[129]Xe NMR Spectroscopy of Deuterium-Labeled Cryptophane-A Xenon Complexes: Investigation of Host−Guest Complexation Dynamics

Thierry Brotin, Anne Lesage, Lyndon Emsley,* and André Collet

Contribution from the École Normale Supérieure de Lyon, Stéréochimie et Interactions Moléculaires, UMR CNRS 5532, 46, Allée d'Italie, F-69364 Lyon Cedex 07, France

*Received August 23, 1999. Revised Manuscript Received December 14, 1999*

Abstract: We have discovered the ability of [129]Xe NMR spectroscopy to discriminate between the xenon complexes of cryptophane-A **1** and its deuterated congeners **2**−**6** in solution. At 238 K, under slow exchange conditions, the upfield shift experienced by the xenon atom upon complexation by **1** (190 ppm) is increased (up to ∼0.6%) when the hosts are deuterated. By using mixtures of deuterated and nondeuterated hosts, such as **1** and **6**, the dynamics of a xenon atom can thus be traced between three different sites (one free and two bound states). We have demonstrated that some of the dynamic features of the exchange between these sites can be extracted from 2D-EXSY experiments, using a suitable kinetic model. We conclude that the exchange of a xenon atom between different hosts occurs by travelling through the solution rather than upon collision of two hosts.

Introduction

The recently discovered xenon@cryptophane-A complex[1] is probably one of the most fascinating examples of a host−guest supermolecule owing its existence solely to van der Waals forces.[2] Its unprecedented high stability ($K \approx 3000$ M^{-1} at 293 K in 1,1,2,2-tetrachloroethane-d_2), combined with the exceptional sensitivity of the [129]Xe nucleus to its environment through NMR experiments,[3] makes this complex a useful tool for studying structural and mechanistic details of molecular recognition phenomena, which may not be easy to observe in other host−guest systems.[4] In this article, we show that the large chemical shift range of [129]Xe makes it possible to discriminate between cryptophane-**A** (**1**) congeners differing only by specific deuterium labeling (see **2**−**6** in Scheme 1). We have experimentally characterized this effect, and we use it to obtain information on the dynamics of xenon binding to cryptophanes, by means of two-dimensional (2D) exchange NMR experiments which allow us to extract relevant rate constants.

Chemical Shift Discrimination. Figure 1(a) shows the one-dimensional (1D) [129]Xe−NMR spectrum of a solution contain-

Scheme 1. Structures of Cryptophane-A (**1**) and Deuterated Cryptophanes **2**−**6**
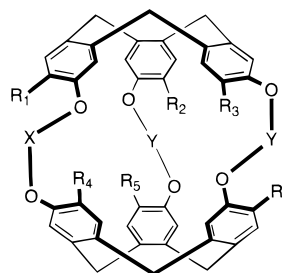
1 : X = CH$_2$CH$_2$; Y = CH$_2$CH$_2$; R$_1$ = OCH$_3$; R$_2$ — R$_6$ = OCH$_3$

