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Self-Complexed Deep Cavitands: Alkyl Chains Coil into a Nearby Cavity

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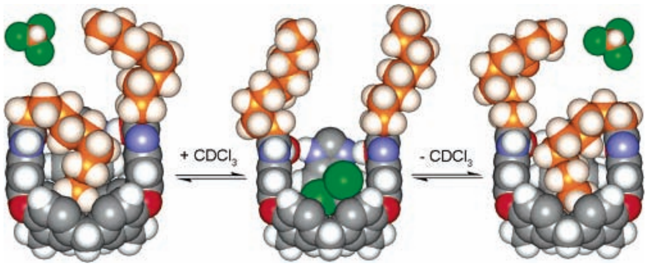
ABSTRACT



A series of self-complexing tetrabenzimidazole cavitands have been synthesized. Alkyl chains appended to the rim helically coil into the cavity in competitive organic solvents. These “flexible arms” exchange with each other, a process shown by 2D NMR to proceed via an intermediate solvent-containing species.

The folding of many natural supramolecular systems incorporates self-fulfillment; that is, sections of proteins fold in on themselves to fill cavities created by the tertiary structure of the macromolecule.[1] Self-complementary supramolecular constructs have the possibility of acting as switches and molecular devices upon an external stimulus.[2] Most self-complexing species involve anchors with strong host complementarity, via charge-based, hydrogen-bonding, or $\pi-\pi$ interactions.[3] Underivatized neutral anchors can bind via the hydrophobic effect (for example, in cyclodextrins)[4] and in some cases can use *inter*molecular associations to form dimers[5] or polymers.[3b] It is rare that an underivatized alkyl chain chooses to occupy a restricted space in organic solvents where there is no hydrophobic stabilization (unless it has no other choice).[6,7]

The entropic penalty occurring from the constriction of a freely moving chain into a defined space leaves long alkyl chains as reluctant guests for supramolecular systems. Here, we report the self-encapsulation of appended alkyl chains

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into the inner space created by a deep, self-folding cavitand.[8] Cavitands of the type shown in Figure 1 fold into a "vaselike" conformation in organic solvents if a hydroxylic cosolvent is present to hold the structure together via hydrogen bonds between the benzimidazole groups at the rim.[9] This creates a cavity with a π-rich, polarizable inner surface which provides stabilization to cations bound inside.[10] So far, these cavitands have proved resistant to binding neutral species; they are only soluble in competitive solvents and as such preferentially bind solvent molecules.[11]

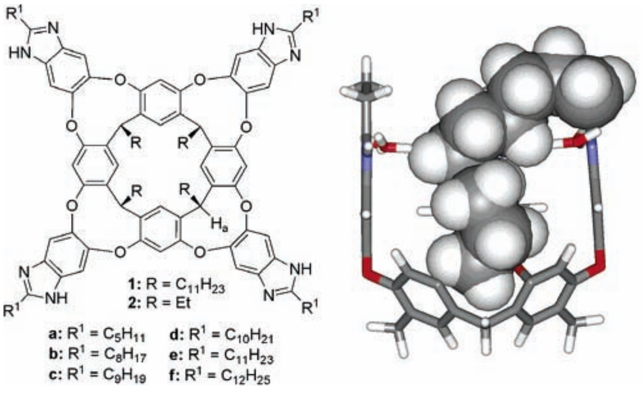

Figure 1. Alkylated cavitands used and a minimized representation (Maestro v7.0.2, AMBER forcefield)[12] of C_{10} cavitand **1d**. Other chains and the front wall were removed for clarity.

Cavitands **1a**−**f** were synthesized by condensation of the corresponding alkyl imidate with the known octamine·HCl cavitand (see Supporting Information).[9a,13] Cavitand **1a** behaved as one would expect from previous reports,[9a] but upon synthesis of the C_8-topped cavitand **1b**, an unexpected result occurred. In water-saturated $CDCl_3$, a number of low-intensity peaks were present in the upfield region of the ^1H NMR spectrum, indicating a small amount of an alkyl chain encapsulated inside the cavity. A range of substrates (R = Et and $C_{11}H_{23}$, R^1 = C_9H_{19}−$C_{12}H_{25}$, $C_{16}H_{33}$) were synthesized, and the relevant ^1H NMR spectra are shown in Figure 2.

