoxaline wall varies for the four carboxamide units and is in the range of 72−96°. Thus, the IR, NMR, and X-ray results classify the intramolecular hydrogen bonds as strong, neutral hydrogen bonds.[39]

We performed computational studies in order to rationalize the conformational properties of cavitands red-**3**−**7**.[33] The structures of cavitands red-**3**−**7** were optimized at the DFT B3LYP/6-31G(d) level of theory (Figure 6, alkyl chains were exchanged by methyl groups). In the ester-based cavitand red-**3**, only two hydroquinone OH groups per cavitand can hydrogen-bond with the COOMe moieties due to steric reasons. In contrast, in cavitand red-**4** all four hydrogen bonds can be established. This result is in accordance with the observation that in cavitand red-**3** the kite form is more favorable, while cavitand red-**4** adopts the vase form in $CDCl_3$ solution. Apparently, the formation of all four hydrogen bonds is required to render the vase form more favorable. However, although all four hydrogen bonds can, in principle, be established in cavitands red-**5**−**7**, only red-7 clearly adopts a vase conformation according to its ^{1}H NMR spectrum. Thus, additional requirements for successful H-bond acceptors must exist. To rationalize why red-7 adopts the vase conformation, while red-**5** and red-**6** do not, we calculated dihedral angle scans (θ) of hypothetical pyridine-, imidazole-, and carboxamide-containing test systems on the MP2/cc-pVTZ//B3LYP/6-31+G(d,p)[40,41] level of theory (Figure 7). For the pyridine wall, the global energy minimum is located at a dihedral angle of 140°, which is consistent with the dihedral angle range of 130−158° observed in the crystal structure of ox-**5** (Figure 5D). For the imidazole and the carboxamide walls, the global minima are located at 130° and 120°, respectively. The formation of intramolecular hydrogen bonds, however, is only possible for dihedral angles θ in the range of 60−100° (blue-colored area in Figure 7). To reach this range at least 1.9 kcal mol^{-1} are required for the pyridine, 1.3 kcal mol^{-1} for the imidazole, and 0.3 kcal mol^{-1} for the carboxamide moiety. This energetic penalty in case of the pyridine and imidazole moieties is presumably so large that remaining in their optimal orientations and establishing intermolecular hydrogen bonds with OH groups of other cavitand molecules might be more favorable. In case of the carboxamide moiety, on the other hand, the conformational energetic penalty is presumably smaller than the energetic gain resulting from the formation of intra-

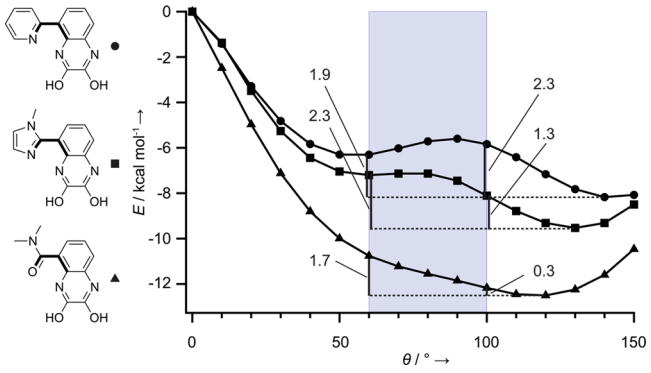

Figure 7. Dihedral angle scans for hypothetical test systems containing the pyridine, imidazole, and carboxamide moieties, performed on the MP2/cc-pVTZ//B3LYP/6-31+G(d,p) level of theory. The highlighted gray area is the dihedral angle range in which H-bonding to the hydroquinone OH groups would be possible in the cavitand systems.

molecular hydrogen bonds. Thus, the additional criterion for an acceptor that is able to stabilize the vase form is the preferential adoption of a dihedral angle in the range of 60−100°.

