Supramolecular Chemistry

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Strong Binding of Hydrocarbons to Cucurbituril Probed by Fluorescent Dye Displacement: A Supramolecular Gas-Sensing Ensemble**

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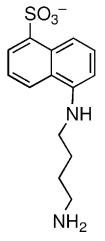
The inclusion of small hydrocarbons into molecular container compounds in solution has received considerable attention.[1–9] It allows for a puristic understanding of the solvophobic driving force for the formation of discrete host–guest complexes[10] and has additional potential for gas storage, uptake, and separation, thus complementing solid-state applications of porous materials[11,12] or surface-immobilized macrocycles.[13] Studies on the precipitation of complexes between the smallest alkanes with α-cyclodextrin date back to the 1950s.[14] Subsequently, synthetic hosts such as cryptophanes,[1] self-assembling capsules,[2–5] and hemicarcerands[6,7] have been investigated for their potential to entrap small hydrocarbons. Herein, we describe a highly sensitive fluorescence-based method for the quantification of volatile hydrocarbons binding with cucurbituril. We observe exceptionally strong, highly selective, and reversible binding in aqueous solution.

Cucurbit[*n*]urils (CB*n*) are water-soluble, highly symmetric pumpkin-shaped synthetic macrocycles,[15,16] and their unique supramolecular chemistry is presently unfolding.[17,18] They are well-established to bind organic ammonium ions through a combination of hydrophobic interactions inside the nonpolar inner cavity and ion–dipole interactions with the carbonyl portals. While a CB5 derivative has been reported to bind very small guests such as methane and acetylene,[12,19] the homologue which holds most promise for hydrocarbon binding is CB6,[20] the original cucurbituril, which possesses an intermediary size to allow inclusion of guests with up to seven heavy atoms into its inner cavity.[18,21] Unfortunately, CB6 has an intrinsically low water solubility of about 30 μM, which complicates the determination of actual binding constants.[21,22] In particular, it prevents ^{1}H NMR titrations, which have been routinely employed in all previous studies on solution-phase gas binding by molecular containers.[1–9] The binding of xenon with CB6 has been studied by ^{129}Xe NMR spectroscopy in the presence of 0.2 M Na_2SO_4,[23] where the solubility is increased (but where also the binding strength suffers). Alternatively, an alkylated CB6 derivative with higher water solubility has been employed, which was also investigated by isothermal titration calorimetry, to afford a binding constant of 3400 M^{-1} with xenon.[24] The binding constants, which we report herein for several simple hydrocarbons, are much larger than those observed for xenon, and, in fact, the largest ones reported for neutral guests with CB6.[18] In several cases, they exceed those previously observed for any molecular container.[1–9]



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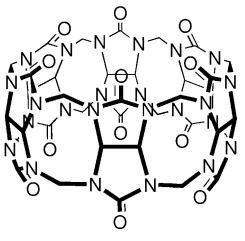

CB6

In the quest for a convenient method to monitor volatile hydrocarbon binding to CB6, we selected an indicator displacement strategy[25] based on our recently developed anchor dye approach.[26] In detail, compound **1** possesses a putrescine anchor for strong binding with CB6,[27] and a microenvironmentally highly sensitive 1-naphtylamine-5-sulfonic acid chromophore to ensure a robust fluorescence response upon binding. Complexation of **1** by CB6 increases its locally excited fluorescence band ($\lambda_{exc} = 283$ nm, $\lambda_{obs} = 334$ nm) by a factor of 50–1000, depending on pH. The binding constants were extracted from direct host–dye fluorescence titrations (see the Supporting Information) to afford values of 4.3×10^7 M^{-1} in 1 mM HCl (pH 3.0) and 2.5×10^3 M^{-1} in 50 mM NaOAc (pH 5.5).

