Host–Guest Systems

Deutsche Ausgabe: DOI: 10.1002/ange.201602671
Internationale Ausgabe: DOI: 10.1002/anie.201602671

Uptake of Hydrocarbons in Aqueous Solution by Encapsulation in Acyclic Cucurbit[*n*]uril-Type Molecular Containers

*Xiaoyong Lu and Lyle Isaacs**

Abstract: *The ability of two water-soluble acyclic cucurbit-[n]uril (CB[n]) type containers, whose hydrophobic cavity is defined by a glycoluril tetramer backbone and terminal aromatic (benzene, naphthalene) sidewalls, to act as solubilizing agents for hydrocarbons in water is described. ^{1}H NMR spectroscopy studies and phase-solubility diagrams establish that the naphthalene-walled container performs as well as, or better than, CB[7] and CB[8] in promoting the uptake of poorly soluble hydrocarbons into aqueous solution through formation of host–hydrocarbon complexes. The naphthalene-walled acyclic CB[n] container is able to extract large hydrocarbons from crude oil into aqueous solution.*

Hydrocarbons (HCs) are of tremendous importance in real-world applications and in fundamental scientific pursuits. For example, the United States consumed about 7 billion barrels of petroleum products in 2014 which was used to power automobiles, heat buildings, generate electricity, and as feedstocks for the chemicals, drugs, and synthetic materials that modern society relies upon.[1] Conversely, accidental release of petroleum products poses a risk to humans, animals, and marine life. The chemistry of HCs lies at the core of modern biochemistry and chemistry. For example, the hydrophobic nature of HCs is responsible for the self-assembly of biological membranes and for the function of biological receptors such as proteins that bind fatty acids.[2] The fundamental properties of HCs (e.g. physical properties, reactivity, conformations) are key topics in all undergraduate organic chemistry courses. Accordingly, chemists and biologists are deeply interested in understanding and controlling the properties of HCs and HC-derived molecules and materials.

Supramolecular chemists have studied the ability of various molecular containers to recognize HCs. For example, the Rebek[3] and Gibb[4] research groups have shown that cavitands bind HCs in water, stabilize otherwise unstable conformations (e.g. helices), and promote chemical reactions. Self-assembled metallocages have also been shown to act as potent receptors for *n*-alkanes and cycloalkanes.[5] Recently, Stoddart and co-workers reported that ExBox acts as a scavenger for polycyclic aromatic HCs.[6] Cucurbit[*n*]uril-based molecular containers (CB[*n*], Figure 1) display a high affinity toward hydrophobic cations and even neutral guest compounds.[7,8] Accordingly, CB[6] has been investigated as a receptor for low-molecular-weight HCs (C_1–C_6),[9] as a porous material for the solid-state sorption of acetylene,[10] and as a component of polyurethane materials for the adsorption of oil–water mixtures.[11] Recently, we introduced acyclic CB[*n*]-type receptors (e.g. **1** and **2**) and their use in biomedical applications.[12,13] Herein we investigate the binding ability of **1** and **2** for HCs in water relative to macrocyclic CB[*n*].

