Behavior of Cesium and Thallium Cations inside a Calixarene Cavity As Probed by Nuclear Spin Relaxation. Evidence of Cation−π Interactions in Water

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Received: March 27, 2009; Revised Manuscript Received: May 6, 2009

We have studied the complexes formed between the *p*-sulfonatocalix[4]arene and cesium or thallium metal cation, first by carbon-13 longitudinal relaxation of the calixarene molecule at two values of the magnetic field **B**₀. From the longitudinal relaxation times of an aromatic carbon directly bonded to a proton, thus subjected essentially to the dipolar interaction with that proton, we could obtain the correlation time describing the reorientation of the CH bond. The rest of this study has demonstrated that it is also the correlation time describing the tumbling of the whole calixarene assembly. From three non-proton-bearing carbons of the aromatic cycles (thus subjected to the chemical shift anisotropy and dipolar mechanisms), we have been able to determine the variation of the chemical shift anisotropy when going from the free to the complex form of the calixarene. These variations not only provide the location of the cation inside the calixarene cavity but also constitute a direct experimental proof of the cation−π interactions. These results are complemented by cesium and thallium relaxation measurements performed again at two values of the magnetic field **B**₀. An estimation of the mean distance between the cation and the calixarene protons could be obtained. These measurements have also revealed an important chemical shift anisotropy of thallium upon complexation.

Introduction

The macrocyclic *p*-sulfonatocalixarenes are able to complex a variety of neutral or charged guests in water.[1,2] The complexes formed between the *p*-sulfonatocalix[4]arene and the metal cations were shown to be strongly charge-dependent. Microcalorimetry[1] and molecular dynamics[3] indeed revealed that the divalent and trivalent metal cations remain outside the host cavity where they do form strong outer-sphere (solvent-mediated) complexes with the SO_3^- groups fixed on the upper rim of the calixarene. The complexation of these multivalent cations was totally entropy-controlled, with thermodynamic parameters ($\Delta_r H° > 0$ and $T\Delta_r S° \gg 0$) reflecting essentially the desolvation of the charged groups upon binding. For a long time, the monovalent metal cations were considered to be not complexed by the *p*-sulfonatocalix[4]arene. However, the formation of very weak but selective complexes was recently evidenced by highly sensitive microcalorimetry.[4] Interestingly, the thermodynamic parameters of complexation ($\Delta_r H° \ll 0$ and $T\Delta_r S° < 0$ or ≈ 0) were in sharp contrast with those observed with multivalent cations, the process being totally enthalpy-controlled, and led to the conclusion that the monovalent metal cations bind inside the cavity where they can interact with the π-electrons of the phenyl groups of the calixarene. The inclusion of Cs^+ was confirmed by ^{133}Cs pulsed-gradient spin echo diffusion data[5] and by a numerical approach combining molecular mechanics and DFT calculations.[6]

In a previous study, we have shown by paramagnetic induced carbon-13 spin relaxation that the two monovalent cations, cesium and thallium, when complexed by the *p*-sulfonatocalix[4]arene, are well inside the cavity, approximately at similar locations, but with, apparently, a greater mobility for thallium.[7] Here, we are able to proceed with samples devoid of paramagnetic impurities to measure calixarene carbon-13 and proton longitudinal relaxation times (T_1) at two different values of the static magnetic field. These results, which are interpreted in terms of dipolar interactions and chemical shift anisotropy, provide a clear picture of the host−guest interactions and, in particular, demonstrate the validity of the cation−π model. Longitudinal and transverse relaxation times (T_1 and T_2) of the cations were also measured and their analysis (again in terms of dipolar interactions and chemical shift anisotropy) confirmed and complemented the information deduced from relaxation of nuclei belonging to the calixarene. In particular, exchange phenomena are unraveled for thallium, but not for cesium.

Experimental Section

The host molecule is the *p*-sulfonatocalix[4]arene (Figure 1). 25,26,27,28-Tetrahydroxy-5,11,17,23-tetrasulfonatocalix[4]arene (SC4) has been purchased from ACROS (hydrate, 95%). Two different batches have been used for the whole study. Indeed, calixarene carbon-13 and proton longitudinal relaxation times (T_1) have been measured at two different values of the static magnetic field on samples devoid of paramagnetic impurities. Conversely, longitudinal and transverse relaxation times (T_1 and T_2) of the cations have been measured earlier on another series of samples, which involve paramagnetic impurities,[7] and it will be demonstrated that the latter species have no significant influence on the cation relaxation times. SC4 has been decol-

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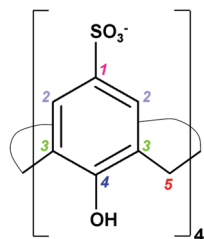† Nancy-Université.
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Calixarene Complexes Studied by NMR Spin Relaxation

J. Phys. Chem. B, Vol. 113, No. 31, 2009 **10801**

Figure 1. Structure of the *p*-sulfonatocalix[4]arene.

orized by adsorption on active carbon and dried under vacuum at 80 °C; its final water content has been checked by potentiometric titration. The cations are produced by the dissociation of CsCl and TlNO$_3$, respectively. CsCl and TlNO$_3$ have been bought from Merck (suprapur and pro analysis grade, respectively); after drying, they have been stored in a desiccator and used without further purification. All the solutions have been prepared by weight in pure D$_2$O (Aldrich, 99.990% D atom) or in (90% H$_2$O)/(10% D$_2$O) mixture. Dissolved oxygen has been removed by bubbling high quality argon for 10 min in sample tubes that have been thereafter sealed.

