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# Electronic and Steric Effects in Binding of Deep Cavitands

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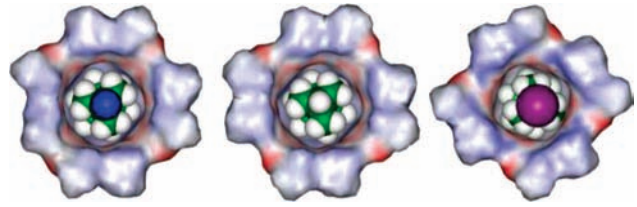
## ABSTRACT



**A deep, self-folding cavitand responds to minor electronic differences between suitably sized adamantane guests. Binding constants range from <0.5 to 4000 $M^{-1}$ for guests as similar as 1-bromoadamantane and 1-cyanoadamantane. The barriers to guest exchange also vary up to 3 kcal $mol^{-1}$.**

Enzymes can detect very small changes in substrate structures,[1] and the discrimination may be through steric or electronic effects. The replacement of hydrogen atoms with fluorine atoms, for example, has large effects on the binding constants of thrombin inhibitors, and these are attributed to variations in electronic rather than steric effects.[2] Functional groups presented to substrates by the folded enzymes are responsible for this selectivity, and some synthetic receptors can reproduce this discrimination. Fully enclosed host capsules can detect subtle differences in guest structure, generally due to changes in "fit"—capsules are responsive to the size and shape complementarity of the substrate.[3] Open-ended receptors such as cyclodextrins or cavitands are often poor at distinguishing between small changes in guest structure; any functionality that is incompatible with the cavity can be directed outward, into the solvent. Here, we report that small changes in a series of adamantane-derived guests have large effects on the properties of the complex with the cavitand. These effects appear electronic in nature rather than steric interactions with the cavitand or its substituents at the cavitand's rim.[4]

Deep cavitands are held in a bowl-shaped conformation by a seam of hydrogen bonds at the open end.[5] They fold around their guests and act as enzyme mimics in a number of senses, including recognition, catalysis, and the ability to

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alter substrate reaction paths.[6] Two previously synthesized cavitands, propionamide **1** and chloromethyl **2** (Figure 1a),[5a]

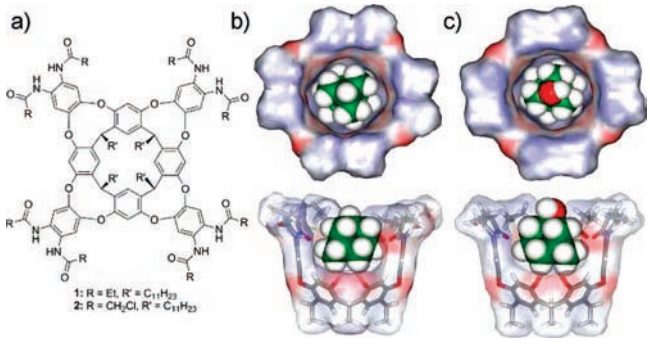


**Figure 1.** (a) Self-folding cavitands **1** and **2**. (b) Two views of the minimized structure of complex **1**•**3a**. (c) Two views of the minimized structure of complex **1**•**3e** (DFT minimization; B3LYP/6-31G* basis set). Some groups are omitted for clarity.

were chosen for this study; they feature nearly identical sizes of the eight secondary amides surrounding the open end. Cavitands **1** and **2** form kinetically stable host/guest complexes with substituted adamantanes in solvents that are not bound in the cavity such as mesitylene-$d_{12}$ or *p*-xylene-$d_{10}$. The adamantane provides a binding "anchor" that fills the space of the cavitand and presents C−H bonds to its aromatic surfaces. Typically, substituents emerge through the opening to the bulk solvent outside.[6a] Figure 1 shows energy-minimized structures (DFT minimization; B3LYP/6-31G* basis set) of the complexes of adamantane **3a** and 1-hydroxyadamantane **3e** in cavitand **1**. At first glance, the contacts between host and guest appear identical. Figure 1c shows that the substituent is remote from the amide seam—the calculated distance between an amide NH and the OH of **3e** is 5.9 Å, far longer than any hydrogen bond. This distance would preclude steric clashes between any small adamantane substituent and the cavitand's rim.

