

Influence of the Cavity Size of Water-Soluble Cryptophanes on Their Binding Properties for Cesium and Thallium Cations

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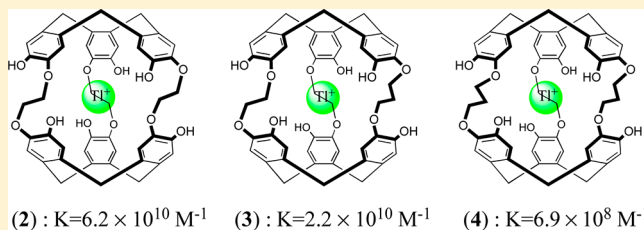
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Supporting Information

ABSTRACT: The binding properties of water-soluble cryptophane **1** toward cesium and thallium cations, in basic solution, have recently been reported. In this Article, we show that water-soluble cryptophane-222 (**2**), cryptophane-223 (**3**), and cryptophane-233 (**4**), bearing zero, one, and two propylene-dioxy linkers, respectively, also efficiently bind these two cations under similar experimental conditions. Their binding properties are thoroughly studied by ¹³³Cs and ²⁰⁵Tl NMR spectroscopy, while the binding constants are determined by isothermal titration calorimetry (ITC) experiments under various experimental conditions. Complexation of cesium and thallium is also evidenced by electronic circular dichroism (ECD) using the enantiopure *MM*-2 compound. This study reveals that the cavity size of the cryptophane is not the main parameter to observe efficient binding. In contrast, the number of phenolate moieties surrounding the cryptophane backbone seems to be pivotal for the complexation of these two cations. These results are important in the field of detoxification.



■ INTRODUCTION

The synthesis of molecular ligands able to selectively trap cesium (Cs) or thallium (Tl) cations at low concentrations in organic or aqueous solvents is of great interest in the field of environmental chemistry. Indeed, cesium and thallium are two very toxic elements that can contaminate air, soils, and water, thereby representing a threat for populations exposed to these elements. For instance, the radioactive ¹³⁷-cesium isotope (¹³⁷Cs) is produced in nuclear reactors and it is one of the most abundant elements present in nuclear waste. ¹³⁷Cs contamination mainly occurs when this radioactive element is accidentally released in the atmosphere after a nuclear accident (Chernobyl 1986, Fukushima-Daiichi 2011). Due to its half-life of 30 years, this element can easily contaminate air, soils and water for a long period of time. On the other hand, thallium has been released to the ecosystem as a byproduct from the extraction of iron, cadmium, and zinc. Thallium is also present in coal ashes produced by coal power stations. It is thus present in significant amount in wastewater discharges released by these stations and can contaminate rivers and groundwater. The high toxicity of this element makes this element a serious threat for the population living near these coal power stations.

Therefore, the synthesis of molecular ligands able to selectively encapsulate cesium and thallium(I) at very low concentrations is of major concern. Various supramolecular systems bearing oxygen atoms within their structure, which can

interact with the cations, (crown-ethers derivatives) or several aromatic rings aimed at stabilizing the complex via π -cation interactions (calixarene derivatives) have been described in the literature.¹ Most of them, exhibit large binding constants in organic solvents (about 10^6 M^{-1})^{1f-i,k,l,r} with cesium, but very few are water-soluble. In addition, the binding constants strongly decrease when water-soluble compounds are used. Hence, it is very important to synthesize new molecular sensors which are soluble in aqueous solutions and which exhibit very high binding constants with cesium and thallium(I).

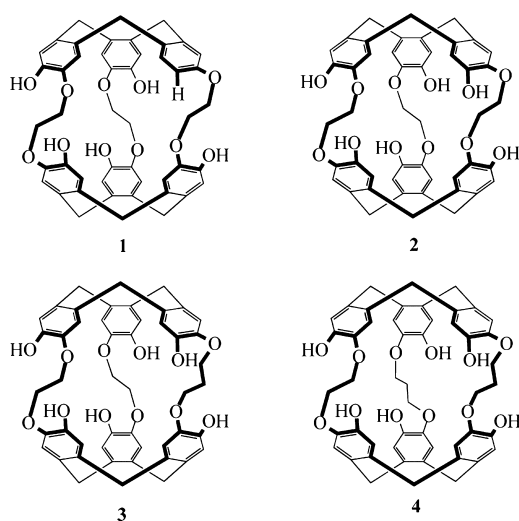
Cryptophane derivatives are hollow molecules able to encapsulate a large range of substrates in organic or aqueous solvents.² For instance, water-soluble cryptophanes can encapsulate small neutral molecules (chiral or achiral), charged molecules (ammonium) or even xenon.³ Recently, we have shown that water-soluble cryptophanes bearing hydroxyl functions could efficiently encapsulate cesium or thallium(I) cations under basic conditions.⁴ The binding constants determined from isothermal titration calorimetry (ITC) experiments are, to our knowledge, the highest values ever found for this kind of host molecule. Thus, cryptophane **1** bearing five hydroxyl groups (Scheme 1) is able to encapsulate

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Scheme 1. Chemical Structure of Water-Soluble Cryptophanes 1–4^a



^aOnly a single enantiomer (*MM*) is shown.

