

Location of a Metallic Cation Complexed in a Calixarene Cavity As Determined by Calixarene ^{13}C Spin Relaxation. Application to Cesium and Thallium Complexed by *p*-Sulfonatocalix[4]arene in Water

Diana Cuc,[†] Sabine Bouguet-Bonnet,[†] Nicole Morel-Desrosiers,[‡] Jean-Pierre Morel,[‡] Pierre Mutzenhardt,[†] and Daniel Canet^{*,†}

Faculté des Sciences et Techniques, Méthodologie RMN (UMR CNRS-UHP 7036; CRM2), Nancy-Université, BP 239, 54506 Vandœuvre-lès Nancy Cedex, France, and Microorganismes: Génome et Environnement (UMR CNRS-UBP 6023), Clermont Université, Chimie Bâtiment 7, 24 avenue des Landais, 63177 Aubière Cedex, France

Received: July 30, 2008; Revised Manuscript Received: December 19, 2008

This study deals with the exact location of the monovalent metal cations Cs^+ and Tl^+ which are complexed by the *p*-sulfonatocalix[4]arene in water. This determination rests on the measurements of longitudinal relaxation times of carbon-13 not directly bonded to protons. The difference between the relaxation times of the free calixarene and of the complex definitely demonstrates that the monovalent metal cation is well inside the calixarene cavity. These features are in fact enhanced by the presence of paramagnetic species which act in a different way in the complexed form. Experimental results also show without any ambiguity that the calixarene cavity is essentially hydrophobic. Finally, it is observed that thallium is more mobile than cesium within the calixarene cavity.

Introduction

The ability of the *p*-sulfonatocalix[4]arene (Figure 1; abbreviated as SC4 in the following) for complexing monovalent metal cations in water is now well established: recent microcalorimetric studies¹ and translational ^{133}Cs diffusion NMR measurements² have not only clearly shown the existence of such complexes but have also led to the consistent determination of the association constants.

Interestingly, the thermodynamic parameters for the binding of the monovalent metal cations¹ have suggested the formation of inclusion complexes,^{3,4} in sharp contrast to the binding of the divalent or trivalent metal cations which occurs outside the calixarene cavity.^{5,6} It was demonstrated that the monovalent metal cations do bind inside the SC4 cavity due to favorable enthalpies of cation– π interactions.¹ This was confirmed, as far as the Cs^+ –SC4 complex is concerned, by ^{133}Cs pulsed-gradient spin echo diffusion data² and also by molecular mechanics coupled with density functional theory (DFT) calculations.⁷

Although those previous works strongly suggested the inclusion of the monovalent metal cation within the calixarene cavity, they could not confirm unambiguously the exact location of the guest. In the present work, we intend to locate experimentally the metal cation by looking at the spin relaxation of nuclei belonging to the calixarene itself. This will be carried out for two monovalent metal cations M^+ that have different sizes and affinities for the *p*-sulfonatocalix[4]arene in water, namely Cs^+ and Tl^+ (the van der Waals radii are 170 pm for Cs^+ and 150 pm for Tl^+ ;⁸ the association constants (molar scale) obtained by NMR for the binding with SC4 are 45 ± 5 for Cs^+ and 245 ± 25 for Tl^+ ⁹).

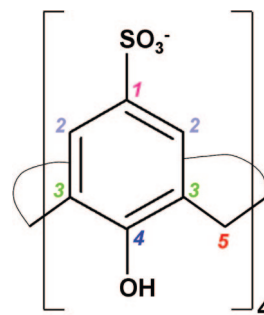


Figure 1. Structure of *p*-sulfonatocalix[4]arene with the numbering used throughout this paper.

Recently, NMR spin relaxation has been used with guest molecules or ions possessing sensitive nuclei (e.g., ^1H , ^{13}C) which probe directly the motion or the location of the guest within the cavity.^{10,11} This is obviously not possible here, and a method of choice would be to measure the dipolar interaction between M^+ and appropriate carbon-13 nuclei via ^{13}C longitudinal spin relaxation. We mean by appropriate a carbon for which the spin relaxation is not dominated by a predominant mechanism which would mask the dipolar interaction with M^+ , as this is the case for proton-bearing carbons. Indeed, due to the dependence upon $1/r^6$ of the dipolar contribution to relaxation rates, it is very unlikely that we could accurately measure, for those carbons bonded to proton(s), the dipolar interaction with M^+ . Of course, the most direct experiment would be of the NOE (Nuclear Overhauser Effect)¹² type implying radio-frequency irradiation at the Larmor frequency of cesium or thallium. This would, however, require a special NMR probe which is not available and anyway would be very difficult to design. Actually, we show below that we are able to determine indirectly a contribution arising from the cation complexation by measuring the relaxation rates of C_1 , C_3 , and C_4 , which are the carbons not directly bonded to proton(s) in

