EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402140

# Resorcin[4]arene-Based Molecular Baskets and Water-Soluble Container Molecules: Synthesis and $^1$H NMR Host–Guest Complexation Studies

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**Keywords:** Supramolecular chemistry / Host–guest systems / Molecular recognition

Resorcin[4]arene-based molecular baskets, with four free or methylene-bridged HO groups, and water-soluble container molecules bearing poly(ethylene glycol) chains of different lengths on the lower rim and cap have been synthesized. These cavitands, topped with *p*-xylylene bridges, feature well-defined cavities capable of encapsulating heteroalicyclic guests. Association constants ($K_a$) were determined by $^1$H NMR spectroscopy for the organic-soluble molecular baskets in $CDCl_3$ and for the water-soluble container molecules in $D_2O/CD_3CN$ (2:1). Opposite guest selectivities were observed in the two environments. Upon complexation, the water-soluble hosts show changes in their $^1$H NMR spectra. In the absence of guests, the *p*-xylylene bridge rotates rapidly on the $^1$H NMR timescale, revealing a time-averaged achiral $C_{2v}$ structure, whereas this rotation is hindered by guest inclusion, resulting in spectra showing a racemic $C_2$-symmetric host, indicative of planar chirality.

## Introduction

In 1982, Cram and co-workers introduced a new class of synthetic organic receptors comprised of resorcin[4]arenes bridged by quinoxaline flaps.[1] These compounds can be switched from a closed *vase* to an open *kite* conformation and inspired organic chemists to develop more complex structures to serve as model systems for biological processes by monitoring their host–guest complexation behavior.[2,3] Studies in organic solvents[4–9] and in aqueous media[10–16] have been reported, with water-soluble cavitands[17] being of special interest for potential medical applications as recently demonstrated by Hooley and co-workers.[18]

Herein we describe the synthesis and binding properties of the molecular baskets **1** and **2** and the water-soluble container molecules **3a**,**b** (Figure 1). In earlier work, we observed that a cleft-type resorcin[4]arene-based cavitand with two flexible quinoxaline wall flaps and four free HO groups in the octol-derived bottom selectively recognizes steroidal substrates in $CDCl_3$.[4] We have now modified this system by introducing rigidly bridged wall flaps to generate the new cavitands **1** and **2** with better defined cavities for host–guest complexation.

In a second approach, we report the synthesis of novel water-soluble container molecules that are prevented by bridges at the top of the molecule from undergoing undesirable dimerization in the *kite* form, which is frequently observed in water for top-open systems.[10,11,15,16] Water solubility is achieved through the covalent attachment of poly(ethylene glycol) (PEG) chains[16,19] in both the legs and the top bridge of cavitands **3a**,**b**. We chose PEG chains over charged water-solubilizing groups such as ammonium,[20] carboxylate,[12] phosphate,[21] or sulfate[20] salts to limit potential interactions with the diverse guests studied in inclusion complexation. We describe how the PEG groups attached to the bridge change the planar chirality properties of the molecule, as reflected in the $^1$H NMR spectra.[22–24]

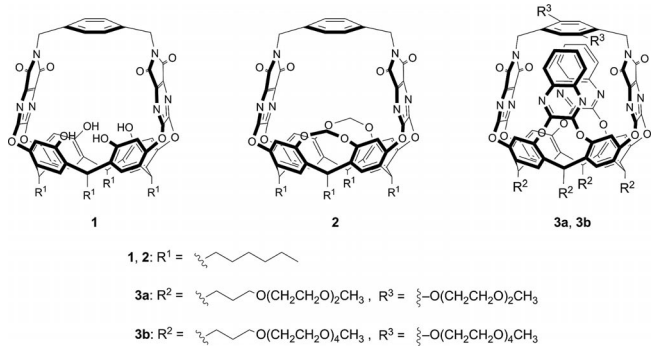


Figure 1. Molecular baskets **1** and **2**, and water-soluble container molecules **3a**,**b**.

## Results and Discussion

### Synthesis of the Receptors

The synthesis of the molecular baskets **1** and **2** is outlined in Scheme 1, A. Under high dilution conditions, octol **4**[25,26] was treated with bridge **5**[9] in the presence of DBU

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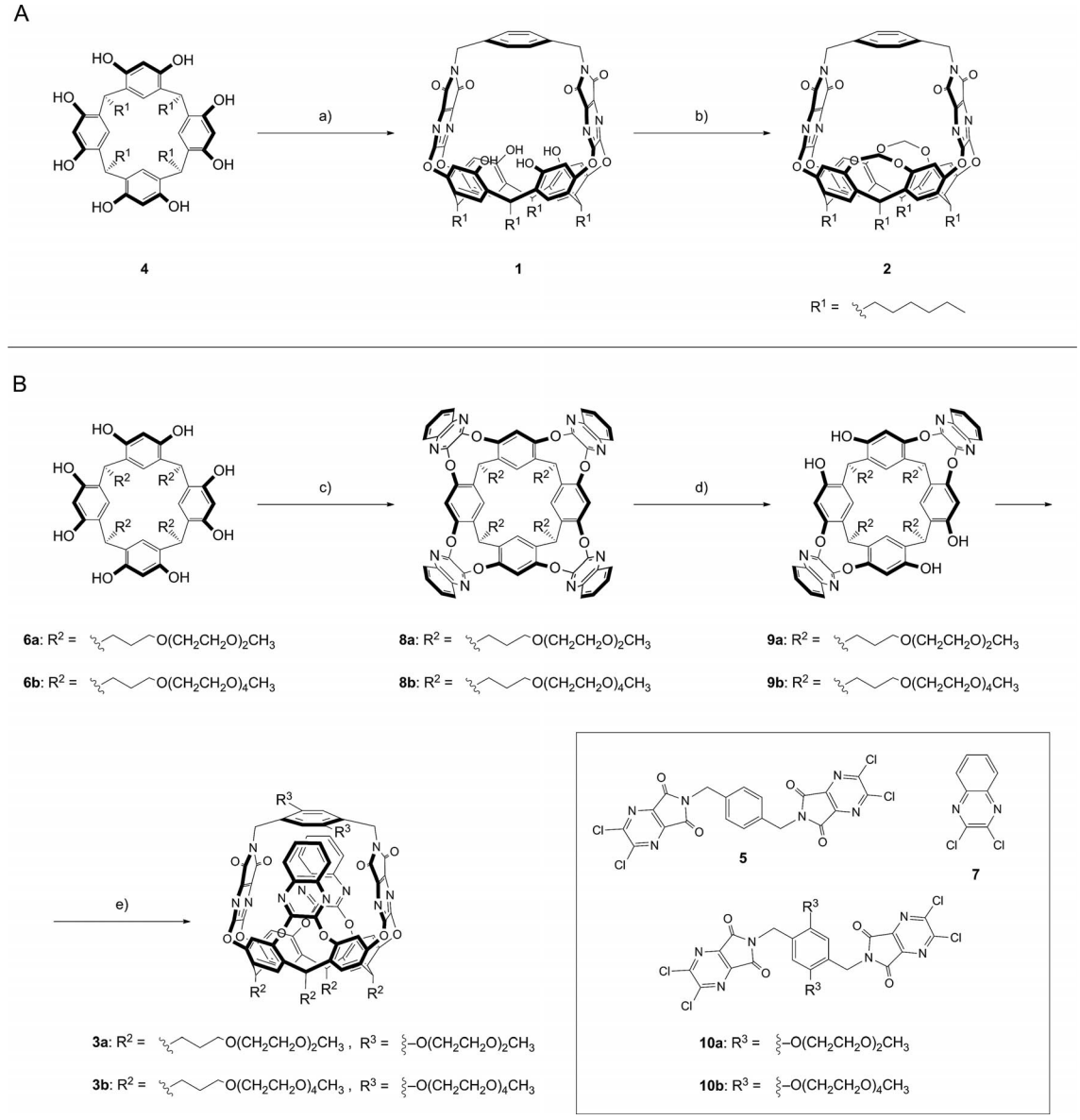
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402140.




