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## Cavitation energies can outperform dispersion interactions

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The accurate dissection of binding energies into their microscopic components is challenging, especially in solution. Here we study the binding of noble gases (He-Xe) with the macrocyclic receptor cucurbit[5]uril in water by displacement of methane and ethane as <sup>1</sup>H NMR probes. We dissect the hydration free energies of the noble gases into an attractive dispersive component and a repulsive one for formation of a cavity in water. This allows us to identify the contributions to host-guest binding and to conclude that the binding process is driven by differential cavitation energies rather than dispersion interactions. The free energy required to create a cavity to accept the noble gas inside the cucurbit[5]uril is much lower than that to create a similarly sized cavity in bulk water. The recovery of the latter cavitation energy drives the overall process, which has implications for the refinement of gas-storage materials and the understanding of biological receptors.

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The formation of host-guest complexes between noble gases and macromolecular receptors has intrigued supramolecular chemists for decades.<sup>1-4</sup> Such noble-gas complexes should present ideal models for the investigation of dispersion interactions, which are presently receiving prominent attention due to the advent of improved theoretical methodologies<sup>5-11</sup> and refined experimental model systems.<sup>12-21</sup> In fact, London dispersion forces are the only attractive intermolecular interaction at work here, because noble gas atoms lack multipole moments and therefore any ability to exert electrostatic forces.<sup>7</sup> To systematically analyze the factors that drive noble gases into macrocyclic cavities, we now report and analyze the binding affinities of He, Ne, Ar, Kr, and Xe with cucurbit[5]uril (**CB5**), a rigid, water-soluble synthetic macrocyclic host (Fig. 1).<sup>22-26</sup>

Access to all noble-gas affinity constants ( $K_a$ ) required a generic spectroscopic methodology other than the highly specific  $^{129}\text{Xe}$  NMR spectroscopy.<sup>3</sup> Indicator displacement assays allow the determination of  $K_a$  values independent of the chemical nature of the analyte.<sup>27, 28</sup> Optical probes, which allowed the convenient determination of the complexation of volatile hydrocarbons by the larger cucurbit[6]uril,<sup>29</sup> proved inapplicable to **CB5** because its cavity volume ( $68 \text{ \AA}^3$ )<sup>28</sup> is too small to encapsulate reporter chromophores. We and others had previously observed a millimolar affinity of methane with **CB5** in aqueous solution.<sup>29-31</sup> Since then, we worked on the optimization of a robust indicator displacement strategy based on methane and ethane as  $^1\text{H}$  NMR probes to determine the binding of small analytes such as noble gases (Fig. 2).

## Results

### Determination of binding constants

As can be seen from the  $^1\text{H}$  NMR spectra (Fig. 2c), methane is in a slow exchange with the corresponding methane•**CB5** complex. This leads to two distinct signals from which the relative integrals and, thus, the binding constants can be determined with high accuracy (Supplementary Sections 2 and 3). The resulting data set for noble-gas binding to **CB5**, obtained by competitive  $^1\text{H}$  NMR experiments with methane or ethane, is shown in Table 1. This macrocycle serves as a receptor for all noble gases and is the first one known to bind He, Ne, Ar, and Kr in aqueous solution. Note that the binding constant of Xe is largest ( $8,700 \text{ M}^{-1}$ ), rendering **CB5** one of the strongest synthetic Xe receptors, only surpassed by a cryptophane ( $17,000 \text{ M}^{-1}$ ).<sup>3</sup> Surprisingly, within the noble gas series, the change to the smaller Kr causes only a decrease in  $K_a$  by a factor of less than four. The step from Kr to Ar causes the largest drop in  $K_a$  (by a factor of seven) but the binding constants for Ne and He level off near a value of  $70\text{--}90 \text{ M}^{-1}$ . Packing coefficients ( $PC$ , Table 1) are readily accessible empirical tools to assess trends in binding affinities. Accordingly, the high binding of Kr and Xe ( $PC = 51\text{--}69\%$ ) can be qualitatively rationalized in terms of Rebek's rule,<sup>23, 32</sup> which predicts the highest affinities near

*PC* values of 55%, while the drop for C<sub>2</sub>H<sub>6</sub> may indicate not only a tight packing (*PC* = 67%) but also an emerging steric repulsion near the constrictive portal regions of the host due to the non-spherical guest structure.