* Corresponding author. Telephone: 33-(0)3-83-68-43-49. Fax: 33-(0)3-83-68-43-47. E-mail: Daniel.Canet@rmn.uhp-nancy.fr.

[†] Nancy-Université.

[‡] Clermont Université.

the considered calixarene molecule. In fact, in the course of this study, we have noticed the presence of a spurious relaxation mechanism due to paramagnetic impurities accompanying calixarene molecule. These paramagnetic species could be residual stable free radicals that have not been detected earlier because they did not perturb the other types of measurements, microcalorimetry for instance. The only way to interpret our data is to assume that part of these paramagnetic species act specifically on the relaxation of the considered carbons in the complexed form. This unexpected feature enhances in fact the effect of complexation upon spin relaxation and, as will be shown below, is the key to the interpretation of our data in terms of cation location with respect to the calixarene cavity.

Theory

In a general way, and assuming fast exchange of M^+ between calixarene cavity and the bulk, the observed longitudinal relaxation rate R_1 (the inverse of the longitudinal relaxation time T_1) of calixarene carbons can be expressed as follows:¹³

$$R_1^{\text{obs}} = pR_1^{\text{complex}} + (1 - p)R_1^{\text{free}} \quad (1)$$

p is the proportion of calixarene molecules containing the cation (deduced from the known association constants which were previously determined by Job's plot methodology^{14,15}), while R_1^{complex} and R_1^{free} stand for relaxation rates of the considered carbon in the two relevant states.

Due to the presence of paramagnetic impurities, the concentration of which is proportional to the quantity of calixarene, any relaxation rate can be written as

$$R_1 = R_{1,0} + \alpha[C] \quad (2)$$

where $R_{1,0}$ would be the part of the relaxation rate independent of calixarene concentration; $[C]$ is the calixarene concentration and α is a coefficient related to the strength of the paramagnetic contribution to the relaxation rate. Inserting eq 2 into eq 1 and rearranging, we obtain

$$R_1^{\text{obs}} = R_{1,0}^{\text{free}} + (R_{1,0}^{\text{complex}} - R_{1,0}^{\text{free}})p + \alpha^{\text{free}}[C] + (\alpha^{\text{complex}} - \alpha^{\text{free}})p[C] \quad (3)$$

For each sample, p and $[C]$ are known and it can be observed that eq 3 has been written in a linear form so that we can determine $R_{1,0}^{\text{free}}$, $(R_{1,0}^{\text{complex}} - R_{1,0}^{\text{free}})$, α^{free} , and $(\alpha^{\text{complex}} - \alpha^{\text{free}})$. We shall denote $(R_{1,0}^{\text{complex}} - R_{1,0}^{\text{free}})$ by ΔR_1 ; it arises from all possible contributions due to complex formation.

Note that, if the calixarene concentration ($[C]$) is kept constant for a given series of samples, eq 1 is retrieved from eq 3 with

$$\begin{aligned} R_1^{\text{complex}} &= R_{1,0}^{\text{complex}} + \alpha^{\text{complex}}[C] \\ R_1^{\text{free}} &= R_{1,0}^{\text{free}} + \alpha^{\text{free}}[C] \end{aligned} \quad (4)$$

In that case, R_1^{complex} and R_1^{free} do not vary from one sample to the other ($[C]$ constant) and are therefore the only parameters to be determined.