2 : X = CH$_2$CH$_2$; Y = CD$_2$CD$_2$; R$_1$ = OCH$_3$; R$_2$ — R$_6$ = OCH$_3$

3 : X = CD$_2$CD$_2$; Y = CD$_2$CD$_2$; R$_1$ = OCH$_3$; R$_2$ — R$_6$ = OCH$_3$

4 : X = CD$_2$CD$_2$; Y = CD$_2$CD$_2$; R$_1$ = OCD$_3$; R$_2$ — R$_6$ = OCH$_3$

5 : X = CD$_2$CD$_2$; Y = CD$_2$CD$_2$; R$_1$ — R$_3$ = OCD$_3$; R$_4$ — R$_6$ = OCH$_3$

6 : X = CD$_2$CD$_2$; Y = CD$_2$CD$_2$; R$_1$ — R$_6$ = OCD$_3$

ing an equimolar amount of cryptophanes **1** and **6** in the presence of an excess of xenon at 293 K. The NMR spectrum displays two broadened peaks at 224.8 ppm and at 66.8 ppm, corresponding respectively to free xenon in the solution and xenon trapped in the cryptophanes. The exchange of xenon between **1**, **6** and the solvent is responsible for the broadening. At 238 K, the rate of exchange decreases significantly, and the low-frequency resonance (Figure 1b) splits into two sharp peaks of the same intensity at about 54.1 and 52.9 ppm. These peaks correspond to xenon atoms encapsulated in hosts **1** and **6,** respectively. The assignment of the signals was simply obtained by using a second solution containing an excess of **6**. Chemical shifts are given with respect to xenon gas at a pressure extrapolated to zero as a reference. This was obtained using the chemical shift reference given by Bartik et al.[1] for free xenon in tetrachloroethane-d_2 (229.5 ppm at 278 K). On this scale we found a chemical shift of 63.0 ppm for a xenon atom

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(2) Cryptophanes and their complexes: (a) Kirchhoff, P. D.; Dutasta, J.-P.; Collet, A.; McCammon, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 381−390 and references therein; (b) Collet, A. In *Comprehensive Supramolecular Chemistry*; Lehn, J−M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., series Eds.; Pergamon: Elmsford, NY,1996; Vol. 2, Vögtle, F., Ed.; Chapter 11, pp 325−365.

(3) (a) Reisse, J. *New. J. Chem.* **1986**, *10*, 665−672 and references therein; (b) Long, H, W.; Gaede, H. C.; Shore, J.; Reven, L.; Bowers, C. R.; Kritzenberger, J.; Pietrass, T.; Pines, A. *J. Am. Chem. Soc.* **1993**, *115*, 8491−8492. (c) Albert, M. S.; Gates, G. D.; Driehuys, B.; Happer, W.; Saam, B.; Springer, C. S. ,Jr.; Wishnia, A. *Nature* **1994**, *370*, 199−201. (d) Moudrakovski, I. L.; Ratcliffe, C. I.; Ripmeester, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 3123−3132.

(4) Recent examples of organic hosts binding xenon: Robbins, T. A.; Knobler, C. B.; Bellew, D. R.; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111−122. Branda, N.; Wyler, R.; Rebek, J. Jr. *Science* **1994**, *263*, 1267−1268. Branda, N.; Grotzfeld, R. M.; Valdes, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85−88. Szabo, T.; Hilmerson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 6193−6194.
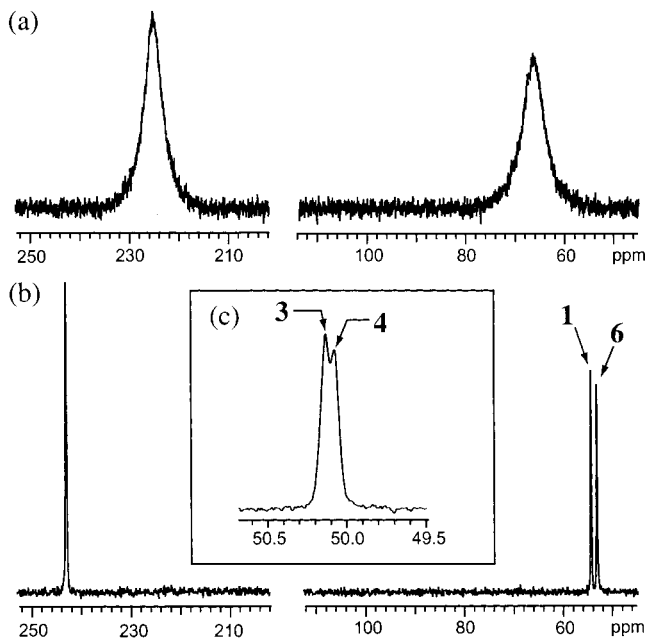
Figure 1. ^{129}Xe NMR spectra of an approximately 0.07 M solution of cryptophanes **1** and **6** in (CDCl$_2$)$_2$, [^{129}Xe]/[Hosts] $\approx$ 2; (a) spectrum recorded at 273 K (15212 scans, Xe pulse width (pw = 12 μs), relaxation delay (d_1 = 4.0 s), an exponential apodization (lb = 4.748) was applied); (b) spectrum recorded at 238 K (462 scans, pw = 8 μs, d_1 = 4.0 s, a Gaussian apodization (gf = 0.045) was applied); (c) ^{129}Xe NMR spectrum of a solution containing hosts **3** and **4** (approximately 1/1) in a mixture of 1,1,2,2-tetrachloroethane-d_2 and toluene (50/50) at 223 K (494 scans, pw = 12 μs, d_1 = 4.0 s, a slight Gaussian apodization (gf = 0.185) was applied, [^{129}Xe]/[Hosts] $\approx$ 2).