The non-vanishing binding for the tiny He atom and comparable binding to that of Ne came as a surprise. Although <sup>4</sup>He is spectroscopically silent, its isotope <sup>3</sup>He is not, such that we were able to use <sup>3</sup>He NMR spectroscopy<sup>1</sup> to corroborate the binding of the lightest noble gas to the macrocyclic cavity in aqueous solution. Indeed, the <sup>3</sup>He NMR spectra showed a small but significant up-field shift (Fig. 2b), indicative of fast exchange. In addition, we observed a decrease in the relaxation time *T*<sub>1</sub> of <sup>3</sup>He in the presence of **CB5**, akin to that observed for methane binding (Supplementary Sections 1 and 7).

An additional series of specialized NMR experiments (Supplementary Section 8) allows us to conclude that the **CB5** cavity is not filled with any slowly exchanging water molecules in aqueous solution, similar to the dry concave binding sites in some proteins and in fluorinated nanoporous materials.<sup>33-36</sup> Although the presence of water molecules in the CB5 cavity that are transiently present or in fast exchange cannot be excluded experimentally, MD calculations with explicit water molecules (Supplementary Section 12) show that water molecules would not be significantly stabilized in the CB5 cavity relative to their immersion in the bulk. This circumstance simplifies our mechanistic analysis, because a desolvation penalty of the inner host cavity does not need to be considered, in a first approximation.

### Interplay between dispersion interactions and the hydrophobic effect

Initially, the situation for the noble-gas data set in Table 1 appeared straightforward since only two interactions are at work: dispersion and hydrophobic ones. Hydrophobic desolvation alone,<sup>37, 38</sup> however, cannot be responsible for the trend of the binding constants, because the least hydrophobic (most water soluble) noble gases display the strongest binding.<sup>29</sup> If the hydrophobic character of the noble gas was dominant, one would expect an approximately 10 times stronger binding for He than that for Xe. Experimentally, however, the binding of He is two orders of magnitude weaker than that of Xe. Accordingly, the premature conclusion would be that dispersion interactions must then be at work, overwhelming the hydrophobic effect. Even more deceiving, the observed free-energy correlation (Fig. 2d) between the logarithmic binding affinities and the molecular polarizabilities (which enter the London dispersion energy formula in the nominator) apparently confirms dispersion interactions as dominant contributor even in a quantitative sense.

It is indeed possible to compare experiment and theory with respect to the absolute dispersion interactions between the noble gases and the macrocycle. Consequently, we conceptually dissected the free energies into five processes according to the Born-Haber cycle shown in Fig. 1c. The first one (*i*) describes the hydration of the noble gas with the associated free energy ( $\Delta G_{\text{hydr}}^{\text{gas}}$ ) being experimentally accessible through the solubilities (Table 1). The second (*ii*)

and third (*iii*) refer to the hydration of the host and the host-noble gas complex; we assume those to be the same,  $\Delta G_{\text{hydr}}^{\text{CB5}} \approx \Delta G_{\text{hydr}}^{\text{CB5-gas}}$ , because the hydration shell around CB5 remains unchanged upon noble-gas encapsulation (Supplementary Fig. 9) and because the inner cavity is poorly hydrated (see above). The fourth one (*iv*) describes the host-guest binding in solution with the associated free energy ( $\Delta G_a$ ), for which experimental values can be directly obtained from the measured  $K_a$  values. The free energy for the fifth process (*v*) follows then from the thermodynamic cycle ( $\Delta G_{\text{gas}}^{\text{exp}} = \Delta G_{\text{hydr}}^{\text{gas,exp}} + \Delta G_a^{\text{exp}}$ ) and presents an experimental estimate of the dispersion-driven gas-phase binding of the noble gas to the host in the gas phase. The resulting  $\Delta G_{\text{gas}}^{\text{exp}}$  values (Table 2) nicely reveal a systematic increase with size and polarizability of the noble gases, corroborating dispersion as the underlying driving force.

