

NMR Investigation of the complexation of neutral guests by cucurbituril

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The effect of acidity on the stability of the complexes of neutral guests with cucurbituril (CB), a synthetic receptor, in aqueous Na₂SO₄ solutions is investigated by ¹²⁹Xe, ¹⁹F and ¹H NMR spectroscopy. The apparent affinity constants of THF and xenon for CB were measured and found to be independent of the pH of the solution. It was also observed that small acids, such as TFA, in their undissociated form can be encapsulated inside the CB cavity. The apparent association constants of THF, Xe and TFA for CB are estimated to be around 1700 M⁻¹, 210 M⁻¹ and 11 M⁻¹, respectively.

Introduction

Cucurbituril (CB) is a macrocyclic cavitand with a hollow core of approximately 5.5 Å diameter in which small molecules can be encapsulated (Fig. 1).^{1,2} The hydrophobic cavity is accessible from the exterior through two carbonyl fringed portals of 4 Å diameter. Its easy synthesis and rigid structure with a hollow core make CB an attractive synthetic receptor. Its host-guest chemistry has however only been studied in strongly acidic aqueous solutions due to its extremely poor solubility in virtually all other solvents. Furthermore, most work has been devoted to the complexation of aliphatic and aromatic ammonium ions which show exceptional affinity towards the receptor. Conclusive evidence for the formation of 1 : 1 complexes with internal complexation of the alkyl or aryl moiety has been obtained from NMR,³ UV spectroscopy⁴ and calorimetric data.⁵ The successful inclusion is attributed to the hydrophobic forces which lead the hydrophobic alkyl or aryl moiety to enter the cavity. The stabilization of the complex is also attributed to the attraction between the cationic head of the ions and the dipoles associated with the carbonyl groups at the portals of cucurbituril. The reported association constants for these ammonium compounds range between 10² and 10⁶ M⁻¹. To our knowledge the only quantitative data reported in the literature regarding the complexation of neutral guests by CB dissolved in acidic aqueous solutions are the work of Buschmann *et al.*,⁶ who recently studied, by calorimetry, the formation of complexes between CB and aliphatic alcohols, acids and nitriles. They reported affinity constants ranging between 200 and 600 M⁻¹.

In recent communications one of us (K. K.) reported that CB dissolves in neutral aqueous solutions in the presence of alkali metal ions.^{7,8} Under these conditions, simple organic molecules such as tetrahydrofuran (THF), cyclopentanone, furan and benzene form stable 1 : 1 host-guest complexes with CB and the affinity constants range between 250 and 8000 M⁻¹. The X-ray structure of CB crystallized from Na₂SO₄ solutions reveals that two sodium ions are coordinated to each portal. These ions

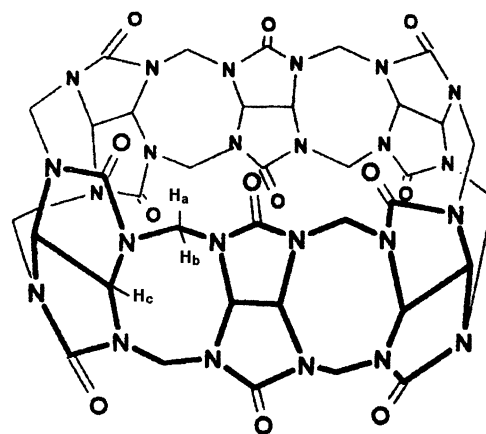


Fig. 1 Structure of cucurbituril (CB) and proton labeling.

along with their coordination water molecules cover each portal of CB like a 'lid on a barrel'. These lids are still present when a neutral guest is encapsulated in the CB cavity. The addition of trifluoroacetic acid (TFA) leads to the release of the encapsulated neutral guest molecules from CB. This phenomenon was tentatively interpreted as being due to the removal of the alkali ion 'lids' by protonation of the carbonyl oxygens under the acidic conditions, thereby permitting the release of the encapsulated guest molecules.⁷

We recently studied by ¹H and ¹²⁹Xe NMR spectroscopy the complexation of CB with what can be considered as the ultimate neutral guest, monoatomic xenon (in aqueous solutions in the presence of sodium ions).⁹ The data clearly show that Xe is reversibly trapped in the cavity to form a 1 : 1 host-guest complex ($K = 210 \pm 15 \text{ M}^{-1}$). Interestingly, the stability of this complex, which cannot be due to H-bonding, electrostatic interactions or charge transfers, is comparable to that of CB complexes with certain aryl- and alkyl-ammonium ions. This study clearly illustrated the role of London dispersive energies in the stabilization of the CB-guest complex. We also

concluded that when xenon is the guest, it is possible that an exchange process corresponding to the displacement of xenon by xenon also takes place ($\text{CB-Xe} + \text{Xe}^* \rightleftharpoons \text{CB-Xe}^* + \text{Xe}$).

