A cavitand with a fluorous rim acts as an amine receptor†

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A deep cavitand featuring eight trifluoroacetyl groups attached to the open end has been synthesized; these functions provide new chemical surfaces and constrict access to the cavitand, yet increase the rates of guest exchange.

Cavitands are concave hosts that bind small molecules of complementary size, shape and chemical surface.[1] Deepened cavitands surround most of a small guest but the open end reduces the selectivity and exposes part of the guest to the external medium.[2] Exquisite selectivities can be achieved using capsules that completely surround the guest(s).[3–7] In contrast, many receptors, both natural and synthetic, present an inwardly-directed component—that is, a functional group that complements a surface feature of the guest.[8] Here we describe a system that incorporates both a cavity for shape recognition and a strongly hydrogen bonding region for amine recognition.[9]

Cavitand **1** is an analog of the known octapropionamide cavitand **2**,[10a] and is synthesized *via* a similar route (see Supplementary Information†). Ordinarily, changing the amide substituents at the cavitand rim has little effect—derivatives of **2** are known with R′ groups that vary in bulk, chirality and electronics, but their binding properties are all generally similar since they share the same lining: eight aromatic surfaces, eight carbonyl groups and the anilide NH's that form a seam of hydrogen bonds.[10] The variable alkyl groups are at the very edge of the cavitand, remote from the binding pocket. Modeling suggests that perfluoro cavitand **1** should be an exception as it displays a different positioning of its CF_3 groups. Steric clashes and Coulombic repulsions force the eight CF_3 groups away from each other, with four groups vertically and four outwardly oriented (Fig. 1c–d). The F_3C–C–N–C torsion angles for the "vertical" and "outward" are calculated to be −139° and 155°, respectively (Fig. 2). This has the effect of partially closing the open end of the cavity, an effect previously shown to control guest binding in water *via* hydrophobic repulsion.[11] Cavitand **1** is soluble in most organic solvents, and forms a C_{4v}-symmetric "vase" conformation in benzene-d_6. The N*H* resonance is observed as one broad peak at $\delta = 13.66$ ppm, almost 4 ppm downfield of the corresponding

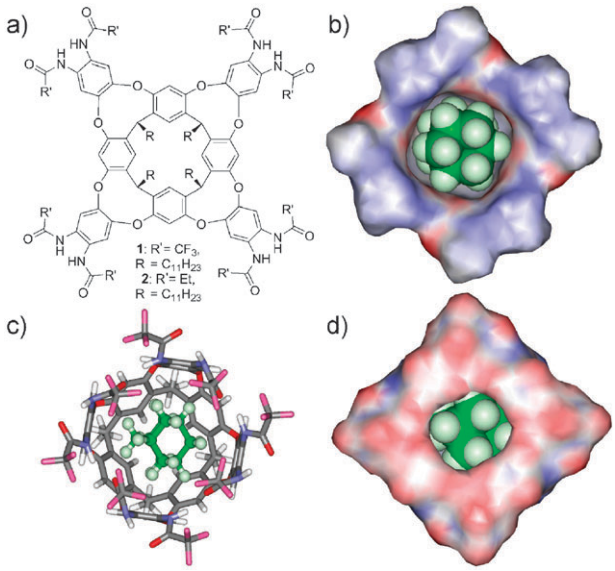

Fig. 1 (a) Modeled structures of perfluorocavitand **1** and octapropionamide cavitand **2**; (b) the complex of **2** with adamantane guest and a van der Waals' surface; (c) the complex of **1** with adamantane guest; (d) the complex of **1** with adamantane guest and a van der Waals' surface (Macromodel; AMBER forcefield).

resonances in **2** ($\delta = 9.6$ ppm in C_6D_6).[10a] The presence of only one broad set of NH peaks (and one peak in the ^{19}F NMR spectrum) suggests the amide seam is rotating rapidly on the NMR timescale. Cooling **1** in toluene-d_8 to 210 K sharpened the N*H* signal considerably, but did not resolve the two different N*H*s, indicating a low barrier to rotation of the amide seam. In **2**, the rate of amide rotation is approximately the same as the rate of guest self-exchange,[10a] with a $\Delta G^{\ddagger} = 17$ kcal mol^{-1}; 2D EXSY spectroscopy shows

