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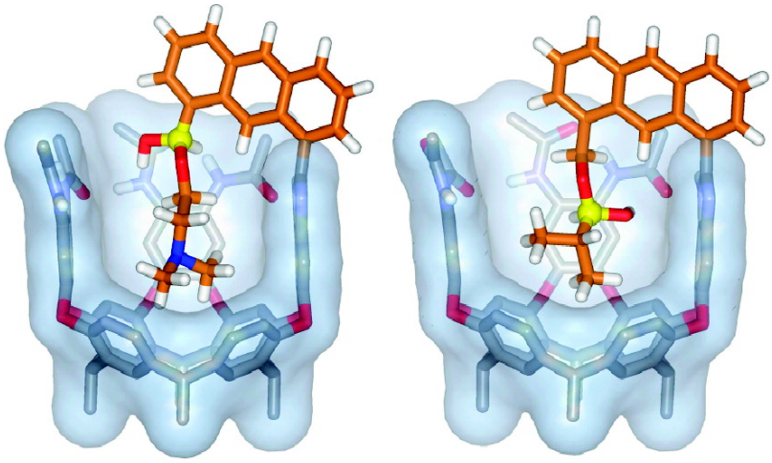

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Cavitands with Introverted Functionality Stabilize Tetrahedral Intermediates

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Abstract: The synthesis and characterization of two deepened cavitand hosts with introverted functionality—functional groups directed into the cavity—is described. Two functions can be introverted, alcohol and aldehyde, and they show the formation of hemiacetals and hemiketals on binding small guests with complementary functional groups. The structures of the bound hemiacetals are determined by 1D and 2D NMR studies. The arrangements of the guests in the cavitands enhance the equilibrium constants of carbonyl additions, K/K_{ctrl}, between 13- and 10^5-fold, compared to their counterparts in solution. The stabilization of the addition products is due to the prior complexation of the guests and the organized solvation provided to the tetrahedral intermediates by a network of secondary amides at the cavitand rim.

Introduction

Reactive intermediates have been stabilized by isolation in covalent carcerands[1] and even reversibly formed capsules.[2] In the former, the intermediates are formed irreversibly from precursors *in situ*,[3] while in the latter the products of unfavorable chemical *equilibria* are amplified by surrounding them in a stabilizing environment. For example, iminium ions are readily observed in capsules that bear multiple negative charges,[4] and labile silanols are protected from hydrolysis in metal/ligand capsules.[5] The covalent participation of host with guest is underrepresented, largely due to the difficulty of functionalizing concave molecular surfaces.[6] In a recent departure, we introduced the cavitand **1** (Figure 1) and showed its "introverted" aldehyde stabilizes intermediate hemiaminals with amines that are accommodated in the cavity.[7] Here we apply it and the derived alcohol **2** to the stabilization and amplification of hemiacetals.

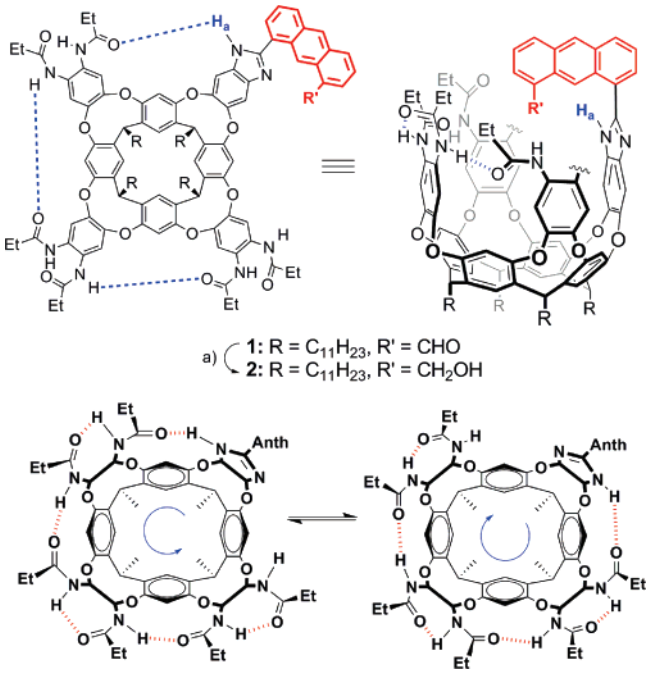

Figure 1. (a) Cavitands used, and a representation of their folded state: $NaBH_4$, THF, 90%. (b) Illustration of the chiral environment created by the hydrogen-bonding pattern at the rim; the exchange is slow on the NMR time scale.

