Intramolecular Hydrogen Bonding Controls the Exchange Rates of Guests in a Cavitand

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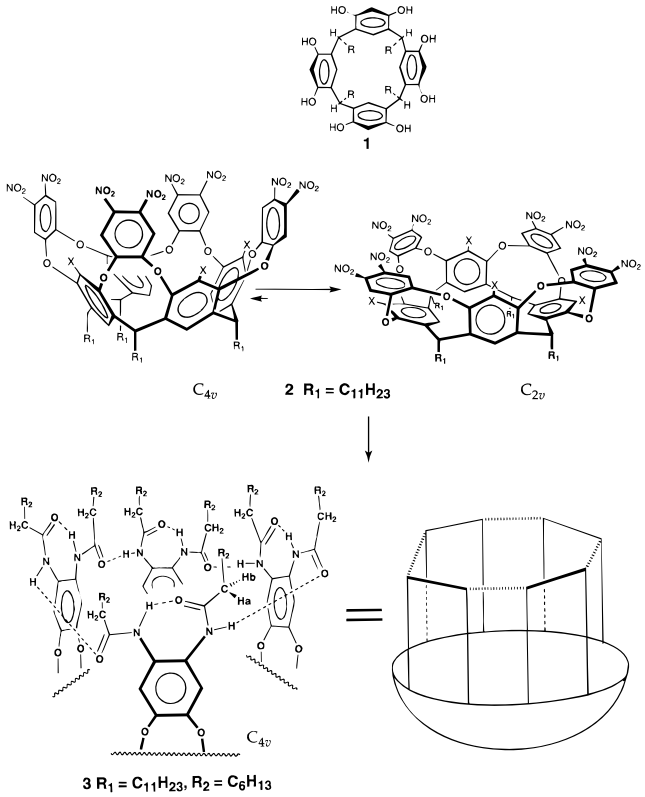
Högberg's resorcinarenes **1** provide practical starting materials for many of the synthetic receptors used in molecular recognition studies.[1] Their easy synthesis, richness of functionality, predictable conformations, and curvature have made them and their calixarene cousins[2] ideal platforms for cavitands,[3] carcerands,[4] velcrands,[5] and various hybrid molecules.[6] Cavitands are especially versatile, binding smaller molecules and solvents in the solid state, in the gas phase, and even in solution.[7] We describe here cavitand complexes that feature unusual kinetic stability in solution and relate their behavior to the effects of hydrogen bonding on conformational dynamics.

The conformational dynamics of cavitands and velcrands have been thoroughly described by Cram.[5] The molecule flutters between C_{4v} and C_{2v} symmetries. The former has all four catechol sides up and features a well-defined vase-like shape that is preferred at higher temperatures. The latter has these sides flipped outward in a kite-like shape and is the dominant conformation at room temperature or below. The barrier to interconversion is typically 10−12 kcal/mol for cavitands with unsubstituted resorcinol rings and 17−19 kcal/mol with 2-alkylated ones.[5] To stabilize the C_{4v} conformation, a purse-string suture of intramolecular hydrogen bonds was stitched along the upper rim of the structure. Specifically, reduction of the octanitro derivative **2** (X = H),[8] prepared similarly to the corresponding Cram cavitand (X = Me),[5a] and subsequent acylation of the amines with excess octanoyl chloride gave octaamide **3** (Scheme 1).[8] The amides present hydrogen bonds that can bridge adjacent rings - *interannular* binding—and are held in place by the 7-membered *intraannular* hydrogen bonds.

Scheme 1



When all of the amides are oriented in the same direction, the hydrogen bonds are coherent and offer the added benefits of cooperativity. The result is a deeper vase, one that resists the conformational change to the kite-like shape.

The ^{1}H NMR spectrum of **3** in various nonpolar solvents showed the earmarks of the C_{4v} conformation[5] at room temperature, including a characteristic methine triplet at ca. 6 ppm. The N−H resonances are far downfield: 10.1 and 9.9 in benzene-d_6, 10.2 and 10.0 in toluene-d_8, 9.9 and 9.7 in *p*-xylene-d_{10}, and 9.9 and 9.1 in $CDCl_3$. These are concentration independent. From the ^{1}H NMR at various temperatures, the temperature coefficients[9] $\Delta\delta/\Delta T$ for the N−H signals were calculated as 1.6×10^{-3} and 4.1×10^{-3} ppm K^{-1} in toluene-d_8 (220−295 K interval) and 0.9×10^{-3} and 3.5×10^{-3} ppm K^{-1} in $CDCl_3$ (250−295 K interval). These values confirm that one of the hydrogen bonds in **3** is less sensitive to temperature and is shielded from external solvent and that the other is somewhat more exposed to the solvent. The two N−H signals coalescence in toluene-d_8 and *p*-xylene-d_{10} at $T_c \approx 87$ °C, and at higher temperatures only one N−H signal was observed. The barrier to interconversion ($\Delta G^{\ddagger}$) of the two types of N−H signals is, accordingly, 17.4 ± 0.5 kcal mol^{-1}. In media more competitive for hydrogen bonds (DMSO-d_6/$CDCl_3$ or DMSO-d_6/*p*-xylene-d_{10} mixtures), the spectra are broad, indicating intermediate rates for the C_{4v} to C_{2v} interconversion. The FTIR spectra of **3** in benzene-d_6 and $CDCl_3$ show only the absorptions of hydrogen-bonded amides at 3233 and 3240 cm^{-1}, and the intensites of these absorption bands are invariant over the concentration range of 20−0.05 mM.