Scheme 1. Synthesis of target compounds **1**, **2**, and **3a**,**b**. Reagents and conditions: a) **5**,[9] DBU, DMA, MW, 140 °C, 1 h, 34%; b) $CH_2ClBr$, DBU, DMA, pressure tube, 80 °C, 2 d, 55%; c) **7**, $K_2CO_3$, DMA, 60 °C, 20 h, 67% (**8a**), 96% (**8b**); d) CsF, catechol, DMF, 80 °C, 1.5 h, 59% (**9a**), 38% (**9b**); e) **10a** or **10b**, quinuclidine, 1,4-dioxane, 60 °C, 40 h, 3% (**3a**), 6% (**3b**). DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene; DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; MW = microwave.

as base to afford tetrol basket **1** in 34% yield. The two pairs of neighboring phenolic groups in **1** were linked through a methylene bridge by using $CH_2ClBr$ and DBU to yield basket **2** in 55% yield.[27–29]

For the synthesis of container molecules **3a**,**b** (Scheme 1, B), PEGylated octols **6a**,**b**[16] were treated under basic conditions with 2,3-dichloroquinoxaline (**7**) to give cavitands **8a**,**b**.[1,27,30,31] Two of the side-flaps were then selectively removed by using CsF and catechol to afford tetrols **9a**,**b**.[4,32] Introduction of the PEGylated bridges **10a**,**b** (for their synthesis, see the Supporting Information) afforded container molecules **3a**,**b** in low yields of 3 and 6%, respectively.[9] All the compounds were fully characterized, with the spectroscopic data fully supporting their molecular structures (see Figures 1SI–24SI in the Supporting Information).

## Host–Guest Binding Studies with Molecular Baskets 1 and 2

Binding studies on molecular basket **1** were performed by using $^1H$ NMR spectroscopy in $CDCl_3$ at 298 K. Several heteroalicyclic substrates as well as cyclohexane and the steroids progesterone and cortisone acetate[4] were used as guests (Figure 2). The side-open cavities of the molecular baskets are readily accessible to small guests, and host–guest exchange kinetics is fast on the $^1H$ NMR timescale at

298 K. Association constants $K_a$ ($M^{-1}$) were obtained from binding titrations, following the complexation-induced change in the chemical shifts of host protons.[33] Detailed protocols are given in the Exp. Sect.

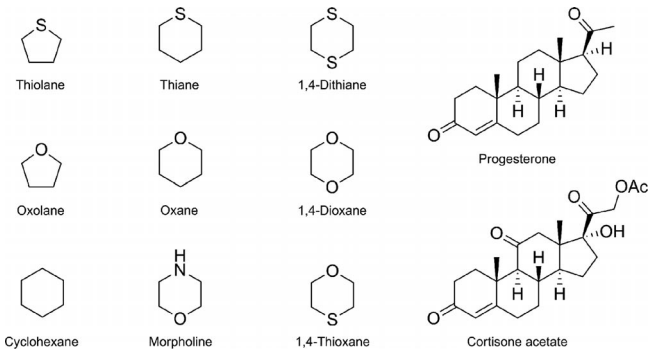



Figure 2. Guest molecules used for binding studies.

$^1$H NMR analysis of molecular basket **1** in [$D_8$]1,4-dioxane at 298 K indicated the presence of a single host species, presumably forming a 1:1 inclusion complex with the solvent (see Figure 1SI, a in the Supporting Information). On the other hand, in $CDCl_3$ at 298 K, two sets of host signals were detected. We rationalized this observation as follows: 1) The host cavity can never be empty, 2) if there is no guest available, or the guest is too small or too large, the cavity has to distort, and 3) in the case of distortion, the $C_{2v}$ symmetry of the host breaks down, previously chemically equivalent protons become different, and more signals appear in the $^1$H NMR spectrum.

We concluded that host **1** in $CDCl_3$ exists in two forms, a $C_{2v}$-symmetric species ($C_{2v}$-**1**) and a $C_1$-symmetric racemate ($C_1$-**1**). These two species are in equilibrium, transformed by twisting a set of diaryl ether bonds (Figure 3, a), and can be clearly differentiated by the resonances of the phenolic HO groups. Whereas $C_{2v}$-**1** shows one signal for all four HO groups, $C_1$-**1** features four individual HO signals (Figure 3, b). By heating the sample to 323 K, only one HO signal can be observed, which indicates fast equilibration on the $^1$H NMR timescale (see Figure 25SI in the Supporting Information).

Upon guest complexation in the titration studies, only one $C_{2v}$-symmetric host is observed, as illustrated in Figure 26SI for the titration with 1,4-dioxane as guest. The obtained titration curves (see Figures 27SI–54SI in the Supporting Information) for molecular basket **1** were evaluated by using the software IGOR Pro.[34] The $K_a$ values determined by monitoring the chemical shift of the HO signal and the average $K_a$ values obtained by monitoring the chemical shifts of the aromatic lower rim and/or methine protons are summarized in Table 1.