A series of substituted adamantane guests were titrated with the cavitands (see Table 1). The guests are similar in size but vary electronically. The parameters listed in Table 1 are binding constants and the energy barriers to self-exchange, values that can be easily determined by NMR techniques ($^1$H NMR integration and 2D EXSY,[7] respectively). As seen in Table 1, binding constants vary widely. Adamantane (**3a**) itself is a rather poor guest ($K_a = 55$ M$^{-1}$), whereas the presence of a fluorine atom (**3i**) or chlorine atom (**3j**) increases the binding constant to 170 and 900 M$^{-1}$, respectively. In contrast, neither bromo- (**3k**) nor iodoadamantane (**3l**) shows any binding affinity whatsoever (at the limit of detection of the NMR spectrometer). These cannot be steric factors; the halogens are small enough to avoid steric clashes with the cavitand walls, and the much larger 1-adamantylmaleimide shows a binding constant of 120 M$^{-1}$.[6a] The presence of hydrogen-bonding groups is not

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**Table 1.** Calculated Binding Constants for the Complexes Formed between Adamantane Guests and Cavitands **1** and **2**. Free Energy Barriers for the Self-Exchange of Guests in Cavitand **1**[a]

| Ad-X | $K_a$ (M$^{-1}$) (**1**)[e] | $K_a$ (M$^{-1}$) (**2**)[e] | $\Delta G^{\ddagger f}$ (kcal mol$^{-1}$) |
|---|---|---|---|
| H (**3a**) | 55 | 3 | 16.3 |
| Et (**3b**) | 515 | 79 | 16.4[b] |
| −C≡CH (**3c**) | 180 | <1 | 16.5[b] |
| −CH=CH$_2$ (**3d**) | 300 | <1 | ND |
| OH (**3e**) | 345 | 32 | 16.9 |
| NH$_2$ (**3f**) | 110 | 88 | 16.8 |
| NHAc (**3g**) | 305 | ND | 16.6 |
| CO$_2$H (**3h**) | 270 | 67 | 17.2 |
| F (**3i**) | 170 | 31 | 17.5 |
| Cl (**3j**) | 900 | 47 | 18.2 |
| Br (**3k**) | <0.5 | ND | ND |
| I (**3l**) | <0.5 | ND | ND |
| N$_3$ (**3m**) | 1650 | 90 | 18.3[c] |
| NCO (**3n**) | 1730 | 109 | 18.9 |
| CN (**3p**) | 4140 | 80 | 19.2[c] |
| NC (**3q**) | 1800 | 72 | 19.3[d] |

[a] 2 mM cavitand, 2 − 10 mM guest in mesitylene-$d_{12}$, 300 K. [b] 2D NMR obtained at 280 K. [c] 2D NMR obtained at 320 K. [d] 2D NMR obtained at 310 K. [e] estimated error ± 10%. [f] estimated error ± 0.2 kcal mol$^{-1}$.

necessarily beneficial; the binding constants for adamantanol, adamantanamine, 1-adamantylacetamide and adamantanecarboxylic acid (**3e**−**h**) are all less than that of chloride **3j** but still larger than adamantane itself. The largest binding constants were to guests **3m**−**q**. The presence of either azide, isocyanate, nitrile, or isonitrile increases the binding affinity significantly: there is an 80-fold difference in binding constant between adamantane and 1-adamantane carbonitrile **3p**. Another telling comparison is between **3c** (1-adamantylacetylene) and nitrile **3p**. The replacement of a C−H group outside of and directed *away* from the cavitand with a nitrogen atom causes a 20-fold increase in binding constant. A sterically neutral change in the guest causes a large change in binding properties.