Returning to eq 3, it will be assumed (and experimentally verified) that $\alpha^{\text{complex}} \approx \alpha^{\text{free}} \approx \alpha$, in such a way that eq 3 can be rewritten as

$$R_1^{\text{obs}} = R_{1,0}^{\text{free}} + \alpha[C] + \Delta R_1 p \quad (5)$$

Before discussing in more detail the values of relaxation rates, it may be of interest to review the relaxation mechanisms¹³ pertaining to the considered aromatic carbons (C_1 , C_3 , and C_4).¹² In addition to the so-called chemical shift anisotropy contribution, R_1^{csa} , which can be important at relatively high magnetic fields (as will be the case here), we have to deal with the dipolar interaction mechanism, leading to a contribution denoted in the following by R_1^{dip} . These interactions can be intramolecular, arising from protons of the calixarene molecule, or intermolecular, arising from water protons or deuterons and, possibly, from paramagnetic species. Altogether, we can write ΔR_1 as arising from these two contributions:

$$\Delta R_1 = \Delta R_1^{\text{csa}} + \Delta R_1^{\text{dip}} \quad (6)$$

At this point, we can recall that any dipolar contribution to the relaxation rate is proportional to $1/r^6$, where r is the distance between the considered carbon and the spin with which it interacts. The effect of molecular motions is accounted for by a factor which decreases when the measurement frequency increases. It must, however, be recognized that this decrease is significant only when very slow molecular motions are present. In our case and to a first approximation, we shall neglect these variations. Conversely, concerning the csa contribution, we assume that, in the present study, it will depend essentially on the square of the measurement frequency besides a factor equal to the square of the shielding anisotropy.

Experimental Section

25,26,27,28-Tetrahydroxy-5,11,17,23-tetrasulfonatocalix[4]-arene (SC4) was purchased from ACROS (hydrate, 95%). Three different batches, designated as SC4_1, SC4_2, and SC4_3, were used for the whole study. SC4 was decolorized by adsorption on active carbon and dried under vacuum at 80 °C; its final water content was checked by potentiometric titration. The cations are produced by the dissociation of CsCl and TiNO_3 , respectively. CsCl and TiNO_3 were bought from Merck (suprapur and pro analysis grade, respectively); after drying, they were stored in a desiccator and used without further purification. All the solutions were prepared by weight in triply distilled H_2O , pure D_2O (Aldrich, 99.990% D atom), or 90% $\text{H}_2\text{O}/10\%$ D_2O mixture. Dissolved oxygen was removed by bubbling high-quality argon for 10 min in sample tubes which were thereafter sealed.

All carbon-13 measurements were performed at 150 MHz and at a temperature of 25 °C with a Bruker Avance DRX spectrometer equipped with a $^1\text{H}/^{13}\text{C}/^{15}\text{N}$ triple cryoprobe operating at 14.1 T. Longitudinal relaxation times were measured with the standard inversion–recovery experiment. Additional measurements were performed at 100 MHz and at 25 °C with a Bruker Avance DRX spectrometer operating at 9.4 T.

Results and Discussion

Before going to calixarene– M^+ complexes, let us consider carbon-13 relaxation rates of the three calixarene batches, SC4_1, SC4_2, and SC4_3, thus, possibly, with different paramagnetic species. These compounds have been dissolved alone in H_2O or D_2O , with the aim to derive information about the role of water in these relaxation studies.¹⁶ Some instructive

TABLE 1: Carbon-13 Longitudinal Relaxation Rates (s⁻¹) of Free Calixarene SC4 in Different Samples (for Numbering, see Figure 1) at 14.1 T and 25 °C^a

sample	C ₁	C ₃	C ₄
SC4_1 in 90% H ₂ O/10% D ₂ O	1.62 ± 0.05	1.27 ± 0.04	1.07 ± 0.03
SC4_2 in pure H ₂ O	0.73 ± 0.04	0.81 ± 0.05	0.64 ± 0.03
SC4_2 in pure D ₂ O	0.77 ± 0.04	0.95 ± 0.05	0.65 ± 0.03
SC4_3 in 90% H ₂ O/10% D ₂ O	0.57 ± 0.02	0.78 ± 0.03	0.58 ± 0.02
SC4_3 in pure D ₂ O	0.67 ± 0.03	0.89 ± 0.04	0.61 ± 0.03

