^{129}Xe and ^{1}H NMR Study of the Reversible Trapping of Xenon by Cryptophane-A in Organic Solution

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Abstract: The interaction of xenon with cryptophane-A in 1,1,2,2-tetrachloroethane-d_2 is investigated by ^{129}Xe and ^{1}H NMR spectroscopy. Xenon is reversibly trapped into the cavity of this host to form a 1 to 1 host−guest complex with an apparent association constant K of the order of at least 3×10^3 M^{-1} at 278 K. The exchange between the free and bound xenon is slow on the ^{129}Xe NMR time scale, and the bound xenon resonance is shifted by approximately 160 ppm to lower frequencies with respect to the free xenon resonance. The xenon complex is at least 4 and 20 times more stable, respectively, than the corresponding chloroform and methane complexes under the same conditions. The stability of this xenon complex appears to be much greater than that of the previously described xenon complex of α-cyclodextrin in water. This is probably due to the combination of three favorable effects: (i) good size matching between the guest and the cryptophane cavity in its most relaxed conformation, resulting in the optimization of the London forces between the highly polarizable guest and the electron rich aromatic rings of the host (enthalpic stabilization); (ii) no rotational or vibrational entropy loss of the monatomic guest in the cryptophane cavity; and (iii) no (or little) entropy loss due to reduction of the conformational freedom of the host. Analysis of the line widths of the signals corresponding to the free and bound xenon as a function of the relative xenon/cryptophane ratio suggests that the incoming xenon atom must displace the departing one to enter the cryptophane cavity, and that the empty cryptophane is not involved in the complexation equilibrium.

Introduction

Recent studies of molecular recognition phenomena have demonstrated that the capture of small neutral and apolar guest species by organic hosts, without the help of hydrophobic forces, is a reachable goal. Cram and co-workers[1] have shown that gases such as O_2, N_2, CO_2, and xenon (Xe) can be trapped by hemicarcerands to form complexes which release their guest slowly on heating. They have proposed the term "constrictive binding" to describe the phenomena where the guest must overcome steric constraints imposed by the host portals in order to enter and leave the host. Rebek and co-workers[2] have captured methane, ethylene, and xenon within the cavity of dimeric hosts which self-assemble in chloroform solution by complementary H-bonding. In this case, the capture and release of the guest involves breaking and re-formation of the dimeric host itself. We have previously described a complex between cryptophane-A (CA, Figure 1) and methane[3] and a complex between cryptophane-A and $CHCl_3$.[4] These complexes form readily in $(CDCl_2)_2$ and exhibit association constants of 130 M^{-1} for methane and 230 M^{-1} for $CHCl_3$ at 300 K, 1 atm. We have found similar results with other cryptophanes of the same size which bind guests ranging from methane to butane in organic solvents.[5] In these cryptophanes, the host windows can open wide enough to allow the guest to enter and depart without experiencing the steric constraints which exist in Cram's hemicarcerands, and a reversible exchange is observed between the free and bound guest. These observations are important for several reasons. They show that purely organic, molecular hosts can be designed to bind virtually any kind of chemical

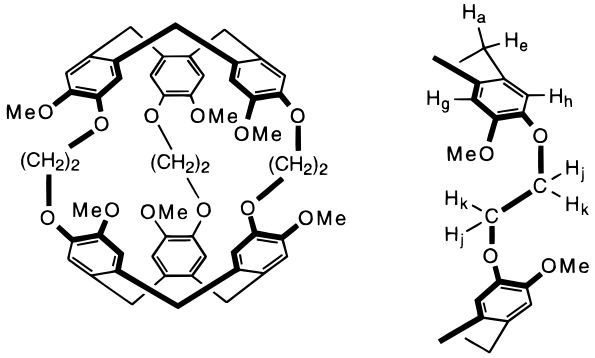

Figure 1. Structure of cryptophane-A and atom labeling.

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species, opening the way to fascinating objectives such as the selective capture of molecular hydrogen and its isotopes, of the noble gases including radon, of small fluorocarbons, etc. They also provide good models for studying host−guest systems which owe their existence solely to van der Waals forces. These forces have long been considered to play a subsidiary role compared to hydrophobic forces and H-bonding in natural or artificial host−guest complexes, and there is certainly a need to clarify some of the current paradigms of this field.

Our present understanding of the complexation properties of these cryptophanes and of related cavitands toward small apolar species is still very limited. Generally speaking, in complexes that form reversibly, the observed equilibrium results from a compromise between host−solvent, guest−solvent, and host−guest interactions, where each of these components can be dissected in a number of ways.[6] For cryptophanes, and particularly in their methane complexes, the relative magnitude of these three contributions is not known very precisely. At a microscopic level, the way in which the guest is bound and released and the associated dynamics of the host itself are important issues, which have been recently addressed by molecular dynamics simulations in the McCammon group.[7,8] These simulations, however, need to be checked against experimental data including association constants, complexation kinetics, and structural information on the host and its complexes, and these data should be complemented with information on the solvent properties.

Our earlier work on cyclodextrins[9] has shown that it is possible, using xenon nuclear magnetic resonance (NMR), to obtain quantitative information concerning complexation. Xenon is a highly polarizable, rather inert but hydrophobic atom, which has a van der Waals radius of approximately 2 Å. Two xenon isotopes are easily accessible to NMR spectroscopy: ^{129}Xe ($I = {}^1/_2$, natural abundance of 26.4%) and ^{131}Xe ($I = {}^3/_2$, 21.2%).[10] The NMR parameters of these isotopes are very sensitive to the environment of the xenon atom, which therefore can be used as a probe of structural and dynamical properties of host−guest complexes in the solid state and in solution.[11]

In the present paper, we report quantitative ^{1}H and ^{129}Xe NMR studies on the reversible binding of xenon to cryptophane-A in $(CDCl_2)_2$. We first focus on the interaction of xenon with the host and then the competition between xenon and chloroform in order to quantify the xenon−cryptophane affinity. The xenon−cryptophane-A complex appears to be much more stable than the chloroform and methane complexes, and is probably the most stable xenon−host complex ever observed in the absence of hydrophobic forces. Finally, we discuss the relative stabilities of these complexes in terms of host−guest interactions and more particularly in terms of the guest occupancy factor, the ordering of the guest in the host cavity, and the flexibility of the host.