First, we investigated the interaction of **1** and **2** with liquid HCs. Aqueous solutions of **1** or **2** (1 mM) were stirred with an excess of poorly soluble HCs until equilibrium was achieved and then examined by ^{1}H NMR spectroscopy. We found that **1** and **2** solubilize and bind the lower HCs ($\leq C_6$) in a 1:1 ratio (see the Supporting Information), but that **2** more efficiently solubilizes higher *n*-alkanes (e.g. *n*-heptane–*n*-dodecane, see the Supporting Information). For example, **2** (1 mM) solubilizes and binds 0.18 mM *n*-decane, whereas **1** only solubilizes 0.011 mM decane. For comparison, CB[7] (1 mM) solubilizes 0.033 mM *n*-decane, and CB[8] (0.23 mM) solubilizes 0.016 mM *n*-decane. Figure 2 a–c shows the ^{1}H NMR spectra for a saturated solution of heptane in water, **1**, and a mixture of **1** and C_7H_{16}, respectively, prepared by extracting the HC into water. The resonances corresponding to H_a–H_d of the guest C_7H_{16} shift upfield upon formation of the **1**·C_7H_{16} complex. This shift indicates they are bound in the cavity of **1**, which constitutes an NMR shielding region by virtue of its aromatic walls and glycoluril tetramer backbone.[14] Conversely, the resonance corresponding to H_m of **1** shifts downfield upon formation of **1**·C_7H_{16}, which reflects the disruption of π-π interactions between the Ar sidewalls in free **1**.[14] Similarly, Figure 2 d–f shows the ^{1}H NMR spectra for aqueous solutions of C_8H_{18}, **2**, and the **2**·C_8H_{18} complex, respectively. Once again, the guest resonances H_a–H_d shift upfield upon complexation, whereas the Ar walls (H_n, H_o) of **2** shift downfield. The larger $\Delta\delta$ values in this system reflect the larger shielding effect of the naphthalene walls of **2** compared to **1**. The resonances for free C_8H_{18} (*) arise from the presence of insoluble droplets of C_8H_{18} in the NMR tube. The assignments of the resonances for the bound guest are based on their COSY spectra (see the Supporting Information). The geometry of the **2**·octane complex was then investigated. Its NOESY spectrum (see the Supporting Information) shows strong cross-peaks between H_b/H_c on the $OC(H_a)_2C(H_b)_2C(H_c)_2SO_3Na$ arms of **2** and the CH_3 groups of octane, thus reflecting their proximity. Analysis of the complexation-induced changes in the chemical shift ($\Delta\delta$) for *n*-octane (H_a: −0.91, H_b: −1.23, H_c: −1.38, H_d: −1.46) confirms that the central CH_2 groups

[*] Dr. X. Lu, Prof. Dr. L. Isaacs
Department of Chemistry and Biochemistry
University of Maryland, College Park
College Park, MD 20742 (USA)
E-mail: LIsaacs@umd.edu

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602671.

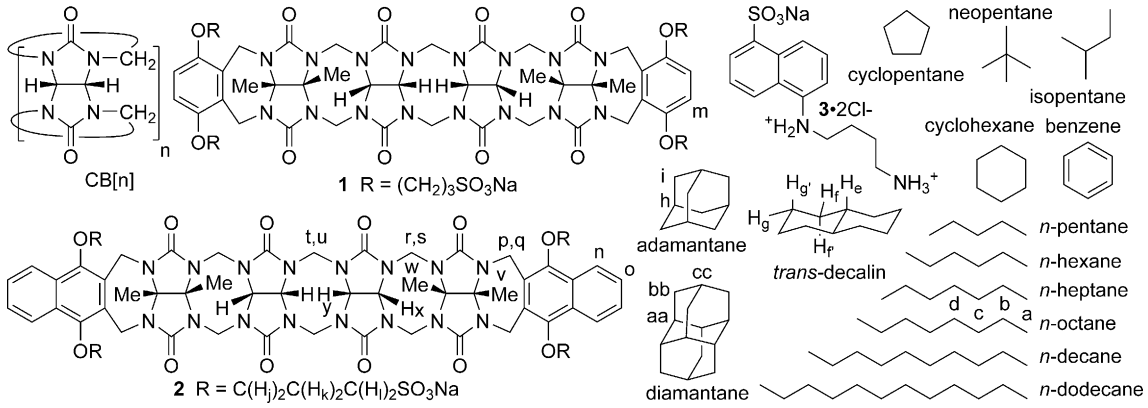

Figure 1. Structures of CB[*n*], hosts **1** and **2**, and HC guests.