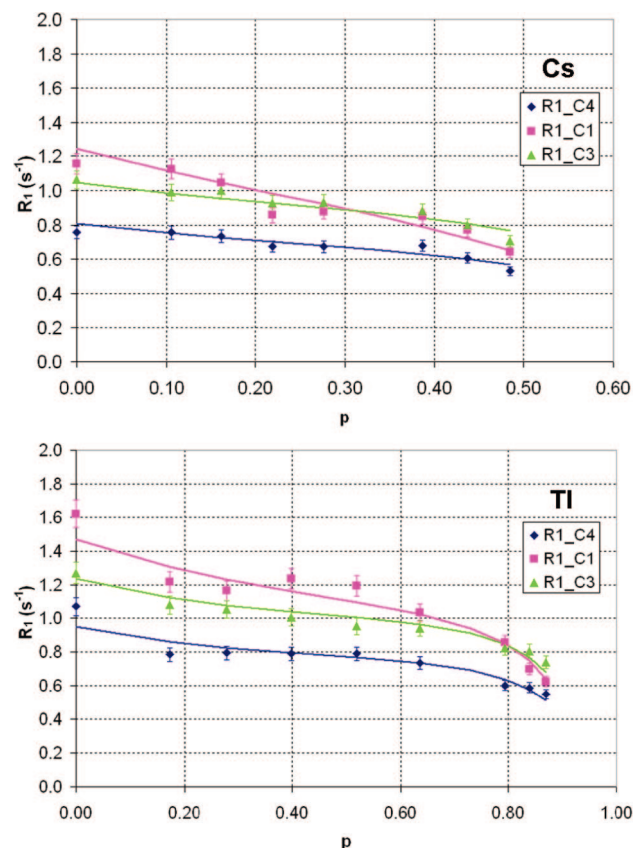
^a SC4_1, SC4_2, and SC4_3 correspond to different batches.**TABLE 2: Concentrations and Proportions (*p*) of Calixarene Molecules Complexing the Metal^a**

[SC4] (mmol/L)	[Cs] (mmol/L)	<i>p</i>	[SC4] (mmol/L)	[Tl] (mmol/L)	<i>p</i>
8.30	24.90	0.48	6.53	32.67	0.87
11.07	22.13	0.44	9.80	29.40	0.84
13.83	19.37	0.39	13.10	26.10	0.79
19.37	13.83	0.28	19.60	19.60	0.64
22.13	11.07	0.22	22.90	16.30	0.52
24.90	8.30	0.16	26.10	13.10	0.40
27.67	5.53	0.11	29.40	9.80	0.28
33.20	0.00	0.00	32.70	6.50	0.17
			39.20	0.00	0.00

^a Samples of the first series, SC4_1 (constant total concentration). $K_a = (45 \pm 5) \text{ L} \cdot \text{mol}^{-1}$ for the complex with Cs and $K_a = (245 \pm 25) \text{ L} \cdot \text{mol}^{-1}$ for the complex with Tl.

conclusions can be drawn from the comparison of the results obtained for the three different samples (gathered in Table 1). The first remark concerns paramagnetic impurities which are less important in SC4_2 than in SC4_1. From the first two rows of Table 1, the difference of paramagnetic contributions can be seen to be 0.89 s^{-1} for C₁, 0.46 s^{-1} for C₃, and 0.43 s^{-1} for C₄. Paramagnetic impurities in SC4_3, if any, appear to be still less important than in SC4_2. As stated in the Introduction, it is safer to rely only on C₁, C₃, and C₄, and it can be noticed that C₁ is more sensitive to paramagnetic impurities than C₃ and C₄. Another very important feature arises from the comparison of C₁, C₃, and C₄ relaxation rates when changing from H₂O to D₂O. If these carbons were subjected to significant dipolar interactions from water, their relaxation rates would drop in D₂O because of the low gyromagnetic ratio of deuterium. We observe just the opposite, and this can be explained by a higher viscosity of D₂O and therefore higher local microviscosities. These features are a first indication of the hydrophobic character at the level of calixarene aromatic cycles, as confirmed by other results presented below.

Samples with Constant Total Concentration (Calixarene + Metal). We turn now to the first series of complexes. For each metal (cesium and thallium), eight to nine samples of variable concentration in calixarene SC4_1 and M⁺ (as indicated above) were prepared in a mixture of 90% H₂O and 10% D₂O. The concentration in calixarene and the quantity *p* (calculated with the association constants indicated above) are given in Table 2 for each sample. Relaxation rates, as measured at 14.1 T, along with the theoretical curves corresponding to eq 5, are displayed in Figure 2. Fits were first performed by linear least squares for each metal (eq 5) and then refined by nonlinear least squares by considering the whole set of data pertaining to both metals. In addition, uncertainties were evaluated by the Monte Carlo method assuming an experimental error of 5% for relaxation rates and 10% for association constants. In the course of the fitting procedure $R_{1,0}^{\text{free}}$ tended to a negative value. This is due to an overwhelming contribution from paramagnetic