encapsulated in cages **1** and **6** (single peak at 278 K) instead of 62.3 ppm as previously reported. The apodization procedure applied and small temperature differences may explain the small difference observed.

Although smaller, a similar effect was observed for compounds **2**, **3**, **4**, and **5**. The highest field signal always corresponds to xenon in deuterated hosts. This isotopic shift reaches 1.19 ppm for the most deuterated host **6**, which represents 0.6% of the overall upfield shift induced by complexation. The discrimination between cryptophanes **3** and **4** (shown in Figure 1c) shows the exceptional sensitivity of this effect for ^{129}Xe, and reflects its capability to probe efficiently and selectively each part of the cavity of cryptophane **A**. To our knowledge no such isotopic effect has been previously reported in host−guest complexes.[5]

Although the physical mechanism of this effect is not clear, we have found experimentally that there is a simple linear relationship (Figure 2b) between the difference in chemical shift between cage **1** and the deuterated hosts (**2**−**6**) as a function of the number deuterium atoms located either in the diethoxyethylene (Nb) bridges or in the methoxy groups (Nm).

This linear relationship was obtained from Figure 2a which shows the chemical shift difference between cryptophanes depending both on the number of deuterium atoms and their location. For instance, discrimination of cages **1** and **2** by xenon shows that a xenon atom encapsulated in a cryptophane having eight deuterium atoms located in the diethoxyethylene bridges is shifted by 0.39 ppm toward low frequency with respect to **1**. A comparison of the xenon chemical shift observed between cages **3** and **5** shows that nine deuterium atoms located in the

(5) An isotopic effect between D$_2$O and H$_2$O for xenon has already been observed. Stengle, T. R.; Reo, N. V.; Williamson, K. L. *J. Phys. Chem.* **1984**, *88*, 3225−3228.
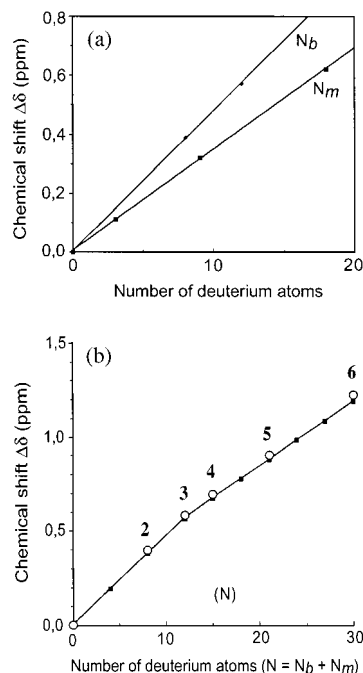