In this paper we report the results from our comprehensive study of the effect of acidity on the complexation of neutral guest molecules by CB. The present results indicate that the explanation that was previously given regarding the freeing of neutral guest from the CB cavity in the presence of acids is not correct.

Results and discussion

^1H NMR spectra were recorded at 298 K for CB solutions containing tetrahydrofuran (THF) in 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ at different pH. D_2SO_4 and NaOD were used to adjust the pH of these solutions ensuring this way that no new species were introduced into the system. The data clearly show, as previously reported,⁷ that THF is complexed by CB but here we observe that the THF complexation affinity is not affected by the acidity of the solution. THF exchange is slow on the ^1H chemical shift timescale at all pH and two sets of signals are observed for both the CB and the THF protons. Integration of these signals yields an affinity constant which is independent of the pH ($1700 \pm 30 \text{ M}^{-1}$). As mentioned in the introduction, in a previous study,⁷ it was observed that when trifluoroacetic acid (TFA) was used to acidify the solutions THF decomplexation occurred as evidenced by the fact that the ^1H NMR signals for the encapsulated THF decreased while those for the free THF increased. The results described here suggest that even if the alkali ion 'lids' of CB are, as previously suggested, removed following the protonation of the portal carbonyl oxygens, this does not influence the stability of the CB-THF complex.

Rebek and co-workers have reported the acid-base control of the encapsulation of guests by a host system in solution.¹⁰ However, in their case the host is a self-assembling dimer which owes its existence to hydrogen-bonding between the two subunits. The hydrogen bonding information needed for the correct assembly is built into the edges of the monomeric subunits and it is easily conceivable that when the groups involved in the H-bonding are protonated the host as such no longer exists and complexed molecules are freed.

It is also possible that with CB, the decomplexation of THF is the result of the competition between THF and TFA for the CB cavity. To monitor the eventual complexation of TFA, ^1H and ^{19}F NMR spectra were recorded for a CB solution ($\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$) containing increasing amounts of TFA. The ^1H NMR spectra exhibit two sets of signals for the CB protons (Fig. 2). The intensity of one set decreases with TFA concentration while the intensity of the other set increases. This suggests that the first set corresponds to the protons of the CB molecules which have not complexed TFA ('empty CB') and the second set to the protons of the CB molecules containing TFA in their cavity. TFA complexation was confirmed by ^{19}F NMR spectroscopy. The ^{19}F spectra of the CB-TFA solutions exhibit an additional signal compared to the ^{19}F spectrum of a TFA solution where only a large signal with its ^{13}C satellites is observed (Fig. 3). The intensity of this additional signal varies with TFA concentration.

TFA complexation is slow on both the ^1H and ^{19}F NMR chemical shift timescales. Assuming that CB forms a 1 : 1 complex with TFA, the concentration of complexed TFA can be obtained from integration in either the ^1H or the ^{19}F NMR spectra (using in the case of ^{19}F one of the ^{13}C satellites of the uncomplexed TFA signal as an internal reference). The ratio of complexed TFA concentration to total CB concentration in solution ($[\text{CB-TFA}]/[\text{CB}]_0$), obtained from integration in the ^{19}F spectra, is plotted in (Fig. 4, curve a) as a function of the ratio of total TFA concentration to total CB concentration ($[\text{TFA}]_0/[\text{CB}]_0$). This curve has a distinct sigmoidal shape which could reflect the fact that negatively charged species are not