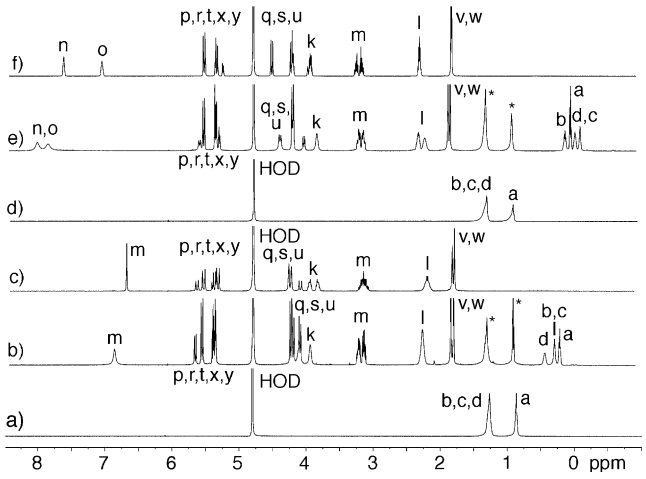

Figure 2. ^{1}H NMR spectra (D_2O, 600 MHz, RT) recorded for: a) *n*-heptane (excess); b) **1** (1.0 mM) and *n*-heptane (excess); c) **1** (1.0 mM); d) *n*-octane (excess); e) **2** (1.0 mM) and *n*-octane (excess); f) host **2** (1.0 mM). * = resonances of droplets of free HC.

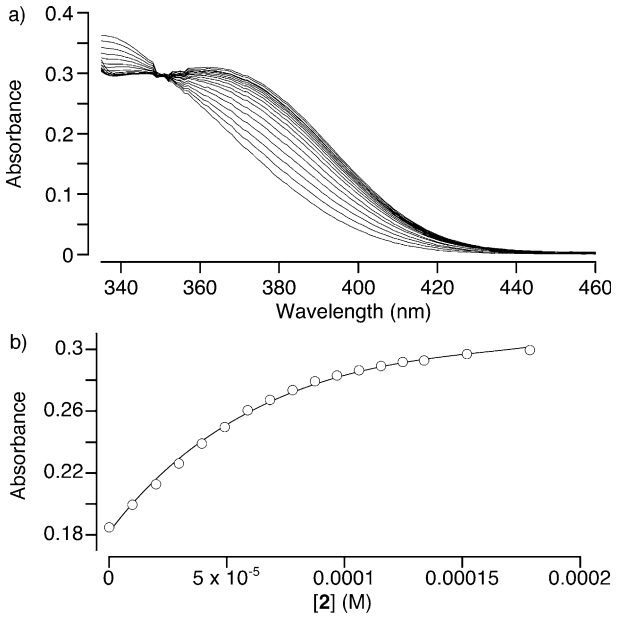

Figure 3. a) UV/Vis spectra from the titration of **3** (50 μM) with **2** (0–179 μM). b) Plot of A_{370} versus [**2**].

reside toward the center of the anisotropic shielding region defined by the cavity of **2,** whereas the terminal CH_3 groups reside in the C=O portal/solubilizing group region. Analogous experiments were performed for the other HCs shown in Figure 1 (see the Supporting Information), which also showed the spectroscopic earmarks of cavity binding. We find that aromatic HCs (e.g. benzene), alicyclic HCs (cyclopentane and cyclohexane), and branched HCs (neopentane and 2-methylbutane) bind inside **1** and **2**, although the exchange kinetics are fast on the ^{1}H NMR time scale and broadened resonances are observed. The situation is different for the linear HCs (C_6H_{14}–$C_{12}H_{26}$) where the resonances for bound guests are sharp and the exchange between free and bound HC is slow on the NMR time scale.