Figure 2. (a) Experimental difference chemical shift $\Delta\delta$, Xe@**i** − Xe@(**j**), between a xenon complexed in a deuterated cryptophane as a function of the difference in the number of deuterium atoms located in the dietoxyethylene bridges (N$_b$) and in the methoxy groups (N$_m$), as described in the text. (b) Difference of chemical shifts between **1** and some hypothetical deuterated cryptophanes (**i**) (squares) bearing deuterium atoms either in the diethoxyethylene bridges and/or in the methoxy groups. The linear relationship $\Delta\delta$ = 0.048 N$_b$ + 0.034 N$_m$, obtained by least-squares fitting of the data in (a) was used to calculate the predicted differences of chemical shift $\Delta\delta$ = (δXe@**1** − δXe@**i**). The experimental differences of chemical shift Xe@**1** − Xe@(**2**−**6**) are also shown (circles).

methyl groups displace the xenon signal by 0.32 ppm toward low frequency. Analyzing these differences for compounds **1**−**6** leads to the experimental points in Figure 2a. We obtain an excellent least-squares fit of these data (r^2 > 0.999, shown in Figure 2a) to a linear dependence on the number of deuterium atoms having the following form:

$$\Delta\delta \, (\text{Xe@}\mathbf{1} - \text{Xe@}\mathbf{i})_{\text{ppm}} = 0.048 \, N_{\text{b}} + 0.034 \, N_{\text{m}}$$

where i = 2−6. From Figure 2b we can see that this simple linear model yields an excellent correlation between predicted and experimental behavior.

Complexation Dynamics. Not only is this effect interesting in itself from a theoretical point of view, possibly shedding light on the subtle structural differences that affect the electronic environment of the xenon atom, but it can also be used for more pragmatic experimental applications. We have taken advantage of this discrimination effect to elucidate some of the dynamic features of the exchange between free xenon and its cryptophane complexes using 2D-EXSY NMR experiments.[6] Examples of the use of EXSY have already been reported, including examples with ^{129}Xe.[7] We performed these experiments using several mixing times (τ_{m}) and obtained relevant rate constants by fitting curves of cross-peak volumes to a model. Note that the large chemical shift scale observed in our case (200 ppm) combined

(6) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546−4553. Meier, B. H.; Ernst, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 6441−6442. Willem, R. *Progr.in Nucl. Magn. Reson. Spectroscopy* **1987**, *20*, 1−94. Perrin. C. L.; Dwyer, T. J. *Chem. Rev.* **1990**, *90*, 935−967 and references therein.
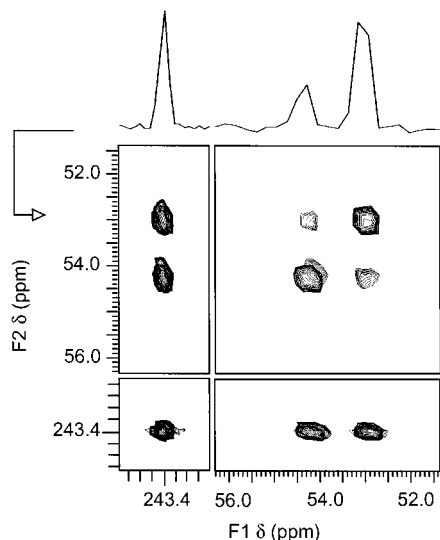
Figure 3. ^{129}Xe 2D-EXSY NMR spectrum of a mixture of cage **1** and **6** in tetrachloroethane-d$_2$. This two-dimensional spectrum was recorded at 238 K using a mixing time $\tau_m = 30$ ms and repetition delay of 4s. Diagonal peaks of free xenon, Xe@**1**, and Xe@**6** are shown, and cross-peaks exchange between them as well. A trace of this 2D spectrum is also shown. Other experimental parameters are given in the Experimental Section.

with the very long relaxation time of the ^{129}Xe atom in solution makes these experiments difficult and time-consuming. A two-dimensional 2D-EXSY spectrum recorded with a mixing time of $\tau_m = 30$ ms is shown in Figure 3. It can be seen, using the experimental conditions given in the Experimental Section below, that exchange between sites can be clearly distinguished with good resolution, especially for the exchange between the two cages **1** and **6**. A trace of this 2D-spectrum is also shown in the figure to provide an appreciation of the signal-to-noise ratio, which is sufficient for good quantification of the data.