Having established that the carboxamide-based cavitand ox-**7** represents a redox-switchable system, we investigated its binding properties in both redox states. Binding studies were performed in mesitylene-d_{12}, a solvent that exhibits a reduced ability to compete with guest molecules for the binding site due to its large size.[42,43] In this context, it should be noted that apolar guest encapsulation is likely to be driven by gains in dispersion interactions with the host or solvophobic effects.[44−46] Cavitand ox-**7**, which is present in the open kite form, showed no binding of small molecules. On the other hand, cavitand red-**7** readily bound a variety of hydrocarbons with slow guest exchange rates on the NMR time scale (Table 1).[38] Within the cycloalkane series, the highest binding constant was measured for cyclooctane (K_a = 83 M^{-1}), which is an unusually large guest for resorcin[4]arene cavitands. This selectivity for large guests was explained by the large opening angle of the quinoxaline walls in red-**7** (see the X-ray structure in Figure 5D). A high association constant for the binding of top-open cavitands to neutral guests was measured for 1,4-cyclohexanedione (K_a = 1080 M^{-1}), which can be explained with very good size-complementarity.

The decomplexation of 1,4-cyclohexanedione from red-**7** proceeds with a rate constant of k_{out} = 10.5 ± 0.2 s^{-1}. This constant corresponds to a Gibbs energy of activation of $\Delta G^{\ddagger}$ = 16.1 ± 0.1 kcal mol^{-1}, which is comparable to other rigid, top-open cavitand systems.[47−50] As rationalized by Rebek and co-workers, the slippage of a guest from a rigid cavitand creates desolvated surfaces in the cavitand interior, which is energetically highly unfavorable.[47,48] Thus, guest escape requires the (at least partial) unfolding of the cavitand, which links the Gibbs energy of activation for guest release to that of cavitand unfolding. In the case of cavitand red-**7**, unfolding requires breaking of the strong hydrogen bonds. This rationale explains how a top-open but hydrogen bond-stabilized rigid container molecule can exhibit considerable association constants and reduced guest exchange rates.

5. REDOX-SWITCHABLE BASKETS WITH ENHANCED ASSOCIATION CONSTANTS AND REDUCED GUEST-EXCHANGE RATES

A molecular gripper should be able to grab and transport its cargo over considerable distances and time scales, requiring it to be able to bind guest molecules with very high association constants and very low guest release rates in their closed states. One possibility to increase association constants and reduce guest exchange rates is the closure of the top of the cavity, leading to steric encapsulation of guests.[51−54] To implement this concept, we prepared the systems illustrated in Figure 8.

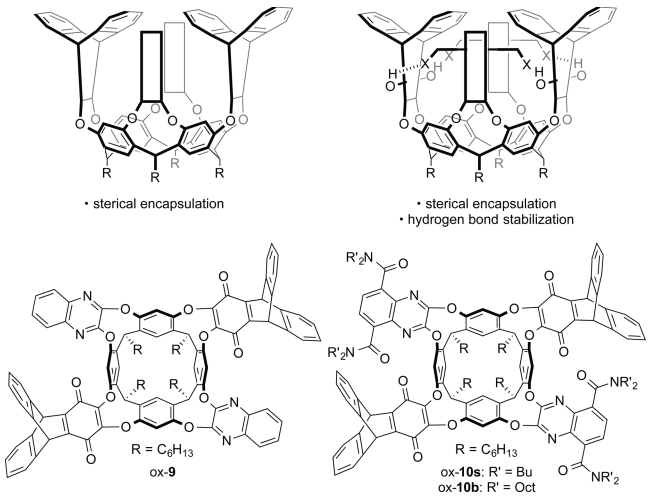

Figure 8. Concept of steric encapsulation for achieving high association constants and low guest-exchange rates. Cavitand ox-**9** served for testing the influence of steric encapsulation, while cavitands ox-**10a,b** incorporated both steric encapsulation and switchable rigidity provided by hydrogen bonds.