After having qualitatively investigated the binding properties of **1** and **2** toward HCs, we performed quantitative measurements of the binding affinity (K_a) of the better-performing container (**2**) toward the HCs. We employed a competitive UV/Vis displacement assay[15] involving **2** and dye **3**. Figure 3a shows the UV/Vis spectra recorded when **3** (50 μM) was titrated with **2** (0–179 μM).[16] The presence of a well-defined isosbestic point provides evidence of a two-state equilibrium between **3** and **2**·**3**. Figure 3b shows a plot of absorbance versus [**2**] fitted to a 1:1 binding model (see the Supporting Information) with $K_a = 3.8 \pm 0.4 \times 10^4\,M^{-1}$. Subsequently, we performed UV/Vis competition assays by titrating solutions of **2** (50 μM) and **3** (50 μM) with each HC up to the solubility limit. Plots of absorbance versus [HC] were fitted to a competition binding model (see the Supporting Information) to yield K_a values for **2** toward benzene ($1.0 \pm 0.2 \times 10^4\,M^{-1}$), *n*-pentane ($8.0 \pm 1.9 \times 10^3\,M^{-1}$), isopentane ($6.6 \pm 1.9 \times 10^3\,M^{-1}$), cyclopentane ($3.0 \pm 0.9 \times 10^3\,M^{-1}$), and cyclohexane ($3.8 \pm 1.2 \times 10^4\,M^{-1}$). The affinity of **2** toward these smaller HCs are modest and fall in the 10^3–$10^4\,M^{-1}$ range. These K_a values are lower than those measured by Nau et al. for CB[6] and the corresponding HCs ($K_a \approx 10^3$–$10^6\,M^{-1}$), which probably reflects their better fit to the smaller CB[6] host.[7,9]

Unfortunately, the extremely poor solubility of the larger HCs in aqueous solution precluded measurements of the

K_a values for **2** by competition methods. Accordingly, we used PSDs[17] for this purpose and to compare **2**, CB[7], and CB[8]. To construct the PSDs we prepared solutions of **2**, CB[7], or CB[8], mixed them with excess liquid HC to achieve equilibrium, and measured the [HC] in water by integration of the ^{1}H NMR signals corresponding to the HC resonances relative to an internal standard. Figure 4 shows the PSDs for

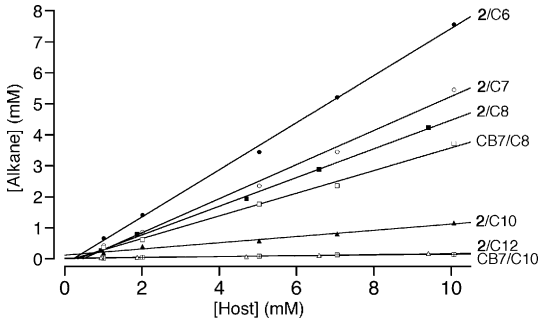

Figure 4. PSDs constructed for host **2** or CB[7] with hexane–dodecane. ●: **2** and *n*-hexane, ○: **2** and *n*-heptane, ■: **2** and *n*-octane, ▲: **2** and *n*-decane, ⊞: **2** and *n*-dodecane; □: CB[7] and *n*-octane; △: CB[7] and *n*-decane.

hexane–dodecane with **2** and for selected HCs with CB[7]. These PSDs are linear (A_L type), which indicates the formation of soluble **2**·HC complexes. A_L-type PSDs are known to obey Equation (1), where S_0 is the inherent