Materials and Methods

Cryptophane-A was synthesized according to a previously described procedure.[12] Deuterated 1,1,2,2-tetrachloroethane $(CDCl_2)_2$ was chosen as solvent because it is too big to be accommodated in the cryptophane cavity, and hence is not a good competitor of the presently considered guests. Chloroform and $(CDCl_2)_2$ were purchased from Aldrich and used without further purification; $(CDCl_2)_2$ was dried on molecular sieves. Xenon gas at natural isotope abundance was purchased from Air Liquide.

Samples were prepared at room temperature. Known volumes (approximately 0.5 mL) of solutions of known concentration of cryptophane-A in $(CDCl_2)_2$ (approximately 0.1 M) were placed in 5 mm J. Young valve NMR tubes of known volume (approximately 2.5 mL). Samples were then degassed by several freeze−thaw cycles on a vacuum line with helium gas during the first two cycles in order to displace any other gases complexed by the cryptophane-A. Xenon gas was then added to the sample by condensation. 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 the experiments undertaken as a function of the total amount of xenon, increments of xenon were added by condensation to the same sample. For the competition experiments, chloroform was added to the sample by condensation after the freeze−thaw cycles and prior to the xenon additions. The chloroform to cryptophane-A ratio in the sample was determined by integration in the proton NMR spectra.

^{129}Xe and ^{1}H spectra were recorded on a Varian UNITY 600 spectrometer equipped with a reverse detection triple probe (^{13}C; ^{15}N; ^{1}H). The ^{13}C channel was tuned to the ^{129}Xe frequency (nominal frequency for ^{129}Xe = 165.997 MHz). ^{1}H spectra were recorded at different temperatures with use of a 90° pulse, a 52 s repetition time, and 8 scans. Digital resolution was 0.18 Hz/point after one level of zero filling. ^{129}Xe spectra were recorded at different temperatures with use of a 30° pulse, a 6 s repetition time, and a spectral width of 42 450 Hz. The number of scans recorded varied from spectrum to spectrum so as to obtain good signal-to-noise ratios. Digital resolution was 0.38 Hz/point after one level of zero filling. Spectra were weighted with an exponential line-broadening corresponding to 10% of the natural line width of the narrowest signal. ^{129}Xe chemical shifts are referenced to the resonance frequency of pure xenon gas extrapolated to zero pressure. Chemical shifts and line widths in the xenon spectra were obtained from Lorentzien fitting of the resonance signals. ^{1}H spectra were simulated by using the *PANIC* software package.

Results and Discussion

Proton and Xenon NMR Studies of Cryptophane-A Solutions in $(CDCl_2)_2$. The ^{1}H spectrum, recorded at 278 K, of a freshly prepared approximately 0.1 M solution of cryptophane-A dissolved in $(CDCl_2)_2$ is shown in Figure 2a. The resonance at 6.00 ppm corresponds to the solvent protons (used as internal reference) and the signal at 1.25 ppm is the resonance of H_2O. Figure 2b is the ^{1}H spectrum, recorded at 278 K, of an approximately 0.1 M solution of cryptophane-A dissolved in $(CDCl_2)_2$ which has been thoroughly degassed on a vacuum line. The chemical shifts of the protons of cryptophane-A are essentially identical with those in Figure 2a but the signals are significantly narrower, and the spacer bridge signals exhibit a fine structure. The water signal now appears at 1.02 ppm. The assignment of the cryptophane signals was straightforward. The resonances of the pseudoaxial and equatorial hydrogens of the methylene bridges H_a and H_e are observed in Figure 2b at 4.49 and 3.31 ppm, respectively (J = 13.7 Hz). The aromatic hydrogens (H_g and H_h) are observed at 6.60 and 6.63 ppm. The resonances corresponding to the protons H_j and H_k of the three OCH_2CH_2O spacer bridges linking the two cyclotriveratrylene

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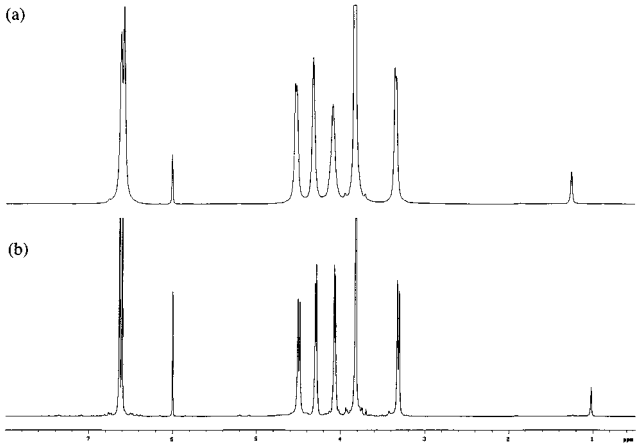

Figure 2. (a) ^{1}H NMR spectrum of a freshly prepared, nondegassed, approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ at 278 K; (b) spectrum of a degassed sample under the same conditions.

subunits, which will be of interest in the present study, are seen at 4.06 and 4.29 ppm. In the presence of an excess of xenon, the spectrum is similar to that of Figure 2b except for the water signal, which has moved to 2.05 ppm. The above observations suggest that water, nitrogen, oxygen, and possibly other impurities of small size present in the freshly prepared solution (coming from the solvent or already present in the cavity of the cryptophane-A molecules in the solid state) are complexed by cryptophane-A. The superposition of the slightly different spectra of these complexes, exchange processes, and the paramagnetic effects of oxygen could explain the broader signals in the freshly dissolved solution. The possibility of competition between these impurities and a particular guest that is being studied has to be kept in mind. For the following studies, all solutions were therefore degassed on a vacuum line by several freeze−thaw cycles with use of helium gas. At this stage, it is worth noting that for the preparation of the cryptophane-A solutions, the molecular weight of empty cryptophane-A (MW = 895.02) was used even though the possibility of preexisting guests in solid-state cryptophane-A cannot be ruled out. If oxygen and nitrogen from air are present at the extent of one molecule per cavity, this will cause an error of less than 3.5% on the cryptophane concentration.