Cavitands ox-**9** and ox-**10a,b** feature two triptycene moieties in a parallel orientation that would enable complete guest encapsulation in the vase forms of the cavitands. Cavitands ox/red-**9** do not possess hydrogen bond acceptor groups, enabling the dissection of the sole influence of steric encapsulation on cavitand binding properties.[29] On the other hand, cavitands ox/red-**10a,b** incorporate both elements: steric encapsulation and switchable rigidity provided by hydrogen bonds.[33]

The conformational and binding properties of cavitands ox/red-**9** are summarized in Figure 9.[29] Both redox states, ox-**9** and red-**9**, are present in the kite conformation in $CDCl_3$ and

Table 1. Association Constants K_a between Cavitand red-7 and Various Guests[a]

guest											
K_a(red-**7**⊃guest) / M^{-1}	13	99	29	3	23	83	47	224	157	42	1080

[a]In mesitylene-d_{12}, 298 K. Determined by integration of the ^{1}H NMR resonances of the relevant species, relative to 1,3,5-trimethoxybenzene as an internal standard. Error in K_a is estimated to be roughly 20%.

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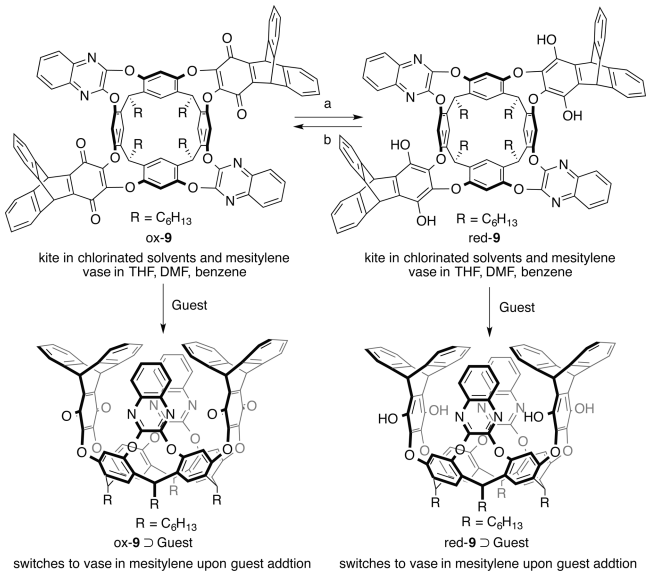

Figure 9. Conformational properties of cavitands ox/red-**9** in the absence and presence of guests: (a) H_2, Pd/C, THF (degassed), 25 °C, 30 min, quantitative; (b) air, quantitative.

mesitylene-d_{12} and in the vase form in THF-d_8, DMF-d_7, and benzene-d_6. This conformational behavior is similar to the parent diquinone system ox/red-**2** and is also valid in the solid state: ox-**9** crystallized in the vase form from DMF and in the kite form from mesitylene-d_{12} (Figure 10). This observation highlights the fact that diquinone cavitands have no pronounced preference for one conformation over the other and that the sole influence of the solvent determines the observed conformation.

While both cavitands, ox-**9** and red-**9**, are present in the kite conformation in pure mesitylene-d_{12}, upon guest addition they both switch to the vase form and encapsulate the guest molecule (Figure 9).[29] The formed complexes are kinetically stable on the NMR time scale. The association constants (K_a) of ox-**9** and red-**9** with the cycloalkane guest series are shown in Table 2. The highest association constants were measured for cyclohexane for both cavitands, reflecting that the cavity volumes of both cavitands are in the medium range compared with other top-closed systems.[23,24,55] Overall, the association constants are rather small, because a kite−vase transition that "costs" binding energy needs to take place for guest encapsulation. On the other hand, these association constants together with the fact that slow guest exchange rates are