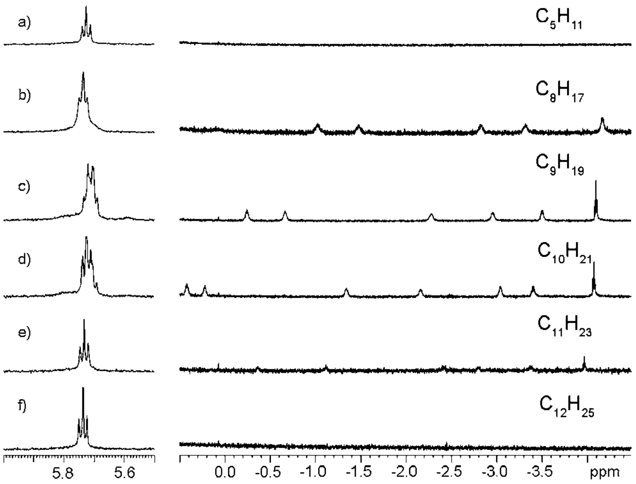

Figure 2. Mid- and upfield regions of the ^1H NMR spectra of alkylated cavitands **1**.

Only four of the substrates show encapsulation of an alkyl chain, and the peaks for an internal guest vary depending upon the chain length. The proportion of alkyl chain encapsulated varied also; the degree of occupancy can be determined by integration of the bound and host peaks and a visual inspection of the methine peak H_a (Figure 1) at δ 5.73. In the case of **1a**, C_5H_{11} is too short and does not occupy the cavity. The ^1H NMR spectrum is consistent with that of a vaselike-shaped cavity, and so **1a** most probably exists with one molecule of $CDCl_3$ inside.[9a] For **1b**, only approximately 10% of the cavitands are occupied by an alkyl chain. C_9H_{19} is the most favorable case with 50% occupancy, whereas $C_{10}H_{21}$ shows 25% occupancy. Encapsulation of the C_{11} chain is less favorable with only 5% occupancy, and C_{12} and C_{16} are not encapsulated at all. The "unoccupied" cavity is not empty and most likely contains one $CDCl_3$ molecule. The different NMR spectra for each alkane length, along with the very similar spectra observed with Et or $C_{11}H_{23}$ feet, suggest an *intramolecular* complexation as shown in Figure 1. In addition, change of concentration (across a range from 0.5 to 4 mM, the solubility limit of **1d**) or temperature (230−330 K, see Supporting Information) did not appreciably alter the NMR spectra. Evidently, it is unfavorable for the cavitand to place its "foot" in the mouth of another.[5] The relatively weak binding is illustrated by the addition of only 2% (w.r.t. $CDCl_3$) CD_3OD, which removes all encapsulation of the alkyl guest, which is consistent with the observation that no guest binding occurs in the corresponding R^1 = H cavitand in CD_2Cl_2/CD_3OD.[8] The presence of small amounts of water (<2%) vs CD_3OD in chloroform could be construed as an increased "hydrophobic effect", but it is insignificant at best. To this date, no suitably sized

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uncharged guest has been observed to bind in these cavitands, even those that bind strongly in water-soluble derivatives via hydrophobic stabilization.[11,14]

The 2D NOESY spectrum of the C_9-topped cavitand **2c** (see Figure 3 and Supporting Information) indicates that the encapsulated alkyl chain undergoes chemical exchange with the alkyl chains appended to the cavitand rim. Evidently, each of the arms exists inside the cavity for a limited period of time and exchanges positions with the others. This explains the nature of the methine signal as seen best in Figure 2c. Here, the methine exists as two overlapping triplets: one from cavitand·$CDCl_3$ and one from cavitand·C_9H_{19}. Cavitand **2c** shows discrete peaks for the internal and external $-CH_3$ groups of the arms, and so the rate of exchange can be monitored by ^{1}H NMR experiments. The 2D NOESY spectrum of **2c** is shown in Figure 3, and integration of the self-exchange cross-peaks observed in this spectrum allows EXSY calculation of rates of in/out exchange (see Supporting Information).[15]