All experiments have been carried out at 25 °C. Proton and carbon-13 T_1 measurements have been performed at two values of the static magnetic field (corresponding to proton frequencies of 600 and 400 MHz) with the standard inversion−recovery sequence on two Bruker Avance spectrometers (the 600 MHz spectrometer is equipped with a cryogenic probe).

Cesium and thallium T_1 and T_2 have been measured at two values of the static magnetic field corresponding respectively to proton resonance frequencies of 400 MHz (Bruker Avance spectrometer) and 200 MHz (homemade spectrometer). For speeding up the experiments in case of large T_1's and for avoiding problems associated with imperfect 180° pulses, T_1 has been systematically measured by the saturation-recovery sequence and, when sensitivity was too low (as it was often the case with the 200 MHz spectrometer), with a method involving only two points of the evolution curve and interleaved scans.[8] T_2 has been measured by a simple Hahn spin echo sequence with the EXORCYCLE phase cycling.[9] Again, when necessary, the two-point methodology has been used.

The association constants have been derived previously from Job plots pertaining to cation chemical shifts ($K = 45 \pm 5$ for cesium and $K = 245 \pm 25$ for thallium)[10] and permit derivation of the relaxation times in the complex state according to the formula: $R^{obs} = pR^{complex} + (1 - p)R^{free}$ (where R is a relaxation rate, which is the inverse of the relaxation time), p being the proportion of systems in the complex state (known from the concentrations and from the association constants). R^{obs} is the observed relaxation rate, $R^{complex}$ is the relaxation rate in the complex (to be determined), and R^{free} is the relaxation rate in a solution where the considered species is alone (determined from an independent measurement).

For cesium and thallium, about 10 measurements (with different concentrations of the cation and of the calixarene, chosen initially for applying the Job's plot methodology;[11] these concentrations can be found in ref 7), have been performed allowing us to derive an accurate value of $R^{complex}$.

Theory

All our experimental relaxation data depend, to a very good approximation, on only two mechanisms: dipolar and chemical shift anisotropy (csa) and possibly the effect of exchange in the

case of T_2. The contributions to the relaxation rates are well-known.[12,13] Those relevant to the present work are listed below.

In the homonuclear case (here protons), the dipolar contribution can be written as

$$R_{1,dip}^{homo} = 3K_{dip}[4\tilde{J}(2\omega_0) + \tilde{J}(\omega_0)] \quad (1)$$

In the heteronuclear case (for instance, A can be a carbon-13 and B a proton), the dipolar contributions can be written as

$$R_{1,dip}^{A} = K_{dip}[6\tilde{J}(\omega_A + \omega_B) + 3\tilde{J}(\omega_A) + \tilde{J}(\omega_A - \omega_B)] \quad (2)$$

$$R_{2,dip}^{A} = K_{dip}\left[3\tilde{J}(\omega_A + \omega_B) + \frac{3}{2}\tilde{J}(\omega_A) + 3\tilde{J}(\omega_B) + \frac{1}{2}\tilde{J}(\omega_A - \omega_B) + 2\tilde{J}(0)\right] \quad (3)$$

With the usual meaning of the various symbols, the constant K_{dip} is written as

$$K_{dip} = \frac{1}{20} \times \left(\frac{\mu_0}{4\pi}\right)^2 \frac{(\gamma_A\gamma_B\hbar^2)^2}{r^6} \quad (4)$$

In the above expressions (and in the following), ω's are resonance frequencies in rad s^{-1} and r is the distance between the two interacting nuclei (A and B in the heteronuclear case). γ_A and γ_B are the gyromagnetic constants, and μ_0 is the vacuum permittivity.

$$R_{1,csa} = \frac{1}{15}\omega_0^2(\Delta\sigma)^2\tilde{J}(\omega_0) \quad (5)$$

$$R_{2,csa} = \frac{1}{15}\omega_0^2(\Delta\sigma)^2\left[\frac{1}{2}\tilde{J}(\omega_0) + \frac{2}{3}\tilde{J}(0)\right] \quad (6)$$

In (5) and (6), $\Delta\sigma$ is the so-called chemical shift anisotropy for a shielding tensor supposed to be of axial symmetry.

In all the above expressions of relaxation rates, $\tilde{J}(\omega)$ are the so-called spectral densities, which describe the reorientational motion to which is subjected the entity carrying the considered spin. Various unsuccessful attempts to proceed with the superposition of two types of motion have shown that, here, only one correlation time τ_c is necessary for the spins of the calixarene molecule (except perhaps for the CH$_2$ groupings, which, in addition to the molecular tumbling motion, may experience internal motions) as well as for the cation spins. This means that the calixarene molecule reorients isotropically and that, to a first approximation, the complexed cations are not subjected to other motions. This could be surprising with regard to several studies[14−16] in which a local motion was unraveled for the guest entity. It should, however, be noted that (i) the host−guest systems are somewhat different from ours (cryptophanes as hosts and small organic molecules as guests) and (ii) the effect of the local motion, according to the so-called Lipari−Szabo approach,[17,18] is weighted by $(1 - S^2)$, where S is an order parameter. Here, the order parameter might be close to unity. Anyhow, in our case, the spectral density has a very simple form:

$$\tilde{J}(\omega) = \frac{2\tau_c}{1 + \omega^2 \tau_c^2} \quad (7)$$

Determination of the Correlation Time: Proton and Carbon-13 Relaxation of the Aromatic CH in the Calixarene Molecule. It can be safely assumed here that protons relax essentially through dipolar interactions with other protons. Let us consider the aromatic proton at the C_2 position (Figure 1), thus in the rigid part of the molecule. It can be safely assumed that the vector joining this proton to other protons in the molecule reorients in the same way as the whole molecular assembly. We can thus hope to determine τ_c from the ratio of relaxation rates measured at two different frequencies (here 600 and 400 MHz). This is because this ratio depends only on τ_c and measurements frequencies as indicated below (see eq 1):

$$\frac{R_1^H(600)}{R_1^H(400)} = \frac{\dfrac{4}{1 + (2\omega_H^{600})^2 \tau_c^2} + \dfrac{1}{1 + (\omega_H^{600})^2 \tau_c^2}}{\dfrac{4}{1 + (2\omega_H^{400})^2 \tau_c^2} + \dfrac{1}{1 + (\omega_H^{400})^2 \tau_c^2}} \quad (8)$$

