Normal hydrocarbons tumble rapidly in a deep, water-soluble cavitand†

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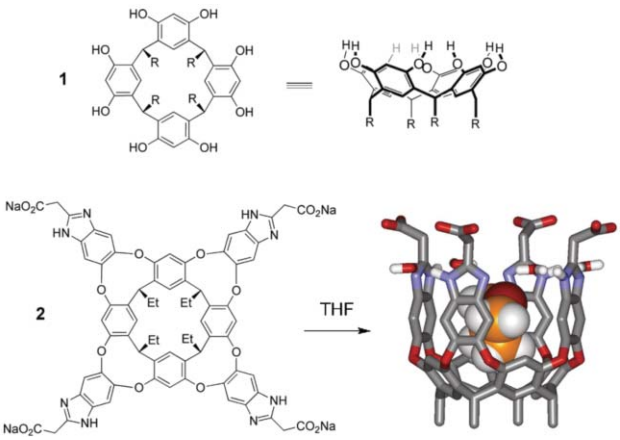
A deep, water-soluble cavitand extracts *n*-alkanes and other water-insoluble species into its cavity *via* hydrophobic forces: alkanes bind in a helical manner, and tumble rapidly on the NMR timescale inside the binding pocket.

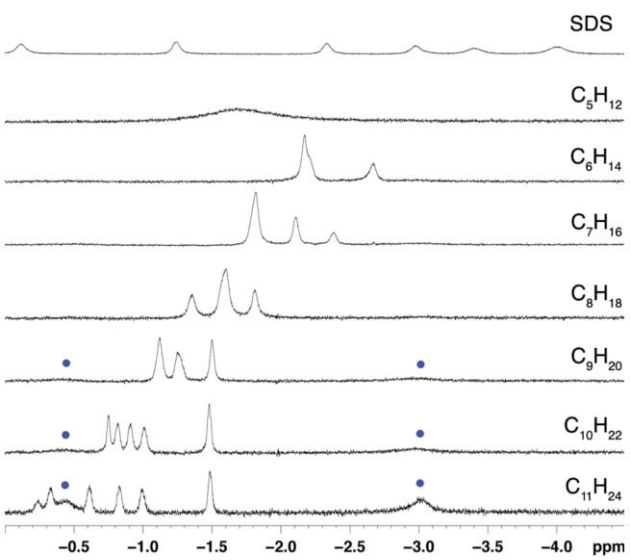
Normal alkanes exist in a variety of shapes in solution but the lowest energy conformation is the one featuring a fully extended chain of carbon atoms. Each bend introduces internal steric clashes which raise the energy[1] and lower the concentration of these conformations. The saturated portion of lipids adopts a conformation which includes multiple bends—but only when it is bound within the hydrophobic pocket of a transfer protein.[2] Here we show that alkanes bound within a synthetic, hydrophobic cavity in water feature up to four successive bends and assume coiled, helical conformations. These coiled alkanes present shapes more complementary to the cavity and bury more hydrophobic surfaces from the aqueous medium than do their extended conformations. Spectroscopic evidence indicates that the coiled alkanes tumble rapidly within the cavity on the NMR timescale. These experiments illustrate that coiling may be a *general* feature of normal alkanes in the structured environments of nature (*i.e.* receptors and enzyme interiors).

The water-soluble tetracarboxylate cavitand **2**[4] (Scheme 1) is an open-ended host readily prepared from the corresponding resorcinarene **1**.[5] The vase-like shape of the cavitand is stabilized by an array of hydrogen bonds incorporating solvent water along its upper rim. These bonds resist the unfolding of the molecule to a flat, kite-like conformation that has no cavity.[6] The cavitand shows millimolar solubility in water imparted largely through its four carboxylates.[7] Most of the atoms that line the interior of the cavity are hydrophobic carbons, incorporated into the eight benzene rings. The cavity presents a surface of polarizable π electrons and is complementary to cations[8,9] or molecules with C–H bonds.[10,11] In aqueous solution, surfactants such as sodium dodecyl sulfate (SDS) and dodecyl phosphatidyl choline (DPC) have similar interactions with synthetic cavitand **2**.[12] Their alkane chains were inserted into the cavity in a helical conformation while the polar head groups remained in the aqueous solvent. The current work shows that even normal alkanes can coil into helices when offered the choice between an aqueous environment or a structured, hydrophobic cavity.

Typical *n*-alkanes (pentane–dodecane) were briefly sonicated with a 2 mM solution of cavitand **2** in D_2O, then the ^1H NMR spectra (600 MHz) were recorded. The spectra (Scheme 2) show that the hydrophobic alkanes are extracted into aqueous solution and bound in the magnetically shielding regions of the cavity. The spectrum of SDS in the cavity is shown as a reference. In the cases of pentane through nonane, there was no free alkane observed in solution—the cavitand extracted only that which it bound. At first glance, the binding mode observed for the alkanes seems unlike that of SDS. The latter is known to bind with its methyl group



Scheme 1 Resorcinarene **1**, its derived water-soluble tetracarboxylate cavitand **2** and a representation of the complex of **2** with THF (Maestro v7.0.1; AMBER force-field;[3] some groups omitted for clarity).