The working principle for gas sensing is depicted in Figure 1. Starting from the pre-assembled highly fluorescent host–dye complex (4 μM CB6 and **1**), the addition of gas results (with an immediate onset signaling fast exchange on the time scale of the experiment) in a continuous displacement of the dye until the saturation limit has been achieved. As can be seen from Figures 1 and 2, the different hydrocarbons showed sizable effects and markedly different fluorescence responses. From the final plateau of the fluorescence intensity and the accurately known (owing to their importance for fossil energies) aqueous solubility of the volatile hydrocarbons, the binding constants were directly calculated by assuming a 1:1 complexation stoichiometry (see the Supporting Information), akin to competition experiments carried out, for example, by ^{1}H NMR spectroscopy.[28] Higher-order complexes were not expected in the solution phase on the basis of packing arguments and even xenon

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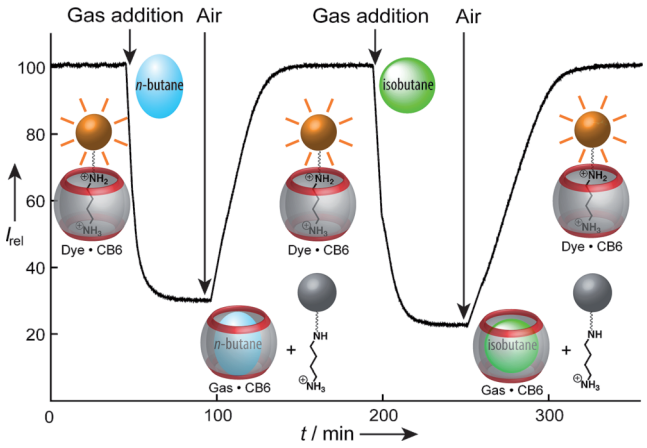

Figure 1. Fluorescence-based approach for gas sensing in aqueous solution. The trace refers to actual experiments with sequential uptake and release of *n*-butane and isobutane.

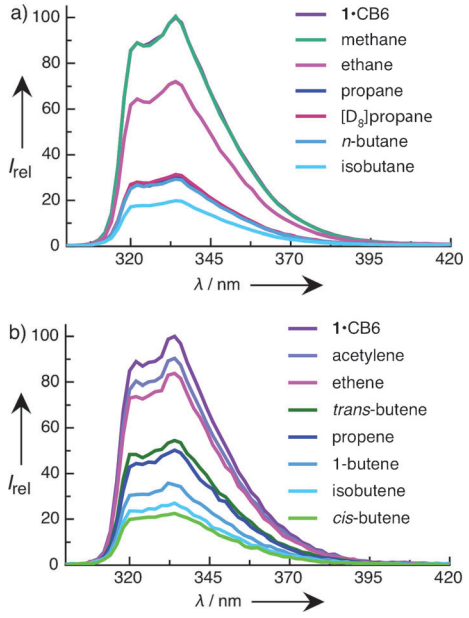

Figure 2. Displacement of dye **1** (4 μM) from CB6 (4 μM) monitored by fluorescence after saturation of aqueous solutions with different gaseous a) alkanes and b) alkenes and acetylene. Measurements in water at pH 3.0, $\lambda_{exc} = 283$ nm. Note that hydrocarbons showing similar displacements may exhibit different binding constants because of varying solubilities (see the Supporting Information).

(volume 43 Å^3) shows only 1:1 binding with CB6.[23,29] Moreover, representative titrations at different gas pressures (and assuming Henry's law, Supporting Information) showed 1:1 binding isotherms and afforded the same binding constants, within error, as those obtained from repeated end-point measurements of the fluorescence intensity of gas-saturated solutions. The accuracy of the fluorescence-based method for measuring binding constants was also cross-checked for other neutral guests such as Xe, SF_6, tetrahydrofuran, furan, cyclopentanone, and benzene (see the Supporting Information), which had been previously studied by NMR spectroscopy in saline solution. Finally, the deep inclusion of the guests inside the CB6 cavity was established by ^{1}H NMR upfield shifts (in the presence of salts to achieve sufficient solubility of CB6; see the Supporting Information).

The binding constants for the different hydrocarbons are shown in Table 1. Most important, because the fluorescence-based method allows the use of very low CB6 concentrations (0.1–4 μM), well below its solubility limit, measurements could not only be performed in 50 mM NaOAc (pH 5.5), but also in salt-free solution at pH 3.0 (1 mM HCl was employed to exclude pH fluctuations in the course of the measurements). The first surprise from the data in Table 1 is that the affinity of simple hydrocarbons to CB6 in water is exceptionally high, contrasting the common conception of CBs as cation–receptor macrocycles.[30] The selectivity of CB6 towards hydrocarbon binding stands out also when compared to previously investigated molecular containers.[1,2,4,9] Figure 3 shows DFT-optimized structures of the corresponding inclusion complexes, which nicely illustrate the hole-size and cavity-height matching of some representative gases.