^{129}Xe NMR spectra of xenon dissolved in pure $(CDCl_2)_2$ were recorded, at 278 K, for various xenon concentrations corresponding to equilibrium xenon pressures of maximum 5 atm. These spectra exhibit a single sharp resonance line whose chemical shift and line width are independent of the xenon pressure (229.5 ppm and 3 Hz, respectively; Figure 3a). ^{129}Xe spectra of an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ containing increasing amounts of xenon were recorded at 278 K. At first the spectrum exhibits a single resonance line at 62.3 ppm (Figure 3b). As the amount of xenon is increased, a second resonance line appears at the expected position for xenon in the solvent (Figure 3c). The most likely explanation for these observations is that encapsulation of xenon in the cryptophane-A cavity occurs and that the exchange process is sufficiently slow to see the NMR resonance lines corresponding to the bound and to the free xenon. The long T_1 relaxation time of dissolved ^{129}Xe and expected differences in the T_1 of the free and the bound xenon make it extremely difficult to determine, from integration of the ^{129}Xe NMR signals, the analytical concentration of xenon in the cryptophane solutions and the ratio of bound to free xenon. The characteristics of the NMR spectra obtained for increasing amounts of xenon are therefore reported in terms of the ratio *n*Xe/*n*CA

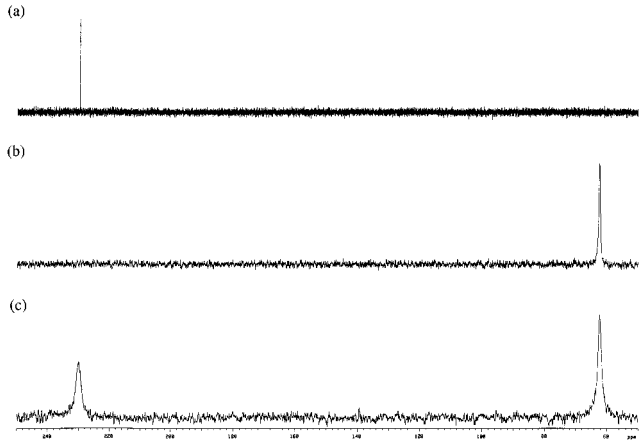

Figure 3. (a) ^{129}Xe NMR spectrum of xenon dissolved in $(CDCl_2)_2$ at 278 K. (b) ^{129}Xe NMR spectrum of xenon dissolved in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ at 278 K (*n*Xe/*n*CA = 0.46). (c) ^{129}Xe NMR spectrum of xenon dissolved in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ at 278 K (*n*Xe/*n*CA = 2.12).

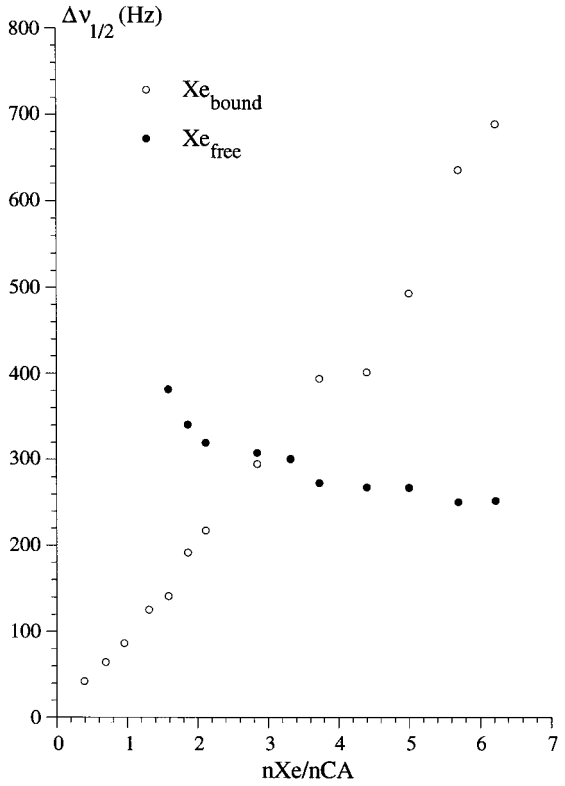

Figure 4. Line width at half-height, displayed as a function of the *n*Xe/*n*CA ratio, of the ^{129}Xe NMR signals of the bound (○) and the free (●) xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ at 278 K.

where *n*Xe is the total number of moles of xenon added to the sealed NMR tube and *n*CA is the number of moles of cryptophane-A in the solution. The possible relation between this value and the analytical concentration of xenon in solution is discussed later.