**Figure 2.** Carbon-13 longitudinal relaxation rates at 14.1 T, plotted as a function of the proportion of calixarene molecules SC4_1 which form a complex with the cesium cation (top) and the thallium cation (bottom) in 90% H₂O/10% D₂O. The total concentration is held constant (see Table 2). Continuous lines were recalculated with parameters (Table 3) deduced from a fit of experimental data according to eq 5 (with $R_{1,0}^{\text{free}} = 0$).**TABLE 3: Parameters Derived from Carbon-13 Longitudinal Relaxation Data (SC4_1; 9.4 and 14.1 T) According to Eq 5^a**

	C ₁	C ₃	C ₄
$\Delta R_1^{\text{Cs}} (\text{s}^{-1}) (150 \text{ MHz})$	0.70 ± 0.07	1.04 ± 0.08	0.75 ± 0.06
$\Delta R_1^{\text{Tl}} (\text{s}^{-1}) (150 \text{ MHz})$	0.46 ± 0.03	0.55 ± 0.03	0.41 ± 0.02
$\alpha (\text{s}^{-1} \cdot \text{mol}^{-1} \cdot \text{L}) (150 \text{ MHz})$	37.48 ± 0.81	31.47 ± 0.68	24.28 ± 0.53
$\Delta R_1^{\text{Cs}} (\text{s}^{-1}) (100 \text{ MHz})$	0.43 ± 0.05	0.60 ± 0.05	0.55 ± 0.05
$\Delta R_1^{\text{Tl}} (\text{s}^{-1}) (100 \text{ MHz})$	0.28 ± 0.02	0.31 ± 0.02	0.23 ± 0.02
$\alpha (\text{s}^{-1} \cdot \text{mol}^{-1} \cdot \text{L}) (100 \text{ MHz})$	32.82 ± 0.68	25.89 ± 0.58	19.04 ± 0.41

^a Uncertainties were evaluated by the Monte Carlo method with 1000 iterations.

relaxation. It was therefore decided that $R_{1,0}^{\text{free}}$ should be negligibly small and could be set to zero (owing to experimental uncertainties). Therefore it was decided to fit only ΔR_1^{Cs} , ΔR_1^{Tl} , and α . Values and uncertainties are gathered in Table 3. It can be seen that the curvature exhibited by the plot of experimental data vs *p* is very satisfactorily reproduced by the recalculated curves (Figure 2). This supports the model represented by eq 5. Also in Table 3 are given the values of ΔR_1^{Cs} and ΔR_1^{Tl} obtained at a field of 9.4 T (raw data are similar to those shown in Figure 2 and have been processed in the same way).

We first discuss the α values which are seen to decrease from C₁ to C₄. This is not surprising because, intuitively, we can assume that the paramagnetic species which are in the solution (thus, those corresponding to α) have less access to the bottom

TABLE 4: Chemical Shift Anisotropy (csa) and Paramagnetic Contributions Derived from ΔR_1 Obtained at Two Values of Magnetic Field (Table 3) According to Eqs 7 and 8

	C_1	C_3	C_4
$\Delta R_1^{\text{csa,Cs}}$ (s^{-1}) (100 MHz)	0.22 ± 0.12	0.36 ± 0.13	0.16 ± 0.11
$\Delta R_1^{\text{para,Cs}}$ (s^{-1})	0.21 ± 0.17	0.24 ± 0.18	0.39 ± 0.16
$\Delta R_1^{\text{csa,Tl}}$ (s^{-1}) (100 MHz)	0.15 ± 0.05	0.19 ± 0.05	0.15 ± 0.04
$\Delta R_1^{\text{para,Tl}}$ (s^{-1})	0.13 ± 0.07	0.12 ± 0.07	0.08 ± 0.06

of the calixarene cavity. This nicely confirms what has been deduced from the comparison of SC4_1 and SC4_2 in aqueous solution.