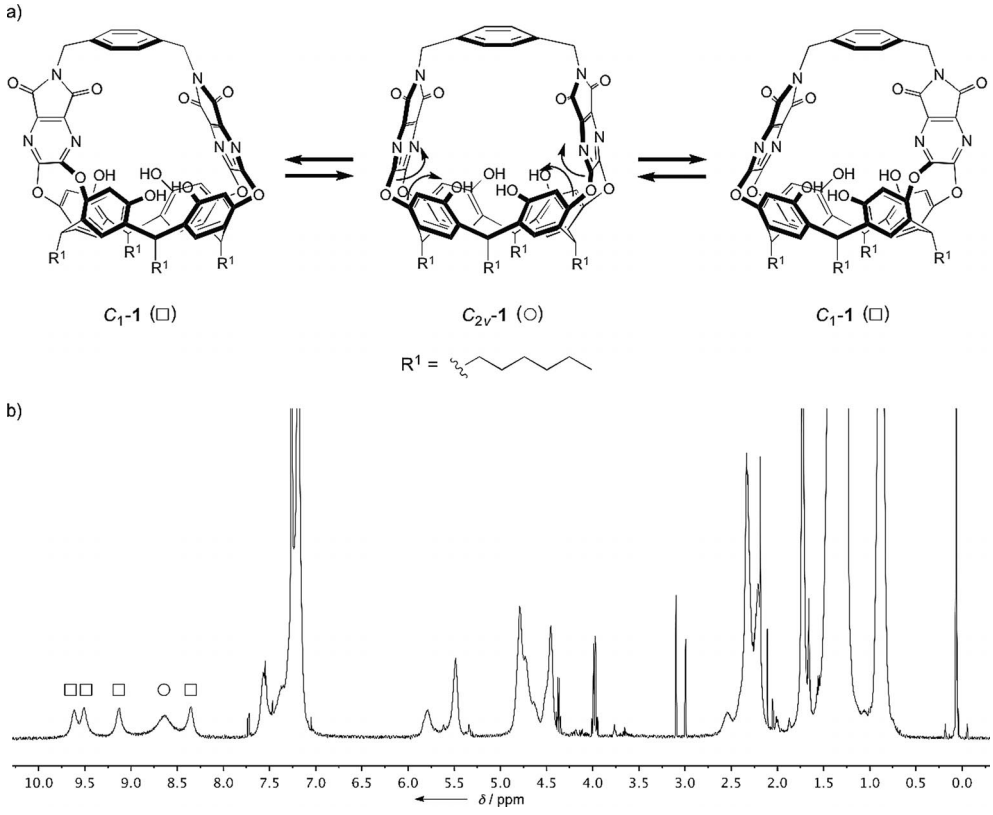



Figure 3. Model explaining the $^1$H NMR observations in $CDCl_3$. a) Host **1** exists in a $C_{2v}$- and a racemic $C_1$-symmetric form, which are in slow equilibrium on the $^1$H NMR timescale at room temperature and below, and are interconverted by twisting diaryl ether bonds. b) $^1$H NMR spectrum (500 MHz, $CDCl_3$, 283 K) of host **1** showing two sets of host signals. Whereas the $C_{2v}$-symmetric conformer only shows one signal for all HO groups, the $C_1$-symmetric conformer generates four different HO resonances.

Table 1. Results of $^1$H NMR titration studies with molecular basket **1** as host in $CDCl_3$ at 298 K. The $K_a$ values obtained are determined from different host protons.

| Guest | $K_a$ [M$^{-1}$][a] | $K_a$ [M$^{-1}$][b] |
|---|---|---|
| 1,4-Dioxane[c] | 43.2 ± 1.5[d] | 15.9 ± 0.2[e] |
| 1,4-Thioxane | 28.7 ± 1.4[d] | 12.2 ± 1.3[e] |
| 1,4-Dithiane | –[f] | –[f] |
| Oxolane | 48.6 ± 2.2[d] | 39.3 ± 8.0[e] |
| Oxane | 38.6 ± 2.3[d] | 27.5 ± 1.4[e] |
| Thiolane | 9.1 ± 0.2[d] | 6.2 ± 2.1[d] |
| Thiane | 9.0 ± 0.3[d] | 8.0 ± 1.3[d] |
| Cyclohexane | –[f] | –[f] |
| Morpholine | –[g] | 710 ± 91[e] |
| Progesterone | –[g] | 43.7 ± 2.2[d] |
| Cortisone acetate | 134 ± 15[d] | 66.8 ± 18.9[e] |

[a] $K_a$ values determined by monitoring the chemical shift of the HO signal. [b] Average $K_a$ values determined by monitoring the chemical shifts of the aromatic lower rim and/or methine protons. [c] Reproducibility was checked in duplicate runs. [d] Standard deviation of titration curve-fitting. [e] Standard deviation of averaged $K_a$ values. [f] No binding was observed. [g] No observable HO signal for evaluation.

In the heteroalicyclic series, the $K_a$ values range from 6.2 M$^{-1}$ for thiolane up to 710 M$^{-1}$ for morpholine. However, the $K_a$ values determined by monitoring the strongly shifting HO signal are larger by a factor of 1.1–2.7 than the average $K_a$ values determined from the more weakly shifting aromatic lower rim and/or methine proton resonances. However, the relative order of binding constants for this set of guests remains the same. A reasonable explanation for the discrepancy between the two sets of data is the higher sensitivity of HO protons due to hydrogen bonding,[35] coming with the drawback of higher possible errors.

Oxygen-containing guests form more stable host–guest complexes than guests containing sulfur, with the binding strength increasing from 1,4-dithiane to 1,4-thioxane to 1,4-dioxane. The steroids progesterone and cortisone acetate show an affinity towards host **1**. According to molecular modeling studies conducted with moloc,[36] they are too big to fit inside the rigidified cavity of **1**, and presumably they undergo side-on hydrogen-bonding interactions with the phenolic HO groups. Morpholine shows the strongest binding but, due to its basicity, causes decomposition of host **1** over time. With cyclohexane as a guest without heteroatoms capable of undergoing polar interactions, no binding was observed.

In addition to dispersion and C–H···π interactions,[37–39] polar interactions contribute to the observed host–guest complexation. We analyzed the complexation of **1** with 1,4-dioxane by using moloc,[36] which suggested that temporary hydrogen bonding of the guest to the phenolic HO groups of the host initiates the formation of the host–guest complex. A subsequent conformational search and energy minimization of the complex using MacroModel (OPLS 2005 force field)[40] followed by further energy minimizations using PM3 in Spartan[41] revealed the preferential orientation of the guest inside the cavity. According to this analysis, 1,4-dioxane binds in a conformation that allows stabilizing orthogonal C–O···C=O interactions[42] with the diazaphthalimide C=O groups, as shown in Figure 4. Geometries showing these interactions were preferred over those in which the guest engages in hydrogen-bonding interactions with the phenolic HO groups.

