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Interaction of Xenon with Cucurbit[5]uril in Water

Gaspard Huber,^{*,[a]} François-Xavier Legrand,^[a] Véronique Lewin,^[b] Delphine Baumann,^[b] Marie-Pierre Heck,^[b] and Patrick Berthault^[a]

There is growing interest in the development of molecular containers dedicated to gas trapping in water. Cucurbit[5]uril (CB[5]), the smallest member of a glycoluril macrocycles family (Figure 1), is able to interact with a large array of guest molecules, among which noble gases.^[1] The interaction of cucurbit[6]uril (CB[6]) with xenon, a promising noble gas for molecular imaging applications,^[2] was investigated in aqueous solution containing acids or salts designed to increase the solubility of the host molecule.^[3] However, it was shown that cations inter-

act with the partial charges on oxygen atoms,^[1] while apolar molecules are encapsulated in the hydrophobic cavity of cucurbiturils.^[4] We already evidenced that the presence of these acids or salts alters the xenon in/out exchange for CB[6] (Figure S1 of the Supporting Information), confirming results obtained with CB*[6] (Figure 1a).^[5] In the literature, observation of xenon binding by cucurbituril derivatives in pure water was previously rendered possible only by grafting substituents, giving MeCB[5]^[6] and CB*[6]^[5] (Figure 1a). In order to understand the thermodynamics and kinetics of xenon binding in CB[5], it seemed thus useful to study samples in deionized water. Although xenon binding in a crystalline form of native CB[5] was observed,^[4] no quantitative kinetics and thermodynamics data were reported for CB[5] or a derivative in aqueous solution. Herein, taking advantage of a solubility not so low in pure water,^[7] we show that CB[5] spontaneously incorporates xenon at 316 K with a quite high binding constant and a low in/out exchange rate. This exchange rate is even measurable at 293 K.

In the presence of xenon, the ¹H NMR spectrum of a D₂O solution of CB[5] exhibits two series of signals characteristic of a slow exchange between two environments, one with and the other without xenon (Figure 1c). The ¹²⁹Xe spectrum shows two signals (Figure 1d) also denoting a slow exchange. The signal at 196 ppm is assigned to free xenon in water and the signal at 225 ppm to xenon encapsulated in CB[5] (Xe@CB[5]), at a chemical shift close to that already observed in a crystal form of the molecule.^[4] The second signal exhibits a linear dependence of chemical shift with temperature between 277 and 334 K, with a slope of 117 ± 3 ppb K⁻¹ (Figure S2, Supporting Information). This may easily be explained by a deeper exploration of the CB[5] cavity by xenon in areas affected by the magnetic anisotropy effect of the carbonyl groups at higher temperatures.

The xenon in/out exchange is also slow on the xenon longitudinal relaxation (*T*₁) timescale. The *T*₁ value of trapped ¹²⁹Xe increases from 15 ± 3 s to 28 ± 5 s when temperature varies from 277 K to 315 K. The rather long *T*₁ confirms previous results on CB*[6]^[5] and reflects the weakness of the proton–xenon dipolar interaction in a system where protons point outwards. The observed *T*₁ value cannot be entirely explained by this mechanism, and other relaxation mechanisms such as chemical shift modulation must also be efficient.

To our knowledge, CB[5] is the first example of a host molecule with which the xenon in/out exchange is slow on the relaxation timescale. This kinetics was characterized in more detail through gas-release experiments. Proton NMR spectra were recorded at repeated time intervals, in a situation where dissolved xenon tends to equilibrate with gaseous xenon.