The mechanism of self-exchange is shown in Figure 2,[5a,12] where the rate-determining step is the unfolding of the

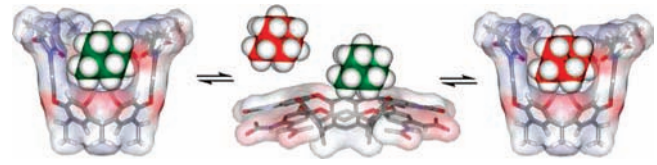

**Figure 2.** Schematic representation of the self-exchange process of adamantane in cavitand **1**.

cavitand. It was suggested that the exchange barrier was mainly due to the breaking of the rim hydrogen bonds, as

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the self-exchange rate of adamantane was similar to the barrier for interconversion of the cycloenantiomers of the amide array.[5a] The two states—folded and unfolded—were first characterized by Cram,[8] but Diederich[9] has recently described a modified cavitand that establishes the existence of a state in which two walls remain up and two are in the out or "kite" conformation. This state may also be involved in the self-exchange reaction.

Table 1 shows the energy barriers to self-exchange ($\Delta G^{\ddagger}$) obtained via calculation (using the Eyring equation) of the rate constants from EXSY NMR.[10] The large differences in $\Delta G^{\ddagger}$ shows that the self-exchange process is not controlled solely by the breaking of the hydrogen bonds, but also by the thermodynamic stability of the adamantane derivative complex. The exchange barriers for the different guests follow a similar trend to the binding constants; adamantane is exchanged fastest, with a barrier of 16.3 kcal mol$^{-1}$, whereas isonitrile **3q** is exchanged slowest, with a barrier of 19.3 kcal mol$^{-1}$; this 3 kcal mol$^{-1}$ difference corresponds to a 100-fold difference in exchange rate. Substituents capable of hydrogen-bonding (namely **3e**−**f**) also have low exchange barriers.

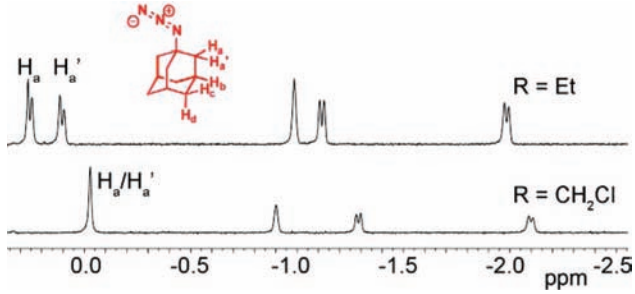


**Figure 3.** Upfield regions of the $^1$H NMR spectra of complexes **1•3m** and **2•3m** (2 mM, mesitylene-$d_{12}$, 300 K). Diastereotopic protons H$_a$/H$_a$′ are distinguished in **1•3m**, but not in **2•3m**.

Chloromethyl cavitand **2** folds in a similar manner to **1**, with the −CH$_2$Cl groups oriented away from the amide seam. Any steric differences between cavitands **1** and **2** are remote from the binding site, but *electronic* differences exist. The chloromethyl groups reduce the strength of the hydrogen bonds as can be seen in the NMR spectrum; rotation of the amides occurs much faster, and the two diastereotopic hydrogens H$_a$/H$_a$′ in **2** are not distinguished. The binding constants in Table 1 corroborate the weakening of the H-bonded seam. All of the binding constants are on the order of 5- to 10-fold smaller than their counterparts in **1**. In addition, the self-exchange of chloroadamantane **3j** in **2** has a barrier of 17.4 kcal mol$^{-1}$; 0.8 kcal mol$^{-1}$ lower than in cavitand **1**.

Self-exchange barriers of 16−19 kcal mol$^{-1}$ are slow enough to provide sharp signals in the $^1$H NMR for both guest and host. Adamantane **3a** tumbles rapidly in the cavity of **1**, showing one sharp peak upfield, whereas **3e**−**q** show all adamantane protons distinguished. The exceptions are for the hydrocarbon-substituted adamantanes **3b**−**d**. At 300 K, broad peaks are observed for acetylene **3c** at chemical shifts similar to those of the other guests **3**. Upon cooling to 280 K, the peaks sharpened, suggesting an intermediate rate of motion. Further cooling had no appreciable effect. The motion can be interpreted with reference to the NMR spectrum of **1•3d** (Figure 4).