The binding free energies in the gas phase were additionally calculated by dispersion-corrected DFT (DFT-D3,  $\Delta G_{\text{gas}}^{\text{DFT}}$  values), DLPNO-CCSD(T), and MP2 calculations (Supplementary Section 13). The absolute agreement between theory and experiment (Table 2) is very good, within 1.7 kcal mol<sup>-1</sup>, which also confirms the validity of the only approximation made ( $\Delta G_{\text{hydr}}^{\text{CB5}} \approx \Delta G_{\text{hydr}}^{\text{CB5-gas}}$ ). Since dispersion interactions are the only attractive interactions in the gas phase, it transpires that the binding is indeed driven by dispersion and that the associated energy is significant, regardless of unfavorable entropic contributions, which can be corrected for (Supplementary Table 11).

## Role of dispersion interactions in solution

Until this point, we have demonstrated that dispersion interactions in the binding of noble gases to **CB5** are indeed very important in the gas phase. But for the solution-phase uncertainty remains: Is the complexation of noble gases by **CB5** really driven by dispersion? Are dispersion interactions really dominant? Our initial reasoning in terms of competition between the hydrophobic effect as a driving force for supramolecular association and dispersion interactions as a separate one has ignored that the hydrophobic effect is itself a conglomerate effect.<sup>42</sup> The solubility of noble gases in water, for example, is determined by two contributors: the (free) energy required to create a cavity in the water structure and, again, the energy gained through dispersion interactions (as the only applicable attractive interaction for noble gases) with the surrounding water shell (Fig. 1d). To draw valid conclusions, the dispersion energy which each noble gas experiences in bulk water needs to be contrasted in absolute terms to the one inside the **CB5** cavity, which in turn should be virtually the same as that experienced in the gas phase.

It is accepted that dispersion interactions as a driving force for association are reduced in solution as compared to the gas phase,<sup>12-19</sup> but the quantitative assessment of this “leveling effect” is difficult. MD calculations with explicit solvent are capable of providing good trends of host-guest binding affinities in aqueous solution,<sup>8, 9</sup> but provide only indirect information on dispersion as a driving force because their absolute contribution is hidden in empirically pa-

parameterized Lennard-Jones potentials which vary from method to method.<sup>6</sup> Electronic-structure methods, on the other hand, can predict direct host-guest interactions in the gas-phase with high accuracy (see Table 2),<sup>5, 10</sup> but the transfer to aqueous solution has involved continuum screening models for the solvent, in which the absolute dispersion energies with the bulk solvent are again convoluted. To achieve a direct comparison, see Table 3, we have used a recently developed continuum solvent model based on dispersion (CSM-D), which has already been tested for noble-gas hydration thermodynamics.<sup>6, 7</sup> This model allows us to quantify the dispersion energies ( $E_{\text{disp}}$ ) that noble gases enjoy in the aqueous bulk and to contrast them to the dispersive stabilization they receive by **CB5**; the latter values were taken from the dispersion-corrected DFT calculations (see Table 2 and Supplementary Table 3). The  $E_{\text{disp}}$  values reported here contain the repulsive (steric, exchange) van der Waals components; these could also be separated out but the pertinent conclusions remain unaffected (Supplementary Section 16).

The conclusion from the computed data in Table 3 is that the encapsulation of the noble gases into **CB5** in water is not driven by dispersion. The dispersion electronic energies are large, but inside **CB5** they fall even somewhat below those in bulk water, by  $1.5 \pm 0.7 \text{ kcal mol}^{-1}$ , with the exception of  $\text{C}_2\text{H}_6$  as a large elongated guest, where steric repulsion inside **CB5** enters the electronic energy term. If dispersion alone would decide on the location of the noble gases they would, in fact, remain in the aqueous bulk, where the interactions are stronger, that is  $\Delta\Delta G_{\text{disp}}$  ca.  $5 \text{ kcal mol}^{-1}$  or  $K_a$  ca.  $< 10^{-3} \text{ M}^{-1}$ .