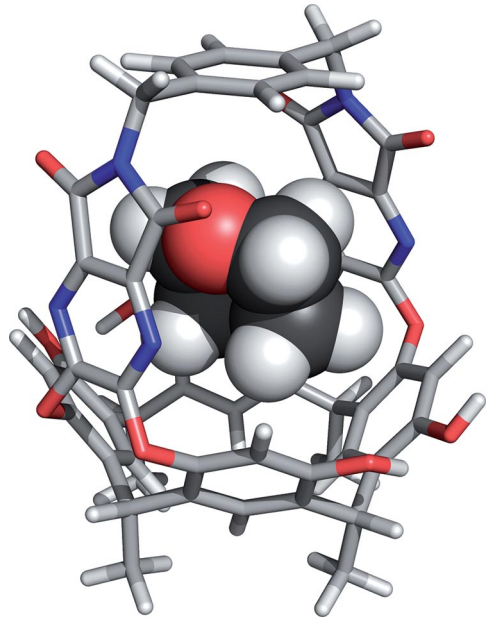


Figure 4. Lowest-energy conformation of molecular basket **1** with encapsulated 1,4-dioxane, calculated by using MacroModel 9.7[40] (OPLS 2005 force field, GB/SA solvation model for $CHCl_3$) and Spartan '14[41] (PM3). The host–guest complex is stabilized by C–O···C=O interactions. For simplification, the hexyl legs have been replaced by methyl groups.

We also performed $^1$H NMR binding titrations with molecular basket **2** in $CDCl_3$ at 298 K using the same series of guests. The pure cavitand showed only one set of signals in $CDCl_3$ (see Figure 55SI in the Supporting Information) as a result of the rigidification caused by the introduction of additional methylene bridges. No significant changes in chemical shift were observed during the titrations ($\Delta\delta < 0.01$ ppm), which indicates no or only very weak host–guest inclusion complexation. Although the removal of the hydrogen-bond-donating HO groups might contribute to the lack of complexation ability of host **2**, we also propose that the two additional methylene bridges enhance the rigidity and reduce the adaptability of the receptor.

## Host–Guest Binding Studies with Water-Soluble Container Molecule 3b

The attachment of PEG chains to our previously described container molecules[9] enhanced their solubility in aqueous media. Although compound **3a** with diethylene glycol chains is soluble in 55:45 MeCN/water, host **3b** with tetraethylene glycol chains readily dissolves in 33:67 MeCN/water. Methanol is a less effective co-solvent, and **3a** dissolves in 86:14 MeOH/water, whereas host **3b** is soluble in 48:52 MeOH/water. The $^1$H NMR spectra of both cavitands in $D_2O/CD_3CN$ show sharp signals. Their methine protons, which are diagnostic of the *vase* and *kite* conformations,

appear below 5 ppm, characteristic of a *vase*-like form. In contrast, their spectra in $D_2O$/MeOD show very broad signals, which are not suitable for an accurate determination of $K_a$ values. We found no evidence in $D_2O/CD_3CN$ for the frequently described host dimerizations in aqueous media.[10,11,15,16] Only traces of dimeric **3a**,**b** were detected by high-resolution matrix-assisted laser desorption/ionization mass spectrometry (HR-MALDI-MS). Dimerization usually involves association of the open *kite* conformation, which cannot be adopted by our basket-type systems with their capping, PEG-garnered *p*-xylylene bridge.

Binding studies by $^1$H NMR spectroscopy were carried out with host **3b** in $D_2O/CD_3CN$ (2:1) at 298 K using barely soluble cyclohexane and the heteroalicyclic guests shown in Figure 2. With four wall flaps, guest access to the cavity is sterically hindered, and slow host–guest exchange kinetics is observed on the $^1$H NMR timescale at 298 K. This enabled the determination of $K_a$ values by integrating the signal intensities of the free and encapsulated guest.[33] Although the signals of bound guests in host **3b** appear in the range of 0.2 to –3.4 ppm and are easily integrable, many signals of the free guests coincide with the resonances of the