Scheme 2 Upfield regions of ^1H NMR spectra of sodium dodecyl sulfate (SDS) and *n*-alkanes (C_5H_{12}–$C_{11}H_{24}$) in a 2 mM solution of **2** in D_2O. (•): encapsulated THF.

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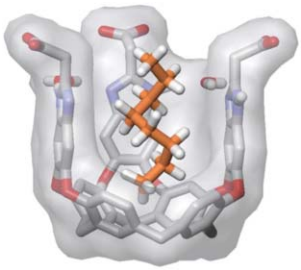
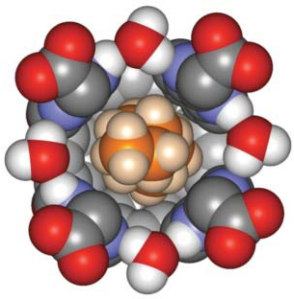


SDS δ observed		Predicted (average) δ's		Octane δ observed	
C_8	1.10				
C_7	0.70				
C_6	-0.20	$C_{8/1}$	-1.63	$C_{8/1}$	-1.59
C_5	-1.30	$C_{7/2}$	-1.33	$C_{7/2}$	-1.35
C_4	-2.30	$C_{6/3}$	-1.58	$C_{6/3}$	-1.59
C_3	-2.95	$C_{5/4}$	-1.80	$C_{5/4}$	-1.83
C_2	-3.35				
C_1	-3.95				

Scheme 3 Depiction of the position of helical alkane residues in **2** correlated with $\Delta\delta$.



Scheme 4 Plan view of the encapsulation of *n*-octane in **2** (Maestro v7.0.1; AMBER force-field;[3] some groups omitted for clarity).

deepest in the cavity ($\Delta\delta \sim -5$ ppm); the next seven methylenes of the alkane chain are coiled inside in a helical manner where their signals are shifted upfield by the anisotropy of the cavitand. The remaining four methylenes and the charged sulfate tail are situated outside the receptor, exposed to solvent water. In contrast, the signals of the *n*-alkanes are broadened, especially for the smaller alkanes, and the $\Delta\delta$ values are not nearly as large as those observed for SDS.

The chemical shifts observed can be explained—even predicted—if the alkanes are coiled in a helical conformation and are not fixed inside the cavity, *but tumbling rapidly* on the NMR timescale. Each of the methyls and methylenes of the alkanes show an averaged chemical shift of two magnetic environments. Scheme 3 shows the expected chemical shifts of each residue bound in cavitand **2** (derived from the observed chemical shifts of SDS). A maximum of 8 carbons can be buried in a helical conformation, fewer in an extended one. The NMR signals of the exposed, terminal groups of nonane–dodecane would be unshifted by binding, and the observed NMR spectra can be calculated by averaging the chemical shift of the two relevant residues (*e.g.* for *n*-octane, $C_1 + C_8$ and $C_2 + C_7$ show the same $\Delta\delta$, *etc.*—see Supplementary Information for calculations†).

The spectrum of pentane is too broadened by the in–out exchange rate to analyze. Also, a change in behavior occurs between octane and nonane: nonane and longer alkanes show two sets of signals for cavitand **2** in the spectra. At low temperature (280 K), signals for resident THF (which are observed at δ −0.4, −3.0 ppm and are an artifact of the synthesis of **2**)[7] can be observed along with those of bound alkane. As the size of the bound alkane increases, the amount extracted into the cavity decreases. C_{11} and C_{12} are bound, but not well—at 300 K significant bound THF is observed, and only after several days of sonication can any bound dodecane be seen.

Unlike SDS, with a polar sulfate group that interacts very strongly and stays within the water solvent, the *n*-alkanes are free to move in the cavity, a process permitted by the space around the coiled alkane (a structure is modeled in Scheme 4). As the alkanes get larger than C_8, they can no longer fit completely inside the cavity, and the benefits of binding due to the hydrophobic effect are lessened. Accordingly, the displacement of THF from the cavity becomes less favorable and a smaller amount of alkane is extracted into the cavitand.

In summary, the binding of normal hydrocarbons is observed in water-soluble tetracarboxylate cavitand **2**, under conditions of slow exchange on the NMR timescale. Guests such as *n*-alkanes that feature poor shape complementarity in their extended conformations coil to fill the space properly and they tumble rapidly on the NMR timescale. Given that the conformations of long alkyl chains in enzyme interiors also show bends and coils among extended regions, this may be viewed as a general mode of binding for substrates taking advantage of hydrophobic stabilization.

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