The finding of lower dispersion interactions of guests inside the cucurbituril interior than in water matches the low bulk polarizability measured repeatedly with solvatochromic and NMR probes inside cucurbiturils.<sup>28, 43</sup> Presumably, and especially in the low-packing regime, the average distances to nearest neighbor atoms (which enter in the sixth power in the denominator of the London dispersion term) are on average longer in the **CB5** complexes due to their rigid macrocyclic structure, while in the aqueous bulk water molecules can always form a tight solvation shell.

### Role of cavitation energies

If dispersion interactions are not dominant, and even disfavor inclusion into **CB5**, then there must be another, overpowering driving force which drives inclusion: the cavitation energies. Before a guest molecule can occupy space either in a solvent or inside a receptor, any (residual) solvent molecules need to be pushed aside or out, creating the required cavity. This is generally an energy-costly process as formally a vacuum is created and non-covalent interactions with neighboring atoms are switched off. The differential cavitation energy needs to be considered, because it contributes markedly to host-guest binding. In solvents, this energy increases with the cohesive energy density, thus it is rather high for bulk water.<sup>44</sup> In contrast, the cavitation energy of concave and shielded macrocyclic cavities may be particularly low if

the cavity water molecules are only poorly hydrogen-bonded to the host and to themselves (this situation was termed “high-energy water molecules”).<sup>11, 37, 45-47</sup> In the case of noble-gas binding to **CB5**, the calculation of the differential cavitation energies is simplified, because the cavity of **CB5** is not or only very weakly hydrated ( $\Delta G_{\text{cavity}}^{\text{CB5}} \approx 0$ , the free energy of creating a cavity in vacuum). The cavitation energies of the noble gases in bulk water can, in turn, be calculated by CSM-D,<sup>7</sup> including their entropic and enthalpic contributions (Supplementary Section 15).<sup>48</sup>

The same cavitation energy, which the noble gas needed to invest to dissolve in water, is recouped when the noble gas is transferred to the cavity of **CB5** and this crucial factor drives the binding (Fig. 1d). In fact, as shown in Table 4, the differential cavitation energies present the only driving force in this experimental test case (negative values) and they also dominate the process in absolute numbers, except for ethane, where steric repulsion contributes in the DFT-D3-calculated dispersion term. The overall association process is given by the sum of the dispersion and cavitation free energies ( $\Delta G_a^{\text{calc}} = \Delta\Delta G_{\text{disp}} + \Delta\Delta G_{\text{cavity}}$ ) and the calculated data compare very well with the experimental ones, with deviations of  $\pm 1 \text{ kcal mol}^{-1}$  for the noble gases. If the cavity of free **CB5** is not dry but rather weakly hydrated (as predicted by MD simulations), an extra correction for a residual cavitation energy of the CB5 cavity would need to be made; this would result in a minor and constant offset (by  $< 1 \text{ kcal mol}^{-1}$  in  $\Delta G_a^{\text{calc}}$ ) across the series.

As can be seen, the good correlation ( $r^2 = 0.97$ ) with polarizability from Fig. 2d is only an apparent one since the cavitation energy and the polarizability of any noble gas are both ultimately tied to its atomic volume. In fact, a correlation with the guest volume instead of the polarizability is equally good (Fig. 2e,  $r^2 = 0.99$ ).

## Discussion

Numerous efforts have been expended to understand the importance of dispersion interactions as a driving force for supramolecular association in solution. Frequently, correlations with polarizability of the guest or with the cohesive energy density of the solvent (including water mixtures or water) have been used to argue either in favor or against a sizable contribution.<sup>13-17, 20</sup> In this noble-gas study, we have selected a homologous series of guests with systematically varying polarizability, for which dispersion interactions are the only attractive ones. This enables a clear-cut dissection of the remaining interactions, an assessment of absolute free-energy contributions, and a direct comparison with theory.