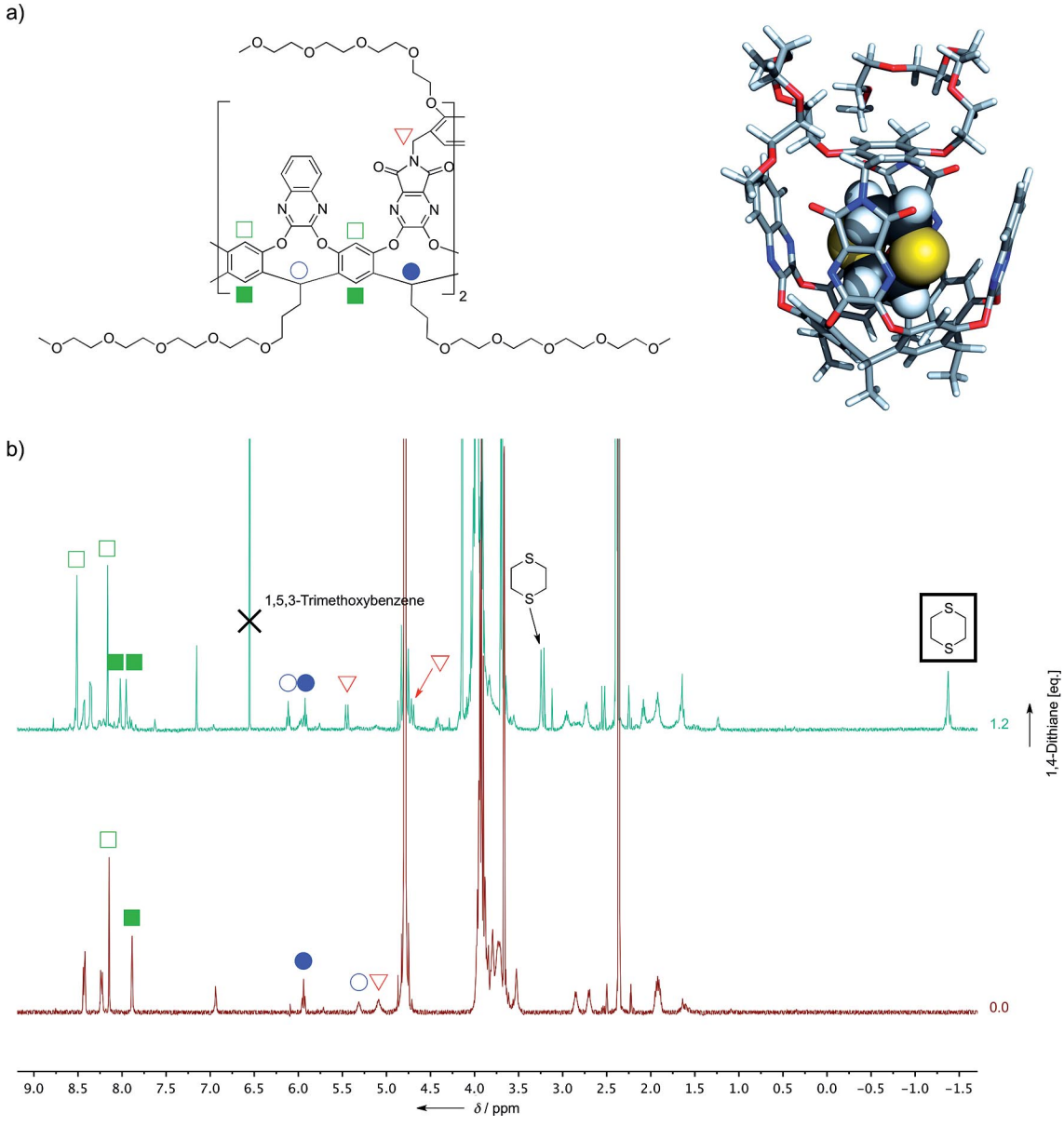



Figure 5. Complexation of 1,4-dithiane by container **3b**. a) Chemical structure of the receptor (left) and lowest-energy conformation of the inclusion complex with PEG chains on the *p*-xylylene bridge and simplified methyl legs (right). MacroModel 9.7[40] (OPLS 2005 force field, GB/SA solvation model for $H_2O$) and Spartan '14[41] (PM3) were used to calculate the structure. b) Monitoring of the complexation process by $^1$H NMR spectroscopy [500 MHz, $D_2O/CD_3CN$ (2:1), 298 K]. The bottom spectrum depicts the free host and the top spectrum shows the complexation of **3b** (0.5 mM) with 1,4-dithiane (1.2 equiv.). The spectrum of the free host reveals a time-averaged $C_{2v}$-symmetric structure with fast rotation of the PEGylated *p*-xylylene bridge. The top spectrum shows a solution of the complex, in which this rotation is slow on the $^1$H NMR timescale, leading to a doubling of resonances in accord with a $C_2$-symmetric host structure.

PEG chains in the host, which makes a proper integration impossible. We circumvented this problem by using 1,3,5-trimethoxybenzene as internal standard, determining by integration only the concentration of the bound guest.[9] The detailed procedure for the $^1$H NMR binding studies is given in the Exp. Sect. All the chemical shifts of the free and encapsulated guests in $D_2O/CD_3CN$ (2:1) at 298 K are shown in Table 1SI in the Supporting Information.

$^1$H NMR binding studies on **3b** were performed at constant host concentration and three different guest concentrations by monitoring the signal ratio of the internal standard and the bound guest. The three individual values of $K_a$ calculated per host–guest complex formed a sequence of decreasing magnitude, and slow host decomposition was observed in the $^1$H NMR spectrum. Therefore we report herein only the $K_a$ values obtained from the first runs, which are summarized in Table 2. The binding study with 1,4-dithiane is shown in Figure 5 (for the study with 1,4-dioxane, see Figure 56SI in the Supporting Information). The guest resonances are strongly shifted upfield upon complexation, from 3.25 ppm in the free guest to –1.37 ppm in the bound state.

Table 2. $^1$H NMR binding studies with container molecule **3b** as host in $D_2O/CD_3CN$ (2:1) at 298 K.

| Guest | $K_a$ [M$^{-1}$] |
|---|---|
| 1,4-Dioxane | 1952 |
| 1,4-Thioxane | 2021 |
| 1,4-Dithiane | 3724 |
| Oxolane | –[a] |
| Oxane | 941 |
| Cyclohexane | 200 |
| Morpholine | –[b] |

[a] No binding was observed. [b] Decomposition of host.

In general, the $K_a$ values range from 200 M$^{-1}$ for cyclohexane up to 3724 M$^{-1}$ for 1,4-dithiane. In aqueous solution, the more soluble, polar oxygen-containing guests form less stable complexes than the less soluble sulfur-containing guests, which have a higher tendency to partition from the aqueous phase into the less polar cavitand interior.[43] The binding strength increases from 1,4-dioxane ($K_a$ = 1952 M$^{-1}$) to 1,4-thioxane ($K_a$ = 2021 M$^{-1}$) to 1,4-dithiane ($K_a$ = 3724 M$^{-1}$). In addition to the enhanced partitioning, S···π interactions[37,39] in the complex seem to contribute to the better binding in the complex, as also suggested by the computer simulations for bound 1,4-dithiane (Figure 5).

Complexation affects the planar chirality properties of the container molecules. Host **3b** adopts a *vase*-like form in both the free and bound state. However, the free *vase* is much more flexible than the complex *vase*. In the free state, the resonances of the methine protons below the two flexible quinoxaline flaps appear at $\delta$ = 5.33 ppm. Upon guest inclusion, the *vase* rigidifies and the methine resonance shifts downfield to 6.11 ppm in the case of 1,4-dithiane (Figure 5), whereas the methine protons under the bridged wall flaps appear at the same position in both the unbound and bound state, at $\delta$ = 5.97 ppm. The host shows one set of signals in the free form, indicative of a time-averaged $C_{2v}$ symmetry, as the absence of guest and greater flexibility allow the PEG-substituted bridge ring to rotate freely on the $^1$H NMR timescale at 298 K. Upon guest inclusion, the resonances of the octol bowl protons, as well as of the $CH_2$ groups in the *p*-xylylene bridge split into two sets of signals (Figure 5 and Figures 57SI and 58SI in the Supporting Information). As a result of the rigidification and the cavity occupancy by the guest, the rotation of the PEG-substituted bridge ring is slowed down, thereby establishing the planar chirality of the host, which now appears as a $C_2$-symmetric structure. The latter is observed in the $^1$H NMR spectrum up to 348 K.

Container molecule **3a** shows the *vase* form in the free state in $D_2O/CD_3CN$ (45:55), and rotation of the *p*-xylylene bridge with its shorter PEG chains is fast on the NMR time scale (see Figure 59SI in the Supporting Information). Similarly to **3b**, inclusion of an appropriate guest, such as 1,4-dioxane, slows down the rotation of the bridge in **3a**, and the spectra of both hosts in [$D_8$]1,4-dioxane (see Figures 3SI, a and 4SI, a) show $C_2$ symmetry as a result of planar chirality.

## Conclusions

Resorcin[4]arene-based molecular baskets with free and methylene-bridged HO groups, as well as water-soluble container molecules bearing PEG chains of different length as legs and as substituents of the *p*-xylylene cap, have been synthesized. Their host–guest complexation behavior was investigated by $^1$H NMR binding studies using a variety of small heteroalicyclic guests. Dispersion and C–H···π interactions, in addition to polar interactions such as C–O···C=O or S···π interactions, stabilize the host–guest complexes, in addition to solvophobic effects in aqueous solution. Complexation studies with molecular basket **1** in $CDCl_3$ revealed better complexation of O-containing than S-containing guests ($K_a$ values: 1,4-dithiane < 1,4-thioxane < 1,4-dioxane), whereas the investigations with the water-soluble container molecule **3b** in $D_2O/CD_3CN$ (2:1) showed the reverse trend. With its higher capacity for guest encapsulation and the aqueous solution favoring apolar binding, the $K_a$ values for the complexes of container **3b** in aqueous solution are greater than those measured for the complexes of the more open cavitand **1** in $CDCl_3$. Complexation by molecular basket **1** in $CDCl_3$ is fast on the $^1$H NMR timescale, whereas the encapsulation of guests by container molecule **3b** is slow. The PEG-substituted *p*-xylylene cap efficiently prevents dimerization of the container molecules in aqueous solution. Guest complexation by hosts **3a**,**b** leads to changes in their $^1$H NMR spectra: Whereas the free hosts appear as time-averaged $C_{2v}$-symmetric structures, complexes with 1,4-dioxane or 1,4-dithiane appear as $C_2$-symmetric, as guest inclusion rigidifies the containers and slows down the rotation of the capping PEG-substituted *p*-xylylene rings, reinforcing the planar chirality of the systems. In future work we intend to com-

bine the knowledge gained on rendering container resorcin[4]arene cavitands soluble with the recently reported redox-triggered switching properties to develop new switchable receptors for use in aqueous solution.[44,45]