The behavior of the model compound **4** (Scheme 2a) supports the interpretation of the structure proposed for **3**. Specifically, a single N−H resonance at ca. 8.7 ppm was observed for **4** in nonpolar solvents at room temperature; a much larger value $\Delta\delta/\Delta T$ for the N−H signal (6.0×10^{-3} ppm K^{-1} in $CDCl_3$, 211−330 K interval) was calculated over a −60 to +60 °C temperature range; the N−H signal is concentration dependent and shifts ca. 0.7 ppm upfield upon dilution from 20 to 0.5

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(8) Selected ^{1}H NMR and COSY spectroscopic data at 25 °C for **2** ($CDCl_3$): δ 7.66, 7.61 (2 × s, 8 H, NO_2-arom) 7.20, 7.06, 6.98, 6.12 (4 × s, 8 H, calix), 3.94 (m, 4 H, CH-methine). For **3** (benzene-d_6): δ 10.06, 9.87 (2 × s, 8 H, NH), 8.04, 7.35 (2 × s, 8 H, C(O)-NH-arom), 7.82, 7.51 (2 × s, 8 H, calix), 6.41 (t, $^3J_{HH}$ = 8.0 Hz, 4 H, CH-methine); MALDI-MS 2531.0 ([M + H]$^+$, calcd for $C_{160}H_{240}N_8O_{16}$). Compound **2** was prepared as described for the analogous cavitand;[5a] other derivatives of **2** and **3** synthesized were $R_1 = C_9H_{19}$ and $C_{10}H_{21}$.

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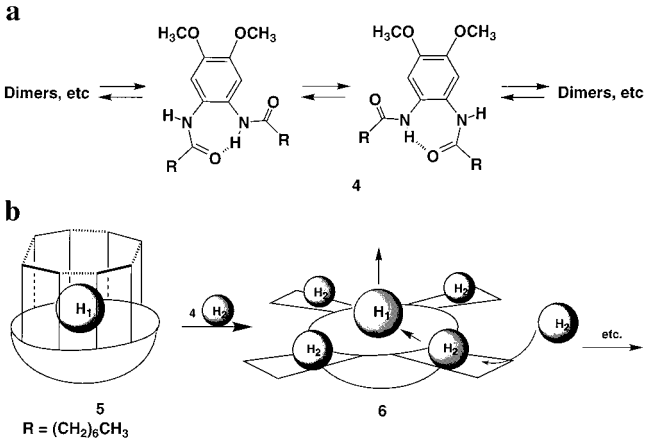
Scheme 2



mM. The FTIR spectra of **4** in benzene-d_6 showed both hydrogen-bonded (3254 cm^{-1}) and free (3389 cm^{-1}) absorptions; their absorption ratios change in the expected concentration-dependent manner toward the monomer upon dilution to 0.05 mM. In short, the model **4**, but not **3**, undergoes fast exchange between two intramolecular hydrogen-bonded structures and, at increased concentrations, forms intermolecular aggregates (Scheme 2b).

The deep cavity of **3** is doubtless solvated, and molecular modeling[10] accommodates one molecule of *p*-xylene and, at best, two molecules of benzene or $CHCl_3$ in its internal volume. The solvent mixtures benzene-d_6/*p*-xylene-d_{10} or benzene-d_6/toluene-d_8 give only one set of signals at 0−25 °C. However, addition of excess adamantane, 1-adamantanamine, and *N*-(1-adamantyl)-acetamide to a solution of **3** in *p*-xylene-d_{10} gives a new set of signals in the NMR spectra—for both the cavitand and the caviplexes of adamantane. The guest species were observed at −0.5 to −1.0 ppm, a feature characteristic of inclusion in a shielded environment and similar to the shifts observed in covalently bound carceplexes.[4,5] The sharp and widely separated signals for free and bound adamantane indicate that exchange of adamantane in and out of the vase **3** is *slow* on the NMR time scale at room temperature. The slow exchange is, to our knowledge, unprecedented for open-cavity receptors. For the adamantanes, hostage and free signals became broad, and the guest signals eventually disappear into the base line at ≥67 °C. The NOESY spectrum of the (**3**−adamantane) complex showed NOE connectivities between the signals of the complexed adamantane with the N−H and the catechol aromatic protons. Accordingly, the hostage molecule is situated in the cavity above the calix[4]resorcinarene platform, as anticipated by the solid-state structures of known caviplexes.[7]