On the other hand, simulations have shown that, in the case of the carbon C_2, the chemical shift anisotropy contribution is small. This is due to the fact that the dipolar interaction with its directly bonded proton is predominant. Therefore, for this carbon-13 we can rely on a ratio similar to the one of eq 8, which, again, will provide τ_c (150 and 100 MHz are the corresponding carbon resonance frequencies):

$$\frac{R_I^C(150)}{R_I^C(100)} = \frac{\dfrac{6}{1 + (\omega_C^{150} + \omega_H^{600})^2 \tau_c^2} + \dfrac{3}{1 + (\omega_C^{150})^2 \tau_c^2} + \dfrac{1}{1 + (\omega_C^{150} - \omega_H^{600})^2 \tau_c^2}}{\dfrac{6}{1 + (\omega_C^{100} + \omega_H^{400})^2 \tau_c^2} + \dfrac{3}{1 + (\omega_C^{100})^2 \tau_c^2} + \dfrac{1}{1 + (\omega_C^{100} - \omega_H^{400})^2 \tau_c^2}} \quad (9)$$

The experimental results are gathered in Table 1 together with the correlation times obtained from eqs 8 and 9. Correlation times deduced from proton relaxation, though of a correct order of magnitude, may be slightly in error due to an intermolecular dipolar contribution that could be indicated by the decrease of the relaxation rates when going from H_2O to D_2O. Obviously, the contribution of intermolecular dipolar interactions to relaxation rates do not involve only the correlation time associated

with the reorientation of the calixarene molecule. This explains the slight difference with the results derived from carbon-13 relaxation rates that arise solely from intramolecular interactions. We notice that complexation affects very little the relaxation rates (this can only be due to a change of the chemical shift anisotropy value; see below) and not at all the derived correlation times. Referring to the Stokes−Einstein equation, we can conclude that the calixarene volume is not significantly modified upon complexation. Owing to experimental uncertainties, we have first determined the following approximate mean values

$$\tau_c = 0.10 \text{ ns in } H_2O$$

$$\tau_c = 0.12 \text{ ns in } D_2O$$

It can be noted that the increase of the correlation time, when D_2O is used, corresponds to the viscosity increase (when going from H_2O to D_2O). Moreover, attempts to determine the chemical shift anisotropy contribution have failed, again because of the preeminent dipolar contribution and because of the experimental uncertainties. According to the results of Table 1 and to reduce the uncertainty on τ_c, we decided to fit simultaneously all the C_2 carbon-13 relaxation rates with the constraint $\tau_c(D_2O) = 1.2\tau_c(H_2O)$ and to determine the uncertainty on τ_c by Monte Carlo calculations. We finally obtained $\tau_c(H_2O) = 0.10 \pm 0.05$ ns. This value will be retained in the following and its relatively large uncertainty will be shown not to affect significantly the main conclusions of the present study. Moreover, to validate this result, we have recalculated, with this value of τ_c, the C−H distance from eq 2. We found 1 Å, slightly lower than the expected value. This is, however, quite satisfactory owing to the absence of vibrational corrections.

Determination of the Chemical Shift Anisotropy of the Non-Proton-Bearing Aromatic Carbons in the Calixarene Molecule. Once we have in hand the correlation time (appropriate for describing the reorientation of the calixarene molecule, either free or in a complex state), we can hope to derive the two contributions, dipolar and chemical shift anisotropy, from only two carbon-13 longitudinal relaxation rates measured at two values of the magnetic field. This is possible here because the dipolar contribution is no longer preeminent (carbons not directly bonded to protons). The two relaxation rates measured at 100 and 150 MHz can be expressed as follows (from eqs 2 and 5).

$$\begin{aligned} R_1(150) &= f_{11}K_{dip} + f_{12}(\Delta\sigma)^2 \\ R_1(100) &= f_{21}K_{dip} + f_{22}(\Delta\sigma)^2 \end{aligned} \quad (10)$$

with

TABLE 1: Determination of the Correlation time τ_c (ns) from the Proton (a) and Carbon-13 (b) Relaxation Rates of the Aromatic CH Moiety in the Calixarene Molecule[a]

solvent	calixarene	$R_1^H(600)$, s^{-1}	$R_1^H(400)$, s^{-1}	$\tau_c^{(a)}$, ns	$R_I^C(150)$, s^{-1}	$R_I^C(100)$, s^{-1}	$\tau_c^{(b)}$, ns
90% H$_2$O 10% D$_2$O	free	0.73 ± 0.02	0.98 ± 0.03	0.14 ± 0.02	3.34 ± 0.09	3.58 ± 0.10	0.10 ± 0.06
D$_2$O		0.65 ± 0.02	0.82 ± 0.02	0.12 ± 0.02	3.42 ± 0.09	3.68 ± 0.10	0.11 ± 0.05
90% H$_2$O 10% D$_2$O	complexCs	0.67 ± 0.02	0.93 ± 0.03	0.16 ± 0.03	3.39 ± 0.09	3.67 ± 0.10	0.11 ± 0.06
D$_2$O		0.62 ± 0.02	0.84 ± 0.02	0.15 ± 0.03	3.83 ± 0.11	4.26 ± 0.11	0.14 ± 0.06
90% H$_2$O 10% D$_2$O	complex Tl	0.76 ± 0.03	0.94 ± 0.04	0.11 ± 0.03	3.17 ± 0.13	3.33 ± 0.14	0.08 ± 0.09
D$_2$O		0.68 ± 0.03	0.87 ± 0.03	0.12 ± 0.03	3.74 ± 0.15	4.11 ± 0.16	0.13 ± 0.10

[a] The measurement frequency in MHz is in parentheses.