The addition reaction of alcohols to carbonyls (eq 1, Figure 2) is reversible, and the formation of hemiacetals can be unfavorable: aliphatic aldehydes form hydrates and hemiacetals readily, but aromatic aldehydes and ketones typically do not.[8] The entropic price of bringing the two reactants together is not always compensated by the new covalent bonds formed. In the case of intramolecular reactions, the entropic price is reduced, and hemiacetals are readily observed; many examples are

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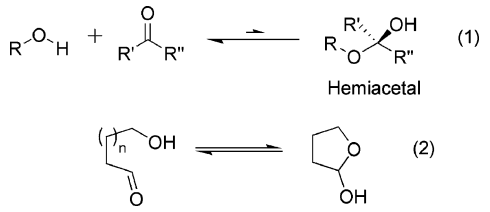

Figure 2. The equilibria in question.

available in the chemistry of carbohydrates (eq 2, Figure 2). The unfavorable additions give the initial intermediates for formation of acetals, a process that can be driven to the products by the removal of the side product, water.[9]

Results and Discussion

Both of the components of the reaction (aldehydes and alcohol) can be incorporated into the cavitand structure (Figure 1), allowing study of the equilibrium from two perspectives by using alcohol or aldehyde guests, respectively. The introverted aldehyde **1** was converted to the corresponding alcohol **2** by reduction with $NaBH_4$. These cavitands are held in the vase-like conformation by the intramolecular hydrogen bonding, and the cavities are large enough to surround a single small-molecule guest and present it with the inwardly directed function. Both cavitands **1** and **2** fold around a competitive solvent such as $CDCl_3$, but in solvents such as mesitylene-d_{12} that do not fit inside, they show broad, undefined ^{1}H NMR spectra. On addition of small aldehydes such as propionaldehyde **3** or isobutyraldehyde **4** to a solution of **2** in mesitylene-d_{12}, the ^{1}H NMR spectra (see Figure 3 and Supporting Information) sharpen considerably and show signals for bound guest. These appear far upfield with shifts due to the magnetically shielded environment created by the many aromatic rings of the cavitand.

Further inspection of the ^{1}H NMR spectrum shows that the bound guest is *covalently* linked to the cavitand. Isobutyraldehyde shows no binding affinity for cavitand **1** (to which it cannot form a covalent bond). When added to **2**, *three* species are formed (Figure 3): two sets of sharp signals corresponding to the two diastereomers formed by covalent addition, and a set of broad signals from a noncovalent complex. The diastereomers arise from the new stereogenic center of the hemiacetal fixed in a chiral environment. The seam of hydrogen bonds around the rim of the cavitand can be either clockwise or counterclockwise and interconverts slowly on the NMR chemical shift time scale (Figure 1b).[6c] (When the guests are noncovalently bound, the complexes exist as two *enantiomers* and show only one set of peaks.) Formation of a covalent complex locks the anthracene arm over the top of the cavitand (in the unbound cavitand, the arm is free to rotate), leading to a signature upfield shift in the amide methyl groups. This orientation of the aromatic group places the amides near the face of the anthracene, causing extra shielding and resonances at $\delta = -0.65$ and -0.69 ppm. These resonances are absent in species that do not form covalent complexes (cyclohexane, cyclohexanol, etc.) The resonances for new hemiacetal CH and OH are obscured by cavitand/free aldehyde peaks and so are not seen. Figure 3 shows the most helpful peaks for assignment in the ^{1}H NMR spectrum: introverted alcohol CH_2 ($H_b/H_{b'}$), cavitand benzimidazole proton H_a, and the deeply bound guest methyl groups ($Me_d/Me_{d'}$) Additional evidence for the covalent linkage is provided by mass spectrometry. Electrospray ionization high-resolution mass spectrometry (ESI-HRMS) of **2·4** gives a mass of 2146.2626 ($M + H^+$), which corresponds to that of the covalent adduct. MS studies of noncovalently bound guests such as cyclohexane show only disassociated cavitand and guest in systems such as this. A modest diastereoselection occurs with a ratio of 1:0.6.[10]