Table 2. Association Constants K_a for the Complexation of Cavitands ox/red-9 and ox/red-10b with Various Guest Molecules[a]

guest	⬡	⬢	⯃	⯄	
K_a(ox-**9**⊃guest) / M^{-1}	3.2	19.2	6.3	n. d.	n. d.
K_a(red-**9**⊃guest) / M^{-1}	0.1	3.2	1.6	n. d.	n. d.
K_a(ox-**10b**⊃guest)[b] / M^{-1}	0.2	2.6	8	2	40
K_a(red-**10b**⊃guest)[b] / M^{-1}	160	300	330	5300	8700

[a]In mesitylene-d_{12}, 298 K. Determined by integration of the ^{1}H NMR resonances of the relevant species, relative to 1,3,5-trimethoxybenzene as an internal standard. Error in K_a is estimated to be roughly 20%. [b]K_a values were corrected to account for the presence of 0.4 equiv of THF remaining after reduction in the cavitand sample.

observed are considerable compared with the top-open system ox/red-**2**, which does not show any binding of small molecules.

Figure 11 shows the conformational and binding properties of cavitands ox/red-**10**. While the oxidized baskets ox-**10** are

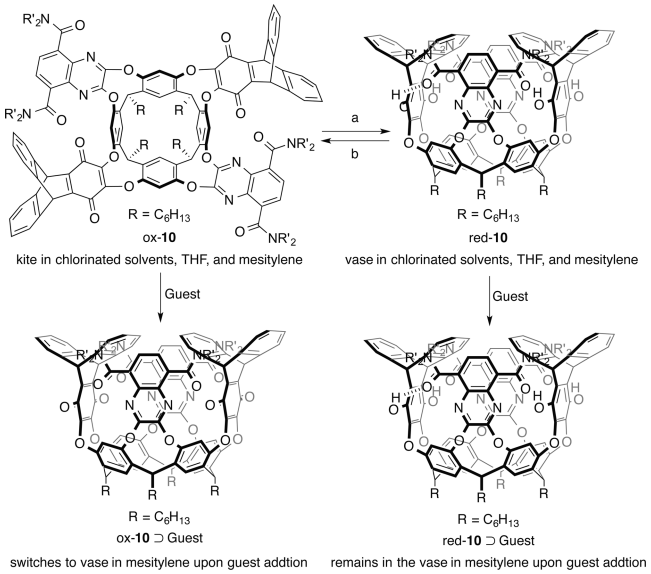

Figure 11. Conformational properties of cavitands ox/red-**10** in the absence and presence of guests: (a) H_2, Pd/C, THF (degassed), 25 °C, 30 min, quantitative; (b) air, quantitative.

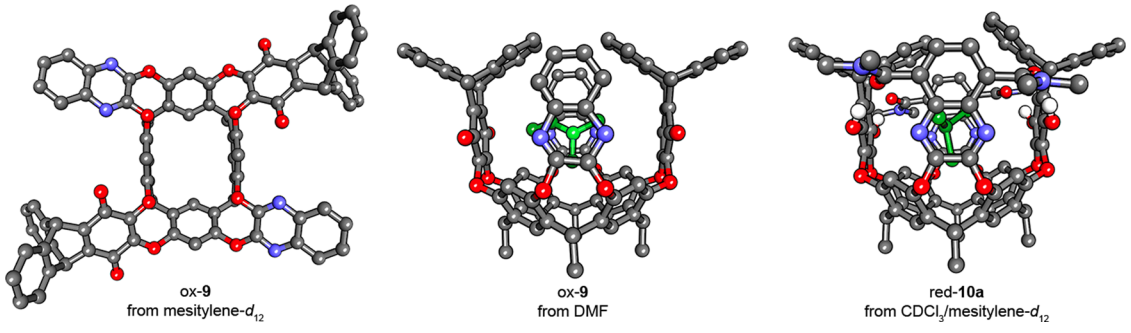

Figure 10. Crystal structures of cavitand ox-**9** crystallized from mesitylene-d_{12} (kite form) and DMF (vase form) and cavitand red-**10a** crystallized from $CDCl_3$/mesitylene-d_{12} (vase form) at 100 K. Solvent molecules residing outside of cavities, *n*-hexyl, *n*-butyl chains, and hydrogen atoms (except on the OH groups of red-**10a**) are omitted for clarity.