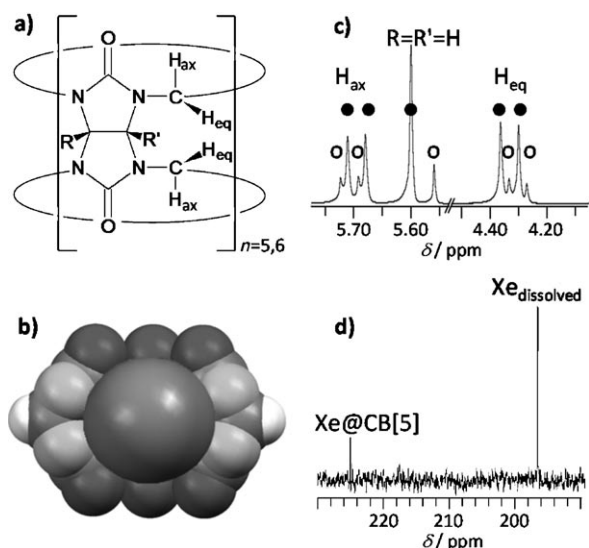


Figure 1. a) General formula of the cucurbiturils cited in the text. CB[5]: $n = 5$, $R = R' = H$; CB[6]: $n = 6$, $R = R' = H$. MeCB[5]: $n = 5$, $R = R' = CH_3$; CB*[6]: $n = 6$, $RR' = (CH_2)_6$. b) Space-fill representation of a crystal structure of CB[5],^[4] with both facing glycoluril units and attached methylene groups removed for clarity. A xenon atom is superimposed in the center of the molecule showing the geometry of the complex. c) ¹H NMR spectrum of a 5.4 mM solution in D₂O of CB[5] under 2.5 atm of xenon at 316 K. Signals assigned to CB[5] entrapping a xenon atom are denoted by ●, while those standing for xenon-free cages are denoted by ○. d) ¹²⁹Xe NMR spectrum of a 0.25 mM D₂O solution of CB[5] under 6 atm of xenon at 316 K at thermodynamic equilibrium, 20 500 scans with a repetition rate of 3.8 s, Fourier transformed with a 6 Hz line broadening.

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Table 1. Kinetics and thermodynamics values of the xenon–CB[5] binding obtained from the gas-release experiment at 316 K as a function of experimental conditions.

Exp. number	1	2	3
[CB[5]] _{total} (mM)	0.25	4.30	5.40
[Xe@CB[5]] _{t=0} ^[a] (mM)	0.23	4.09	4.87
P Xe _{t=0} ^[b] (atm)	0	1	0
k_{in} ^[c] (h ⁻¹ M ⁻¹)	94 (57–123)	105 (56–144)	168 (136–228)
k_{out} ^[d] (10 ⁻³ h ⁻¹)	84 (73–94)	68 (56–91)	127 (102–154)
K ^[e] (M ⁻¹)	1120 (800–1350)	1540 (950–1600)	1320 (1250–1500)

[a] Concentration of CB[5] hosting a xenon atom at $t=0$. This concentration decreases in the course of all experiments. [b] Xenon pressure at $t=0$. [c] Elemental kinetic constant of xenon encapsulation. [d] Elemental kinetic constant of xenon release. [e] Binding constant calculated from the ratio k_{in}/k_{out} . As k_{in} and k_{out} are highly correlated in the fit procedure, the resulting binding constant is quite precisely known. Estimate of experimental errors are in parenthesis.

Then, elemental kinetic constants of xenon encapsulation (k_{in}) and release (k_{out}) were fitted from a model (see the Experimental Section for more details). The binding constant K was deduced from the k_{in}/k_{out} ratio. The results are reported for various CB[5] concentrations in Table 1 and illustrated in Figure 2. For experiment 2, the binding constant value has also been confirmed from ^1H and ^{129}Xe spectra, after the thermodynamic equilibrium has been reached. The obtained value, 1250 M⁻¹ at 316 K agrees with the value extracted from the gas-release experiment.

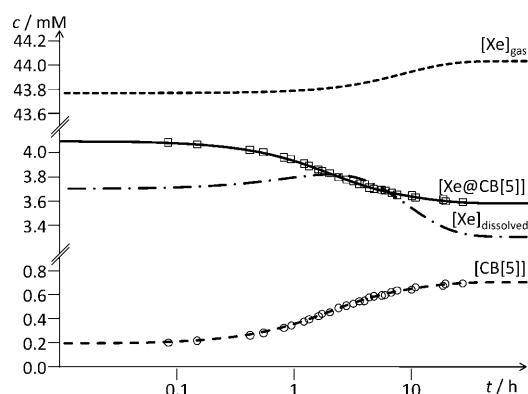


Figure 2. Concentrations of CB[5] (○) and Xe@CB[5] (□) deduced from the ^1H spectra, as a function of time in a gas-release experiment. In this experiment, the xenon pressure was decreased from 6 to 1 atm and the NMR tube was shaken. It corresponds to experiment 2 in Table 1. The curves represent the concentration of each species in the tube, according to the 1:1 model described in the Experimental Section.