These results expose the importance of differential cavitation energies in host-guest binding and establish a clear-cut case where they are dominant. This case is an extreme one, because it involves a rather weakly polarizable host with a poorly solvated cavity for which the cavitation energy is negligible. Larger cavities may be solvated to variable degrees with high-energy water molecules and the differential cavitation energy as a driving force will then be



lower. Eventually, as the cavities become very large (here cavity water molecules form “bulk-like water clusters”) or when multiple interactions with surrounding bulk water molecules take place as is the case for water molecules near planar or convex surfaces, it may vanish.<sup>20, 37, 49</sup>

The interpretations with respect to the importance of dispersion interactions in solution are more involved. Surprisingly, especially in the low-packing domain and with macrocycles displaying low polarizabilities, they may even destabilize host-guest complexes relative to the solvation of the individual species. As the differential cavitation energies become smaller, as the packing coefficients become larger, and as the polarizability of the macrocycles increases – for example when hemicarcerands are utilized instead of cucurbiturils<sup>50</sup> – dispersion interactions with the guests are likely to become dominant in solution as well. They will not generally be negligible.<sup>15, 20</sup>

We advocate that calculations of dispersion interactions in solution always require an explicit consideration of the discrete dispersion terms not only in the host-guest complex but also in bulk solution. While the latter have not yet become available from MD or COSMO calculations where host-guest affinities in solution were predicted,<sup>5, 8-11</sup> dispersion energies for solute-solvent interactions are accessible, for example, through the CSM-D method.<sup>11,12</sup> In addition, the determination of the free energies for formation of a cavity to accommodate the guest in size and shape is always required both in the solvent and in the receptor site, because they contribute significantly to the driving force, or are even dominant as shown herein. Discrete high-energy water molecules must also be considered, because they contribute directly to the cavitation energy as driving force: a high energy of the encapsulated water molecules is equivalent to a low cavitation energy inside the macrocycle and therefore a large differential cavitation energy relative to the aqueous bulk.

## Methods

<sup>1</sup>H NMR measurements were carried on a JEOL JNM-ECA400 spectrometer using a scan repetition time of 60 s in the presence of methane (Supplementary Fig. 1) or 90 s in the presence of ethane, a spectral width of 7503 Hz, a digital resolution of 0.23 Hz per point before zero-filling, and 128-256 scans. The longitudinal relaxation time (T<sub>1</sub>) of methane and ethane in D<sub>2</sub>O were found to be around 16 s and 19 s, respectively. Upon complexation of the hydrocarbon probes with **CB5**, shorter relaxation times of 1.6 s and 1.3 s, respectively, were observed. Proton NMR data were processed with MestReNova software, an exponential apodization function equivalent to 1.0 Hz line broadening and zero-filled by a factor of 2 were applied before Fourier transformation. Phase and baseline were corrected manually. The integral region of the protons covered their corresponding <sup>13</sup>C satellites. Binding constants (*K<sub>a</sub>*) of the hydrocarbon gases, *i.e.*, CH<sub>4</sub>, C<sub>2</sub>H<sub>6</sub> and C<sub>2</sub>H<sub>4</sub> were obtained according to the direct binding model of 1:1 complexation (equation 1, taking CH<sub>4</sub> as an example), where *R* is the <sup>1</sup>H NMR integral ratio of bound and free CH<sub>4</sub>. The concentration of each species can be calculated directly from



the  $^1\text{H}$  NMR integral, because of the slow exchange characteristic of the complexation on the NMR time scale for the **CB5**-hydrocarbon complexes (Supplementary Fig. 2). Because the experiments were carried out under 1 atm of the gas, the concentration of the dissolved, unbound gas is equal to its solubility in water.

$$K_{\text{CH}_4@\text{CB5}} = \frac{[\text{CH}_4]_{\text{bound}}}{[\text{CB5}]_{\text{free}}[\text{CH}_4]_{\text{free}}} = \frac{R}{[\text{CB5}]_{\text{total}} - R \times [\text{CH}_4]_{\text{free}}} \quad \text{with } R = \frac{[\text{CH}_4]_{\text{bound}}}{[\text{CH}_4]_{\text{free}}} \quad (1)$$