Of course, the parameter of interest is ΔR_1 , and the first striking feature comes from the large values of ΔR_1^{Cs} and ΔR_1^{Tl} , as well as from their large difference. A first attempt would be to consider that they originate from the dipolar interaction between the considered carbon-13 and the metal. A simple calculation performed with a typical distance of 3 Å (deduced from an approximate geometry) leads to an effective correlation time (characterizing the molecular motions). We arrive at values of the order of 0.3 μs for thallium and 30 μs for cesium. These values are obviously unrealistic, and one is thus forced to look for other mechanisms, namely, as already considered, interaction with paramagnetic species and chemical shift anisotropy. The presence of paramagnetic species was already demonstrated from the relaxation rates of the three series of samples, and because we have at hand measurements performed at two different frequencies (namely 150 and 100 MHz), it should be possible to evaluate the two contributions ΔR_1^{csa} and ΔR_1^{para} (which stands here for ΔR_1^{dip} , as the dipolar interactions arising from the unpaired electrons of paramagnetic species can be assumed to be largely dominant). According to the approximation indicated above, we can write

$$\Delta R_1^{\text{csa}}(150) = \left(\frac{\omega_c^{150}}{\omega_c^{100}} \right)^2 \Delta R_1^{\text{csa}}(100) \quad \text{and} \quad \Delta R_1^{\text{para}}(150) = \Delta R_1^{\text{para}}(100) = \Delta R_1^{\text{para}}$$

and consequently

$$\Delta R_1^{\text{csa}}(100) = \frac{\Delta R_1(150) - \Delta R_1(100)}{\left(\frac{\omega_c^{150}}{\omega_c^{100}} \right)^2 - 1} \quad (7)$$

Likewise

$$\Delta R_1^{\text{para}} = \Delta R_1(100) - \Delta R_1^{\text{csa}}(100) \quad (8)$$

The values deduced from eqs 7 and 8 are given in Table 4. Owing to the large uncertainties, it is obvious that they provide only trends, and it can be seen that, although the paramagnetic contribution is important, it competes with the csa contribution. Nevertheless, these results, along with the global ΔR_1 values, clearly indicate that both cations lie, in the complex, at the bottom of the cavity. On the other hand, perturbation to the carbon relaxation is less important in the case of complexes with thallium than for complexes with cesium. This is probably related to faster exchange in the case of thallium.

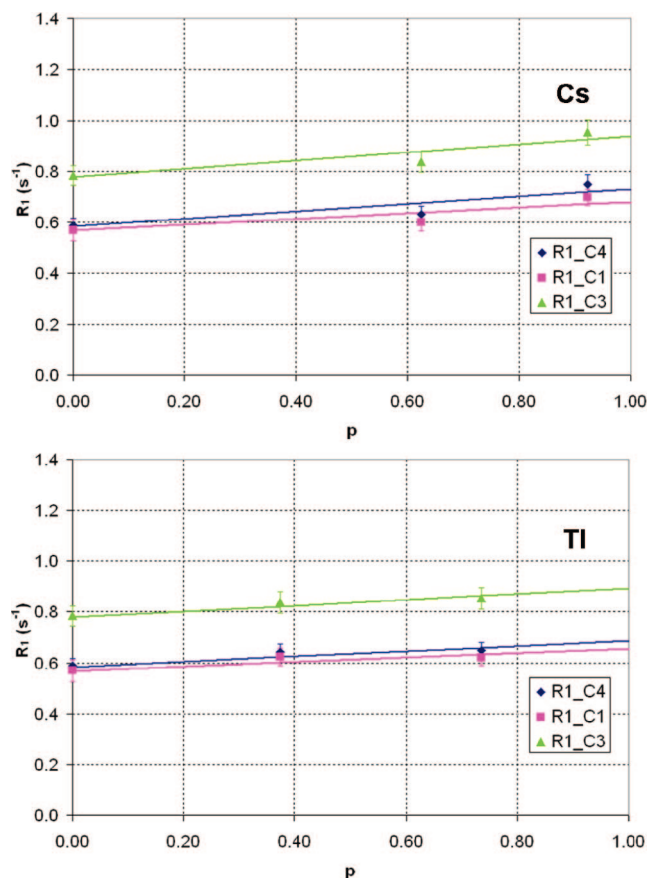


Figure 3. Carbon-13 longitudinal relaxation rates at 14.1 T, plotted as a function of the proportion of calixarene molecules SC4_3 which form a complex with the cesium cation (top) and the thallium cation (bottom) in 90% H₂O/10% D₂O. The calixarene concentration is held constant so that the data representation is linear and can be fitted according to eq 1, thus providing directly R_1^{free} and R_1^{complex} (Table 5). Samples of SC4_3 in D₂O lead to similar results.