Table 1: Binding constants of hydrocarbons with CB6.

	Hydrocarbon [Volume/Å^3][b]	PC[c] [%]	K [10^3 M^{-1}][a] Water pH 3.0[d]	NaOAc pH 5.5
C1	methane [29]	20	< 2	< 0.05
C2	ethane [45]	32	24[e]	2.6 ± 0.7
	ethene [41]	29	3.9	0.25[e]
	acetylene [35]	25	0.11[e]	0.047[e]
C3	propane [63]	44	180[e]	10
	[D$_8$]propane [63]	44	160[f]	–
	propene [58]	41	25[e]	1.4
C4	*n*-butane [80]	56	280	4.4
	1-butene [75]	53	79	1.3
	cis-butene [74]	52	150	2.1
	trans-butene [74]	52	21	0.32
	isobutane [79]	56	850	23
	[D$_{10}$]isobutane [79]	56	910[f]	–
	isobutene [75]	53	84	1.9
C5	*n*-pentane [96]	68	9 ± 4	0.14
	isopentane [96]	68	15 ± 5	0.30
	neopentane [96]	68	< 2	< 0.05
	cyclopentane [86]	61	1300 ± 300	25 ± 10
≥ C6	higher alkanes[g] [> 102]	> 72	< 2	< 0.05

[a] Determined by competitive fluorescence displacement with the **1**·CB6 reporter pair at 298 K; the error in data is 20% unless specified differently. [b] Obtained from AM1-optimized geometries. [c] Packing coefficient, obtained by dividing the guest volume by the inner cavity volume of CB6 (142 Å^3, from ref. [18]). [d] Adjusted with 1 mM HCl. [e] 10% error. [f] Measurement relative to protiated form. [g] *n*-Hexane, isohexane, 2,3-dimethylbutane, cyclohexane, and *n*-heptane.

Gases, which were known to bind—although with unknown affinity—to CB5,[12] (CH_4 but also Ar, Kr, N_2, and O_2) did not show any detectable binding with CB6. Isobutane and cyclopentane are bound strongest, with bindings constants close to 10^6 M^{-1}. Different hexanes and larger alkanes caused no fluorescence displacement at all, suggesting a more than two orders of magnitude lower affinity, which is consistent with the previously measured very low binding of

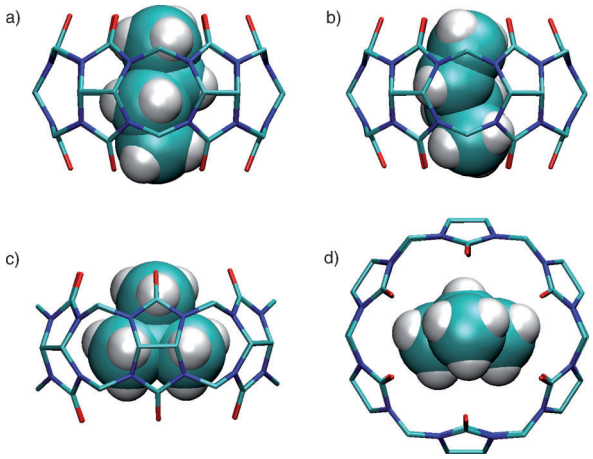

Figure 3. Optimized geometries of the CB6 complexes with a) *n*-butane, b) 1-butene, c) isobutane (side view), and d) isobutane (top view) at the B3LYP/6-31G** level of theory (gas phase).

a neutral cyclohexane derivative ($10\,M^{-1}$).[21] As might be expected from the spherical void, CB6 preferentially includes branched and cyclic hydrocarbons (isobutane > *n*-butane and cyclopentane ≫ *n*-pentane), which reveals an interesting constitutional selectivity.