The binding constants for the other gases (noble gases and  $\text{N}_2$ ) were obtained by a competitive method (equation 2), taking the known affinities of methane and ethane as references. In order to obtain accurate binding constants by a competitive binding method, the unknown gas should have a similar binding constant to that of the reference system. Thus, the binding constants of the stronger binding gases were determined with  $\text{CH}_4$  as reference ( $K_{\text{CH}_4@\text{CB5}} = 1610 \pm 80 \text{ M}^{-1}$ ,  $[\text{CB5}] = 1.39 \text{ mM}$ ) and those with a low affinity ( $< 100 \text{ M}^{-1}$ ) were determined with  $\text{C}_2\text{H}_6$  as the reference ( $K_{\text{C}_2\text{H}_6@\text{CB5}} = 24.3 \pm 0.3 \text{ M}^{-1}$ ,  $[\text{CB5}] = 16 \text{ mM}$ ) via:

$$K_{\text{gas}} = \frac{[\text{gas}]_{\text{bound}}}{[\text{gas}]_{\text{free}} \times [\text{CB5}]_{\text{free}}} = \frac{K_{\text{CH}_4@\text{CB5}} \times \left( \frac{[\text{CB5}]_{\text{total}}}{R} - [\text{CH}_4]_{\text{free}} \right) - 1}{[\text{gas}]_{\text{free}}} \quad (2)$$

Details of the  $^3\text{He}$  NMR experiments and computational data can be found in the Supplementary Information.

## Data availability statement

All the data supporting the findings of this study are available within the Article and its Supplementary Information and from the corresponding authors upon reasonable request.

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### **Author contributions**

F.B. initiated this project with W.M.N. The manuscript was written by S.H., F.B., and W.M.N. and commented on by all the authors. All gas-binding experiments by  $^1\text{H}$  NMR were conducted by S.H. and F.B. in the laboratories of W.M.N.  $^3\text{He}$  NMR experiments were carried out by R.E.H. and water-suppression NMR experiments were carried out by A.D.S. Quantum-chemical calculations were carried out by N.V., L.Z. and T.H. and the CSM-D ones by T.T.D.

### **Additional information**

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at [www.nature.com/reprints](http://www.nature.com/reprints). Correspondence and requests for materials should be addressed to F.B. and W.M.N. (experiments, general), N.V. and T.H. (DFT), and T.T.D (CSM-D).

### **Competing interests**

The authors declare no competing interests.

## Fig. Captions

Figure 1 | Host **CB5**, noble gas guests, and host-guest complex formation. a, Structural representation of **CB5** and space-filling model of the **CB5**•Kr complex (white, H; blue, N; red, O; cyan, C). b, size comparison of the van der Waals volumes along the noble gas series, c Schematic representation of the binding equilibria of noble gases with **CB5** in the gas phase and in solution with the pertinent free energy designations for the different steps of this Born-Haber cycle, d, schematic representation of the conceptual dissection of the binding process into (i) relocation of the noble gas from bulk water into the **CB5** macrocycle with the associated dispersion free energy difference  $\Delta\Delta G_{\text{disp}}$  and (ii) collapse of the resulting cavity in bulk water with the associated recovery of the cavitation free energy  $\Delta\Delta G_{\text{cavity}}$ , and e, bar graph with the computed individual contributions ( $\Delta\Delta G_{\text{disp}}$ ,  $\Delta\Delta G_{\text{cavity}}$ ) and the calculated *versus* experimental values for  $\Delta G_a$  for the noble gas series (extrapolated value for Rn, see Fig. 2); the errors for the experimental values (see Table 2) would fall within the widths of the data points.

Figure 2 | Experimental data for binding of noble gases to **CB5**. a, truncated structure of **CB5** with proton assignments. b,  $^3\text{He}$  NMR spectral shift of dissolved helium (0.38 mM in  $\text{D}_2\text{O}$ ) upon addition of **CB5** (10 mM). c,  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ) spectra for representative **CB5**-gas binding experiments, namely (i) dissolved  $\text{CH}_4$ , (ii) **CB5** (1.39 mM) in the presence of dissolved  $\text{CH}_4$  (1.45 mM), and (iii) **CB5** (1.39 mM) in the presence of both, dissolved  $\text{CH}_4$  (0.75 mM) and Ar (0.73 mM). d,e, Plots of experimental binding constants (log scale, solid circles) for noble gases with **CB5** vs polarizabilities (d) and atomic volumes (e);  $K_a$  values for Rn (open circles) are linearly extrapolated.