$$K_a = \frac{\text{slope}}{S_0(1-\text{slope})} \quad (1)$$

solubility of the HC, slope is the slope of the PSD, and K_a is the binding constant for the **2**·HC complex.[17] Table 1 gives the K_a values calculated for the **2**·HC, CB[7]·HC, and CB[8]·HC complexes using S_0 values from the literature[18] and the experimentally determined PSD slope values. The binding affinity of **2** toward the larger HCs falls in the 10^5–10^6 M^{-1} range. Binding affinities in the 10^5–10^6 M^{-1} range are quite substantial for unfunctionalized HC guests, and indicate a substantial hydrophobic driving force in the recognition properties of **2**. For example, Figure 4 shows that **2** performs as well as CB[7] as a solubilizing agent for octane (**2**: slope 0.43, CB[7]: slope 0.42) and substantially better for decane (**2**: slope 0.10, CB[7]: slope 0.016). We surmise that the ability of **2** to flex its glycoluril tetramer backbone allows it to better accommodate a compact conformation of decane relative to CB[7]. Consistent with this interpretation is the observation that the larger CB[8] container performs (PSD slope = 0.10) as well as **2** toward *n*-decane. A related trend is seen for *n*-dodecane, where CB[8] (slope = 0.11) is better than **2** (slope = 0.016), which in turn is comparable to CB[7] (slope = 0.014). We conclude that an important determinant of the K_a value and, therefore, PSD slope with **2**, CB[7], and CB[8] are the sizes of the hydrophobic cavity of the host and the size of the guest. Given that the high host–guest binding affinity of CB[*n*]·guest complexes is largely due to the release of encapsulated high-energy water molecules,[7,8] it is reasonable to posit—despite the structural perturbation of the naphthalene sidewalls—the high-energy nature of the water molecules inside uncomplexed **2**. Quite surprisingly, the hydrophobic driving force for binding HCs inside **2** is comparable to that of CB[7] and CB[8], irrespective of whether it originates from encapsulated high-energy water molecules or enhanced van der Waals interactions that occur with the aromatic walls of host **2**.

A further consideration, besides the K_a value and the PSD slope when comparing the solubilizing abilities of **2**, CB[7], and CB[8], is the inherent solubilities of the hosts and the highest concentrations of HC that can be achieved. According to both of these measures, the solubilizing abilities of **2** exceed those of CB[7] and CB[8]. For example, the inherent solubility of **2** (18 mM) is slightly higher than CB[7] (reported as 5 mM[7] and 20–30 mM[20]; ca. 10 mM in our hands) and much higher than CB[8] (250 μM in our hands). Accordingly, even though CB[8] binds more tightly to *n*-decane than **2**, the maximum concentration of *n*-decane obtained with CB[8] is 0.016 mM but reaches 1.15 mM for **2**. In addition, the PSD plot for CB[8] with *n*-decane reaches a plateau above [CB[8]] = 0.18 mM, which reflects the poor solubility of the CB[8]·*n*-decane complex, as confirmed by the partial precipitation of the CB[8]·*n*-decane complex (see the Supporting Information). Significantly higher concentrations of decalin, adamantane, and diamantane are also obtained using **2** as the solubilizing agent compared to CB[8], because of the low inherent solubility of CB[8] (see the Supporting Information).

Having delineated the comparable binding affinities of **2**, CB[7], and CB[8] toward *n*-alkanes, we wanted to test whether similar trends would hold for the privileged binding scaffolds of (acyclic) CB[*n*]-type receptors.[13,14,21] Figure 5 shows the ^{1}H NMR spectra recorded for *trans*-decalin,

Table 1: K_a and S_0 values of HCs towards **2**, CB[7], and CB[8] in D_2O.

Guest[a]	S_0 [mM][18,19]	**2** K_a/ 10^4 [M^{-1}]	slope	[HC] max [mM]	CB[7] K_a/ 10^4 [M^{-1}]	slope	[HC] max [mM]	CB[8] K_a/ 10^4 [M^{-1}]	slope	[HC] max [mM]
n-hexane	0.13	2.6	0.76	7.6	–	–		–	–	–
n-heptane	0.024	5.3	0.55	5.5	2.7	0.39	2.3	1.4	0.26	0.071
n-octane	0.0064	13	0.43	4.2	12	0.42	3.7	9.5	0.37	0.081
n-decane	1.1×10^{-4}	110	0.10	1.15	18	0.016	0.16	110	0.10	0.016
n-dodecane	2.2×10^{-5}	74	0.016	0.12	67	0.014	0.12	550	0.11	0.016
trans-decalin	6.4×10^{-3}	72	0.82	8.1	13	0.45	2.0	57	0.73	0.11
adamantane	7.8×10^{-4}	1700	0.92	9.2	520	0.79	3.6	37	0.23	0.083
diamantane	1.3×10^{-5}	1000	0.12	1.3	300	0.04	0.4	1500	0.16	0.028