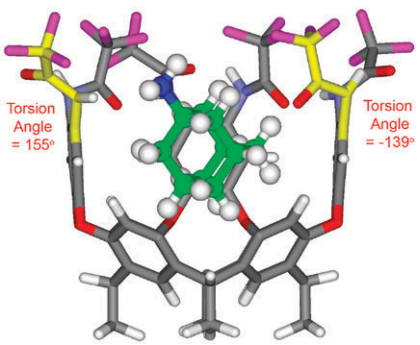

Fig. 2 Modeled structure of the complex of **1** with adamantane guest, indicating the two torsion angles for the trifluoroacetamide groups.

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that the barrier to self-exchange of tetrahydropyran in **1** (mesitylene-d_{12}) is 16.4 kcal mol^{-1}. There is an energetic component to the self-exchange barrier due to the London dispersion forces between guest and the host walls. This "lower limit" of exchange rate is reached in cavitand **1**; the rotation of the amide seam is fast, but the exchange barrier is approximately the same as for octamide **2**.[12]

The guest binding properties of **1** are most easily studied in non-competitive solvents such as *p*-xylene-d_{10} or mesitylene-d_{12}. The binding constants of the kinetically stable complexes can be determined by integration of free and bound peaks in the ^{1}H NMR spectra (see electronic supplementary information for details†). Substituted adamantane derivatives are well known to be the best guests for these systems[13] but unexpectedly, most common adamantane derivatives showed no binding affinity for the cavitand. The exceptions were 1-adamantanamine and 1-adamantane-methylamine, which bound quite strongly (50 M^{-1}, 5 M^{-1} respectively). Even 1-adamantanol showed no affinity. Other guests were tested, with the results shown in Table 1. A wide variety of amines were also taken up in mesitylene-d_{12} with binding constants as high as 425 M^{-1}. Integration of the peaks for bound and free cavitand and guest indicated a 1 : 1 binding stoichiometry, consistent with literature precedent for similar cavitands.[10] Cyclic amines are the best guests, and they even show affinity for the cavitand in $CDCl_3$ and benzene-d_6 (although not in acetone-d_6). Very few noncationic guests are bound in **2** in $CDCl_3$ or benzene-d_6, as these solvents compete for the space and at *ca.* 10 M concentrations are bound instead. Uncharacteristically, *N*-alkylamines were also bound. While acyclic hydrocarbon chains can be bound in water-soluble cavitands or enclosed capsules,[14] they are not bound in organic-soluble cavitands of this type (*e.g.* **2**). In the extended form they are too narrow to fill the space, and evidently the energetic cost of coiling overcomes the attractive interactions gained. With the effective amine : octamide hydrogen bonding, amines from hexylamine–octylamine are bound in the cavity, and the alkyl chains adopt a helically coiled conformation.[14b] As the molecule gets larger, the binding constant drops as steric clashes at the rim are encountered; nonylamine is not bound. The relative basicity of the amines does not appear to have a dominant effect on the binding constant. Rather, it is the shape of the guest molecule that determines the binding constant; alteration of the guest amine's basicity cannot be achieved without altering the shape complementarity of the guest, and so accurate determination of the effect of changing basicity is not possible.

Table 1 Binding constants for guests in host cavitand **1**

Guest	K_a/M^{-1}[a]	Guest	K_a/M^{-1}[a]
Isobutylamine	0[d]	1-Adamantanamine	50
n-Butylamine	0[d]	1-Chloroadamantane	0
n-Pentylamine	0[d]	1-Adamantyl-acetamide	0
n-Hexylamine	385	Adamantane	3
	5[b]	1-Adamantanol	0
	1[c]	1-Cyanoadamantane	0
n-Heptylamine	85	1-Adamantane-methylamine	5
n-Octylamine	7		
Isooctylamine	220		
c-Octylamine	425	Hexane	10
Pyrrolidine	0[d]	Isooctane	<0.5
Morpholine	130	Cyclohexane	150
N-Methylmorpholine	100	*n*-$C_5H_{11}OH$	15
Piperidine	280	*n*-$C_6H_{13}OH$	30
N-Methylpiperidine	220	*n*-$C_8H_{17}OH$	0
2-Methylpiperidine	0	Tetrahydropyran	150
c-$C_6H_{11}CH_2NH_2$	300	Cyclopropylamine	0[d]
	160[b]	Cyclobutylamine	0[d]
	55[c]	$CH_3(CH_2)_4CO_2H$	0

[a] Determined by integration of the ^{1}H NMR spectrum of a 1.8 mM solution in mesitylene-d_{12}, 300 K. [b] In benzene-d_6. [c] In $CDCl_3$. [d] Addition caused precipitation of the cavitand (see text).