The isobutyraldehyde has modest affinity for **2**, and some of the cavitand exists in a flexible, partially folded state, resulting in broad NMR signals. A 2D NOESY spectrum of the complex (see Supporting Information) shows chemical exchange cross-peaks between the broad guest signals at $\delta = -2.4$ and -2.7 and the signals for free isobutyraldehyde at $\delta = 0.95, 0.75$. No exchange was seen between free isobutyraldehyde and the peaks for either diastereomer of the hemiacetal. Also, Figure 4 shows that the two diastereomers display no exchange between each other, indicating that the hemiacetals are not undergoing interconversion on the NMR time scale.[11]

Integration of the signals for free and bound cavitand allows determination of the equilibrium constant for hemiacetal formation. The calculation used the signals for the methine H_a which are not broadened in the unoccupied cavitand. Other small aldehydes also form hemiacetals inside cavitand **2**, as shown in Table 1. Propionaldehyde **3**, *n*-butyraldehyde **5**, and cyclohexane carboxaldehyde **6** all form covalent complexes in mesitylene solution, as seen by ESI-HRMS and the appearance of characteristic ^{1}H NMR peaks (see Supporting Information). As the reactions do not reach equilibrium immediately, the solutions were allowed to equilibrate over a period of 4 h before NMR analysis. The smaller substrates (**3** and **5**) show no binding without covalent bond formation, but **6** is a good guest even without hemiacetal formation, and so two species can be seen in the ^{1}H NMR spectrum (see Supporting Information). Surprisingly, there is no requirement for acid or base catalysis other than that provided by the nearby secondary amides—or the reactants themselves. The reaction takes place in a region of organized weak hydrogen bonds in a nonpolar solvent, conditions that contribute to the sluggish equilibration observed.

We examined the solution counterparts to these systems to arrive at a measure of the effects of the cavitand. In the absence of the cavitand, a solution of 0.8 M of each aldehyde and benzyl alcohol in deuterated benzene shows much smaller concentrations of the corresponding hemiacetals in the NMR spectra. The relative enhancement of the equilibrium, K_{eq}/K_{ctrl}, is shown in Table 1, and varies from 13-fold for **5** to 138-fold for isobutyraldehyde **4**. It was also possible to observe enhanced formation of a hemi*ketal*. Upon addition of cyclohexanone to **2**, a noncovalent complex forms on mixing. The hemiketal grows in over a period of days to give roughly equal amounts of covalent and noncovalent species. To our knowledge, hemiketals of cyclohexanone are unreported in solution. As a

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(10) This ratio is similar to that seen in a related introverted ester: Purse, B. W.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 2530−2534.

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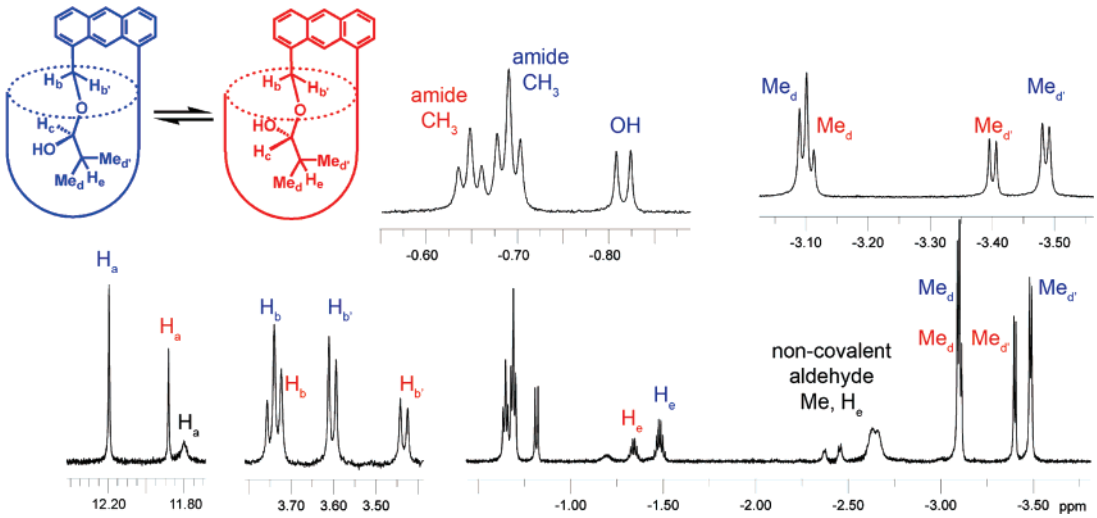


Figure 3. Selected regions of ^{1}H NMR spectrum of hemiacetal formed by addition of isobutyraldehyde to alcohol **2**.