The association constants for 1:1 complexation were calculated from the integration of the NMR spectra; their values are all modest and in the range of $K = 40 \pm 10$ M^{-1} at 295 K, which gives $\Delta G°$ values of 2.0 ± 0.3 kcal mol^{-1}. In benzene-d_6 and $CDCl_3$, the binding affinities are an order of magnitude lower, $\Delta G°$ values of 0.5 ± 0.1 kcal mol^{-1} at 295 K were found. Attempts to complex ferrocene and 1(*R*)-(−)-camphorquinone showed no evidence of inclusion by NMR.

At first glance, the slow exchange is a surprising result: the open end of the vase is seemingly unobstructed and adamantane's dimensions are easily accommodated by the distance (~10 Å) between opposite catechol walls (Figure 1). The problem, we submit, is in the mechanism of hostage exchange. The vase-like molecule is doubtless occupied by solvent in its resting state. Obviously, the solvent must be gone by the time the adamantane takes residence. What is the lowest energy pathway for exchange of occupants into and out of the vase?

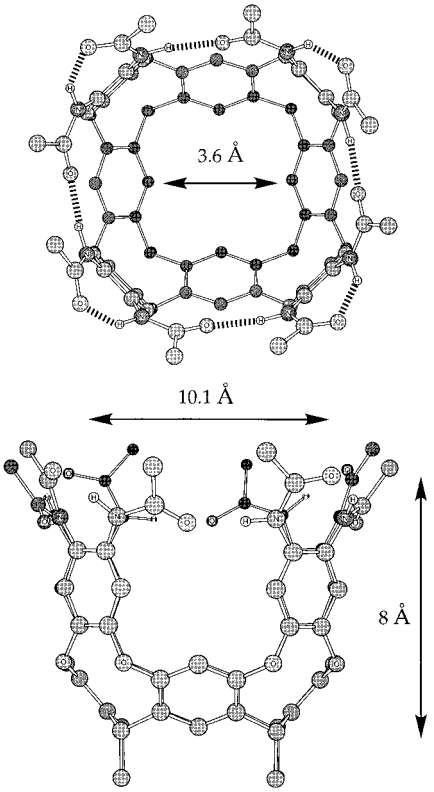


Figure 1. Energy-minimized (MM2) depiction of the hydrogen-bonded structure **3**. The alkyl chains and some hydrogens are omitted for clarity.

Entry from the bottom of the structure is not feasible since only 3.6 Å separate the two opposite hydrogen atoms (Figure 1). Intuitively, pulling a solvent molecule out would seem prohibitive in energy: the interior becomes desolvated as an (abhorrent?) vacuum is created. Squeezing two molecules past each other as they pass in opposite directions inside the vase is also unlikely: there just is not enough room. This leaves no alternative but to pull apart the vase along the lines of the conformational dynamics described above (Scheme 2b). To support this mechanism, the EXSY experiment on the adamantane complex with **3** in *p*-xylene-d_{10} was performed, and the activation barrier ($\Delta G^{\ddagger}$) for the exchange between the free and complexed guest of 16.9 ± 0.4 kcal mol^{-1} at 295 K was found ($k = 2 \pm 1$ s^{-1}), a barrier that coincides with the interconversion barrier between two amide signals. The loss of the four interannular hydrogen bonds raises the price of this motion, as does organization of solvent on the newly exposed surfaces. The proposed sequence is shown in Scheme 2b, where H represents solvent or hostage and only the changes in solvation of the concave surfaces are outlined. The process is depicted as orderly *displacement* from the periphery toward the center of the assembly, but the flow in the opposite direction or direct displacment from the central species in **6** is just as likely and, at this level of resolution, indistinguishable. Refolding the system in the reverse of the sequence completes the exchange process.

In conclusion, a completely closed surface is not necessary for sizable energetic barriers to the exchange of hostages. All that is needed is limited access:one door to the cavity. Even such a minimal system requires a sequence of events for exchange that is far from simple. The process is much more complicated in biological macromolecules, but the same considerations are expected to apply.

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