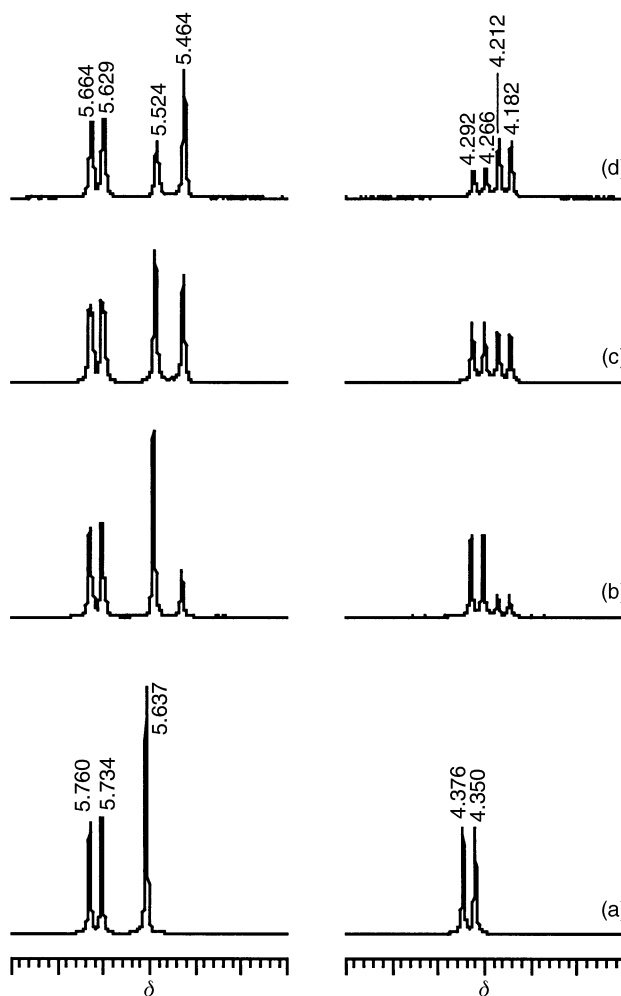


Fig. 2 ^1H NMR spectra at 298 K of a CB solution in 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ with (a) no TFA; (b) $[\text{TFA}]_0/[\text{CB}]_0 = 20$; (c) $[\text{TFA}]_0/[\text{CB}]_0 = 30$; (d) $[\text{TFA}]_0/[\text{CB}]_0 = 40$. The resonance frequencies are slightly affected by the acidity of the solution which increases with the amount of added guest.

complexed by CB and it is only the non-dissociated form of TFA which can be encapsulated inside the CB cavity. This hypothesis is confirmed by the fact that when the solution is acidified with D_2SO_4 and the fraction of non-dissociated TFA increases, the $[\text{CB-TFA}]/[\text{CB}]_0$ ratio increases (Fig. 4, curve b). CB is known to complex cations and these data clearly suggest that it does not complex anions.

It is possible to obtain an expression for the affinity constant of CB for TFA (K) by combining the expression for the acidity constant of TFA (K_a) and the mass balance equations for CB and TFA. The affinity constant is a function of the known quantities K_a ($\text{p}K_a = 0.18$), $[\text{CB}]_0$, $[\text{TFA}]_0$ and the pH and also of the concentration of complexed TFA, which can be obtained from integration in the ^1H or ^{19}F NMR spectra. K was calculated for the solutions corresponding to the data points in (Fig. 4a) and an average value of $11 \pm 2 \text{ M}^{-1}$ was obtained. The apparent affinity constant of CB for TFA is very small and all quantitative data regarding the complexation of TFA by CB must therefore be interpreted with care. Indeed, impurities present in trace amounts in the solution could be efficient competitors of TFA for the CB cavity. The small value for the CB-TFA apparent affinity constant explains why, in the previously reported study,⁷ it was necessary to add large amounts of TFA to the CB-THF systems to achieve complete decomplexation of THF.