**Table 1** | Association constants ( $K_a$ ) of gases with **CB5**, their packing coefficients ( $PC$ ) in the corresponding inclusion complexes, molecular volumes ( $V$ ), polarizabilities ( $\alpha$ ), and aqueous solubilities ( $S_{\text{gas}}$ ).

gas	$K_a$ ( $\text{M}^{-1}$ )	$V$ ( $\text{\AA}^3$ )	$PC$ (%)	$\alpha$ ( $\text{\AA}^3$ )	$S_{\text{gas}}$ (mM)
He	87±1	12	17	0.21	0.39
Ne	72±1	15	23	0.40	0.46
Ar	360±25	23	34	1.64	1.4
Kr	2390±55	35	51	2.48	2.5
Xe	8700±2100	42	62	4.04	4.3
Rn	[35000±20000]	47	69	5.3	9.3
CH <sub>4</sub>	1610±80	28	42	2.59	1.4
C <sub>2</sub> H <sub>4</sub>	206±11	41	60	4.25	4.8
C <sub>2</sub> H <sub>6</sub>	24.3±0.3	46	67	4.45	1.9
N <sub>2</sub>	430±30	28	42	1.74	1.3

$K_a$  values were determined by  $^1\text{H}$  NMR experiments at 22 °C in  $\text{D}_2\text{O}$  according to eq. 1 with methane as probe and 1.39 mM **CB5**, except for He and Ne, where ethane was used as probe with 16.2 mM **CB5**, and except for the hydrocarbon gases, which were determined directly, see Supplementary Sections 1 and 2. The errors refer to fixed reference  $K_a$  values of 1610  $\text{M}^{-1}$  for methane and 24.3  $\text{M}^{-1}$  for ethane, that is, they consider integration and gas concentration errors only.  $PC$  values were calculated as described in the Supplementary Section 6. Polarizabilities were taken from ref. 39. Solubility in water taken from ref. 40, 41. The  $K_a$  value for Rn was obtained by linear extrapolations, see Fig. 2d,e; it is included as a prediction, since it will eventually become available in laboratories equipped to work with this radioactive element, see ref. 4.



**Table 2 |** Thermodynamics of gas binding to **CB5** in the gas phase<sup>a</sup> calculated from a thermodynamic cycle (Fig. 1c) and by DFT-D3

Gas	$\Delta G_a^{\text{exp } b}$	$\Delta G_{\text{hydr}}^{\text{gas,exp } c}$	$\Delta G_{\text{gas}}^{\text{exp } d}$	$\Delta G_{\text{gas}}^{\text{DFT } e}$
He	-2.6	2.7	<b>0.1</b>	<b>1.8</b>
Ne	-2.5	2.6	<b>0.1</b>	<b>0.5</b>
Ar	-3.5	2.0	<b>-1.5</b>	<b>-1.4</b>
Kr	-4.6	1.6	<b>-3.0</b>	<b>-3.2</b>
Xe	-5.4	1.3	<b>-4.1</b>	<b>-4.9</b>
Rn	[-6.2]	0.9	<b>-5.3</b>	<b>-6.6</b>
CH <sub>4</sub>	-4.4	2.0	<b>-2.4</b>	<b>-2.3</b>
C <sub>2</sub> H <sub>6</sub>	-1.9	1.8	<b>-0.1</b>	<b>0.4</b>

<sup>a</sup> In kcal mol<sup>-1</sup>. <sup>b</sup>  $\Delta G_a^{\text{exp}} = -RT \ln K_a$ , with  $K_a$  values from Table 1 (extrapolated value for Rn); errors  $\pm 0.1$ , except Xe ( $\pm 0.2$ ). <sup>c</sup> From Supplementary Table 8. <sup>d</sup> The experimental free binding energy in the gas phase was calculated from two experimental values via  $\Delta G_{\text{gas}}^{\text{exp}} = \Delta G_{\text{hydr}}^{\text{gas,exp}} + \Delta G_a^{\text{exp}}$ . <sup>e</sup> DFT-D3 values from Supplementary Table 3.