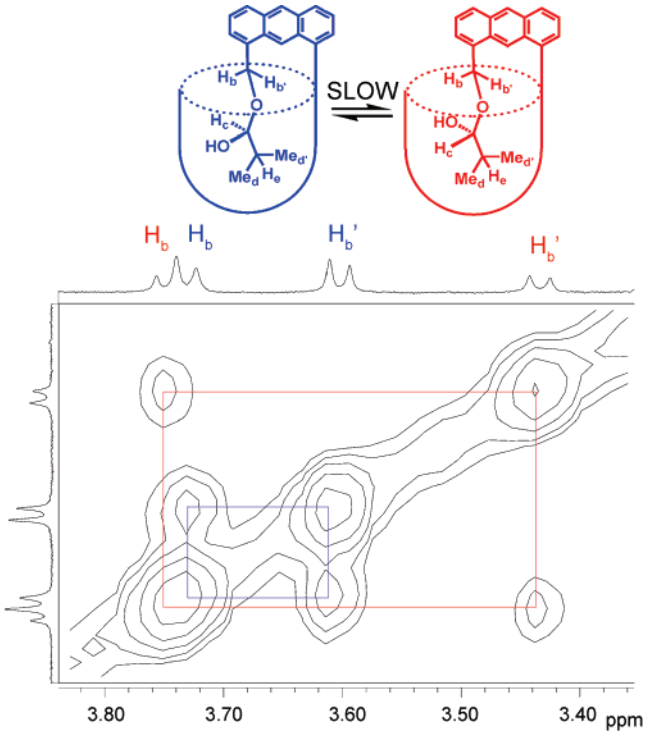
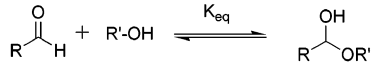


Figure 4. Expansion of the 2D NOESY spectrum of the complex **2**·**4** formed by exposure of cavitand **2** to isobutyraldehyde **4**, 600 MHz, mesitylene-d_{12}, 300 K, 300 ms mixing time. This region shows NOE cross-peaks between benzyl protons H_b and H_b' (same color), but no exchange correlation between H_b of different diastereomers (different colors).

Table 1. Enhancement of Equilibrium Constants[a] for Various Substrates



Entry	R-CHO	Alcohol	K_{eq} (M^{-1})	K_{ctrl} (M^{-1})	K_{eq}/K_{ctrl}
1[b,c]	Et **3**	**2**	30	0.86	35
2[b,c]	i-Pr **4**	**2**	51	0.37	138
3[b,c]	n-Pr **5**	**2**	11	0.34	13
4[b,c]	C_6H_{11} **6**	**2**	35	0.28	125
5[b,c]	 **7**	**2**	21	<0.001	$> 10^5$
6[b,c]	**1**	 **8**	31	~0.005	5800
7[b,d]	**1**	 **9**	42	<0.001	$> 10^5$
8[b,e]	**1**	 **10**	33	<0.001	$> 10^5$

[a] K_{eq} = [hemiacetal]/([cavitand][guest]). [b] K_{eq} determined with $[cavitand]_0$ = 1.5 mM and $[guest]_0$ = 10 mM. [c] K_{ctrl} for reaction of benzyl alcohol and desired aldehyde in benzene-d_6, $[PhCH_2OH]_0 = [RCHO]_0$ = 0.8 M. [d] K_{ctrl} for reaction of benzaldehyde and desired alcohol in benzene-d_6, $[PhCHO]_0 = [ROH]_0$ = 0.5 M. [e] $[PhCHO]_0 = [ROH]_0$ = 15 mM.

result, a limit was estimated based upon the detection limits of the spectrometer (Table 1), and enhancement of the addition reaction inside **2** is $>10^5$.