The affinity of Xe for CB also does not seem to be affected by the pH of the solution. We recently reported the ^1H and ^{129}Xe NMR study of the complexation of Xe by CB in a 0.2 M

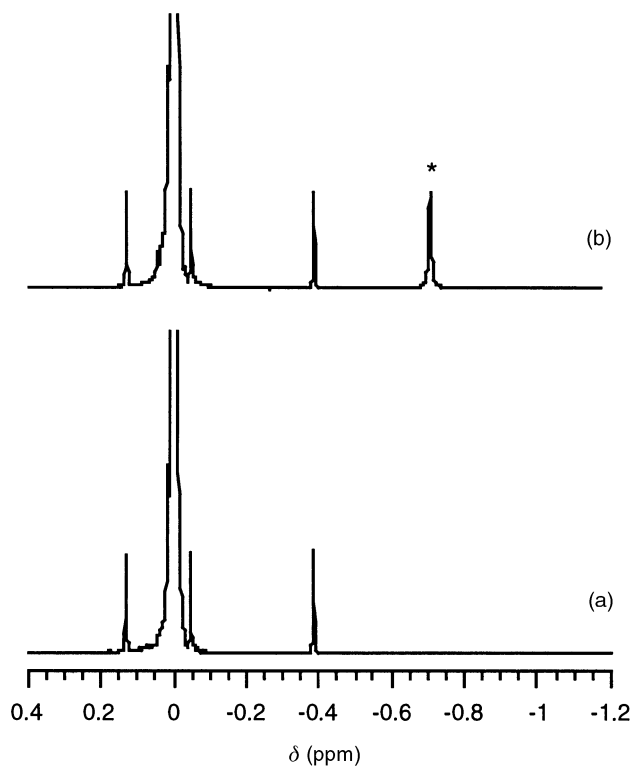


Fig. 3 ^{19}F NMR spectra at 298 K of TFA in (a) 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$; (b) CB solution in 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ with $[\text{TFA}]_0/[\text{CB}]_0 = 40$. The signal with a star corresponds to the complexed TFA.

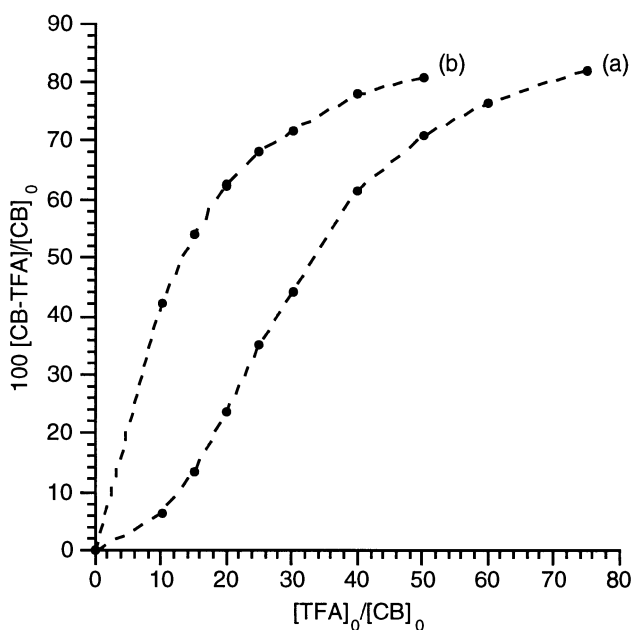


Fig. 4 Variation of $[\text{TFA-CB}]/[\text{CB}]_0$ as a function of $[\text{TFA}]_0/[\text{CB}]_0$ in (a) 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$; (b) 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ with 0.4 M D_2SO_4 . The dashed lines have been added as a visual aid.

$\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ solution.⁹ Xe exchange was observed to be fast on the ^1H NMR chemical shift timescale but it was possible to determine the apparent affinity constant of Xe for CB from the variation of the observed ^1H chemical shifts as a function of xenon concentration. Under more acidic conditions (0.5 M D_2SO_4) the ^1H spectra exhibit, as before, a single set of signals and analysis of the variation of the chemical shifts with xenon concentration (Fig. 5) yields a value of $220 \pm 30 \text{ M}^{-1}$ for the apparent affinity constant which is identical, within experimental error, to the one obtained for the CB-Xe system under less acidic conditions ($210 \pm 15 \text{ M}^{-1}$).