The evolution of the line widths of the observed xenon resonance lines are shown, in Figure 4, as a function of the *n*Xe/*n*CA ratio. The line width of the bound xenon increases with increasing *n*Xe/*n*CA ratios and extreme broadening causes the resonance line to disappear. The line width of the free xenon decreases with increasing *n*Xe/*n*CA ratios and seems to reach a constant value of approximately 250 Hz. A small decrease

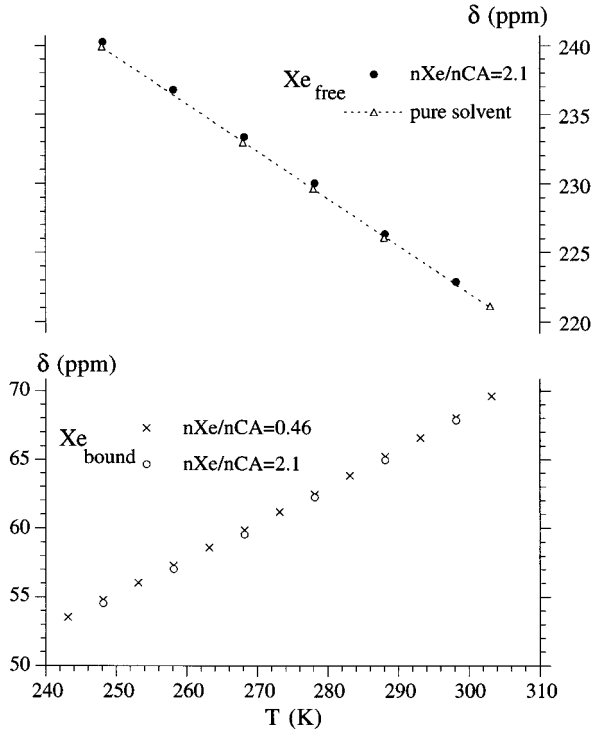

Figure 5. ^{129}Xe NMR chemical shift displayed as a function of temperature of (Δ) xenon dissolved in $(CDCl_2)_2$, (●) free xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 2.12), (○) bound xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 2.12), and (×) bound xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 0.46).

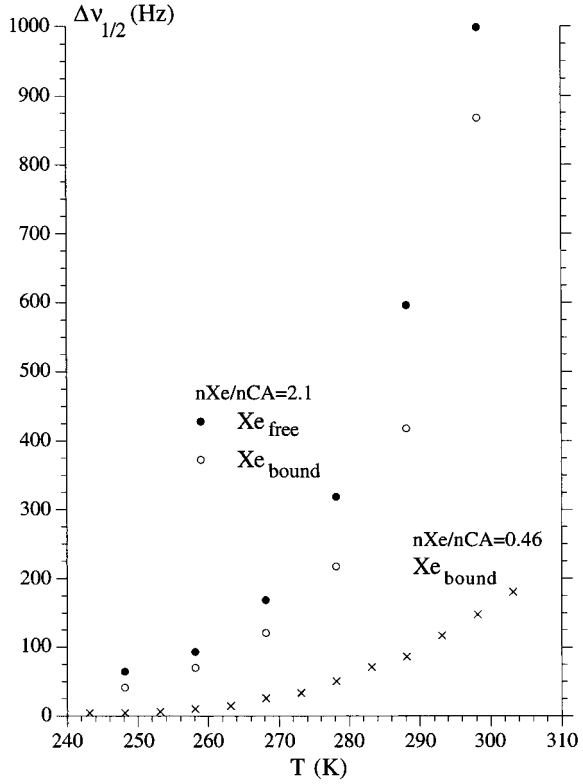

Figure 6. Line width at half-height, displayed as a function of temperature, of the ^{129}Xe NMR signals corresponding to (●) free xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 2.12); (o) bound xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 2.12), and (×) bound xenon in an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ (*n*Xe/*n*CA = 0.46).

in the chemical shift of the bound xenon is observed (less than 0.2 ppm) for *n*Xe/*n*CA ratios in the range 0 to 1 (results not shown). For *n*Xe/*n*CA ratios larger than 1, the chemical shift of the bound and of the free xenon is essentially constant (variations are of the same order of magnitude as the variation due to experimental errors).

^{129}Xe spectra were recorded at various temperatures, ranging between 253 and 303 K, for samples with a *n*Xe/*n*CA ratio of approximately 0.5 and 2.0. For the complete range of temperatures studied, both resonance lines are observed for the sample with the higher *n*Xe/*n*CA ratio while only the resonance line corresponding to the bound xenon is observed for the sample with the smaller ratio. The chemical shifts and line widths for these samples are shown, in Figures 5 and 6, as a function of temperature. The temperature dependence of the xenon chemical shift in the pure solvent is also shown in Figure 5. The chemical shift of the resonance corresponding to the free xenon (sample with *n*Xe/*n*CA ≈ 2) increases linearly as the temperature decreases as does the chemical shift of xenon in the pure solvent. For the bound xenon, the chemical shift in both samples decreases as the temperature decreases. These variations in chemical shift cannot be due to a change in the xenon concentration resulting from variation in solubility with temperature since, as mentioned previously, the ^{129}Xe chemical shift of both bound and free xenon and of xenon in the pure solvent is essentially independent of xenon concentration. The line widths decrease in a nonlinear manner as the temperature decreases (Figure 6). For the sample with the larger *n*Xe/*n*CA ratio the line widths of both the free and the bound xenon remain significantly larger than the line width of xenon dissolved in the pure solvent. This latter line width is due to field inhomogeneities and temperature instabilities. The signal of the bound xenon in the sample with the smaller *n*Xe/*n*CA ratio, however, reaches a value similar to the line width observed in the pure solvent. This suggests that, at lower temperatures, the conditions of infinitely slow exchange are attained for this sample.