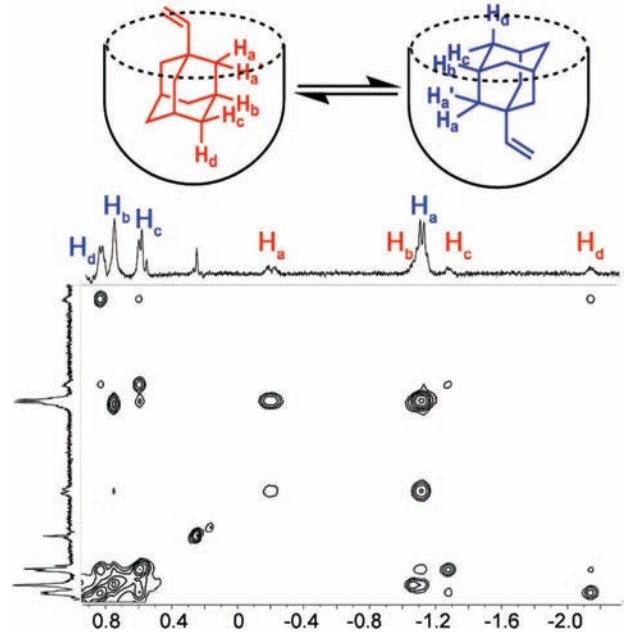


**Figure 4.** Upfield region of the 2D NOESY NMR spectrum of complex **1•3d** (2 mM, mesitylene-$d_{12}$, 260 K) illustrating exchange peaks between the two carceroisomers.

The $^1$H NMR spectrum of vinyladamantane complex **1•3d** gave very broad guest peaks at 300 K in the same way as **1•3c**, but when cooled to 260 K, *two* host/guest complexes were observed. 2D NOESY experiments confirmed that the two species showed chemical exchange peaks at 260 K, but no crosspeaks were observed with the excess guest outside the cavity. This indicates that the two species are carceroisomers[11] of **1•3d**, with one complex having the vinyl group directed to the solvent as usual, and the other with the vinyl group deep in the base of the cavity. The interconversion is an equilibrium process and occurs *inside* the cavity; guest tumbling is a lower energy process than guest in/out exchange. The ratio of vinyl "outside" to vinyl "inside" isomers is 1:7. This broadening of peaks for slowly tumbling molecules has been previously observed for long rigid guests such as *trans*-decalin in a water-soluble analogue of **1**.[12]

(9) Gottschalk, T.; Jaun, B.; Diederich, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 260–264.

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(12) Hooley, R. J.; van Anda, H. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 13464–13473.

Eyring analysis of the exchange peaks gives a $\Delta G^{\ddagger}$ (tumbling) = 14.2 kcal mol$^{-1}$. It was not possible to obtain a suitable NOESY spectrum where in/out crosspeaks could be integrated, but if we assume that the in/out exchange rate is similar to that of **3c**, then the barrier to tumbling (presumably by a "breathing" motion of the cavitand)[12,13] is ~2 kcal mol$^{-1}$ lower than that for in/out exchange.

In contrast, 1-ethyladamantane **3b** adopts only one conformation, where the ethyl group is deep in the cavity (see Supporting Information for spectra). No other conformation was observed, and the in/out exchange barrier is 16.4 kcal mol$^{-1}$, similar to that of **3c**. This orientation is unprecedented; the authors are not aware of any examples of adamantanes bound "upside-down" inside a deep cavitand. The tapered bottom of the cavitand may provide a partial answer for the selectivity of **1** for different guests. As shown in Figure 5a,

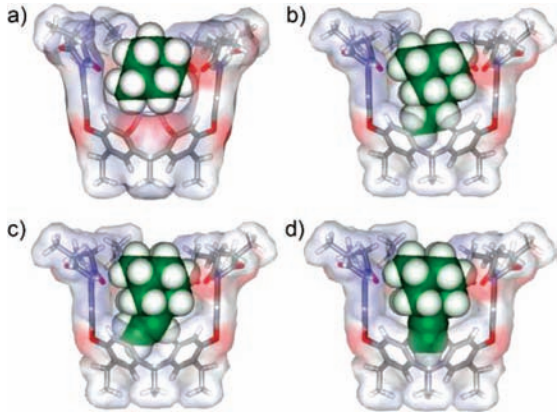


**Figure 5.** Minimized structures of guests (a) **3a**, (b) **3b**, and (c) **3d** in cavitand **1** and (d) a representation of the complex of "inverted" **3c** with **1** (some groups are omitted for clarity).