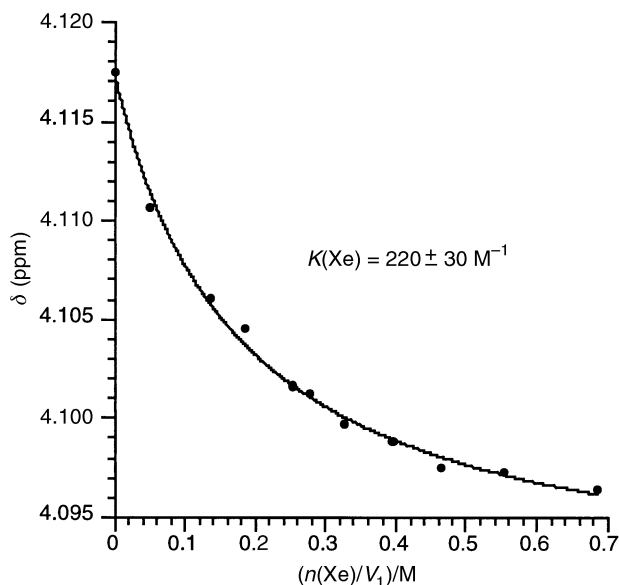


Fig. 5 Variation of the equatorial CB proton chemical shift (δ) as a function of $n(\text{Xe})/V_1$ ($n(\text{Xe})$ is the total number of moles of xenon and V_1 is the volume of the liquid phase in the sealed NMR tube) for CB dissolved in 0.2 M $\text{Na}_2\text{SO}_4\text{-D}_2\text{O}$ with 0.5 M D_2SO_4 . The curve corresponds to the model previously reported.⁹

Contrary to what was previously observed under less acidic conditions,⁹ where two resonance lines are observed in the ^{129}Xe NMR spectrum of the CB-Xe system ($\delta = 190 \text{ ppm}$ for Xe in the solvent, $\delta = 122 \text{ ppm}$ for complexed Xe), the ^{129}Xe NMR spectrum of the CB-Xe system under acidic conditions (0.5 M D_2SO_4) exhibits only one resonance line (linewidth around 50 Hz) which is at the chemical shift of xenon in the solvent (free xenon). Since the ^1H NMR data clearly show that xenon complexation occurs under acidic conditions, the absence of a resonance line for the complexed xenon in the ^{129}Xe NMR spectra could be due to the exchange dynamics. If xenon exchange is fast on the ^{129}Xe NMR chemical shift timescale, a single resonance line is expected at the chemical shift corresponding to the weighted average of the chemical shifts for the free and complexed xenon. With an apparent affinity constant of around 200 M^{-1} and a difference between the chemical shifts of the free and the complexed xenon of around 70 ppm, this chemical shift should however be distinctly different from the chemical shift of the free xenon. It is possible that under these new experimental conditions xenon exchange is still slow on the ^{129}Xe timescale but that the resonance line for the complexed xenon is too broad for the signal to be observed. In our previous study we observed that the linewidth of the resonance corresponding to the complexed xenon increases in a linear manner with the xenon : CB ratio (from around 200 Hz to about 800 Hz) while the linewidth of the resonance line of the uncomplexed xenon remains constant (around 500 Hz). Based on previous work from our laboratory,¹¹ these observations lead us to conclude that an exchange process corresponding to the displacement of xenon by xenon takes place. For such a complex exchange process it is difficult to predict the effects of a small change in the exchange kinetics, especially considering the extreme sensitivity of the xenon NMR parameters to environmental conditions,¹² but it is possible that a small change in rate constants could lead to a significant change in the xenon linewidths. Also, the CB concentration is one order of magnitude smaller in this study than in the previous study (due to the lower solubility of CB in the presence of D_2SO_4) and the linewidths of the complexed xenon are expected to be larger (larger xenon : CB ratios) and of the free xenon narrower. This is indeed what is observed for the latter signal.

In conclusion, our results show that the affinity of guests, such as THF or xenon, for CB dissolved in an aqueous alkaline

salt solution is not influenced by the acidity of the solution. Since it is likely that at low pH the carbonyls at the CB portals are protonated, our results indicate that, contrary to an earlier interpretation, the stability of the host–guest complexes is not affected by the eventual presence of sodium ions coordinated to the carbonyl groups of the host portals.