Contrary to k_{out} , k_{in} slightly increases with CB[5] concentration (Table 1). Therefore, a mechanism in which a second CB[5] molecule is involved in the binding kinetics by pushing a xenon atom in another CB[5] molecule cannot be excluded as an additional mechanism. Miyahara and co-workers^[6] hypothesized the intervention of water molecules in the xenon binding of MeCB[5], after they observed that the noble gas was not bound in the solid phase, but in water at 353 K. In our case, the existence of a minor influence of a second CB[5] molecule is supported by another observation. In the course of the gas-

release experiment, the bound xenon chemical shift decreases linearly with the proportion of CB[5] cages filled with a xenon atom (Figure S3). As a very slow exchange has a fully negligible influence on chemical shifts, this observation proves that the environment of the Xe@CB[5] complex changes in the course of the kinetics. A reasonable explanation is that the CB[5] molecules interact with each other, in a different way depending on whether they bind or not a xenon atom, inducing the observed chemical shift variations.

Playing with the dependence of xenon solubility with temperature, another experiment has been performed, where a 4.3 mM solution of CB[5] equilibrated with 1 atm xenon was subjected to a sudden decrease in temperature, from 316 K to 293 K. From the model, k_{in} and k_{out} were evaluated to 9.0 h⁻¹ M⁻¹ (lower and upper limits of 7.7 and 19.0 h⁻¹ M⁻¹, respectively) and 2.1 × 10⁻³ h⁻¹ (between 1.5 and 5.3 × 10⁻³ h⁻¹), respectively. k_{out} decreases more than k_{in} when temperature decreases, leading to a binding constant of 4200 ± 1000 M⁻¹ at 293 K, a value higher than that at 316 K. As a matter of comparison, k_{out} was measured from the encapsulated xenon signal line width, for a saturated solution of CB[6] under atmospheric pressure of hyperpolarized xenon at 316 K (Figure S4, Supporting Information). A value of 3 × 10⁷ h⁻¹ was found, more than 10⁸ times higher than when CB[5] is concerned. This obviously comes from the available space left at the level of the oxygen atoms, defining the portals, smaller for CB[5] (2.4 Å) than for CB[6] (3.9 Å).^[7a] Xenon, with a van der Waals diameter of 4.3 Å, is only slightly impeded in encapsulation and release in CB[6] but much more in CB[5]. Moreover, the high rigidity of cucurbiturils, demonstrated in a recent molecular dynamics simulation in CB[6],^[8] strongly lowers the probability for xenon to pass through the portals when they are much smaller than its diameter. This effects is far less sensitive in cryptophanes, another family of cage molecules subjected to higher internal dynamics.^[9] For CB[5], the xenon binding constant, not significantly affected by the host concentration, decreases with temperature. At room temperature, it is higher than those reported for a CB*[6]^[5] and constitutes the highest xenon–cucurbituril binding constant ever reported.

Hyperpolarized xenon experiments also give some clues on the xenon–CB[5] interaction. The one-scan ^{129}Xe spectrum in a 0.25 mM solution of CB[5] at 316 K and under 1 atm of xenon displays only one signal assigned to free xenon in solution (Figure S5, Supporting Information), despite a signal-to-noise ratio of 10 000. The absence of a second signal is expected, since k_{in} is lower than xenon relaxation. Interestingly, the 660 s T_1 value is similar to that of xenon in pure D₂O. This indicates that there is no strong superficial site of CB[5] where xenon is

stabilized a time (more than 1 ns) sufficient to induce significant dipolar relaxation with protons of CB[5].

In conclusion, xenon is spontaneously but slowly trapped by CB[5] even at room temperature. The high dependence of the exchange kinetics with temperature denotes a high enthalpy of the transition state, which is related to the high rigidity of the CB[5] structure. One can take advantage of the high sensitivity of the xenon release rate to temperature to entrap the noble gas in solution at high temperature and to keep it there while quickly cooling the solution. Comparison of in/out exchange kinetics of xenon in CB[5] and CB[6] points out the crucial importance of the portal size of cucurbiturils. Thus, the synthesis of new cucurbiturils with slightly different portal sizes would constitute a strategy for selective encapsulation of gases of economical or ecological interest, such as methane or radon.