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present in the kite form in $CDCl_3$ and mesitylene-d_{12}, the reduced baskets red-**10** switch to a rigid, hydrogen bond-stabilized vase form in these solvents.[33] An X-ray crystal structure of the *N*,*N*-dibutyl-substituted cavitand red-**10a** from $CDCl_3$/mesitylene-d_{12} was obtained, showing the cavitand in the vase form (Figure 10). Although three mesitylene-d_{12} molecules are present in the unit cell, the cavity is filled with a $CDCl_3$ molecule. The average O···O distance between the amide and the OH oxygen atoms is 2.73 Å. The torsion angle between the C═O moiety and the quinoxaline wall varies for the four amide units and is in the range of 75−96°.

For binding studies, the *N*,*N*-dioctyl-substituted system ox/red-**10b** was employed because of its enhanced solubility in mesitylene-d_{12} compared with ox/red-**10a**.[33] As for ox/red-**9**, cavitand ox-**10b** is present in the kite form in mesitylene-d_{12} and undergoes a guest-induced kite−vase switching upon guest addition (Figure 11). The K_a values of ox-**10b** are in the range of 10^{-1}−10^{1} M^{-1} and therefore on the same order of magnitude as those of ox/red-**9** (Table 2). On the other hand, cavitand red-**10b** is preorganized in the vase form for guest uptake and achieves much higher association constants in the range of 10^{2}−10^{4} M^{-1}. Thus, modulation of the redox state of cavitand **10b** switches its association constants by a factor of 10^{2}−10^{3}. The sole influence of the triptycene moiety is revealed by comparing triptycene-based red-**10b** and naphthoquinone-based red-**7**; replacing the naphthoquinone by the triptycene moiety increases K_a values by a factor of 10^{1}−10^{2}.

Bridging the top of the cavity by triptycene moieties and stabilizing the vase form by hydrogen bonds has also a large impact on guest uptake and release kinetics.[33] The first-order rate constant for cyclooctane uptake by red-**10b** is k_{in} = (5.4 ± 0.3) × 10^{-4} s^{-1} ($\Delta G^{\ddagger}_{298K}$ = 21.9 kcal mol^{-1}) and for cyclohexane release k_{out} = (5.3 ± 0.2) × 10^{-5} s^{-1} ($\Delta G^{\ddagger}_{298K}$ = 23.3 kcal mol^{-1}). Figure 12 shows a comparison of guest-release rates, k_{out}, for different cavitands. The rate constant (k_{out} = (5.3 ± 0.2) × 10^{-5} s^{-1}, cyclohexane) measured for red-**10b** is the smallest value ever reported for a cavitand system. Compared with the top-open, hydrogen bond-stabilized cavitands red-**7** (k_{out} = (10.5 ± 0.2) s^{-1}, 1,4-cyclohexanedione) and the Rebek system **11** (k_{out} = (2 ± 1) s^{-1}, adamantane),[47,48] it can be concluded that closing the top of a hydrogen bond-stabilized cavitand reduces the guest-release rate by a factor of 10^{4}−10^{5}. Comparing cavitand red-**10b** to the top-closed but not hydrogen bond-stabilized cavitand **12** (k_{out} = 2.5 × 10^{-3} s^{-1}, cyclohexane)[23] allows the conclusion that additionally rigidifying a closed system by hydrogen bonds can reduce the guest-release rate by a factor of 10^{2}.

6. SUMMARY AND OUTLOOK

In summary, we have developed cavitands whose conformational and binding properties can be influenced by redox interconversion, presenting an example of how a molecular switch can be engineered in a stepwise manner with the assistance of molecular design, synthesis, ^{1}H NMR spectroscopy, X-ray crystallography, and computational studies.