Fig. 2 shows the representation of bound adamantanamine in **1**, showing the amino group angled towards the acidic N*H*s at the rim. This is not intended as a static picture; the amides rotate rapidly between conformations, and the guest rotates rapidly in the pocket, but it shows a "snapshot" of the preferred orientation of bound guest.

If the guest amine is too small to fill the cavity (*e.g.* *n*-Bu, *i*-Bu, *c*-Pr), the cavitand–amine salt complex precipitates from solution and no peaks are seen in the ^{1}H NMR. This effect also has little correlation with relative basicity, as the effect is not seen for longer primary amines. When the cavitand is folded around a guest, no precipitation is seen; this holds either for strongly bound amine guests, or for the addition of amines to strong host : guest complexes (**1** in benzene-d_6, for example). The trifluoroacetanilide group is acidic; the pK_a (DMSO) of trifluoroacetanilide itself is 12.6,[15] which is comparable to that of *n*-$BuNH_3^+$ (11.1). This indicates that some deprotonation should occur, and the insolubility of the salt drives the deprotonation. The precipitate redissolves if an aliquot of ethanol-d_6 is added to the NMR sample, suggesting no covalent reaction has occurred (*e.g.* amide cleavage). It must be pointed out, however, that the precipitate could be due to an indeterminate aggregation effect.

Certain non-amines are bound, if they fit inside the cavity. Cyclohexane, tetrahydropyran, *n*-hexane and 1-hexanol all form complexes with **1**, with weaker binding constants than the correspondingly-sized amines. Hexanol, pentanol and hexane tumble rapidly on the NMR timescale (Fig. 3),[16] whereas their amine counterparts do not.

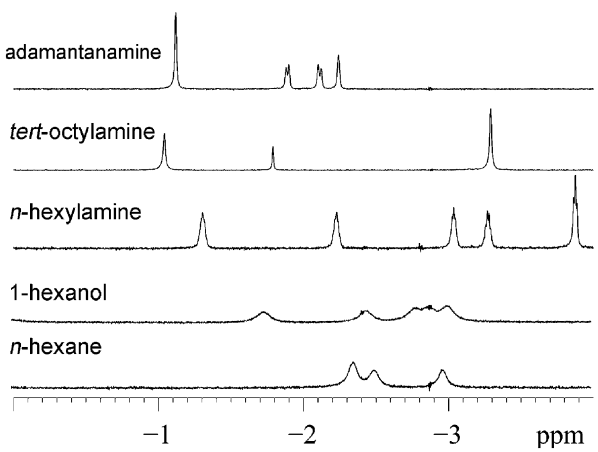

Fig. 3 Upfield regions of ^{1}H NMR spectra of 6 mM guest in a 1.8 mM solution of **1** in mesitylene-d_{12}.

Cavitand **1** is a "two-site" receptor—the cavity binds species as usual with the correct shape complementarity—but the second site is a relatively acidic perfluoroacetamide seam. This both closes off the rim of the cavitand (providing selectivity for smaller guests) and provides strong hydrogen bonding to guests that position a complementary basic lone pair in the vicinity. Even flexible amines are oriented in the binding pocket with the lone pair towards the acidified rim. This region closes off the rim of the cavitand, providing selectivity for smaller guests. Weaker lone pairs such as those on oxygen or chlorine do not provide enough basicity for binding. Alcohols of the correct size to fit beneath the rim are not oriented towards it; they tumble in the cavity.

In conclusion, a deep cavitand presents two domains for the control of guest binding. The combination provides selectivity for amines and small guests that other self-folding cavitands cannot. Explorations of the effects of the fluorous region on recognition are underway.

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12 Tetrahydropyran is not bound by **2**, so the published figure for self-exchange of adamantane (a poor guest for **1**) is used here (ref. 10*a*).

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