Note that the 2D-EXSY spectra we observe are always symmetric about the main diagonal (i.e., both cross-peaks in a pair have the same volume). This indicates that the experimental conditions were sufficient to avoid any problems with non-uniform preparation of the magnetization due to a too rapid repetition rate which could complicate the quantification of the spectra.[8] This is because the exchange between sites on the ~10 ms time scale leads to a mean value of T_1 (in the tens of seconds range) *which is the same for all three sites*.

Under these conditions the cross-peak volumes in the two-dimensional spectrum are directly proportional to the exponential of the **R** matrix that contains all of the rate constants describing the host–guest exchange processes and the relaxation times of the probe nucleus

$$I_{ij}(\tau_m) = M^0_j \left[\exp\left(-\mathbf{R}\tau_m\right)\right]_{ij}$$

where $I_{ij}(\tau_m)$ are the intensities of diagonal and off-diagonal peaks at mixing time τ_m and M^0_j are the equilibrium magnetizations. The spin lattice relaxation time T_1 of ^{129}Xe in 1,1,2,2-tetrachloroethane and in cryptophane **1** had previously been

(7) See, for instance, ref 3d and references therein. See also: Tomaselli, M.; Meier, B. H.; Robyr, P.; Syter, U. W.; Ernst, R. R. *Chem. Phys. Lett.* **1993**, *205*, 145−152. Larsen, R. G.; Shore, J.; Schmidt-Rohr, K.; Emsley, L.; Long, H.; Pines, A.; Janicke, M.; Chmelka, B. F. *Chem. Phys. Lett.* **1993**, *214*, 220−226.

(8) Bremer, J.; Mendz, G. L.; Moore, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 4691−4696. Köck, M.; Griesinger, C. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 332−334. Geppert, T.; Köck, M.; Reggelin, M.; Griessinger, C. *J. Magn. Reson.* **1995**, *B107*, 91−93.
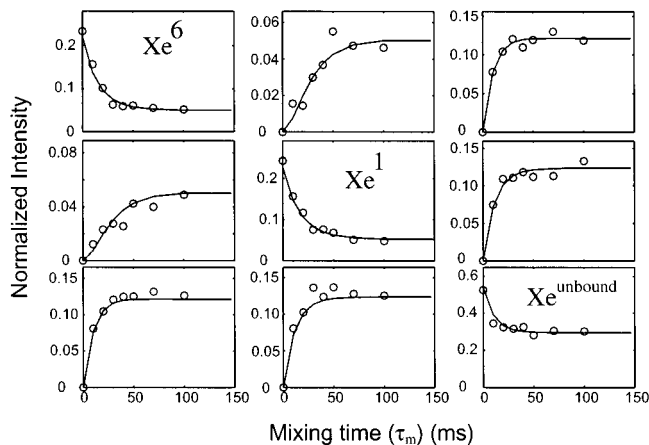

Figure 4. Normalized peak volumes as a function of the mixing time (τ_m). Each panel of the figure shows the volume for a particular peak. Diagonal peaks are shown diagonally and are correlated by the corresponding cross-peaks. Experimental data are represented by dots, and the solid lines represent the best fit of the data (obtained by least-squares fitting using a program kindly provided by D. Sakellariou).