Future challenges will consist of the functionalization of the switchable cavitand system at the upper rim (walls), because introduction of functionalities would contribute to broadening of the potential application areas of the newly developed switches. Top functionalization, for example, could pave the way for extended redox-switchable tubes, which would be able to trap larger guest molecules. Another important future research direction is the development of redox-switchable

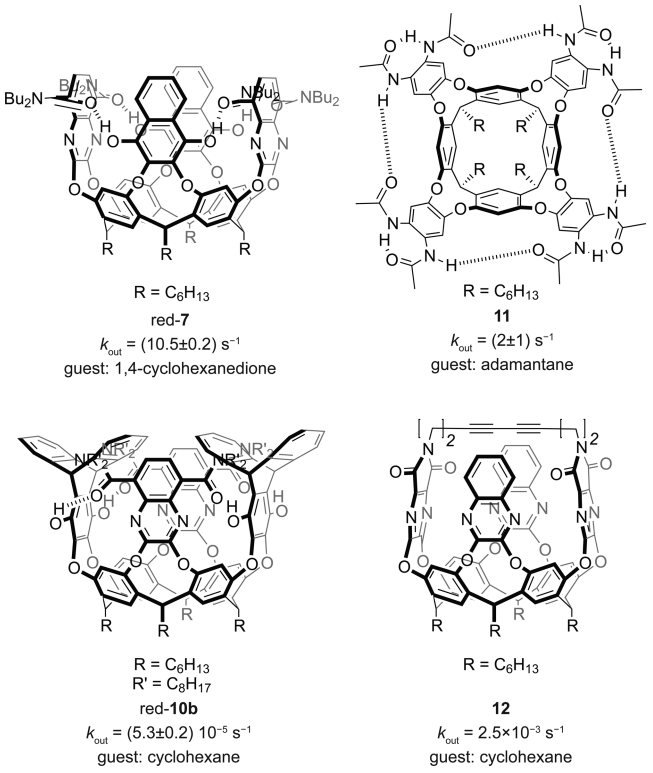

Figure 12. Comparison of guest-release rates k_{out} for different cavitands.

cavitands that would not rely on an external proton source for the switching process. This goal could be achieved by a clever redesign of the quinone-based cavitands, rendering the switching process feasible in purely aprotic media. This development would also set the stage for photoredox-switchable cavitands. Finally, suitable functionalization at the lower rim (legs) would allow interfacing redox-switchable cavitands with metal surfaces and studying their function as molecular grippers.

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Notes

The authors declare no competing financial interest.

Biographies

Igor Pochorovski was born in the Ukraine (1985). He obtained his Bachelor's degree in chemistry and biochemistry from the LMU Munich, then spent a summer as a visiting researcher at UC Berkeley working in the group of Prof. F. D. Toste. After completing his Master's studies at ETH Zurich, he joined Prof. F. Diederich for his Ph.D. (2010−2013), where he was working in the field of

supramolecular chemistry. Since 2014, he is a postdoctoral scholar with Prof. Z. Bao in the Department of Chemical Engineering at Stanford University, working in the field of organic electronics.

François Diederich was born in the Grand-Duchy of Luxemburg (1952) and studied chemistry at the University of Heidelberg (1971−1977). He joined Prof. H. A. Staab at the Max-Planck-Institut für Medizinische Forschung in Heidelberg for his doctoral dissertation (1977−1979). After postdoctoral studies with Prof. O. L. Chapman at UCLA (1979−1981), he returned to Heidelberg for his Habilitation (1981−1985). Subsequently, he joined the Faculty in the Department of Chemistry and Biochemistry at UCLA where he became Full Professor in 1989. Since 1992, he has been Professor in the Laboratory of Organic Chemistry in the Department of Chemistry and Applied Biosciences at ETH Zurich.

■ DEDICATION

Dedicated to Prof. Ken Houk on the occasion of his 70th birthday.

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