Calixarene Complexes Studied by NMR Spin Relaxation

J. Phys. Chem. B, Vol. 113, No. 31, 2009 **10803**

$$f_{11} = 2\tau_c \left[\frac{6}{1 + (\omega_C^{150} + \omega_H^{600})^2 \tau_c^2} + \frac{3}{1 + (\omega_C^{150})^2 \tau_c^2} + \frac{1}{1 + (\omega_C^{150} - \omega_H^{600})^2 \tau_c^2} \right]$$

$$f_{12} = \frac{2\tau_c}{15} \frac{(\omega_C^{150})^2}{1 + (\omega_C^{150})^2 \tau_c^2}$$

$$f_{21} = 2\tau_c \left[\frac{6}{1 + (\omega_C^{100} + \omega_H^{400})^2 \tau_c^2} + \frac{3}{1 + (\omega_C^{100})^2 \tau_c^2} + \frac{1}{1 + (\omega_C^{100} - \omega_H^{400})^2 \tau_c^2} \right]$$

$$f_{22} = \frac{2\tau_c}{15} \frac{(\omega_C^{100})^2}{1 + (\omega_C^{100})^2 \tau_c^2}$$

$$(11)$$

Solving eqs 10 yields

$$\Delta\sigma = \sqrt{\frac{f_{11}R_1(100) - f_{21}R_1(150)}{f_{11}f_{22} - f_{21}f_{12}}}$$

$$K_{dip} = \frac{R_1(100) - f_{22}(csa)^2}{f_{21}}$$

$$(12)$$

Experimental data along with results in terms of $\Delta\sigma$ and K_{dip} are gathered in Tables 2−4 for the carbons C_1, C_3, and C_4 (Figure 1).

Let us recall that these three carbons are not directly bonded to a proton; as a consequence, the chemical shift anisotropy values should be reliable. Moreover, we notice that the $\Delta\sigma$ deduced from (12) does not depend, as expected, on the solvent (H_2O or D_2O). This is also true for K_{dip}, which also does not seem to depend on the presence of the metal inside the cavity. We consequently assume that K_{dip} is the same for the free and complex states and can be fitted globally. Uncertainties on $\Delta\sigma$ and on K_{dip} are derived again from Monte Carlo calculations. K_{dip} arises from several dipolar interactions that can be evaluated from a known average structure of the calixarene molecule (derived from molecular modelisation). Calculated values,

reported in the last row of Table 5, are remarkably close to the experimental values. This is a further proof of the consistency of our experimental determinations.

In addition, we have calculated $\Delta\sigma$ mean values for the free calixarene, for the complex calixarene@cesium and for the complex calixarene@thallium. Results are also reported in Table 5 together with the carbon $\Delta\sigma$ variation for both complexes. First, it can be observed that the correct order of magnitude is retrieved for $\Delta\sigma$.[19] Second, it is the variation of $\Delta\sigma$ (when going from the free state to the complex) that provides invaluable information. This variation is obviously due to a change in the electronic distribution around the considered carbons. It indicates clearly that the cation is inside the cavity but also that it is the π electronic distribution that is altered since, in these aromatic cycles, $\Delta\sigma$ originates mainly from this π electronic distribution. The latter considerations are therefore a proof of the cation−π interaction. The differences in the $\Delta\sigma$ variations for the two cations will be discussed later.

Cesium Relaxation. The experimental results for R_1 and R_2 as a function of p are shown in Figure 2 ($R^{complex}$ and R^{free} are obtained from the linear fit of $R^{obs} = pR^{complex} + (1 - p)R^{free}$), and the relevant parameters are reported in Table 6. We first consider the comparison between R_1 and R_2 data. As experimental uncertainties are larger for R_2 data than for R_1 data, we conclude that there is no significant difference between these two sets of data. As a consequence, we conclude that possible exchange phenomena are not detectable by spin relaxation and that it is sufficient to discuss the R_1 data (which should be more accurate than R_2 data). As the $R_1^{complex}$ is larger at the smallest magnetic field, dipolar relaxation is likely to be the dominant mechanism (since for chemical shift anisotropy, relaxation rates increase when the magnetic field increases). Because we are dealing with samples containing paramagnetic species, a first assumption could be that cesium relaxation is dominated by dipolar interactions with the unpaired electrons. In that case, the spectral densities $\tilde{J}(\omega_{Cs} + \omega_e)$ and $\tilde{J}(\omega_{Cs} - \omega_e)$ in eq 2 (ω_{Cs} and ω_e standing respectively for the cesium and electron resonance frequencies) would simply vanish due to the large value of ω_e. We would therefore be left with the term $3\tilde{J}(\omega_{Cs})$ in eq 2. Denoting by $R_1^{complex}(53)$ and $R_1^{complex}(26)$ the longitudinal relaxation rates at the two considered values of the magnetic field (9.4 and 4.7 T, respectively, 53 and 26 MHz