The resonance frequency of 62.3 ppm observed at 278 K for xenon inside the cavity of cryptophane-A is unusually low for xenon in a host−xenon complex in solution (difference in chemical shift between the bound and the free xenon: $\Delta\delta \approx 160$ ppm). Previous studies of molecular cages with xenon NMR have been reported. As mentioned above, Cram and his colleagues[1] obtained a stable hemicarcerand−xenon complex ($K \approx 200$ M^{-1}) and Rebek and co-workers[2] reported the binding of xenon within the dimeric capsule formed by two self-complementary units. When referenced to the resonance frequency of pure xenon gas extrapolated to zero pressure, the chemical shifts of their bound xenons are 116 ($\Delta\delta \approx 101$) and 198 ($\Delta\delta \approx 19$) ppm, respectively. The six benzene rings of cryptophane-A provide a shielding environment for a guest inside the cavity. This ring current effect is dominating for protons (shifts to lower frequencies of up to 4.5 ppm are observed for the protons of different guests of cryptophane-A in $(CDCl_2)_2$)[13] but is not the major contribution for xenon. Due to the large polarizable electron cloud of xenon, the effect of intermolecular interactions (van der Waals interactions in particular) is much more important than the effect due to the

(13) Proton shifts to lower frequencies observed for some cryptophane-A complexes in $(CDCl_2)_2$: CH_4, 4.50 ppm; C_2H_6, 3.95 ppm; CH_2Cl_2, 4.33 ppm; CH_2Br_2: 4.28 ppm; CHFClBr, 4.43 ppm; CHF_2Cl, 4.59 ppm; $CHCl_3$, 4.33 ppm.

anisotropy in the molecular magnetic susceptibility (the σ_a contribution in the Buckingham expansion).[14] The latter effect is in the range of a few ppm while the former covers hundreds of ppm.[15]

The temperature dependence observed for the chemical shifts of the free and the bound xenon cannot be the consequence of the slowing down of the exchange process. Indeed, the temperature dependence of the chemical shift of the free xenon is identical to the temperature dependence observed for xenon dissolved in the pure solvent (Figure 5). Furthermore, the chemical shift of the bound xenon decreases in a continuous manner with decreasing temperature even when the line widths suggest that the infinitely slow exchange regime has been reached (Figures 5 and 6). The temperature dependence of the chemical shift of xenon in the cryptophane-A cavity is thus intrinsic to the properties of the inclusion complex and it is not the one usually observed for xenon in the solution, gas, and solid states. In pure solvents a decrease in chemical shift is observed when the temperature is increased.[16] In mixtures of xenon and various gases, the most frequently observed temperature dependence is a decrease in chemical shift with increasing temperatures.[17] An increase in chemical shift with temperature is however reported for mixtures of xenon with CO and with N_2. In zeolite Na*A* the temperature dependence of the xenon chemical shift depends on the xenon loading.[18] The chemical shift decreases with temperature for low loading and increases with temperature for high loading corresponding, in this case, to occupancy factors greater than 20% (this factor was calculated considering four xenon atoms of 4.32 Å diameter in the zeolite Na*A* cavity which has a diameter of 11.5 Å).[19] The temperature dependence of the chemical shift for high loading is explained by the fact that at higher temperatures repulsive configurations, which lead to large deshielding effects, can be sampled and that this sampling is enhanced if the xenon is in a confined space. The xenon in the cryptophane-A cavity has an occupation factor around 65%,[20] and the explanation used for the zeolites could apply to this case as well. However, contrary to the zeolite cavity, the cryptophane is not rigid and the size and shape of the cavity as well as the cross section of the windows giving access to the cavity may fluctuate as a function of the dynamics of the OCH_2CH_2O spacer bridges which can adopt gauche or anti conformations, and of the peripheral methoxy groups which can rotate almost freely. Thus the temperature dependence of the chemical shift of the bound xenon in cryptophane-A might also be a consequence of the effect of the temperature on the cryptophane dynamics.

The temperature dependence of the line widths (Figure 6) indicates that the broadening of the ^{129}Xe NMR signals observed in a solution of cryptophane-A is essentially a consequence of exchange processes; the other contributions to the line widths are only significant at the lowest temperatures and lowest xenon concentrations. The residence time of xenon in the cryptophane cavity, τ_{in}, can therefore be estimated directly from the line width by using the relation $\Delta\nu_{1/2} = (\pi\tau)^{-1}$. From the data in Figure 4 (278 K), τ_{in} is found to vary between 8 (at the lowest Xe concentration) and 0.5 ms (at the highest Xe concentration). The dependence of τ_{in} on the concentration of xenon (or equivalently, the dependence of the line width of the bound xenon on the *n*Xe/*n*CA ratio, Figure 4) indicates that the exchange process is more complex than the simple equilibrium

$$\mathrm{Xe} + \mathrm{CA} \rightleftharpoons \mathrm{CA{-}Xe}$$

For such a process in slow exchange, it is expected that the chemical shift of the bound and of the free xenon and the line width of the bound xenon are independent of xenon concentration.[21] In the present study the chemical shifts of the bound and free xenon are independent of the *n*Xe/*n*CA ratio but the line width of the bound xenon varies essentially in a linear manner with the *n*Xe/*n*CA ratio. For concentrations of xenon for which essentially all the cryptophane-A cavities are filled, a degenerate exchange process such as

$$\mathrm{Xe^*} + \mathrm{CA\text{-}Xe} \underset{k_d}{\overset{k_d}{\rightleftharpoons}} \mathrm{CA\text{-}Xe^*} + \mathrm{Xe}$$

is able to explain the observed data. The contribution of this process to the line width is $2k_d[Xe_{free}]/\pi$ for the NMR signal of Xe_{bound}, a contribution that is proportional to the xenon concentration once all the cryptophane-A cavities are filled, and $2k_d[Xe_{bound}]/\pi$ for Xe_{free}, which is constant when there is an excess of xenon ($[Xe_{bound}] = [CA] = 0.1$ M). These behaviors agree with the experimental observations (Figure 4), and from the value of 250 Hz found for the line width of Xe_{free} at high Xe concentration, k_d is estimated to be 3900 M^{-1} s^{-1} at 278 K in $(CDCl_2)_2$. For lower concentrations of xenon this same type of exchange process could occur with other small molecules present in the solution and which can also be complexed by cryptophane-A (helium was used in the degassing procedure and can still be present in the final sample, together with a small amount of water). The idea that the decomplexation of xenon, leaving an empty cavity, is not energetically favorable is supported by a recent molecular dynamics simulation of the behavior of a closely related host (cryptophane-C) in $CHCl_3$ solution.[8]