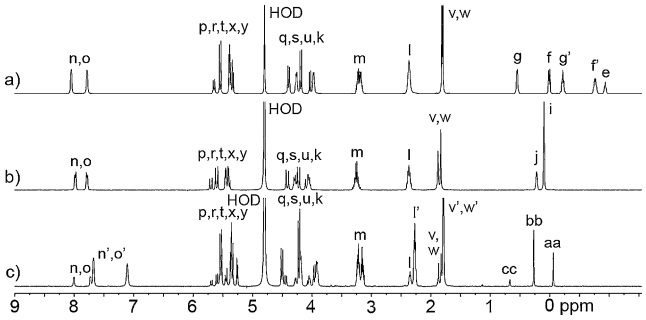

Figure 5. ^{1}H NMR spectra (600 MHz, D_2O, RT) for HCs treated with **2**: a) *trans*-decalin, b) adamantane, c) diamantane.

adamantane, and diamantane solubilized with **2**. The significant upfield shifts of the HC resonances reflect their encapsulation inside the shielding region of **2** defined by the glycoluril tetramer backbone and the aromatic naphthalene sidewalls. The 1:1 nature of the **2**·octane, **2**·*trans*-decalin, and **2**·adamantane complexes were confirmed by DOSY spectroscopy, which gives diffusion coefficients that are comparable to uncomplexed **2** (see the Supporting Information). Next, we measured the PSDs for **2**, CB[7], and CB[8] toward *trans*-decalin, adamantine, and diamantane (Table 1, see also the Supporting Information). Remarkably, the solubilizing abilities of **2** are superior to CB[7] or CB[8] in terms of both the PSD slope and $[HC]_{max}$ for both *trans*-decalin and adamantane. In the case of diamantane, the PSD slopes and K_a values follow the order CB[8] > **2** > CB[7]. Of particular note is that the calculated K_a values of **2**·adamantane and **2**·diamantane exceed $10^7\,M^{-1}$, which highlights the remarkable potent hydrophobic driving force achieved by **2**, which is comparable to or larger than that achieved with CB[*n*].

Given the affinity of **2** toward HCs, we explored its ability to extract components of crude oil into water. A crude oil sample (1.0 mL) from Nigeria, West Africa, containing an unknown composition of HCs (^{1}H NMR in $CDCl_3$, Figure 6a), was added to a solution of **2** (5.0 mM, 2 mL) in D_2O and shaken for 10 h at 25 °C. The aqueous phase was separated, filtered (0.45 μm polyethersulfone membrane), and analyzed by ^{1}H NMR spectroscopy (Figure 6c). The aqueous solution was mixed with $CDCl_3$ to break the **2**·HC complex and extract the HCs into the organic solution for ^{1}H NMR analysis (Figure 6b). On the basis of the ^{1}H NMR spectroscopy result (Figure 6c) it is clear that host **2** enhances the water solubility of crude oil samples through formation of a **2**·HC complex. From the resonances in the $\delta = 1.5$ to -1.0 ppm range, aliphatic HCs are the major components of the extract, although resonances for aromatic compounds are also visible (Figure 6c, $\delta = 6.5$–5.7 ppm). The aromatic resonances are barely visible in the ^{1}H NMR spectrum of the crude oil sample, which suggests that **2** is somewhat selective toward aromatic guests, which is in accord with previous recognition studies of **2** toward insoluble drugs.[14] The HC content of the $CDCl_3$ extract was analyzed by GC-MS and compared to a standard sample containing decane, dodecane, and tetradecane (Figure 6d,e). The assignment of molecular formulas in Figure 6e were done by comparison with the