Experimental Section

CB[5] and CB[6] were purchased from Sigma Aldrich. Xenon 86% enriched in isotope 129 was purchased from Cortecnet, France. Spectra were acquired on a Bruker Avance DRX500 spectrometer equipped with an inverse broad band probehead with z-gradient. The ^{129}Xe spectra were referenced to the signal of gaseous xenon at 0 ppm. The ^1H spectra were referenced to the HDO signal at 4.572 ppm at 316 K.

Solutions of CB[5] (0.25–5.4 mM) in D_2O were prepared and placed into 5 mm NMR tubes of known volume equipped with Teflon valves from Young Scientific Glassware Ltd. These solutions were thoroughly degassed through successive freeze–pump–thaw cycles. Only for the hyperpolarized xenon experiments, xenon was polarized by optical pumping, using the spin-exchange method through our home-built apparatus.^[10] For thermally polarized xenon and related proton experiments, a known quantity of gas was added into the NMR tube. After a vigorous shaking of the tube at the target temperature, series of ^1H were recorded during the equilibrium phase of the species.

For experiments at 316 K (Table 1), the most accurate results were obtained by starting from a sample containing xenon at several atmospheres and stored few days at the target temperature. Then xenon was quickly evacuated from the tube until it was at a known pressure, and ^1H NMR spectra were recorded at time intervals. Given the low xenon in/out rates, the concentrations were considered constant during the acquisition of a spectrum. The signals of the equatorial protons (R and R' in Figure 1a) were chosen for the integration procedure. Then, these concentrations were fitted according to Equations (1)–(4), assuming a 1:1 complex between xenon and CB[5]:



where Xe_d and Xe_g are, respectively, water-dissolved and gas-phase xenon, k_in , k_out , k_e and k_d are rate coefficients of elemental kinetic equations of respectively xenon encapsulating (k_enc) or releasing (k_rel) from CB[5] cavity, evaporating (k_ev) or dissolving (k_dis). k_e end

k_d should verify $s = k_\text{d}/k_\text{e}$, where s is the solubility of xenon in water at a given temperature,^[11] assumed to be negligibly modified by the presence of CB[5], as it is observed in the presence of millimolar concentrations of salts.^[3] For each experiment, six parameters were fitted using the Solver macro of Excel 2007, namely $[\text{Xe}_\text{d}]$, $[\text{Xe}_\text{g}]$, $[\text{CB}[5]]$ at $t = 0$, k_in , k_out and k_e . Experimental errors on k_in and k_out were estimated by finding values that double the sum of the square of the differences between experimental data and those obtained from the fit while optimizing the five other parameters.

The binding constants K were obtained by using two methods. In the first one they resulted from the fitting of proton kinetics data, as $K = k_\text{in}/k_\text{out}$. The second came from the analysis of proton and xenon spectra recorded at equilibrium. The ^{129}Xe spectra were acquired in non-quantitative conditions, so the peak area values were corrected from the T_1 measured from the inversion–reconversion method for $\text{Xe@CB}[5]$ for 5.4 mM CB[5] concentration and by the monitoring of the hyperpolarized signal after small flip angle pulses for dissolved xenon. The ^1H spectrum gave the ratio $\alpha = [\text{Xe@CB}[5]]/[\text{CB}[5]]$. The ^{129}Xe spectrum gave the ratio $\beta = [\text{Xe@CB}[5]]/[\text{Xe}_\text{d}]$. The knowledge of the total concentration of CB[5], $[\text{CB}[5]]_\text{t}$ gave K by using $K = \beta(1 + \alpha)/[\text{CB}[5]]_\text{t}$.

A suspension of CB[6] (0.6 mg) in D_2O (1 mL) was filtered to give a saturated solution. A hyperpolarized xenon spectrum recorded on this solution was recorded at 316 K under a xenon pressure of 1 atm. A slow exchange on the xenon chemical shift time scale is observed (Figure S4). The k_out value of xenon bound to CB[6] was obtained from the line width of its characteristic signal.

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Keywords: cucurbiturils • host–guest systems • kinetics • NMR spectroscopy • xenon

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