This study highlights the complexity of the cucurbituril–guest system, even in the case of a simple guest like THF or xenon. In fact, many if not all host–guest systems are much more complex than they appear at first, because it is still extremely difficult to discuss matters quantitatively in terms of non-bonded interactions. Indeed, it is not only the host–guest interactions which must be considered but also the solvent–guest and solvent–host interactions since they are of the same strength as host–guest interactions. If the host and (or) the guest can interact with cations, as in the case discussed here, these additional interactions cannot be neglected. If an acid is added, the complexity of the problem increases because the protonation energies are of the same order of magnitude as the other interactions. Last but not least, since it is the standard free energy which is needed to fully explain a host–guest complexation, it is also necessary to take into account the entropy contributions associated with the various interactions. It is obvious that the knowledge that we possess for the numerous terms is insufficient for us to be able to give a general and exhaustive interpretation of the experimental association constants which, moreover, are apparent constants because empty hosts probably never exist. The only way to contribute to the knowledge of these supramolecular host–guest–solvent systems is to undertake comparative studies. The use of xenon in this context as a ‘spherical, non-polar, inert’ guest allows the exclusion of factors which, *a priori*, could never be ignored with polyatomic guests such as THF.

Experimental

Cucurbituril (CB) was synthesized according to procedures previously described in the literature.¹ Na₂SO₄, D₂SO₄, trifluoroacetic acid (TFA), tetrahydrofuran (THF), D₂O and NaOD were purchased from Aldrich and used without further purification. Xenon gas at natural abundance was purchased from Air Liquide (Belgium).

For the study of THF complexation as a function of pH, 2.5 × 10⁻³ M samples of CB in 0.2 M Na₂SO₄–D₂O with [THF]/[CB] equal to 1 were prepared at different pH. D₂SO₄ and NaOD were used to obtain pH values ranging between 0 and 12. The one-dimensional ¹H NMR spectrum of each sample was recorded at 298 K on a Varian UNITY600 spectrometer. For the study of TFA complexation (pK_a = 0.18), 8 × 10⁻³ M samples of CB in 0.2 M Na₂SO₄–D₂O containing different amounts of TFA were prepared ([TFA]/[CB] ranging between 1 and 100). The ¹H and ¹⁹F NMR spectra of these samples were recorded at 298 K on a Varian UNITY600 spectrometer. D₂SO₄ was then added to each sample (addition of less than 15 µl of pure D₂SO₄ into each 500 µl sample) and the NMR spectra were once again recorded. For the study of xenon complexation by CB in the presence of D₂SO₄, a known volume (approximately 1.5 ml) of a 2.5 × 10⁻³ M CB solution in 0.2 M Na₂SO₄–D₂O and 0.5 M D₂SO₄ was placed in a 10 mm high pressure NMR tube. The solution was then degassed by several freeze–thaw cycles on a vacuum line. Up to 10 atm of xenon gas were condensed into the sample. The total amount of xenon added was known precisely from the difference between the weight of the sample after xenon addition and the weight of

the degassed sample. For each xenon concentration, ¹²⁹Xe and ¹H NMR spectra were recorded at 298 K on a Bruker AMX360 spectrometer.

One-dimensional ¹H NMR spectra were recorded on a Varian UNITY600 spectrometer using a 90° pulse, a 12 s repetition time, a spectral width of 6000 Hz, a minimum of 32 scans and a digital resolution of 0.16 Hz per point after one level of zero filling. On the Bruker AMX360 spectrometer, one-dimensional ¹H spectra were recorded using a 90° pulse, a 10 s repetition time, 64 scans, a spectral width of 1250 Hz and a digital resolution of 0.08 Hz per point after one level of zero filling. The longitudinal relaxation times of all the THF and CB protons were measured and found to be less than 2 s. ¹⁹F NMR spectra were recorded on the Varian UNITY600 spectrometer using a 90° pulse, a 15 s repetition time, a spectral width of 28200 Hz, 64 scans and a digital resolution of 0.25 Hz per point after one level of zero filling. The ¹⁹F chemical shifts are referenced to the ¹⁹F chemical shift of the TFA in the solvent. ¹²⁹Xe spectra were recorded on the Bruker AMX360 spectrometer (nominal frequency 99.64 MHz) with a 30° pulse, a 5 s repetition time, a spectral width of 20 000 Hz and a digital resolution of 0.61 Hz per point. The number of scans recorded varied from spectrum to spectrum so as to obtain reasonable signal-to-noise ratios. The ¹²⁹Xe chemical shifts are referenced to the frequency of pure xenon gas extrapolated to zero pressure.

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