The size selectivity can be illustrated by considering the packing coefficients (PCs) of the different gases (Table 1).[18] As can be seen, a maximum is reached for isobutane and cyclopentane with guest volumes of 79–86 Å^3, corresponding to a packing coefficient of 56–61 %, in good agreement with Rebek's 55 % solution.[2,3,31] The affinity drops expectedly for smaller and larger guests, corresponding to a too loose or too tight packing. CB6 also differentiates well between saturated and unsaturated hydrocarbons: alkenes show a four–ten times weaker binding. This drop is unlikely to be due to the minimal size variation (5–10 %, Table 1), but rather to the three–five times higher water solubility of alkenes, which reduces the driving force for inclusion. The same trend applies for acetylene, which has not only a factor of nine higher water solubility than ethylene, but also a more than a factor of 30 lower affinity to CB6. Stereoselective binding is also observed, as revealed by the seven times larger binding of *cis*-butene versus its *trans* form, a stereochemical effect, which manifests itself on the larger-molecule scale in the preferential binding of a *cis*-azobenzene with the homologous CB7.[32] The comparison of the four butene isomers is particularly intriguing. They display virtually the same water solubilities and volumes, and are consequently capable of displacing the same number of very-high-energy water molecules from the cavity of CB6.[18] Also attractive van der Waals interactions are expected to be comparable because of their comparable polarizability, which leaves the observed order (*cis*-butene > isobutene ≈ 1-butene > *trans*-butene) presently unaccounted for.

Neopentane is equally large as isopentane and 2,3-diazabicyclo[2.2.1]hept-2-ene (all 96 Å^3) and shows additionally an essentially perfect shape fitting. Nevertheless, only the last two guests show sizable binding with CB6 (Table 1 and Ref. [21]). The absence of binding of neopentane must consequently be due to a kinetic effect, that is, the tight cucurbituril portals block the ingression of the most bulky guest (constrictive binding).[6,21,33] Indeed, already Mock and Shih have shown that neopentylammonium does not form inclusion complexes with CB6.[34]

Alkali cations affect the thermodynamics and kinetics of binding of guest molecules to cation–receptor macrocycles in an adverse fashion.[22,27,35,36] Nevertheless, the addition of salts is routinely applied when working with CB6 to increase solubility and enable NMR measurements.[15,21,28,35] Even though salts are not expected to interact with the inert nonpolar hydrocarbons investigated herein, they destabilize the resulting host–guest complexes. In detail, the binding constants dropped by one–two orders of magnitude in the presence of 50 mM Na^+ ions, which are known to bind to the carbonyl portals, and thereby compete with the binding of guests. Our data also reveal a guest-size dependence: The C4 and C5 hydrocarbons show the most pronounced drop in binding constant in the presence of salt. This is well in line with a steric hindrance, where the sodium ions bound to the portals interfere strongly with the binding of large guests (Figure 3), and only weakly with smaller ones such as the C2 hydrocarbons. From a conceptual viewpoint, the differential salt effects set precedent that cations do not only lead to much smaller absolute binding constants, but that they also adulterate the intrinsic selectivity of CB6. For example, in the presence of sodium, ethane, *cis*-butene, and isobutene appear to have the same affinity for CB6, while in its absence the true selectivity order emerges, with *cis*-butene > isobutene > ethane. The different gases do therefore not only show different absolute fluorescence responses, but also exhibit characteristic salt effects towards the fluorescent sensing ensemble. The possibility to modulate the binding constant by simple addition of salts (or other competitors for CB6 such as cadaverine) offers, on the other hand, the possibility to effectively trigger the release of an encapsulated analyte.[21,26]

The apparent isotope effects for complexation of perdeuterated propane and perdeuterated isobutane with CB6 were determined by relative measurements. The resulting values (K'_H/K'_D, assuming identical solubilities of the isotopomers)[37] were 1.1 ± 0.1 and 0.9 ± 0.1 (Table 1) and are therefore negligible within experimental error. Significant deuterium isotope effects have been occasionally observed on host–guest complexation equilibria (0.98–0.58),[38] but in all previously investigated cases the binding was driven by C–H···π interactions between the aromatic guest and aromatic host, which respond sensitively, through variations of the partition function caused by changes of the C–H versus C–D vibrational energies, to deuterium isotope effects. The complexation of hydrocarbons by CB6 does not involve specific interactions of the C–H and C–D bonds, such that the observed absence of a sizable deuterium isotope effect can be well accounted for.