TABLE 2: Experimental Results for the Calixarene Carbon-13 C_1 Together with the Molecular Parameters Derived from Eqs 10−12[a]

solvent	calixarene	$R_1^C(150)$, s^{-1}	$R_1^C(100)$, s^{-1}	$\Delta\sigma$, ppm	K_{dip}, 10^9 s^{-2}
90% H$_2$O 10% D$_2$O	free	0.57 ± 0.02	0.37 ± 0.01	174.6 ± 11.2	0.11 ± 0.02
D$_2$O		0.66 ± 0.02	0.41 ± 0.01		
90% H$_2$O 10% D$_2$O	complexCs	0.68 ± 0.02	0.44 ± 0.01	200.7 ± 12.1	
D$_2$O		0.79 ± 0.02	0.51 ± 0.01		
90% H$_2$O 10% D$_2$O	complex Tl	0.66 ± 0.03	0.42 ± 0.02	196.3 ± 12.7	
D$_2$O		0.77 ± 0.03	0.50 ± 0.02		

[a] Measurement frequencies in MHz are in parentheses.

TABLE 3: Experimental Results for the Calixarene Carbon-13 C_3 Together with the Molecular Parameters Derived from Eqs 10−12[a]

solvent	calixarene	$R_1^C(150)$, s^{-1}	$R_1^C(100)$, s^{-1}	$\Delta\sigma$, ppm	K_{dip}, 10^9 s^{-2}
90% H$_2$O 10% D$_2$O	free	0.78 ± 0.02	0.51 ± 0.01	199.6 ± 11.3	0.16 ± 0.02
D$_2$O		0.89 ± 0.02	0.56 ± 0.02		
90% H$_2$O 10% D$_2$O	complexCs	0.94 ± 0.03	0.62 ± 0.02	232.4 ± 12.8	
D$_2$O		1.07 ± 0.03	0.70 ± 0.02		
90% H$_2$O 10% D$_2$O	complex Tl	0.89 ± 0.03	0.56 ± 0.02	224.3 ± 12.8	
D$_2$O		1.02 ± 0.04	0.63 ± 0.02		

[a] Measurement frequencies in MHz are in parentheses.

TABLE 4: Experimental Results for the Calixarene Carbon-13 C_4 Together with the Molecular Parameters Derived from Eqs 10−12[a]

solvent	calixarene	$R_1^C(150)$, s^{-1}	$R_1^C(100)$, s^{-1}	$\Delta\sigma$, ppm	K_{dip}, 10^9 s^{-2}
90% H_2O 10% D_2O	free	0.58 ± 0.02	0.38 ± 0.01	179.8 ± 10.7	0.08 ± 0.01
D_2O		0.61 ± 0.02	0.32 ± 0.01		
90% H_2O 10% D_2O	complexCs	0.73 ± 0.02	0.46 ± 0.01	207.1 ± 12.2	
D_2O		0.72 ± 0.02	0.43 ± 0.01		
90% H_2O 10% D_2O	complex Tl	0.69 ± 0.03	0.40 ± 0.02	197.3 ± 11.9	
D_2O		0.67 ± 0.03	0.41 ± 0.02		

[a] Measurement frequencies in MHz are in parentheses.

TABLE 5: Mean $\Delta\sigma$ Values (ppm) of the Three Aromatic Carbons Not Directly Bonded to a Proton (in the Considered Calixarene Free Molecule or in Its Complexes) and Values of the Parameter K_{dip} ($\times 10^9$ s^{-2}), Which Indicates the Strength of the Dipolar Interactions Sensed by These Nuclei[a]

	C_1	C_3	C_4
$\Delta\sigma$ free (ppm)	174.6 ± 11.2	199.6 ± 11.3	179.8 ± 10.7
$\Delta\sigma$ complex Cs (ppm)	200.7 ± 12.1	232.4 ± 12.8	207.1 ± 12.2
variation/free	$(15.0 \pm 3.6)\%$	$(16.4 \pm 2.3)\%$	$(15.2 \pm 1.9)\%$
$\Delta\sigma$ complex Tl (ppm)	196.3 ± 12.7	224.3 ± 12.8	197.3 ± 11.9
variation/free	$(12.5 \pm 4.0)\%$	$(12.3 \pm 2.5)\%$	$(9.7 \pm 2.1)\%$
K_{dip} exp ($\times 10^9$ s^{-2})	0.11 ± 0.02	0.16 ± 0.02	0.08 ± 0.01
K_{dip} calc ($\times 10^9$ s^{-2})	0.10	0.16	0.08

[a] In the last row are reported K_{dip} values calculated from an average calixarene structure (see text).

being the cesium resonance frequencies), we would obtain for their ratio

$$\frac{R_1^{complex}(53)}{R_1^{complex}(26)} = \frac{1 + (\omega_{Cs}^{26})^2\tau_c^2}{1 + (\omega_{Cs}^{53})^2\tau_c^2} \quad (13)$$

With an experimental ratio of 0.92 (calculated from the data in Table 6), we would arrive at a correlation time of about 1 ns, thus an order of magnitude larger than the calixarene reorientation correlation time. This is very unlikely, especially because exchange phenomena (which could alter the effective correlation time[13]) are not detectable. Indeed, if additional motions are present, the effective correlation time cannot be larger than the host correlation time (0.1 ns). As a matter of fact, we reach consistent results by assuming that dipolar interactions with protons are responsible for the observed experimental data. With this second assumption, the ratio of eq 13 becomes

$$\frac{R_1^{complex}(53)}{R_1^{complex}(26)} = \frac{\dfrac{6}{1 + (\omega_{Cs}^{53} + \omega_H^{400})^2\tau_c^2} + \dfrac{3}{1 + (\omega_{Cs}^{53})^2\tau_c^2} + \dfrac{1}{1 + (\omega_{Cs}^{53} - \omega_H^{400})^2\tau_c^2}}{\dfrac{6}{1 + (\omega_{Cs}^{26} + \omega_H^{200})^2\tau_c^2} + \dfrac{3}{1 + (\omega_{Cs}^{26})^2\tau_c^2} + \dfrac{1}{1 + (\omega_{Cs}^{26} - \omega_H^{200})^2\tau_c^2}} \quad (14)$$