## Experimental Section

**General Details and Synthetic Procedures:** Octol **4**,[25] PEGylated octol **6b**,[11,16] and bridge **5**[9] were prepared according to literature procedures. 2,3-Dichloroquinoxaline (**7**) was bought from ABCR. The experimental details for the synthesis and characterization of compounds **1**, **2**, **3a**, and **3b** are described in this manuscript, for the synthesis and characterization of compounds **6a**, **8a**,**b**, **9a**,**b**, and **10a**,**b**, see the Supporting Information. The atom numbering used to assign the $^1$H NMR signals and the naming of the compounds by phane nomenclature[46,47] are reported in the Supporting Information.

**Molecular Basket 1:** A solution of octol **4**[25] (25 mg, 30 μmol) and arene-bridge **5**[9] (16 mg, 30 μmol) in DMA (10 mL) was treated with DBU (22.8 μL, 150 μmol) and stirred at 140 °C under MW irradiation for 1 h. A spatula of $SiO_2$ (200 mg) was added, the mixture was evaporated (HV, 50 °C), and the crude purified through a short FC plug ($SiO_2$; $CH_2Cl_2$/EtOAc, 8:2) to yield **1** (15 mg, 34%) as a slightly yellow solid. $R_f$ = 0.70 ($SiO_2$; $CH_2Cl_2$/EtOAc, 8:2), m.p. >250 °C (decomp.). $^1$H NMR (500 MHz, [D$_8$]1,4-dioxane): $\delta$ = 0.89 [t, $J$ = 6.9 Hz, 6 H, $H_3C(6'_l)$; partial overlap with next resonance], 0.90 [t, $J$ = 7.0 Hz, 6 H, $H_3C(6_l)$], 1.25–1.43 [m, 32 H, $H_2C(2'_l$–$5'_l$, $2_l$–$5_l)$], 2.15 [q, $J$ = 8.1 Hz, 4 H, $H_2C(1'_l)$], 2.23 [q, $J$ = 7.8 Hz, 4 H, $H_2C(1_l)$], 4.36 [t, $J$ = 7.8 Hz, 2 H, H–C($1_r$)], 4.73 [s, 4 H, $H_2C(4'_f)$], 5.42 [t, $J$ = 8.1 Hz, 2 H, H–C($1'_r$)], 7.04 [s, 4 H, H–C($5_r$)], 7.19 [s, 4 H, H–C($2_r$)], 7.33 [s, 4 H, H–C($6'_f$)], 8.58 (s, 4 H, HO) ppm. $^{13}$C NMR (125 MHz, [D$_8$]1,4-dioxane): $\delta$ = 14.43, 23.36, 23.38, 28.76, 30.01, 30.07, 30.42, 32.66, 32.69, 33.52, 33.63, 34.05, 34.46, 41.67, 111.78, 124.13, 130.76, 130.97, 131.49, 137.48, 143.18, 153.00, 153.57, 158.82, 163.64 ppm (one signal missing due to overlap). IR (ATR): $\tilde{\nu}$ = 3337 (br, w), 2926 (m), 2856 (m), 1791 (w), 1733 (s), 1613 (w), 1585 (w), 1489 (m), 1434 (m), 1370 (s), 1337 (s), 1280 (m), 1224 (m), 1199 (s), 1169 (m), 1132 (m), 1073 (s), 923 (m), 905 (m), 857 (m), 800 (m), 740 (m), 637 (m) cm$^{-1}$. HRMS (MALDI-TOF, DCTB): $m/z$ (%) = 1255.5157 (20) [M + K]$^+$ (calcd. for $C_{72}H_{76}KN_6O_{12}^+$ 1255.5153), 1241.5484 (28), 1240.5451 (67), 1239.5415 (84) [M + Na]$^+$ (calcd. for $C_{72}H_{76}N_6NaO_{12}^+$ 1239.5413), 1219.5665 (34), 1218.5625 (75), 1217.5578 (100) [M + H]$^+$ (calcd. for $C_{72}H_{77}N_6O_{12}^+$ 1217.5594), 1216.5517 (50) [M]$^+$ (calcd. for $C_{72}H_{76}N_6O_{12}^+$ 1216.5521), 663.4537 (72), 354.1700 (86).

**Molecular Basket 2:** A solution of **1** (97 mg, 80 μmol) in DMA (12 mL) was treated with $CH_2ClBr$ (218 μL, 3.19 mmol) and DBU (60.1 μL, 400 μmol) and stirred in a pressure tube at 80 °C for 2 d [with extra $CH_2ClBr$ (218 μL, 3.19 mmol) after 24 h]. A spatula of $SiO_2$ (300 mg) was added, the mixture was evaporated (HV, 50 °C), and the crude purified through a short FC plug ($SiO_2$; $CH_2Cl_2$/EtOAc, 9.5:0.5) to yield **2** (54 mg, 55%) as a slightly yellow solid. $R_f$ = 0.74 ($SiO_2$; $CH_2Cl_2$/EtOAc, 95:5), m.p. >218 °C (decomp.). $^1$H NMR (500 MHz, [D$_8$]1,4-dioxane): $\delta$ = 0.89 [t, $J$ = 6.9 Hz, 6 H, $H_3C(6'_l)$], 0.92 [t, $J$ = 6.9 Hz, 6 H, $H_3C(6_l)$], 1.25–1.51 [m, 32 H, $H_2C(2'_l$–$5'_l$, $2_l$–$5_l)$], 2.18 [q, $J$ = 8.2 Hz, 4 H, $H_2C(1'_l)$], 2.28 [q, $J$ = 8.0 Hz, 4 H, $H_2C(1_l)$], 4.05 and 5.75 [2d, $J$ = 8.0 Hz, 4 H, $H_2C(8_r)$], 4.79 [s, 4 H, $H_2C(4'_f)$; partial overlap with next resonance], 4.80 [t, $J$ = 8.0 Hz, 2 H, H–C($1_r$)], 5.56 [t, $J$ = 8.2 Hz, 2 H, H–C($1'_r$)], 7.20 [s, 4 H, H–C($2_r$)], 7.22 [s, 4 H, H–C($5_r$)], 7.41 [s, 4 H, H–C($6'_f$)] ppm. $^{13}$C NMR (125 MHz, [D$_8$]1,4-dioxane): $\delta$ = 14.39, 14.46, 23.35, 23.36, 28.54, 28.57, 30.11, 30.12, 30.40, 32.51, 32.72, 33.06, 34.58, 37.03, 41.86, 100.22, 118.63, 122.61, 131.31, 136.36, 137.48, 140.69, 143.24, 152.92, 156.22, 158.63, 163.20 ppm. IR (ATR): $\tilde{\nu}$ = 2927 (m), 2856 (m), 1793 (w), 1735 (s), 1607 (w), 1578 (w), 1538 (w), 1487 (m), 1439 (m), 1368 (s), 1337 (s), 1277 (m), 1198 (s), 1152 (m), 1138 (m), 1069 (m), 970 (s), 923 (m), 891 (m), 798 (m), 739 (m), 718 (m), 633 (s) cm$^{-1}$. HRMS (MALDI-TOF, DCTB): $m/z$ (%) = 1279.5150 (9) [M + K]$^+$ (calcd. for $C_{74}H_{76}KN_6O_{12}^+$ 1279.5153), 1265.5477 (11), 1264.5442 (24), 1263.5410 (30) [M + Na]$^+$ (calcd. for $C_{74}H_{76}N_6NaO_{12}^+$ 1263.5413), 685.4356 (87), 437.1934 (100), 354.1699 (40).