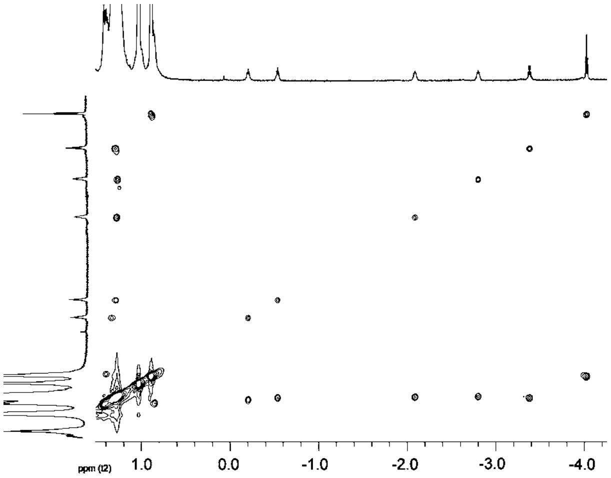

Figure 3. Upfield region of the 2D NOESY spectrum of cavitand **2c**, indicating chemical exchange between bound and free alkyl chains.

The rate k_{out} of the encapsulated arm leaving the cavity is 0.37 s^{-1}, whereas the corresponding k_{in} of arm encapsulation is 4.7 s^{-1}. Accounting for the fact that the population of the external alkyl chain is 3 times that of internal guest, the "in" rate is 4 times that of the "out" rate.

There are two plausible mechanisms for self-exchange: a single concerted S_N2-like step or a two-step dissociative S_N1-like mechanism. For the S_N2 mechanism, one external guest arm would push the encapsulated arm out as it is itself bound in one concerted process. In the dissociative mechanism, as illustrated in Figure 4, the bound arm is released with the resulting vacuum filled by one or more small solvent molecules. The solvent is then expunged upon encapsulation of another alkyl chain. Because the in and out rates are different, there is a propensity for solvent-occupied cavitands; the dissociative mechanism is likely here. The slow out step involves replacement of the arm in the cavity by a molecule of $CDCl_3$, and the replacement of a poor $CDCl_3$ guest by another arm occurs much faster. If the mechanism occurred by a single concerted step, the in and out rates should be the same. The weak hydrogen bonds holding the cavitand in the folded form allow the complex to "breathe", easing the transition between complexes.[16]

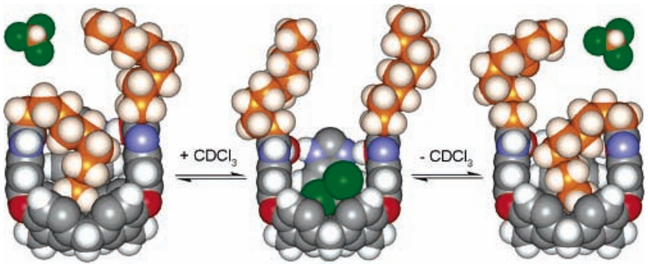

Figure 4. Representation of the exchange mechanism showing the intermediate $CDCl_3$-containing cavitand **2c** (Maestro v7.0.2, AMBER forcefield).[12] Other chains and the front wall were removed for clarity.

If the NOESY spectrum is viewed at a greater vertical intensity, NOE cross-peaks between the residues of the encapsulated arm can be seen (see Figure 5). The long-range NOEs between the terminal methyl group at δ -4.15 and the fourth encapsulated residue at δ -2.30 suggest that the arm exists in a helically coiled conformation. The packing

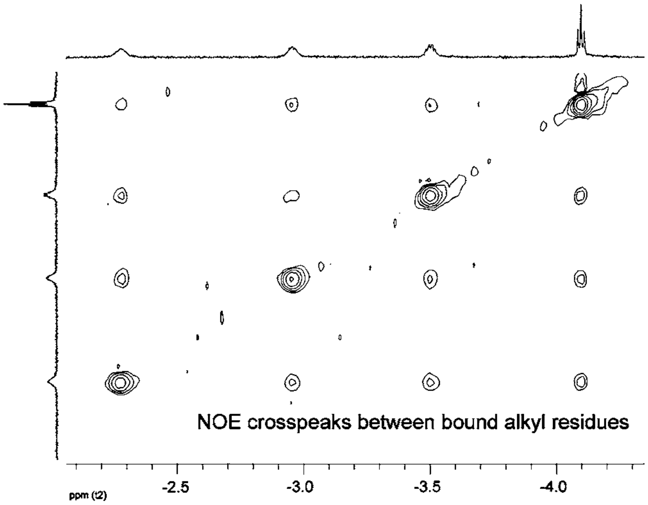

Figure 5. Upfield region of the 2D NOESY spectrum of cavitand **2c**, indicating NOE cross-peaks between the four deepest carbons of the encapsulated alkyl chain.