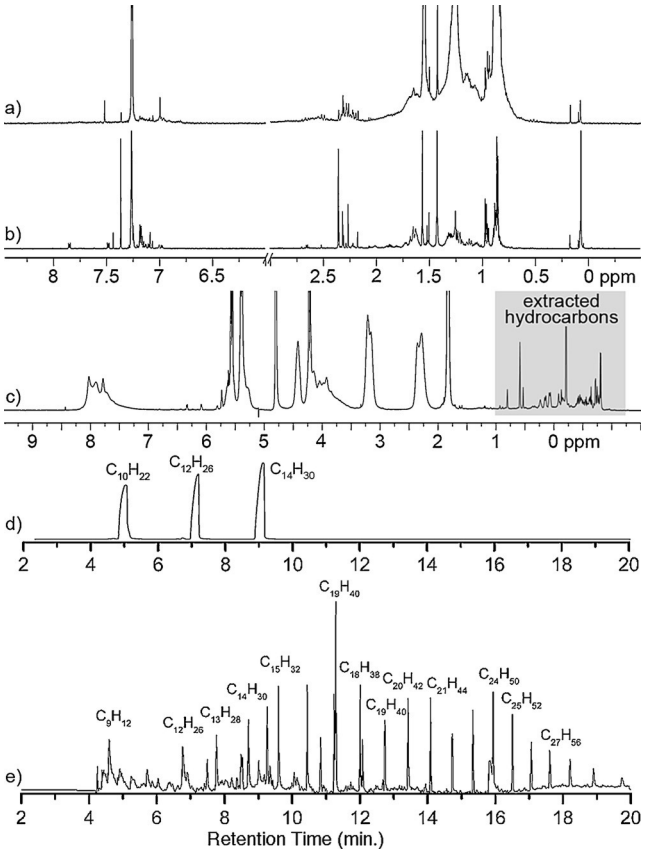

Figure 6. ^{1}H NMR spectra (400 MHz, RT) for: a) a crude oil sample in $CDCl_3$, b) oil sample obtained by back-extraction of the solubilized HCs into $CDCl_3$, c) host **2** (5 mM) extract of the crude oil sample in D_2O. GC-MS chromatograms of: d) *n*-decane, *n*-dodecane, and *n*-tetradecane standards, e) oil extracted by **2** back-extracted into $CDCl_3$.

National Institute of Standards and Technology database. The observation of the larger HCs (e.g. up to $C_{27}H_{56}$) in the extract establishes the potent molecular recognition capability of **2** toward a broad range of HCs, although the geometry and stoichiometry of the complexes with higher HCs remains to be determined.

In summary, we have investigated the binding ability of **2**, CB[7], and CB[8] toward HCs by ^{1}H NMR and UV/Vis spectroscopy as well as by PSDs. Host **2** promotes the uptake of HCs in aqueous solution as well as or better than CB[7] in terms of the PSD slope and $[HC]_{max}$. The high solubility of **2** allows it to outperform CB[8] in terms of the $[HC]_{max}$ achieved. In conclusion, we find that the hydrophobic driving force for binding inside acyclic CB[*n*]-type receptor **2**—despite the structural perturbation upon the introduction of the naphthalene walls—is comparable to those of CB[7] and CB[8], which are well known for their remarkable binding affinities through the release of high-energy water molecules upon complexation.[7,8] The excellent solubility of acyclic CB[*n*] and the ability to tailor their structures by synthetic chemistry[14] suggests future application for the separation, sequestration, and transformation of gaseous and liquid HCs.

Acknowledgements

We thank the NSF (CHE-1404911) for financial support.