Competition Studies. Since it is almost impossible to make sure that He, H_2O, and other potential guests (N_2, O_2, etc.) are totally removed by the degassing procedure, it is difficult to know which equilibria must be considered to derive quantitative data regarding the complexation of xenon by the cryptophane. It was therefore decided to perform competition experiments involving xenon and another guest known to form a complex with cryptophane-A in $(CDCl_2)_2$. Chloroform was a reasonable choice for this study, because the ^{1}H resonance of the bound species is shifted by approximately 4.3 ppm to lower frequencies with respect to the resonance of the free species and is clearly visible in the proton spectrum, and as mentioned above its apparent binding constant in this solvent is relatively large (860 M^{-1} at 278 K).[22]

The ^{1}H spectrum at 278 K of a 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ containing 8 equiv of $CHCl_3$ was first recorded (Figure 7a). The use of such a guest excess ensures that more than 99% of the host molecules are filled with a chloroform molecule. This spectrum is significantly different

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(19) See ref 11b.
(20) The volume of the cryptophane cavity with its three spacer bridges in anti conformation has been estimated at 81.5 Å^3 (see ref 3); this figure should probably be reduced by ca. 20% (i.e., ca. 65 Å^3) when the spacer bridges are in their energetically more favorable *gauche* conformation.
(21) Sudmeier, J. L.; Eveloch, J. L.; Jonsson, N. B.-H. *J. Magn. Reson.* **1980**, *37*, 377−390.
(22) See ref 4. The value of *K* at 278 K is derived from the value at 300 K (230 M^{-1}) and the enthalpy ($\Delta H° = -34.3$ kJ mol^{-1}) and entropy ($\Delta S° = -67$ J mol^{-1} K^{-1}) of complexation (from ref 3).

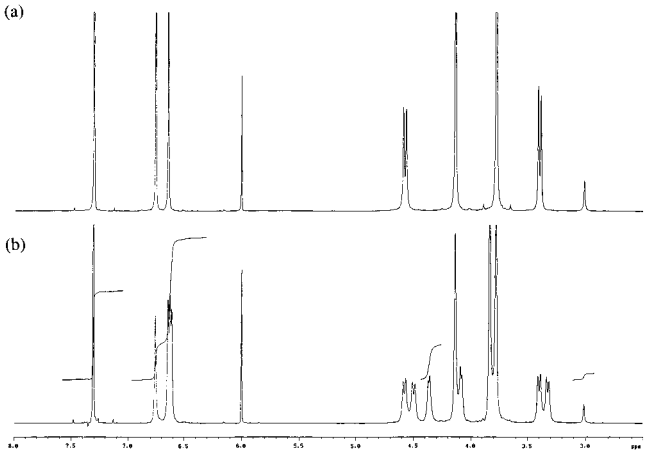

Figure 7. (a) ^{1}H NMR spectrum at 278 K of an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ containing 8 equiv of $CHCl_3$. (b) Spectrum under the same conditions of the same sample containing xenon:*n*Xe/*n*CA = 3.6. Integration curves drawn above the signals were used to determine the concentration of free and bound $CHCl_3$ and of bound xenon (see text).

from the spectrum of degassed cryptophane-A (Figure 2b), with the spacer bridge protons now appearing as a singlet at 4.13 ppm. The exchange between bound and free $CHCl_3$ is slow; their resonance signals appear at 3.01 and 7.31 ppm, respectively. We then recorded the ^{1}H spectra of this solution to which increasing amounts of xenon were added. A second set of signals, corresponding to the proton resonances of the cryptophane−xenon complex, appears in the spectra (Figure 7b). These new signals indicate that there is an exchange between complexed $CHCl_3$ and Xe, and that this exchange, as seen by the cryptophane protons, is slow. For the range of *n*Xe/*n*Ca ratios investigated (from 0 to 11) the new set of signals never completely replaces the old one, and this circumstance facilitated the evaluation of the relative affinities of these two guests for the host. This evaluation was made from relevant signals in the proton spectra (Figure 7b; signals with the integration). The $[CHCl_3]_{bound}/[CA]$ and $[CHCl_3]_{free}/[CA]$ ratios were obtained from the integration of the signals at 3.01 and 7.31 ppm, respectively, and the $[Xe]_{bound}/[CA]$ ratio was determined from the proton signals at 4.36 ppm which correspond to one of the multiplets of the OCH_2CH_2O spacer bridge protons (H_j or H_k) in the cryptophane−xenon complex. These integrals were normalized by setting the integration of the aromatic protons H_g and H_h from both complexes ($\delta \approx 6.6$ and 6.8 ppm) to 12 in each spectrum. Figure 8shows the evolution of these ratios as a function of the *n*Xe/*n*CA ratio. When no xenon has been added to the solution the $[CHCl_3]_{bound}/[CA]$ ratio is equal to one, confirming that in this solution all the cavities contain one molecule of $CHCl_3$. Assuming that the observed equilibrium corresponds to

$$CHCl_{3\ bound} + Xe_{free} \rightleftharpoons CHCl_{3\ free} + Xe_{bound}$$

the relative affinity of cryptophane-A for xenon and for $CHCl_3$ in $(CDCl_2)_2$ is given by eq 1, where only the concentration of free xenon, $[Xe]_{free}$, is unknown.

$$K = \frac{[CHCl_3]_{free}}{[CHCl_3]_{bound}} \frac{[Xe]_{bound}}{[Xe]_{free}} \qquad (1)$$

It is however possible to express this quantity in terms of the total amount of xenon present in the NMR tube, *n*Xe (or *n*Xe/*n*CA). Assuming (i) that $[Xe]_{free}$ is proportional to the amount