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of an alkyl chain into a helical coil introduces 0.55−0.65 kcal mol^{-1} strain per gauche interaction.[17,18] The maximization of CH−π contacts between the host and guest overcomes this enthalpic penalty, along with the entropic cost of restricting the chain in the confined cavity.

The first observed example of a coiled alkane in a deep self-folding cavity of this type was that of sodium dodecyl sulfate (SDS) binding in a water-soluble tetracarboxylate derivative of **1**.[19] When the encapsulated region of the C_9 cavitand **2c** is overlaid with the similar region of that ^1H NMR spectrum (Figure 6), one can see the similarities and differences. The C_9 cavitand **2c** shows six upfield-shifted residues from encapsulation, and in the case of SDS, eight encapsulated residues are shifted upfield by the magnetic anisotropy of the similarly sized cavitand. The terminal methyl group is situated at the base of the cavity in each case and as such occurs at similar $\Delta\delta$. The next three residues are also consistent with a fully coiled alkane in each case and share similar chemical shifts.

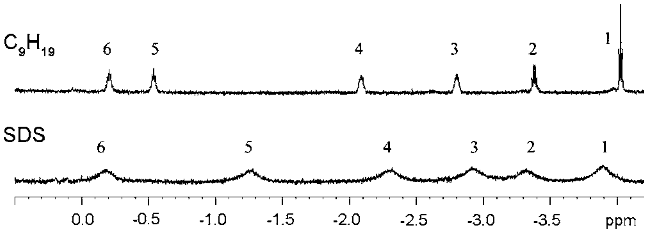

Figure 6. Upfield region of the ^1H NMR spectra of C_9-topped cavitand **2c** and that of SDS helically coiled in an analogous, water-soluble tetracarboxylate cavitand.[19]

Closer to the cavitand rim, however, the structures of the complexes diverge. Residue 5 of the encapsulated C_9 arm shows its signal further downfield than the equivalent methylenes of SDS, and the three unobserved residues have not been significantly shifted from the bulk cavitand signals and remain hidden. Cavitands **2b**,**d**,**e** also show significant variances in δ for residues 5−7. The locations of the encapsulated arm methylenes nearer to the rim are evidently different from those of SDS and also vary depending on chain length. The covalent attachment forces the methylenes closer to the wall, resulting in an altered chemical shift pattern. The peaks for the encapsulated arms are also considerably sharper than those for SDS. This may be caused by rapid in/out exchange of the attached arms, but the EXSY experiments (vide supra) show that in/out exchange is slow on the NMR time scale. Heating the sample to 330 K causes a slight broadening of peaks, again suggesting slow in/out exchange at room temperature that increases with temperature. It is most likely that SDS is more flexible in the cavity, and it shows intermediate in/out exchange. The nature of SDS binding[13,19,20] has precluded quantitative study of its exchange rate, but binding of *n*-alkanes gives sharper (although still slightly broadened) peaks due to their very slow exchange,[11a] with *no* coupling patterns observed. With no covalent attachment to the cavity, SDS and *n*-alkanes can move more freely in the cavity along the vertical axis, causing an additional broadening of the NMR signals. The encapsulated arm, covalently attached at the rim, is more restricted in its vertical motion, and hence sharper peaks, including coupling patterns, are observed. Interestingly, the NMR spectra do not show different shifts for the protons on each CH_2 group. Upon coiling into a helix, these protons become diastereotopic and conceivably distinguishable by NMR. The lack of splitting suggests that the arm is interconverting between the two possible coiled forms rapidly on the NMR time scale. This interconversion is extremely rapid: even at 230 K, the individual forms could not be observed, as was the case in capsules.[21]

In conclusion, a new type of self-complexing cavitand has been synthesized, with *n*-alkane chains appended to the rim which fold into the cavity itself. The four chains exchange at rates observable on the NMR time scale via an intermediate solvent-containing species as shown by 2D NMR experiments. Further studies on the applicability of this type of system as a sensor or trigger for external processes are underway.

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

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