Given the enhancements in equilibrium constant for the addition of aldehydes to **2**, we expected a similar effect for the addition of alcohols to **1**. Unfortunately, the addition of small alcohols such as propanol, *tert*-butanol, and isoamyl alcohol to a solution of **1** in mesitylene-d_{12} showed no folded cavitand, even after 2 weeks. With larger alcohols that have better size and shape complementarity for the cavitand (cyclohexanol, cyclooctanol, and 1-adamantanol), host−guest complexes were seen, but no visible hemiacetal formation occurred. No peaks for upfield-shifted amide methyl groups were seen, so it is most likely that the aldehyde arm was oriented outside the cavity, to lower steric clashes with the guest. The equilibrium constant for this process lies so far toward the reactants that even cavitand binding does not reveal products at millimolar concentrations. In an attempt to add further stabilization to the hemiacetal,[8b,12,13] we introduced additional H-bonds using *N*,*N*-dimethylethanolamine **8**, *trans*-1,2-cyclohexanediol **9**, and *trans*-1,2-cyclopentanediol **10**.

On addition of 10 equiv of alcohol **8** to **1**, a new complex was indeed formed. *N*,*N*-Dimethylethanolamine is a poor guest for the cavity without covalent attachment, and so again two species are present: the bound hemiacetal and unoccupied cavitand, which displays broad, unassignable ^{1}H NMR signals. In this case, the resonance for the hemiacetal CH is not obscured

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(13) Bone, R.; Cullis, P.; Wolfenden, R. *J. Am. Chem. Soc.* **1983**, *105*, 1339−1343.

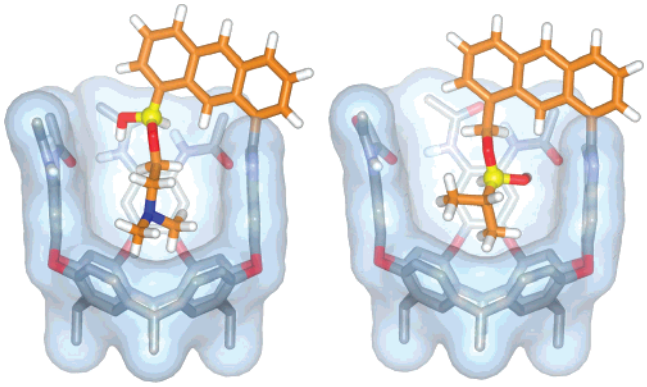


Figure 5. Minimized representations of (a) hemiacetal derived from combination of **1** and *N*,*N*-dimethylethanolamine **8** and (b) hemiacetal derived from combination of **2** and isobutyraldehyde **4** (Maestro v. 7.0.2, MMFFs forcefield).

by background and is seen as two singlets (for the two diastereomers), $\delta = 4.78$ and 4.50 ppm. No coupling is seen to the OH, which is consistent with the spectra for related hemiaminals.[7] The diastereomeric ratio in this case is 2:1. When the equilibrium constant of hemiacetal formation in the cavitand was calculated and compared to that for the reaction of benzaldehyde and *N*,*N*-dimethylethanolamine, we were pleased to see a significant enhancement in hemiacetal formation: $K_{eq}/K_{ctrl} = 5800$, far greater than observed for cavitand **2**. The presence of a second H-bond acceptor has an effect on these equilibria in free solution: whereas no appreciable hemiacetal formation was observed for the reaction of 0.5 M benzaldehyde and cyclohexanol in benzene, the combination of **8** with benzaldehyde gave barely observable amounts of hemiacetal,[8b] allowing crude determination of the equilibrium constant.

N,*N*-Dimethylaminopropanol and 1,2-thiomethylethanol showed no binding affinity or hemiacetal formation, but the cyclic diols **9** and **10** did form hemiacetals in cavitand **1** with K_{eq} similar to that of **7**. In these cases, however, no hemiacetal formation was observed in the control reaction with benzaldehyde; presumably the OH group, being a weaker H-bond acceptor than NMe_2, does not provide enough stabilization of the hemiacetal to form sufficient concentration to be visible by ^{1}H NMR. As a result, an upper limit was estimated on the basis of the detection limits of the spectrometer (Table 1). This crude estimation leads to large enhancements in K_{eq}, possibly even larger than for **1·8**. The formation of hemiacetals with **10** was extremely slow; only after 4 days at 23 °C was equilibrium reached. In this case, diol **10** is large enough to form a strong noncovalent complex with **1** prior to hemiacetal formation, as seen by sharp signals for folded cavitand (see Supporting Information).