With the correlation time corresponding to the calixarene reorientation (0.1 ns), we find 0.96 instead of the experimental value of 0.92. The order of magnitude is therefore correct, and

this makes possible the determination of the distance between cesium and the calixarene protons (see below). Nevertheless, the major conclusion is that cesium is mainly subjected to dipolar interactions with calixarene protons and not to dipolar interactions with unpaired electrons of paramagnetic species. This is in contrast with calixarene carbons that are, for a large part, subjected to these paramagnetic species.[7] We are therefore forced to admit that, in the complex, the latter are close to the aromatic cycles and remote from the metal. This will be assumed for thallium as well (next section). We can thus attempt to interpret the data by postulating that there is a single relaxation mechanism stemming from dipolar interactions. With such a hypothesis and taking into account the 16 protons belonging to the calixarene molecule, the dipolar contributions to the two relaxation rates (in the complex form) at 26 and 53 MHz can be written as

$$R_1^{dip}(26) = 16K_{dip}2\tau_c\left(\frac{6}{1 + (\omega_{Cs}^{26} + \omega_H^{200})^2\tau_c^2} + \frac{3}{1 + (\omega_{Cs}^{26})^2\tau_c^2} + \frac{1}{1 + (\omega_{Cs}^{26} - \omega_H^{200})^2\tau_c^2}\right) \quad (15)$$

$$R_1^{dip}(53) = 16K_{dip}2\tau_c\left(\frac{6}{1 + (\omega_{Cs}^{53} + \omega_H^{400})^2\tau_c^2} + \frac{3}{1 + (\omega_{Cs}^{53})^2\tau_c^2} + \frac{1}{1 + (\omega_{Cs}^{53} - \omega_H^{400})^2\tau_c^2}\right) \quad (16)$$

The distance r, which is involved in K_{dip} (see (12)), can be considered as a sort of mean distance between cesium and the calixarene protons. As in previous calculations, τ_c has been set at 0.1 ns and K_{dip} has been fitted from experimental data at the two magnetic field values, yielding $r = 1.50$ Å. We thus find the correct order of magnitude of r. It must be emphasized that the latter value is only a coarse approximation of a sort of mean distance. This is because the meaning of r corresponds to the following equation: $1/r = [\Sigma_i(1/r_i^6)]^{1/6}$, where r_i is the distance between the metal and the ith proton of the calixarene molecule. With this value of r and within experimental uncertainties, we are able to retrieve relaxation rate values close to the experimental ones. This is a clear evidence that chemical shift anisotropy does not contribute to cesium relaxation rates. Conversely, we cannot exclude minor contributions from paramagnetic relaxation (see above) and/or from quadrupolar relaxation (cesium has a spin 7/2). This would not radically change our conclusions except that the value found for r could be underestimated. As a matter of fact, owing to the consistency of our results, the quadrupolar contribution is probably very weak. This could arise from a small electronic field gradient resulting from a quasi symmetric environment of the cesium cation.

Calixarene Complexes Studied by NMR Spin Relaxation

J. Phys. Chem. B, Vol. 113, No. 31, 2009 **10805**
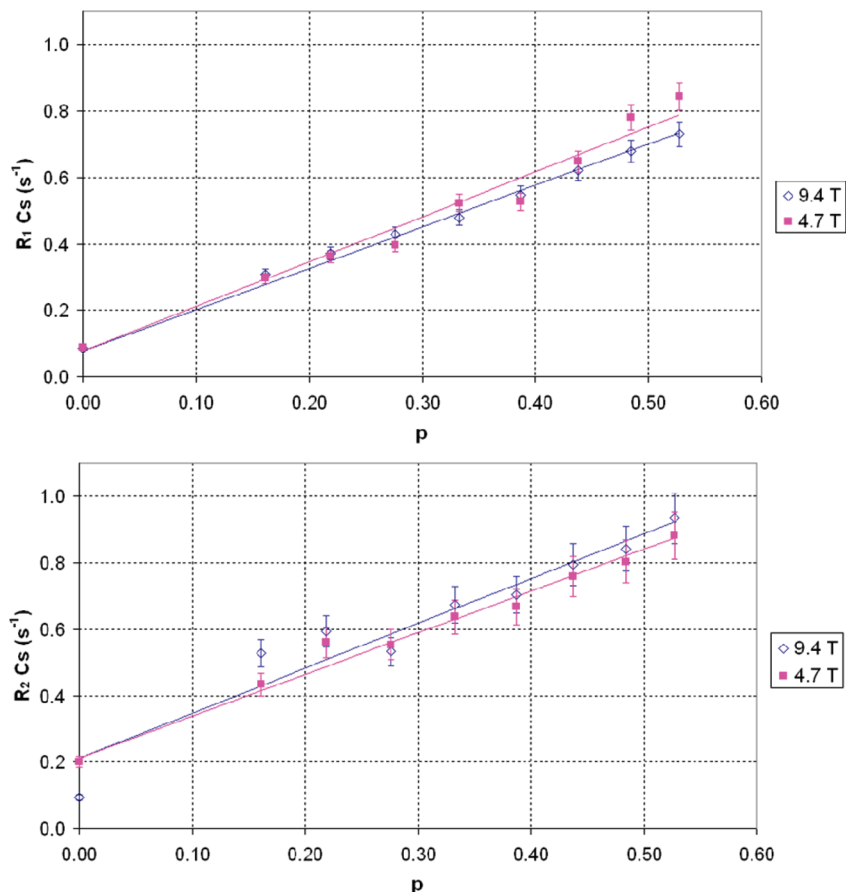
Figure 2. Relaxation rates (s^{-1}) of cesium as a function of the complex proportion at two values of the magnetic field (4.7 and 9.4 T). Top: longitudinal relaxation rates. Bottom: transverse relaxation rates.