**Container Molecule 3a:** A solution of tetrol **9a** (200 mg, 145 μmol) in dry 1,4-dioxane (370 mL) was treated with a spatula of molecular sieves (3 Å) and a solution of quinuclidine (67.6 mg, 608 μmol) in dry 1,4-dioxane (10 mL), and the mixture was heated to 60 °C. A solution of bridge **10a** (118 mg, 152 μmol) in dry 1,4-dioxane (20 mL) was added over 40 min, and stirring was continued at 60 °C for 40 h. The mixture was filtered through a short plug of $SiO_2$, the filtrate treated with a spatula of silica (500 mg), evaporated, and the crude purified by MPLC ($SiO_2$; $CH_2Cl_2$/THF/MeOH, 96:2:2 to 92:4:4 in 30 min, 92:4:4 for 20 min, 40 mL min$^{-1}$) and HPLC (diol-phase; Nucl. 7 OH, Macherey–Nagel; $n$-hexane/$CH_2Cl_2$/THF/MeOH, 75:25:2:2, 18 mL min$^{-1}$) to yield **3a** (8 mg, 3%) as a yellow waxy solid. $R_f$ = 0.22 ($SiO_2$; $CH_2Cl_2$/THF/MeOH, 92:4:4). $^1$H NMR (600 MHz, [D$_8$]1,4-dioxane): $\delta$ = 1.55 [quint., $J$ = 8.2 Hz, 4 H, $H_2C(2'_l)$], 1.68 [quint., $J$ = 7.2 Hz, 4 H, $H_2C(2_l)$], 2.29 [q, $J$ = 8.2 Hz, 4 H, $H_2C(1'_l)$], 2.40–2.47 [m, 4 H, $H_2C(1_l)$], 3.25 [s, 6 H, $H_3C(15'_f)$], 3.27 [s, 6 H, $H_3C(8'_l)$], 3.28 [s, 6 H, $H_3C(8_l)$], 3.41–3.88 [m, 56 H, $H_2C(3'_l$–$7'_l$, $3_l$–$7_l$, $11'_f$–$14'_f)$], 4.29 and 5.08 [2d, $J$ = 13.6 Hz, 4 H, $H_2C(4'_f)$], 5.46 [t, $J$ = 8.3 Hz, 2 H, H–C($1_r$)], 5.61 [t, $J$ = 8.2 Hz, 2 H, H–C($1'_r$)], 6.75 [s, 2 H, H–C($7'_f$)], 7.34 and 7.39 [2s, 4 H, H–C($2'_r$, $2_r$)], 7.81–7.83 and 7.87–7.90 [2m, 4 H, H–C($4_f$, $5_f$)], 7.86 and 8.00 [2s, 4 H, H–C($5'_r$, $5_r$)], 8.12–8.15 [m, 4 H, H–C($3_f$, $6_f$)] ppm. $^{13}$C NMR (150 MHz, [D$_8$]1,4-dioxane): $\delta$ = 27.98, 28.46, 28.74, 30.35, 34.47, 35.06, 36.54, 58.90, 58.91, 70.13, 70.74, 70.94, 70.97, 71.04, 71.14, 71.18, 71.20, 71.26, 71.31, 72.72, 72.75, 72.83, 118.46, 118.65, 119.17, 123.87, 125.06, 127.95, 129.05, 129.08, 130.62, 131.36, 136.29, 136.52, 136.80, 136.81, 140.24, 140.37, 143.14, 143.57, 151.61, 152.08, 152.38, 152.96, 153.15, 153.50, 153.78, 157.82, 157.90, 161.64, 164.01 ppm (two signals missing due to overlap). IR (ATR): $\tilde{\nu}$ = 3478 (br, w), 2870 (m), 1793 (w), 1734 (m), 1657 (w), 1569 (w), 1511 (w), 1483 (m), 1444 (m), 1410 (s), 1364 (s), 1330 (s), 1261 (m), 1197 (s), 1160 (m), 1139 (s), 1088 (br, s), 1020 (m), 944 (m), 907 (m), 877 (m), 851 (m), 762 (m), 673 (m), 603 (m) cm$^{-1}$. HRMS (MALDI-TOF, DCTB): $m/z$ (%) = 4042.5299 (7) [2M + Na]$^+$ (calcd. for $C_{212}H_{232}N_{20}NaO_{60}^+$ 4042.5615), 2034.7848 (25), 2033.7816 (58), 2032.7777 (100), 2031.7734 (87) [M + Na]$^+$ (calcd. for $C_{106}H_{116}N_{10}NaO_{30}^+$ 2031.7751), 2011.7966 (24), 2010.7918 (48), 2009.7872 (70), 2008.7826 (54) [M]$^+$ (calcd. for $C_{106}H_{116}N_{10}O_{30}^+$ 2008.7853).