Samples with Constant Calixarene Concentration (SC4_2, SC4_3). As already indicated, the analysis of carbon-13 relaxation times will be easier if calixarene concentration is held constant since data can simply be interpreted according to eq 1. A linear representation (R_1 vs p) should be obtained, yielding R_1^{complex} and R_1^{free} .

We first studied a series of samples made with SC4_2, the second batch of calixarene (the first one, SC4_1, being no longer available) at fixed calixarene concentration (39.2 mmol/L in D₂O) and with metal concentrations (five samples for cesium and five samples for thallium) yielding p values in the same range as those investigated in the first series of samples (see Table 2). This was primarily performed to check the validity of eq 1. Perfect linear representations were obtained (not shown). However, the range of cesium concentration (and therefore of p values) was not sufficient to determine R_1^{complex} and R_1^{free} accurately.

The validity of eq 1 being firmly established, we then decided to proceed only with three concentrations for each metal covering the widest range, in H₂O and also in D₂O. Unfortunately, at that time, SC4_2 turned out to be unavailable and we had to turn to a third batch of calixarene (SC4_3). Part of the experimental results are shown in Figure 3 along with the best straight lines fitting these data. Equation 1 appears perfectly valid, and the parameters of interest are reported in Table 5. Compared to the results of SC4_1 and concerning the perturbations at the level of C_1 , C_3 , and C_4 , the same trends are observed

TABLE 5: Relaxation Rates (s⁻¹) Derived from Carbon-13 Longitudinal Relaxation Data (SC4_3, 14.1 T) According to Eq 1^a

	C ₁	C ₃	C ₄
R_1^{free} (90% H ₂ O/10% D ₂ O)	0.57 ± 0.03	0.78 ± 0.04	0.58 ± 0.03
$R_1^{\text{complex,Cs}}$ (90% H ₂ O/10% D ₂ O)	0.68 ± 0.03	0.94 ± 0.04	0.73 ± 0.03
ΔR_1^{Cs} (90% H ₂ O/10% D ₂ O)	0.11 ± 0.06	0.16 ± 0.08	0.15 ± 0.06
$R_1^{\text{complex,Tl}}$ (90% H ₂ O/10% D ₂ O)	0.66 ± 0.04	0.89 ± 0.06	0.69 ± 0.04
ΔR_1^{Tl} (90% H ₂ O/10% D ₂ O)	0.09 ± 0.07	0.11 ± 0.10	0.11 ± 0.07
R_1^{free} (D ₂ O)	0.66 ± 0.03	0.89 ± 0.04	0.61 ± 0.03
$R_1^{\text{complex,Cs}}$ (D ₂ O)	0.79 ± 0.03	1.07 ± 0.05	0.72 ± 0.03
ΔR_1^{Cs} (D ₂ O)	0.13 ± 0.06	0.18 ± 0.09	0.11 ± 0.03
$R_1^{\text{complex,Tl}}$ (D ₂ O)	0.77 ± 0.05	1.02 ± 0.06	0.67 ± 0.05
ΔR_1^{Tl} (D ₂ O)	0.11 ± 0.08	0.13 ± 0.10	0.06 ± 0.08

^a Uncertainties were evaluated by the Monte Carlo method with 1000 iterations. The solvent is indicated in parentheses.

although with less amplitude. This is due to the lack of paramagnetic species (or to a much lesser amount). Thus, the only significant contribution arises from csa, and a thorough analysis of its variation (when going to the complexed form) will be the subject of a future publication. Nevertheless, these results validate perfectly the conclusions reached with the first series of samples (SC4_1). Another important conclusion arises from the comparison of samples for which H₂O or D₂O was used. R_1^{complex} follows the same evolution as R_1^{free} , i.e., a slight increase of the relaxation rate when going from H₂O to D₂O. As already explained, this cannot be due to dipolar interactions with water protons or deuterons (it would be the opposite behavior). This indicates again the absence of water inside the cavity and probably around the aromatic cycles. This is further confirmed by the values of ($R_1^{\text{complex}} - R_1^{\text{free}}$) which are, within experimental uncertainties, the same when D₂O and H₂O are used. This demonstrates that water plays no role in the complexation process: (i) it is not expelled from the calixarene cavity (of course, since its presence is very unlikely); (ii) it does not accompany the cation when it enters the cavity. Interestingly, the simulations⁷ carried out by coupling the molecular mechanics method with DFT calculations indicated that the bottom of the cavity of the calixarene is desolvated when Cs⁺ is inserted into the cavity, with the first water molecules being located at 4 Å, in the vicinity of the sulfonate groups; although this structure must be taken with caution because of the several compromises that were necessary to achieve the simulation, it appears to be in line with the experimental observations presented here.