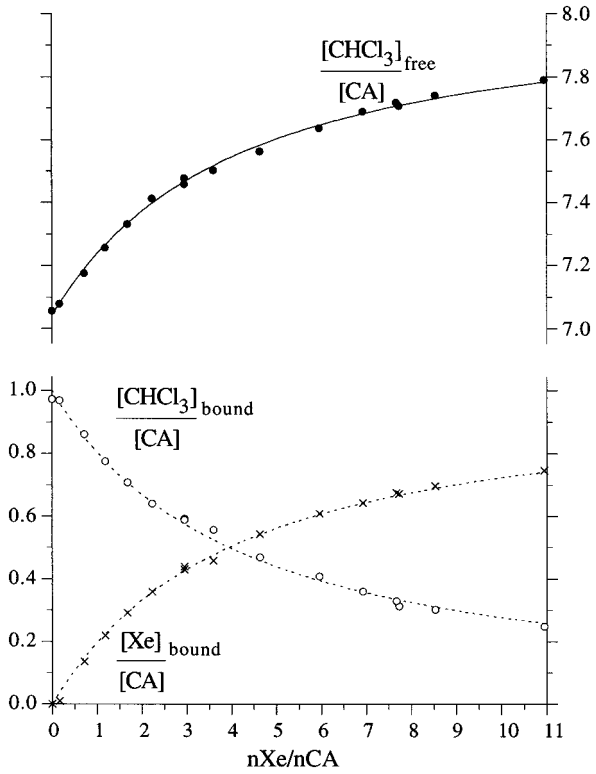

Figure 8. Concentration, as a function of the *n*Xe/*n*CA ratio, of free $CHCl_3$ (●), bound $CHCl_3$ (○), and bound xenon (×) divided by the concentration of crytophane-A. Data were obtained from integration in the ^{1}H NMR spectra of an approximately 0.1 M solution of cryptophane-A in $(CDCl_2)_2$ containing 8 equiv of $CHCl_3$ and increasing amounts of xenon. The curves were calculated with eq 4, the mass balance equations for chloroform and for cryptophane-A, and a value of 2.19 for *Kg* (see text).

of xenon in the gas phase above the solution, nXe_{gas} (Henry's law), (ii) that $[Xe]_{free}$ corresponds to the solubility of xenon in the pure solvent, and (iii) that xenon is a perfect gas, $[Xe]_{free}$ is given by eq 2,

$$[Xe]_{free} = \frac{nXe_{free}}{V_{liq}} = H\frac{nXe_{gas}}{V_{gas}} \qquad \text{with} \qquad H = RT[Xe]^\circ \quad (2)$$

where V_{liq} and V_{gas} are the volumes of the liquid and gas phases in the NMR tube and [Xe]° is the solubility of xenon in the pure solvent, at temperature *T*, for a partial pressure in xenon gas of 1 atm. By using the mass balance equation for xenon ($nXe_{gas} = nXe - nXe_{free} - nXe_{bound}$), eq 2 leads to eq 3.

$$[Xe]_{free} = g[CA]\left(\frac{nXe}{nCa} - \frac{[Xe]_{bound}}{[CA]}\right) \qquad \text{with}$$

$$g = \frac{(V_{liq}/V_{gas})H}{1 + (V_{liq}/V_{gas})H} \quad (3)$$

The expression of the equilibrium constant can be rewritten, using eq 3, and expressed in terms of the *n*Xe/*n*CA ratio and the experimental quantities shown in Figure 8:

$$Kg = \frac{([CHCl_3]_{free}/[CA])}{([CHCl_3]_{bound}/[CA])} \frac{([Xe]_{bound}/[CA])}{(nXe/nCA - [Xe]_{bound}/[CA])} \quad (4)$$

The product *Kg* was determined by using this expression and the experimental data measured for *n*Xe/*n*CA ratios greater than

1 (the experimental error associated with the integration of the NMR signal makes the $[Xe]_{bound}/[CA]$ values unreliable for very low contents in xenon; this only concerns the first three data points in Figure 8). The mean value and standard deviation for the 13 estimations of *Kg* are 2.19 and 0.10, respectively. This value has been used to recalculate the evolution of $[Xe]_{bound}/[CA]$, $[CHCl_3]_{bound}/[CA]$, and $[CHCl_3]_{free}/[CA]$ as a function of *n*Xe/*n*CA (using eq 4 and the mass balance equations for chloroform and for cryptophane-A). These curves are displayed in Figure 8 and are found to be in very good agreement with the experimental data points. The equilibrium constant, *K*, can be obtained if the factor *g* is known, but this requires a value for [Xe]°, the solubility of xenon in the pure solvent. Solubility data for xenon in chlorinated solvents are rather scarce and the value in $(CDCl_2)_2$ was not found in the literature. For xenon solubilities ranging between 0.1 and 0.2 M (the choice of this range is justified by the fact that the solubility of xenon in chloroform is 0.14 M at 298 K),[23] and for the experimental V_{liq}/V_{gas} ratio of 0.31, *g* varies at 278 K between 0.4 and 0.6. The ratio of the equilibrium constants then ranges between 5.5 and 3.7. In other terms, the affinity of cryptophane-A for xenon is 4 to 5 times larger than its affinity for chloroform, in $(CDCl_2)_2$ at 278 K. Since as stated above the apparent affinity constant for $CHCl_3$ has been determined to be 860 M^{-1} in $(CDCl_2)_2$ at 278 K, the apparent affinity constant of cryptophane-A for xenon is thus certainly larger than 3×10^3 M^{-1}, a figure about 20 times larger than its affinity for methane ($K = 131$ M^{-1} for methane at 278 K).[24] This is the most stable complex observed so far in this solvent between cryptophane-A and a neutral molecule at (or close to) room temperature (the previous record was the dichloromethane complex, with $K = 475$ M^{-1} at 300 K).[4]