How can the cavitand amplify the concentration of labile species inside? The cavitand's environment must preferentially recognize and stabilize the tetrahedral intermediate through hydrogen-bonding and other attractive interactions with the seam of the cavitand's amides. This situation is regarded as commonplace in biological catalysis, where the catalytic site is capable of shifting equilibria toward unstable intermediates. The adduct between **1** and **8**, as shown in Figure 5a, positions the new tetrahedral center particularly close to the amide rim, where both hydrogen bond donors and acceptors are available and permanently fixed in place through synthesis. The adducts with cavitand **2** have their tetrahedral centers positioned deeper in the cavity due to the extra methylene group on the anthracene (e.g., Figure 5b). There, the hydrogen-bonding benefit and the stabilization are diminished but still significant.

Modeling indicates that the H-bond acceptor nitrogen in **1·8** (Figure 5a) does not necessarily participate in an intramolecular hydrogen bond with the hemiacetal OH; the NMe_2 group is positioned near the base of the cavity (as corroborated by their ^{1}H NMR signals; $\Delta\delta = -3.6$ ppm). Why the hemiacetal **1·8** is formed and other small alcohols show no reaction is unclear, but evidently the newly formed OH is favored by its positioning in the cavitand. Diols **9** and **10** most probably involve an extra intramolecular H-bond to the second hydroxyl; in these cases, the donor is not used to occupy the cavitand base. The extremely slow rate of equilibration of **1·10** can be rationalized by the poor angle of attack of the larger guest. The mechanism of hemiacetal formation (i.e., whether the nucleophilic addition occurs before or after the binding event) is not clear and most probably varies depending upon the nature of the guest. Diol **10** forms a kinetically stable noncovalent complex prior to addition, and in that case, hemiacetal formation is significantly slower than for guests **3**−**8**. Orientation of the alcohol for attack is unfavorable; thus, a large kinetic barrier to addition exists. The smaller guests that do not preorganize the cavitand rely on addition prior to rapid folding; this addition step has no restrictions on angle of attack and so is faster, even though the entropy of collision must be overcome.

Conclusions

The introverted functions lead to direct observations of intermediates in the liquid phase at ambient temperatures and at equilibrium. The hemiacetal products of aldehydes and alcohols can be observed in the cavitand and are significantly amplified from their counterparts in free solution. Biological macromolecules also use binding forces to stabilize reactive intermediates, and covalent complexes have been proposed as leading to the greatest rate enhancements.[14] The concept of enhancing the concentration of reactive intermediates offers great potential for applications in supramolecular reactions and catalysis.

Experimental Section

1D and 2D NMR spectra were recorded on a Bruker DRX-600 spectrometer. Proton (^{1}H) chemical shifts, reported in parts per million (ppm), were indirectly referenced to external tetramethylsilane employing resonances due to trace monoprotio solvent as an internal reference. The 2D NOESY spectra of the cavitands were recorded at 300 K at 600 MHz with the phase-sensitive NOESY-GP pulse sequence including a gradient pulse supplied with the Bruker software. Each of the 512 F1 increments was the accumulation of 36 scans. Before Fourier transformation, the FIDs were multiplied by a 90° sine square function in both the F2 and the F1 domains. 1K_1K real data points were used, with a resolution of 1 Hz/point. Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA) and used without further purification. High-resolution electrospray ionization time-of-flight (TOF) spectra were acquired on an Agilent ESI-TOF mass spectrometer. Anhydrous solvents were used as obtained from Acros Organics. Guests **3**−**10**, cyclohexanol, cyclooctanol, and 1-adamantanol were obtained from Aldrich Chemical Co. and were used as received. Cavitand **1** was synthesized according to the published procedure.[7]

Synthesis of Introverted Alcohol Cavitand 2. $NaBH_4$ (10 mg, 0.26 mmol) was added to a solution of aldehyde **1**[1] (24 mg, 11.6 μmol) in

(14) Zhang, X.; Houk, K. N. *Acc. Chem. Res.* **2005**, *38*, 379−385. Chen, J.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 327−329.