Conclusions

The findings of this work can be summarized as follows:

1. As expected, the SC4 cavity is essentially hydrophobic; this has been proven by the absence of water in any instance (with or without cation). SC4 can be dissolved in water thanks to its sulfonate and hydroxyl groups.

2. SC4 is able to complex the two monovalent cations cesium and thallium. Our results show that the cations are well inside the calixarene cavity. This is further confirmed by the separation of the two contributions (paramagnetic and csa).

3. Cesium possesses less mobility than thallium within the calixarene cavity. This can be related to different exchange rates.

These conclusions are drawn from simple carbon-13 NMR relaxation measurements. Their relevance comes, however, from a proper choice of carbons in the calixarene molecule (not bonded to hydrogen(s) to avoid a dominant relaxation mechanism) and from the fact that one calixarene sample possessed by chance paramagnetic impurities which, again by chance, do not act in the same way when the cation is complexed by the calixarene. This has the virtue of enhancing dipolar interactions, thus leading to the visualization of the cation location within the calixarene cavity. In fact, this property is almost as old as NMR and is well-known for its ability to enhance relaxation rates of nuclei in the vicinity of the paramagnetic species.¹⁷

Acknowledgment. NMR experiments have been performed in part at the service de Biophysicochimie et des Interactions moléculaires (UHP). D.C. is supported by a Ph.D. French ministerial fellowship.

References and Notes

- (1) Morel, J. P.; Morel-Desrosiers, N. *Org. Biomol. Chem.* **2006**, *4*, 462–465.
- (2) Cuc, D.; Canet, D.; Morel, J. P.; Morel-Desrosiers, N.; Mutzenhardt, P. *ChemPhysChem* **2007**, *8*, 643–645.
- (3) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420–5426.
- (4) Perret, F.; Morel, J. P.; Morel-Desrosiers, N. *Supramol. Chem.* **2003**, *15*, 199–206.
- (5) Bonal, C.; Israël, Y.; Morel, J. P.; Morel-Desrosiers, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1075–1078.
- (6) Mendes, A.; Bonal, C.; Morel-Desrosiers, N.; Morel, J. P.; Malfreyt, P. *J. Phys. Chem. B* **2002**, *106*, 4516–4524.
- (7) Ghoufi, A.; Archirel, P.; Morel, J. P.; Morel-Desrosiers, N.; Boutin, A.; Malfreyt, P. *ChemPhysChem* **2007**, *8*, 1648–1656.
- (8) Marcus, I. *Ion Properties*; Marcel Dekker: New York, 1997.
- (9) Cuc, D. Ph.D. Thesis, Henri Poincaré-Nancy I University, 2008.
- (10) Tosner, Z.; Lang, J.; Sandstrom, D.; Petrov, O.; Kowalewski, J. *J. Phys. Chem. A* **2002**, *106*, 8870–8875.
- (11) Kriz, J.; Dybal, J.; Makrlík, E.; Budka, J. *Magn. Reson. Chem.* **2008**, *46*, 235–243.
- (12) Kowalewski, J.; Ericsson, A.; Vestin, R. *J. Magn. Reson.* **1978**, *31*, 165.
- (13) Kowalewski, J.; Maler, L. *Nuclear spin relaxation in liquids: Theory, experiments and Applications*; Taylor & Francis: London, 2006; p 39.
- (14) Job, P. *Ann. Chim.* **1928**, *9*, 113–203.
- (15) Connors, K. A. *Binding Constants. The Measurement of Molecular Complex Stability*; Wiley: New York, 1987; pp 24–28.
- (16) Seba, H. B.; Thureau, P.; Ancian, B.; Thevand, A. *Magn. Reson. Chem.* **2006**, *44*, 1109–1117.
- (17) Banci, L.; Bertini, I.; Luchinat, C. *Nuclear and Electron Relaxation. The Magnetic Nucleus-Unpaired Electron Coupling in Solution*; VCH: New York, 1991.

JP8067816