In conclusion, we have applied for the first time a fluorescent dye displacement approach to the real-time monitoring of gas binding. Volatile hydrocarbons bind very tightly and selectively to cucurbituril in water. The set of binding constants is the most extensive one so far obtained for the binding of nonpolar neutral guests with cucurbiturils, and

the largest one for complexation of gaseous hydrocarbons to macrocycles in general. It will serve as a benchmark, in particular since the measurements refer to aqueous solution, for the choice of force fields and solvation models in MD simulations in an effort to reproduce hydrophobic effects in supramolecular host–guest binding phenomena. The affinity data provide the thermodynamic foundation for patented claims,[20] and practical applications of the differential binding of CB6 towards different gases are indeed not far-fetched. For example, even though commercial neopentane is already highly pure (99%), it contained traces of an unknown impurity at approximately 1.66 ppm (Figure 4), which accumulated upon prolonged bubbling. Addition of solid CB6 to a D_2O solution of neopentane resulted in the selective removal of the impurity. Neopentane is too large to be encapsulated and, hence, very effectively purified.

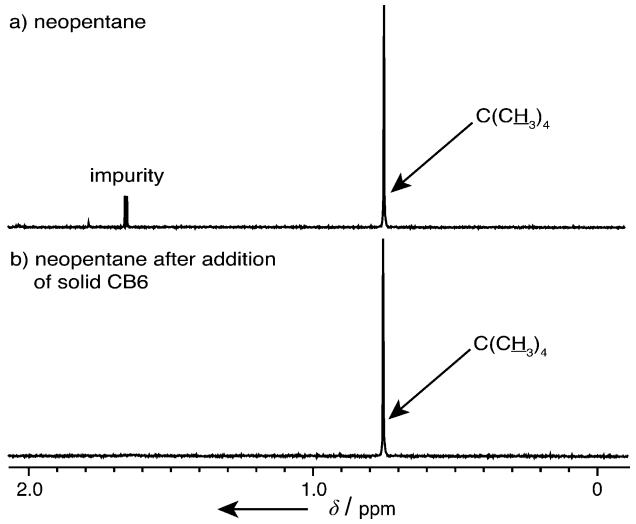

Figure 4. ^{1}H NMR spectra of neopentane-saturated D_2O before and after addition of CB6.

Experimental Section

Gases of highest commercial purity (≥99%) were purchased from Air Liquide, Germany, except for *cis*- and *trans*-butene (Sigma–Aldrich, Germany), neopentane (ChemSampCo, USA), [D_8]propane (ISOTEC, USA), and [D_{10}]2-methylpropane (CDN Isotopes, Canada). Liquid hydrocarbons were from Sigma–Aldrich, Germany. CB6 was synthesized as reported[15,16] and an independently prepared sample (which afforded the same results) was kindly provided by Dr. H.-J. Buschmann. Fluorescence measurements were done with a Varian Eclipse fluorometer at 25.0 ± 0.1 °C (using an external Peltier thermostat). Experiments for the sensing of gaseous hydrocarbons and noble gases were performed in a rubber-sealed long-neck quartz cuvette. The different gases were administered to the aqueous mixture containing the **1**·CB6 complex by slowly purging (ca. 1 bubble per second) with a needle. For the online monitoring of the uptake of volatile liquid analytes, we employed N_2 as carrier gas for transferring the hydrocarbons of interest through the gas phase into the aqueous solution containing the reporter pair until the solubility limit was reached. Experiments at varying gas pressures were performed by deaerating a home-built cuvette by three freeze–pump–thaw cycles and subsequently dosing different gas pressures on a vacuum manifold, as detailed in our previous gas-phase work.[39] Acetylene was also dosed in this manner (instead of bubbling) to avoid the accumulation of acetone, an ubiquitous stabilizer in acetylene samples. For those hydrocarbons, which showed no immediate effect on the fluorescence signal, the solutions were exposed for a prolonged time (several hours) to exclude the possibility of a slower guest exchange kinetics being responsible for the absence of binding.

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