Keywords: cucurbit[*n*]uril · host–guest systems · hydrocarbons · hydrophobic effect · supramolecular chemistry

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8076–8080
Angew. Chem. **2016**, *128*, 8208–8212

[1] US Energy Information Administration. http://www.eia.gov/tools/faqs/faq.cfm?id=41&t=6 (accessed Feb. **2016**).
[2] A. W. Zimmerman, J. H. Veerkamp, *Cell. Mol. Life Sci.* **2002**, *59*, 1096–1116; L. Stryer, *Biochemistry*, W. H. Freeman and Co., New York, **1995**.
[3] R. J. Hooley, H. J. Van Anda, J. J. Rebek, *J. Am. Chem. Soc.* **2007**, *129*, 13464–13473; J. Rebek, *Acc. Chem. Res.* **2009**, *42*, 1660–1668.
[4] C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2006**, *128*, 16498–16499; S. Liu, D. H. Russell, N. F. Zinnel, B. C. Gibb, *J. Am. Chem. Soc.* **2013**, *135*, 4314–4324.
[5] S. M. Biros, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 12094–12095; T. Ogoshi, R. Sueto, K. Yoshikoshi, Y. Sakata, S. Akine, T.-A. Yamagishi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9849–9852; *Angew. Chem.* **2015**, *127*, 9987–9990; T. K. Ronson, C. Giri, N. Kodiah Beyeh, A. Minkkinen, F. Topic, J. J. Holstein, K. Rissanen, J. R. Nitschke, *Chem. Eur. J.* **2013**, *19*, 3374–3382.
[6] J. C. Barnes, M. Juricek, N. L. Strutt, M. Frasconi, S. Sampath, M. A. Giesener, P. L. McGrier, C. J. Bruns, C. L. Stern, A. A. Sarjeant, J. F. Stoddart, *J. Am. Chem. Soc.* **2013**, *135*, 183–192.
[7] W. M. Nau, M. Florea, K. I. Assaf, *Isr. J. Chem.* **2011**, *51*, 559–577.
[8] F. Biedermann, V. D. Uzunova, O. A. Scherman, W. M. Nau, A. De Simone, *J. Am. Chem. Soc.* **2012**, *134*, 15318–15323.
[9] M. Florea, W. M. Nau, *Angew. Chem. Int. Ed.* **2011**, *50*, 9338–9342; *Angew. Chem.* **2011**, *123*, 9510–9514.
[10] S. Lim, H. Kim, N. Selvapalam, K.-J. Kim, S. J. Cho, G. Seo, K. Kim, *Angew. Chem. Int. Ed.* **2008**, *47*, 3352–3355; *Angew. Chem.* **2008**, *120*, 3400–3403.
[11] F. C. Sousa e Silva, S. M. de Lima, G. J.-F. Demets, *RSC Adv.* **2014**, *4*, 58796–58799.
[12] D. Ma, G. Hettiarachchi, D. Nguyen, B. Zhang, J. B. Wittenberg, P. Y. Zavalij, V. Briken, L. Isaacs, *Nat. Chem.* **2012**, *4*, 503–510.
[13] D. Ma, B. Zhang, U. Hoffmann, M. G. Sundrup, M. Eikermann, L. Isaacs, *Angew. Chem. Int. Ed.* **2012**, *51*, 11358–11362; *Angew. Chem.* **2012**, *124*, 11520–11524.
[14] B. Zhang, L. Isaacs, *J. Med. Chem.* **2014**, *57*, 9554–9563.
[15] L. You, D. Zha, E. V. Anslyn, *Chem. Rev.* **2015**, *115*, 7840–7892.
[16] Direct ^{1}H NMR titrations were technically challenging because of the volatility of the smaller alkanes and the insolubility of the larger alkanes.
[17] T. Higuchi, K. A. Connors, *Adv. Anal. Chem. Inst.* **1965**, *4*, 117–212.
[18] W. M. Haynes, *CRC Handbook of Chemistry and Physics*, 96th ed., CRC Press, Boca Raton, FL, **2015**.
[19] P. Karásek, J. Planeta, M. Roth, *J. Chem. Eng. Data* **2008**, *53*, 816–819.
[20] J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621–630.
[21] D. Shetty, J. K. Khedkar, K. M. Park, K. Kim, *Chem. Soc. Rev.* **2015**, *44*, 8747–8761; K. I. Assaf, W. M. Nau, *Chem. Soc. Rev.* **2015**, *44*, 394–418.

Received: March 16, 2016
Published online: May 11, 2016