Thallium Relaxation. Experimental results are shown in Figure 3, and parameters extracted from these results are given in Table 6 (thallium resonance frequencies are 230 and 115 MHz, at magnetic field values identical to those of the cesium study).

The striking feature of the R_1 results is the increase with the magnetic field value. This indicates unambiguously a preeminent contribution from chemical shift anisotropy, which adds to the dipolar interactions with protons of the calixarene molecule. Thus, longitudinal relaxation rates can be interpreted according to the following expressions

$$R_1^{complex}(115) = 16K_{dip}2\tau_c\left(\frac{6}{1+(\omega_{Tl}^{115}+\omega_H^{200})^2\tau_c^2}+\right.$$
$$\left.\frac{3}{1+(\omega_{Tl}^{115})^2\tau_c^2}+\frac{1}{1+(\omega_{Tl}^{115}-\omega_H^{200})^2\tau_c^2}\right)+$$
$$\Delta\sigma^2\frac{2\tau_c}{15}\frac{(\omega_{Tl}^{115})^2}{1+(\omega_{Tl}^{115})^2\tau_c^2} \quad (17)$$

$$R_1^{complex}(230) = 16K_{dip}2\tau_c\left(\frac{6}{1+(\omega_{Tl}^{230}+\omega_H^{400})^2\tau_c^2}+\right.$$
$$\left.\frac{3}{1+(\omega_{Tl}^{230})^2\tau_c^2}+\frac{1}{1+(\omega_{Tl}^{230}-\omega_H^{400})^2\tau_c^2}\right)+$$
$$\Delta\sigma^2\frac{2\tau_c}{15}\frac{(\omega_{Tl}^{230})^2}{1+(\omega_{Tl}^{230})^2\tau_c^2} \quad (18)$$

With, as before, $\tau_c = 0.1$ ns (various attempts with smaller τ_c did not lead to consistent results), we can solve these two

equations and obtain K_{dip} and $\Delta\sigma$. From K_{dip}, we obtain a mean distance of 1.94 Å between the thallium cation and the calixarene protons (this distance, as for cesium, could be underestimated). Note that this distance is larger than in the case of cesium. This could be expected from the properties of the cations and also because exchange phenomena are much faster for thallium than for cesium (see below). We find a chemical shift anisotropy value of 468 ppm. This relatively large value is attributable to the important thallium chemical shift range, which is related to a significant deformation of the electronic distribution.

We turn now to transverse relaxation. The high value of the corresponding relaxation rates (see Table 6) indicate an important contribution from chemical exchange, which can be evaluated by

$$R_2^{exch} = R_2^{obs} - R_2^{dip} - R_2^{csa} \quad (19)$$

R_2^{obs} is the experimental relaxation rates; R_2^{dip} and R_2^{csa} have been calculated from formulas 3 and 6 using the values of $\langle r_{Tl,H}\rangle$ and $\Delta\sigma$ given in Table 6. The values of R_2^{exch} are reported in Table 6 and are seen to be relatively large. On the other hand, if the exchange rate was similar for thallium and cesium, we would expect a cesium relaxation rate of about 25 s^{-1} owing to the chemical shift differences between the two forms (110.5 ppm for thallium and 12.4 ppm for cesium).[10] As this is not the case ($R_2 \cong R_1$), this confirms that exchange phenomena do not affect cesium transverse relaxation whereas they are predominant for thallium transverse relaxation. For the latter, proportionality with the square of $\mathbf{B}_0$ was expected in the case of fast exchange.

TABLE 6: Cesium and Thallium Relaxation Data along with the Complexation Parameters of Interest Derived from These Data^a

metal	$R_1(9.4T)$, s^{-1}	$R_1(4.7T)$, s^{-1}	$\langle r_{M,H}\rangle$, Å	$\Delta\sigma$, ppm	$R_2(9.4T)$, s^{-1}	$R_2(4.7T)$, s^{-1}	$R_2^{exch}(9.4T)$, s^{-1}	$R_2^{exch}(4.7T)$, s^{-1}
Cs free	0.08 ± 0.01	0.08 ± 0.01			0.21 ± 0.02	0.21 ± 0.02		
complex Cs	1.32 ± 0.08	1.43 ± 0.08	1.50 ± 0.04		1.57 ± 0.15	1.47 ± 0.10		
Tl free	1.13 ± 0.12	1.13 ± 0.12			21.0 ± 2.8	21.0 ± 2.8		
complex Tl	11.28 ± 0.44	7.11 ± 0.28	1.94 ± 0.06	468 ± 40	274.4 ± 10.7	140.2 ± 5.6	263.0 ± 10.7	133.9 ± 5.5