THF (5 mL) at 0 °C, and the resulting mixture was stirred for 30 min. The reaction was quenched by addition of a saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give a pale yellow solid. Flash column chromatograpy of the crude residue (SiO_2, CH_2Cl_2:EtOAc 4:1) afforded **2** as a white solid (21 mg, 90%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.87 (s, 1H), 9.88 (s, 1H), 9.85 (s, 1H), 9.29 (s, 1H), 9.00 (s, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 8.43 (m, 1H), 8.12 (d, J = 9.8 Hz, 1H), 8.08 (m, 1H), 7.95 (s, 1H), 7.93 (s, 1H), 7.85 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.51 (m, 3H), 7.43 (m, 2H), 7.35−7.14 (m, 11H), 5.79 (m, 3H), 5.65 (m, 1H), 4.48 (m, 2H), 3.72 (m, 1H), 2.61−2.13 (m, 14H), 1.85−1.25 (m, 83H), 1.20 (t, J = 8.4 Hz, 3H), 1.14 (t, J = 8.4 Hz, 3H), 0.92 (m, 12H), 0.38 (t, J = 8.4 Hz, 3H), 0.32 (m, J = 8.4 Hz, 3H); HRMS (ESI) calcd for $C_{130}H_{161}N_8O_{15}$ $[M + H]^+$ 2074.2075, found 2074.2041.

General Procedure for Hemiacetal Formation. Aldehyde **1** (1.8 mg, 9 × 10^{-4} mmol) or alcohol **2** was dissolved in mesitylene-d_{12} (600 μL) and added to a 5 mM high-field NMR tube. Guest (aldehyde or alcohol, ~1.25 μL in 25 μL of mesitylene-d_{12}) was added via syringe, the NMR tube shaken to allow mixing, and the mixture analyzed by ^{1}H NMR. After complete equilibration (4 h to 1 week), the complexes were analyzed by ^{1}H NMR and ESI-HRMS to determine K_{eq} (see below). The ^{1}H NMR spectra (containing excess guest) for each product are shown in the Supporting Information.

ESI-HRMS analysis for hemiacetal **2·3** (from alcohol **2** and propionaldehyde **3**): calcd for $C_{133}H_{167}N_8O_{16}$ ($M + H^+$) 2132.2494, found 2132.2487.

ESI-HRMS analysis for hemiacetal **2·4** (from alcohol **2** and isobutyraldehyde **4**): calcd for $C_{134}H_{169}N_8O_{16}$ ($M + H^+$) 2146.2650, found 2146.2626.

ESI-HRMS analysis for hemiacetal **2·5** (from alcohol **2** and butyraldehyde **5**): calcd for $C_{134}H_{169}N_8O_{16}$ ($M + H^+$) 2146.2650, found 2146.2638.

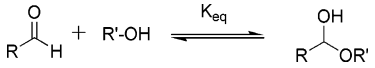
ESI-HRMS analysis for hemiacetal **2·6** (from alcohol **2** and cyclohexylcarboxaldehyde **6**): calcd for $C_{137}H_{173}N_8O_{16}$ ($M + H^+$) 2186.2693, found 2186.2955.

ESI-HRMS analysis for hemiacetal **1·8** (from aldehyde **1** and *N*,*N*-dimethylethanolamine **8**): calcd for $C_{134}H_{170}N_9O_{16}$ ($M + H^+$) 2161.2759, found 2161.2714.

ESI-HRMS analysis for hemiacetal **1·9** (from aldehyde **1** and (1*R*,2*R*)-*trans*-cyclohexanediol **9**): calcd for $C_{136}H_{171}N_8O_{17}$ ($M + H^+$) 2188.2756, found 2188.2724.

ESI-HRMS analysis for hemiacetal **1·10** (from aldehyde **1** and *trans*-cyclopentanediol **10**): calcd for $C_{135}H_{169}N_8O_{17}$ ($M + H^+$) 2174.2600, found 2174.2607.

Determination of Equilibrium Constants.



For the reaction above, K_{eq} = [HA]/([ROH][RCHO]), where [HA] is the equilibrium concentration of hemiacetal, [ROH] is the equilibrium concentration of alcohol, and [RCHO] is the equilibrium concentration of aldehyde, all in M^{-1}. Concentrations were measured by integration of the appropriate signals in the ^{1}H NMR spectrum after complete equilibration had occurred.

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Supporting Information Available: ^{1}H NMR and NOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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