there is space in the cavity that could accommodate a small substituent. The acetylene group in **3c** is too narrow to fill the space well, and its "down" carceroisomer is not seen. Even though adamantane substituents such as Br, OH or $NH_2$ could fill this space well, electrostatic repulsions between their lone pairs and the electron-rich surface of the cavity leads to their "upwards" orientation. The thin layer of positive charge present in the C−H bonds of vinyl and ethyl groups provides a good electronic match with the polarizable aromatic walls,[14] and those groups are positioned "downwards" to optimally match the space (Figure 5). The proper filling of space with congruent shapes is a steric effect.

Nitrile **3p**, the most strongly bound guest, shows the furthest upfield peaks in its $^1$H NMR spectrum (Figure 6), especially for axial proton $H_d$, suggesting that it is positioned deepest in

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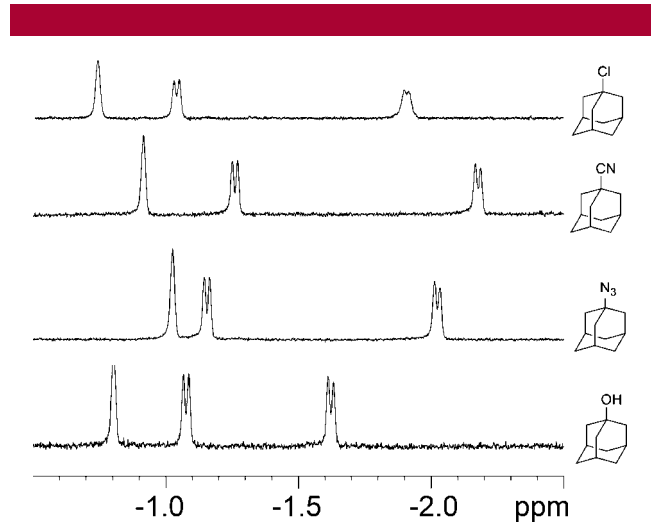


**Figure 6.** Upfield regions of the $^1$H NMR spectra of complexes **1•3j**, **1•3p**, **1•3m**, and **1•3e** (2 mM, mesitylene-$d_{12}$, 300 K).

the cavity; it is well-known that larger upfield shifts equate to increased cavity depth and closeness to the walls.[6g] In contrast, adamantanol **3e** shows peaks at a less negative $\delta$, suggesting a higher position in the cavity with weaker binding. The reasons for this difference are not at all clear. It does appear that the cavitand possesses a "two-site" binding capability; London Dispersion forces between the binding anchor and the cavitand walls, and electrostatic interactions between the substituent and the amides on the rim. Adamantane has no functional group to interact with the amides and consequently has a weaker binding affinity. Interactions with electron-rich substituents (donating lone pairs and hydrocarbons) are less favorable than with electron-poor species (nitrile, etc.) The hydrocarbon-substituted guests can prevent unfavorable interactions by orienting themselves toward the base of the cavity.

In conclusion, we have encountered unusual selectivity between similarly sized guests bound in a deep, self-folding cavitand. Binding constants range from <0.5 to 4000 M$^{-1}$ for guests as similar as 1-bromoadamantane and 1-adamantanecarbonitrile and appear to be electronic in nature. This range is also reflected in the energetic barriers to self-exchange. The tapered space deep in the cavitand is unable to accommodate the roughly spherical shape of adamantane, but small hydrocarbon substituents can fit in this space in an orientation previously unseen in these cavitands. These effects appear to be steric in nature.

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**Supporting Information Available:** Experimental details, 1D NMR spectra, and 2D NMR kinetics data. This material is available free of charge via the Internet at http://pubs.acs.org.

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