^{a} $\langle r_{M,H}\rangle$ stands for the mean distance between the metal and the calixarene protons as defined in text; $\Delta\sigma$ is the chemical shift anisotropy value of the metal in the complexed form. R_2^{exch} represents the contribution of exchange to the transverse relaxation rate.
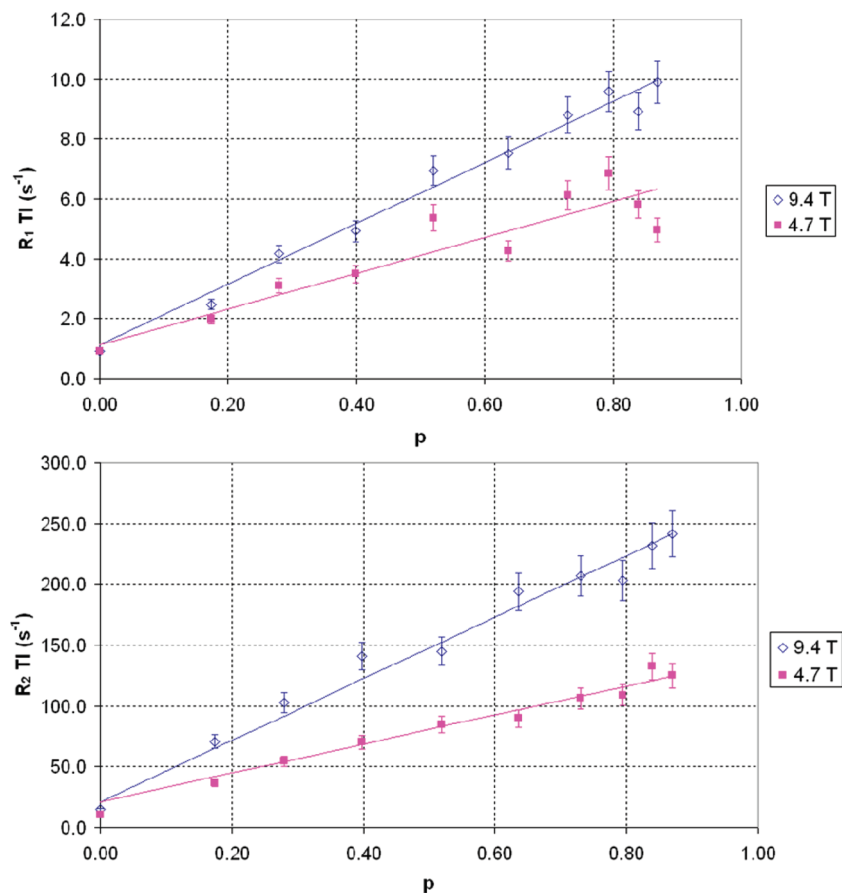
Figure 3. Relaxation rates (s^{-1}) of thallium as a function of the complex proportion at two values of the magnetic field (4.7 and 9.4 T). Top: longitudinal relaxation rates. Bottom: transverse relaxation rates.

This dependence is not observed here, maybe due to various approximations and/or uncertainties.

Conclusion

Through calixarene carbon-13 relaxation, cesium relaxation, and thallium relaxation, we arrive at a consistent picture of the considered complexes. Carbon-13 chemical shift anisotropy variations not only demonstrate unambiguously the cation$-\pi$ interactions but also show that the two cations are similarly located in the cavity at the level of the aromatic cycles. Exchange phenomena affecting thallium could be responsible for a smaller variation of chemical shift anisotropy compared to that for cesium. Indeed, chemical shift anisotropy is very sensitive to the electronic distribution. The fact that this anisotropy increases in the complex form indicates clearly a deformation of the electronic cloud. This is necessarily due to the vicinity of the cation and its specific interaction with aromatic cycles, i.e., the so-called cation$-\pi$ interaction.

The above results have required the estimation of a correlation time describing the reorientation of the whole assembly; this

has been achieved through carbon-13 longitudinal relaxation of the CH group in the aromatic cycle. It turns out that this correlation time is also valid for exploiting the relaxation times of the cations themselves. Longitudinal relaxation times of the cations do confirm, at least qualitatively, what has been deduced from calixarene carbon-13 relaxation measurements. We have also been able to estimate a sort of mean distance between the cation and the calixarene protons. This distance, which might be underestimated, is slightly larger for thallium than for cesium; this can be put in line with the ionic radii of the two cations, the smallest cation being the most mobile and therefore prone to be the most remote. This metal$-$proton distance is actually the mean distance between the metal and a virtual proton, which, from geometrical considerations, is necessarily located on the symmetry axis of the calixarene and inside the cavity. The short distances measured in both cases indicate therefore that metal ions are located inside the cavity. On the other hand, upon complexation, a large chemical shift anisotropy has been observed in the case of thallium in contrast with cesium for which we have been unable to detect any csa contribution,

Calixarene Complexes Studied by NMR Spin Relaxation

J. Phys. Chem. B, Vol. 113, No. 31, 2009 **10807**

probably due to a much smaller gyromagnetic constant. Anyhow, a difference in polarizability could also explain this feature.

Previously, it was shown by both microcalorimetry[4] and NMR[5,10] that, in water, the stability constant of the *p*-sulfonatocalix[4]arene complex with Tl^+ is much larger than that with Cs^+. Although Tl^+ is more strongly solvated than Cs^+,[20] it is also more strongly complexed because its interactions with the phenyl rings of the calixarene cavity are more important (the $Tl^+-\pi$ interactions are stronger because the polarizability of Tl^+ is twice that of Cs^+ [20]). These thermodynamic findings, which do characterize the equilibrium state of the system, are not in contradiction with the results presented here, which shed light on the kinetic aspects of the complex formation by showing that the exchange is faster for Tl^+ than for Cs^+: the thermodynamic properties at equilibrium cannot be related to the exchange rates in a simple manner because the latter do in fact reflect the activation parameters of the exchange processes, which are complex and highly dependent on the ion, in particular on its hydration structure.

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