Scheme 2. Pseudo-First-Order Kinetic Model Contributing to Cross-peaks in 2D-EXSY Experiments
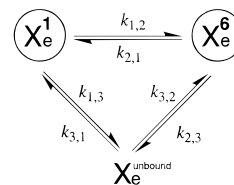
reported to be several hundreds of seconds and 16 s, respectively.[9] Since relaxation originates mainly from dipole–dipole interactions between xenon and protons in the cage, a longer value for T_1 is expected in the deuterated hosts. Since these times are very long compared to the mixing times used in these studies, we can neglect relaxation during τ_m. This leads to a simplification, where the **R** matrix is only a function of the rate constants of the pseudo-first-order three-site exchange process depicted in Scheme 2.

$$\mathbf{R} = \begin{pmatrix} -(k_{1,2} + k_{1,3}) & k_{2,1} & k_{3,1} \\ k_{1,2} & -(k_{2,1} + k_{2,3}) & k_{3,2} \\ k_{1,3} & k_{2,3} & -(k_{3,1} + k_{3,2}) \end{pmatrix}$$

Since deuteration should not affect, to a very good degree of approximation, the complexing properties of the hosts, similar values for the rate constants $k_{3,1}$ and $k_{3,2}$, as well as $k_{1,3}$ and $k_{2,3}$, are expected.[10] The complete set of individual rate constants and initial magnetizations in our experiments was determined by fitting the observed intensities versus τ_m. The experimental points and best fit curves are shown in Figure 4. The values of the initial magnetizations and of the rate constants that we obtain are given in Table 1.

The fit of these curves agrees fairly well with the experimental data and, as expected, $k_{1,3} \approx k_{2,3}$ and $k_{3,1} \approx k_{3,2}$ within experimental error. Note that the errors involved in the quantification of these experiments are difficult to evaluate

(9) Luhmer, M.; Goodson, B. M.; Song, Y. Q.; Laws, D. D.; Kaiser, L.; Cyrier, M. C.; Pines, A. *J. Am. Chem. Soc.* **1999**, *121*, 3502−3512.

(10) Note that the equilibrium condition implies $k_{3,1}/k_{1,3} = M^0_3/M^0_1$; $k_{3,2}/k_{2,3} = M^0_3/M^0_2$; and $k_{2,1}/k_{1,2} = M^0_2/M^0_1$ where M^0_1, M^0_2, M^0_3 are respectively the initial magnetization ($\tau_m = 0$) of xenon bound to cage **1**, xenon bound to cage **6**, and xenon in solution. The **R** matrix may be calculated numerically by solving the following system: $R = -(\ln A_{ij})/\tau_m$ where $A_{ij} = I_{ij}(\tau_m)/M^0_j$ is the experimental matrix of normalized intensities.

Table 1. Rate Constants k_{ij} (± 5 s^{-1}) and Initial Magnetizations M^0_i Obtained from ^{129}Xe EXSY Experiments at 238 K in 1,1,2,2-tetrachloroethane-d_2 in the Presence of a 1:1 Mixture of Hosts **1** and **6** (0.07 M)

$k_{i,j}$ (s^{-1})	M^0_i
$k_{1,2} = 1.8$	$M^0_1 = 0.22$
$k_{2,1} = 1.9$	
$k_{1,3} = 50$	$M^0_2 = 0.23$
$k_{3,1} = 25$	
$k_{2,3} = 44$	$M^0_3 = 0.54$
$k_{3,2} = 22$	

quantitatively. The experimental error of ± 5 s^{-1} is a conservative estimate (note that the fitting gives a much more precise value than this, but that the precision of the fit does not represent the accuracy of the measurement). In Scheme 2, we have assumed that the transfer of a given ^{129}Xe atom from host **1** to host **6** may occur in two different ways. One process implies the diffusion of ^{129}Xe through the solution, whereas the other occurs through collision between **1** and **6**. The fact that $k_{1,3}$ and $k_{2,3}$ are found to be much greater than $k_{1,2}$ clearly shows that, in the presence of an excess of ^{129}Xe, the collision mechanism does not contribute significantly to the exchange process, which is dominated by interactions between free xenon and the cryptophanes.[11] Thus, in the particular set of conditions used in our experiments, a given xenon atom moves from one cryptophane to another on an average of several tens of times per second. One remaining question is whether the xenon atom binds to a cryptophane by pushing out another bound xenon or whether it can only enter an empty cryptophane (the concentration of empty hosts is actually very low, due to the large binding constant and the presence of an excess of xenon). The present experiments do not provide this information, which would require determination of the reaction order. In principle this could be achieved by performing similar EXSY experiments at several initial reactant concentrations.[12] More detailed host–guest interactions studies using this new method will be reported in due course.