**Container Molecule 3b:** A solution of tetrol **9b** (200 mg, 115 μmol) in dry 1,4-dioxane (370 mL) was treated with a spatula of molecular sieves (3 Å) and a solution of quinuclidine (55.5 mg, 484 μmol) in dry 1,4-dioxane (10 mL), and the mixture was heated to 60 °C. A solution of bridge **10b** (115 mg, 121 μmol) in dry 1,4-dioxane (20 mL) was added over 40 min, and stirring was continued at 60 °C for 40 h. The mixture was filtered through a short plug of $SiO_2$, the filtrate treated with a spatula of silica (500 mg), evaporated, and the crude purified by MPLC ($SiO_2$; $CH_2Cl_2$/THF/MeOH, 94:3:3 to 90:5:5 in 30 min, 90:5:5 for 20 min, 40 mL min$^{-1}$) and HPLC (CN-phase; LiChrospher 100 CN 5 μm, Merck; THF, 18 mL min$^{-1}$) to yield **3b** (18 mg, 6%) as a slightly yellow oil. $R_f$ = 0.13 ($SiO_2$; $CH_2Cl_2$/THF/MeOH, 90:5:5). $^1$H NMR (600 MHz,

[$D_8$]1,4-dioxane): $\delta$ = 1.55 [quint., $J$ = 7.6 Hz, 4 H, $H_2C(2'_l)$], 1.68 [quint., $J$ = 6.6 Hz, 4 H, $H_2C(2_l)$], 2.31 [q, $J$ = 7.6 Hz, 4 H, $H_2C(1'_l)$], 2.44–2.51 [m, 4 H, $H_2C(1_l)$], 3.26 [s, 12 H, $H_3C(12'_l, 12_l)$], 3.27 [s, 6 H, $H_3C(19'_f)$], 3.42–3.88 [m, 104 H, $H_2C(3'_l–11'_l, 3_l–11_l, 11'_f–18'_f)$], 4.29 and 5.08 [2d, $J$ = 13.7 Hz, 4 H, $H_2C(4'_f)$], 5.47 [t, $J$ = 8.2 Hz, 2 H, H–C($1_r$)], 5.59 [t, $J$ = 7.6 Hz, 2 H, H–C($1'_r$)], 6.73 [s, 2 H, H–C($7'_f$)], 7.42 and 7.46 [2s, 4 H, H–C($2'_r$, $2_r$)], 7.82–7.85 and 7.89–7.92 [2m, 4 H, H–C($4_f$, $5_f$)], 7.85 and 8.00 [2s, 4 H, H–C($5'_r$, $5_r$)], 8.13–8.15 [m, 4 H, H–C($3_f$, $6_f$)] ppm. $^{13}$C NMR (150 MHz, [$D_8$]1,4-dioxane): $\delta$ = 27.95, 28.46, 28.69, 30.27, 34.44, 35.07, 36.58, 58.90, 70.08, 70.79, 70.84, 70.91, 70.93, 71.03, 71.11, 71.25, 71.28, 71.30, 71.32, 71.45, 72.69, 118.39, 118.56, 119.02, 124.22, 125.36, 127.91, 129.04, 129.11, 130.74, 131.49, 136.46, 136.60, 136.85, 136.92, 140.22, 140.34, 143.14, 143.56, 151.52, 152.15, 152.43, 152.88, 153.07, 153.45, 153.73, 157.82, 157.89, 161.70, 164.07 ppm (15 signals missing due to overlap). IR (ATR): $\tilde{\nu}$ = 3507 (br, w), 2868 (m), 1793 (w), 1735 (m), 1571 (w), 1484 (m), 1411 (m), 1365 (s), 1332 (s), 1254 (m), 1197 (m), 1095 (br, s), 944 (m), 851 (m), 761 (m), 603 (m) cm$^{-1}$. HRMS (MALDI-TOF, DCTB): $m/z$ (%) = 5100.2919 (11) [2 M + Na]$^+$ (calcd. for $C_{260}H_{328}N_{20}NaO_{84}^+$ 5100.1906), 2563.0999 (38), 2562.0956 (76), 2561.0914 (100), 2560.0888 (63) [M + Na]$^+$ (calcd. for $C_{130}H_{164}N_{10}NaO_{42}^+$ 2560.0897).

**NMR Titrations with Molecular Baskets 1 and 2:** $^1$H NMR titrations were performed at 298 K with a Bruker AV III 500 spectrometer (500 MHz) in $CDCl_3$ (99.8 atom-% D, stored over molecular sieves (4 Å) and filtered through basic $Al_2O_3$ before use) purchased from Armar. For the experiments, host **1** or **2** was dissolved in $CDCl_3$ (about $1 \times 10^{-3}$ M) and an aliquot of this solution was used to dissolve the guest (about $2.5 \times 10^{-1}$ M). During the titration, the host solution was successively treated with guest solution by syringe (about 11 additions) so that the host concentration remained constant and the guest concentration gradually increased (about 0.5–100 equiv.). $^1$H NMR spectra were recorded after each addition and the change in chemical shift ($\delta$) of different host protons was recorded as a function of guest concentration. The titration curves obtained were evaluated by using the software IGOR Pro[34] to give the corresponding $K_a$ values (Table 1).

**NMR Binding Studies with Container Molecule 3b:** $^1$H NMR binding studies were performed at 298 K with a Bruker AV III 500 spectrometer (500 MHz) in a mixture of $D_2O$ (99.8 atom-% D) and $CD_3CN$ (99.8 atom-% D) purchased from Armar. For the experiments, host **3b** was dissolved in $D_2O/CD_3CN$ (2:1, about $5 \times 10^{-4}$ M), an aliquot of this solution was used to dissolve the guest (about $2.5 \times 10^{-2}$ M, depending on solubility) and another aliquot to dissolve 1,3,5-trimethoxybenzene (about $3 \times 10^{-2}$ M) as an internal standard. During the binding studies, the host solution was treated with a solution of the internal standard (about 1.0 equiv.) and successively with the guest solution by syringe (0.8, 1.0, and 1.2 equiv.) so that the host concentration remained constant and the guest concentration gradually increased. $^1$H NMR spectra were recorded after each guest addition, and the concentrations of the free and encapsulated guest were calculated by integration of the peak areas of the internal standard and encapsulated guest, considering the corresponding number of protons and concentration of the internal standard as well as the total amount of guest. The $K_a$ values were calculated according to $K_a$ = [HG]/([H][G]) (Table 2).

**Computational Simulations of Host–Guest Complexation:** The complexation of molecular basket **1** with 1,4-dioxane was simulated by using the MAB force field in moloc,[36] verifying the formation of temporary hydrogen bonds between guest and phenolic HO groups of the host. The complex was further investigated by using MacroModel 9.7[40] [conformational search, Monte–Carlo Multiple Minimum (MCMM) algorithm, OPLS 2005 force field, GB/SA solvation model for $CHCl_3$, followed by energy minimization, Polak-Ribière Conjugate Gradient (PRCG) algorithm]. Afterwards, the host–guest complex was further energy-minimized by using PM3 in Spartan '14.[41] Complexation of container molecule **3b** with encapsulated 1,4-dithiane was investigated by using MacroModel 9.7[40] and Spartan '14[41] as described above by using the GB/SA solvation model for $H_2O$.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and characterization of the precursors to the container molecules, as well as NMR spectra for all compounds; method for the $^1$H NMR assignments of the molecules and applied phane nomenclature; additional tables and figures.

## Acknowledgments

This work was supported by a grant from the Swiss National Science Foundation.

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Received: February 24, 2014
Published Online: April 17, 2014

  