**Table 3 |** Dispersion electronic energies and free energies of gases immersed in water and complexed inside **CB5**, all in kcal mol<sup>-1</sup>.

Gas	$\Delta E_{\text{disp}}^{\text{H2O}}$	$\Delta E_{\text{disp}}^{\text{CB5}}$	$\Delta\Delta E_{\text{disp}}$	$\Delta G_{\text{disp}}^{\text{H2O}}$	$\Delta G_{\text{disp}}^{\text{CB5}}$	$\Delta\Delta G_{\text{disp}}$
He	-2.0	-1.2	<b>0.8</b>	-1.6	1.8	<b>3.4</b>
Ne	-3.6	-2.5	<b>1.1</b>	-2.9	0.5	<b>3.4</b>
Ar	-8.3	-6.4	<b>1.9</b>	-6.7	-1.4	<b>5.3</b>
Kr	-9.8	-8.4	<b>1.4</b>	-8.0	-3.2	<b>4.8</b>
Xe	-12.2	-10.1	<b>2.2</b>	-10.0	-4.9	<b>5.1</b>
Rn	-13.9	-12.3	<b>1.6</b>	-11.3	-6.6	<b>4.7</b>
CH <sub>4</sub>	-11.1	-9.4	<b>1.7</b>	-9.0	-2.3	<b>6.7</b>
C <sub>2</sub> H <sub>6</sub>	-14.9	-9.7	<b>5.2</b>	-12.2	0.4	<b>12.6</b>

Thermodynamic quantities in H<sub>2</sub>O were determined by CSM-D (taking  $\Delta E_{\text{disp}}^{\text{H2O}} = \Delta H_{\text{disp}}^{\text{H2O}}$ ) and those inside **CB5** by DFT-D3 calculations in the gas phase, see Supplementary Tables 3 and 7.  $\Delta\Delta E_{\text{disp}} = \Delta E_{\text{disp}}^{\text{CB5}} - \Delta E_{\text{disp}}^{\text{H2O}}$ .  $\Delta\Delta G_{\text{disp}} = \Delta G_{\text{disp}}^{\text{CB5}} - \Delta G_{\text{disp}}^{\text{H2O}}$ .

**Table 4 |** Calculated differential cavitation and dispersion free energy components in the binding of gases to **CB5** and calculated as well as experimental complexation free energies, all in kcal mol<sup>-1</sup>.

Gas	$\Delta\Delta G_{\text{disp}}$	$\Delta\Delta G_{\text{cavity}}$	$\Delta G_{\text{a}}^{\text{calc}}$	$\Delta G_{\text{a}}^{\text{exp}}$
He	3.4	-5.1	<b>-1.7</b>	<b>-2.6</b>
Ne	3.4	-5.7	<b>-2.3</b>	<b>-2.5</b>
Ar	5.3	-7.8	<b>-2.5</b>	<b>-3.5</b>
Kr	4.8	-9.0	<b>-4.2</b>	<b>-4.6</b>
Xe	5.1	-10.2	<b>-5.1</b>	<b>-5.4</b>
Rn	4.7	-10.9	<b>-6.2</b>	<b>[-6.2]</b>
CH <sub>4</sub>	6.7	-8.8	<b>-2.1</b>	<b>-4.4</b>
C <sub>2</sub> H <sub>6</sub>	12.6	-11.3	<b>1.3</b>	<b>-1.9</b>

$\Delta\Delta G_{\text{disp}}$  from Table 3.  $\Delta\Delta G_{\text{cavity}}$  values obtained by CSM-D, assuming  $\Delta\Delta G_{\text{cavity}} \approx -\Delta G_{\text{cavity}}^{\text{H}_2\text{O}}$ , see Supplementary Table 7.  $\Delta G_{\text{a}}^{\text{calc}} = \Delta\Delta G_{\text{disp}} + \Delta\Delta G_{\text{cavity}}$ .  $\Delta G_{\text{a}}^{\text{exp}} = -RT \ln K_{\text{a}}$ , with  $K_{\text{a}}$  values from Table 1 (extrapolated value for Rn).