Conclusions

First, we have discovered that chemical shifts of complexed xenon are sensitive to the level of deuteration of the host. More surprisingly, we find that in a series of compounds varying in the level of deuteration the xenon chemical shift change can be predicted by using a simple linear dependence on the number of deuterium atoms and their location in the host. We expect that the reproduction of our experimental observations by theory will represent something of a challenge and could provide significant details about the nature of the host–guest interactions.

Second, one cannot normally study exchange between identical molecules. We have made use of the discrimination effect to study the exchange of xenon between molecules differing only in their level of deuteration. This provides us with a unique window on complexation dynamics. In the experiments presented here we were able to show that exchange between cages takes place exclusively by xenon molecules travelling through solution and that direct transfer in a collision type mechanism does not take place at a measurable rate.

Further studies of this type will undoubtedly continue to reveal further information about host–guest interactions and dynamics.

Experimental Section

Cryptophane-A **1** was prepared by means of a slightly modified known procedure.[13] Deuterated cryptophanes **2**–**6** were similarly prepared[14] by a multistep reaction starting from 3,4-dihydroxybenzaldehyde and using mehyl iodide-d_3 and 1,2-dibromoethane-d_2 as sources of deuterium. All of the spectroscopic data of deuterated compounds were in good agreement with the proposed structures. The NMR sample was prepared by mixing the same amount of cages **1** and **6** (100 mg of each) in a minimum quantity of 1,1,2,2-tetrachloroethane. The solvent was stripped off, and the operation was repeated to remove any bound substrate remaining from the synthesis (mostly, CHCl$_3$). Then 1,1,2,2-tetrachloroethane-d_2 was added, and the solution was poured into a 10 mm NMR tube. Xenon gas (^{129}Xe, natural abundance, 26.4%) was then bubbled through the solution. The NMR tube was then frozen in liquid nitrogen and sealed under vacuum. The overall cryptophane concentration was [C] ≈ 0.07 M (using a mean molecular weight for **1** and **6**, M $= 910.105$ g mol^{-1}).

NMR Measurements. ^{129}Xe NMR experiments were carried out at 138.4 MHz (proton frequency 500 MHz) on a Varian Unity$^+$ spectrometer using a 10 mm double resonance probe. Two-dimensional EXSY spectra were acquired with a standard 3-pulse sequence.[6] The spectra were recorded at 238 K, and the sample was kept for about 2 h at this temperature before starting the 2D experiments. The mixing times were varied in the range 0.001–500 ms. The relaxation delay was set to 4 s, and the length of the 90° pulse was 12 μs. Quadrature detection was achieved in the F1 dimension using the States method.[15] A total of 2048 t_1 increments with eight scans each were collected for each 2D spectrum. Prior to Fourier transformation, shifted sine bell apodization functions were used in both dimensions, and zero filling to 4096 points was applied. For data processing and integration the VNMR software (Varian) was used. For each 2D data set, the intensities of the peaks were normalized (for a given τ_m, each diagonal and off diagonal peak was divided by the total spectral intensity) to take into account instrumental variation between experiments which were performed on different days.

(11) The introduction of small rate constants for $k_{1,2}$ (and the reverse constant) (1 or 2 orders of magnitude smaller than $k_{1,3}$) does not change significantly the fit of the experimental data.

(12) A similar problem is given when studying isotopic exchange reaction. See, for example: Logan, S. R. *Fundamentals of Chemical Kinetics*; Longman: Harlow, UK, 1996; Section 3.8. Logan, S. R. *J. Chem. Educ.* **1990**, *67*, 371–373.

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(15) States, D. J.; Haberkon, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286–292.