The cryptophane complexes are reversibly formed, and the magnitude of their binding constants will depend on the balance between solvent−guest, host−guest, and solvent−host interactions. In the present case, we assume that the solvent−host interactions play a minor role since $(CDCl_2)_2$ cannot enter the cryptophane-A cavity due to its size.[25] Differences in the solvent−guest interactions certainly convey a significant contribution to the discrimination between CH_4, Xe, and $CHCl_3$, but the importance of these effects cannot yet be quantified due to the lack of relevant data. In any case solvophobic forces due to cavitation effects,[26] which would normally increase in strength with the guest size, do not account for the observed trend. Until this question is clarified, we can only discuss the relative stabilities of the methane, chloroform, and xenon complexes with crytophane-A in terms of differences in the host−guest interactions. Xenon (42 Å^3) is smaller than chloroform (72 Å^3) and larger than methane (29 Å^3). The chloroform complex exhibits a large stabilizing enthalpy of formation ($\Delta H° = -34.3$ kJ mol^{-1}) and a large destabilizing entropy of formation ($\Delta S° = -67$ J mol^{-1} K^{-1}).[27] These values suggest a very ordered, crystal-like complex, and this view has recently been substantiated by X-ray studies of the analogous complex between chloroform and cryptophane-A6 (EtO instead of MeO groups attached to the cryptophane benzene rings).[5] This structure shows that the 3-fold axis of chloroform is aligned with that of the host to form a perfectly ordered and closely packed structure. Moreover, in this complex the host OCH_2-CH_2O spacer bridges exist in an anti conformation, giving the cavity its maximum possible extension (ca. 82 Å^3) to accommodate the comparatively bulky guest. This extension, however, is perhaps insufficient, and this leads to a particularly tight supermolecule, with a large occupancy factor.[28] The tight character of this complex also implies that the conformational freedom of the host itself must be significantly reduced with respect to complexes of smaller guests. On the other side, the methane complex is stabilized both enthalpically ($\Delta H° = -6.7$ kJ mol^{-1}) and entropically ($\Delta S° = +17$ K mol^{-1} K^{-1}), and it is likely that in this complex the host spacer bridges adopt the most stable gauche conformation. This conformation gives the cryptophane cavity its minimum size (ca. 65 Å^3), but this size is still too large for this guest, which is certainly moving almost freely in the cavity. For the xenon complex the enthalpic and entropic contributions have not been evaluated, but comparison of the resolution enhanced ^1H signals of the OCH_2CH_2O units in the Xe complex to simulated signals for an AA′BB′ system in the gauche ($J_{AB'} = J_{A'B} = 4$ Hz) or in the anti conformation ($J_{AB'} = J_{A'B} = 9$ Hz) suggests that the spacer bridges also adopt a gauche conformation in this complex. The occupancy factor of xenon in the cryptophane cavity would thus be around 65%, which is a quite reasonable number for such a complex, meaning that it is neither too tight (as is the chloroform complex) nor too loose (as is the methane complex). In summary, and with the reservation concerning the contribution of guest−solvent interactions, the particularly large affinity of cryptophane-A for xenon seems to originate from the following three main reasons: (i) a good size matching between the guest and the cryptophane cavity in its most relaxed conformation—this should result in the optimization of the London forces between the highly polarizable guest and the electron rich aromatic rings of the host (enthalpic stabilization); (ii) xenon being a spherical monatomic species, there is no rotational or vibrational entropy loss on complexation; and (iii) the host being unstrained there is no (or little) entropy loss due to reduction of its conformational freedom. Statement (iii) also applies for methane and there should also be little rotational entropy loss on complexation because of the its low occupancy factor in the cavity. Statement (i), however, does not apply and the weak enthalpic stabilization of the methane complex is perhaps due to solvophobic effects. Statement (i) applies to the chloroform complex, with the restriction that the host adopts a slightly less favorable conformation. The relative destabilization of this complex at room temperature seems to result from entropic factors, associated with the greater rigidity of the host, and the loss of reorientational degrees of freedom of the guest. In a previous paper dealing with the binding of acetylcholine to various cryptophane hosts,[29] we have concluded that a relatively loose association, rather than a tight lock and key pairing, was required to achieve a strong binding of quaternary ammonium guests to their aromatic receptors. This requirement seems to be general for host−guest complexes that do not involve H-bonding of the

(23) *IUPAC Solubility Data Series*; Ed. Clever, H. L., Ed.; Pergamon Press: New York, 1979; Vol. 2, p 176.

(24) See ref 4. The value of *K* at 278 K is derived from the value at 300 K (130 M^{-1}) and the enthalpy ($\Delta H° = -6.7$ kJ mol^{-1}) and entropy ($\Delta S° = +17$ J mol^{-1} K^{-1}) of complexation (from ref 3).

(25) The van der Waals volume of this solvent is around 104 Å^3 and we have never observed the complexation of neutral guests of size greater that isobutane (80 Å^3) in this cryptophane or in cryptophanes of the same size.

(26) Dejaegere, A.; Claessens, M.; Luhmer, M.; Bardiaux, M.; Reisse, J. *J. Phys. Chem.* **1988**, *92* 7093−7097.

(27) See ref 3 and Collet, A. Cryptophanes. In *Comprehensive Supramolecular Chemistry;* Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Vol. 2 Ed. Vögtle, F.; Pergamon: New York, 1996, Chapter 11, pp 325−365.

(28) Based on a spherical cavity of 82 Å^3, the occupancy factor of the chloroform molecule would be as large as 88%, a figure that is certainly overestimated but nevertheless reflects the "lock and key" structure of the complex. In a close-packed crystal the packing coefficient, i.e., the molecular volume divided by the cell volume, rarely exceeds 75%.

(29) Garel, L.; Lozach, B.; Dutasta, J.-P.; Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652−11653.

partners, such as those involving neutral and apolar species. It implies that not only the guest, but also the host, must keep enough motional or conformational freedom when the complex is formed to avoid too much entropic destabilization at ambient temperature.

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