Cs⁺ with a binding constant, *K*, of $5.3 \times 10^8 \text{ M}^{-1}$ in NaOH/H₂O (0.1 M) solution at 298 K. The affinity of **1** for the thallium cation is even stronger ($K = 2.9 \times 10^9 \text{ M}^{-1}$) in the same experimental conditions, due to the higher polarizability of this cation.⁵ This binding process has been also associated with a strong modification of the chiroptical properties of the host as observed by electronic circular dichroism (ECD) and vibrational circular dichroism (VCD). In addition, both ¹³³Cs and ²⁰⁵Tl NMR spectroscopy revealed strongly shifted NMR signals for the encapsulated species due to the shielding of the six aromatic benzene rings surrounding the Cs⁺ or Tl⁺ cations.

Even though a lot of data were collected during the last two years about the complexation of Cs⁺ and Tl⁺ cations by water-soluble cryptophanes,⁴ some questions concerning these host–guest complexes still arise. For instance, the importance of the presence of phenolate groups in the stabilization of these complexes has not been clearly established. Indeed, these molecules are only soluble under basic conditions, and the synthesis of cryptophanes bearing hydroxyl functions, soluble in water at neutral pH, has to be achieved. The size of the cavity of the cryptophane is also another parameter that could affect significantly the binding properties of these host molecules toward Cs⁺ and Tl⁺ cations.

In this Article, we wish to investigate in details the influence of the cavity size of cryptophane on the binding properties of cesium and thallium(I) cations. Water-soluble cryptophanes **2**, **3**, and **4** bearing six hydroxyl functions on the aromatic rings and different numbers of ethylenedioxy and propylenedioxy linkers have been prepared (Scheme 1). By replacing ethylenedioxy linkers by propylenedioxy linkers, it has been possible to modulate the size of the inner cavity from $V_{\text{vdw}} = 95 \text{ \AA}^3$ (cryptophane **2**) to $V_{\text{vdw}} = 117 \text{ \AA}^3$ (cryptophane **4**). The ability of these cryptophanes to bind Cs⁺ and Tl⁺ cations has been revealed by ¹³³Cs and ²⁰⁵Tl NMR spectroscopy. The binding constants have been measured by ITC experiments at 298 K under several experimental conditions. The effect of the nature of the solution (LiOH/H₂O, NaOH/H₂O and KOH/H₂O) and the concentration of the basic solution (0.1 and 1 M) has been thoroughly investigated. Finally, the enantiopure *MM*-2 derivative has been prepared to investigate the spectral

changes occurring during the binding process by ECD spectroscopy. These data have been compared to those previously obtained for cryptophane **1**.

■ EXPERIMENTAL SECTION

Synthesis of Cryptophanes 2, 3 and 4. The cryptophanes **2**, **3**, and **4** were prepared according to a known procedure starting from the respective hexa-methoxy cryptophanes.^{3d,6} Particular attention was paid to the purification of the compounds. The synthetic route to obtain enantiopure cryptophane *MM*-2 was previously reported.^{3f} Cryptophane **5**, bearing three propylenedioxy linkers, was also prepared according to a known procedure.⁷ The ¹H NMR spectra of compounds **2**–**5** are given in the Supporting Information (S1–S4).

UV–Vis and ECD Measurements. UV–vis and ECD spectra were recorded at 293 K, using a 1.0 cm path length quartz cell. The concentration of *MM*-2 was in the range of 10^{-5} M in basic H₂O solutions (0.1 M solutions of NaOH and KOH). Additional ECD spectra were recorded at higher concentrations (1 and 3 M) in NaOH and KOH. Spectra were recorded in the 220–400 nm spectral range with a 0.5 nm increment and a 1 s integration time. Spectra were processed with standard spectrometer software and baseline corrected without smoothing. Spectral units are expressed in difference in molar extinction coefficients.

ITC Experiments. Isothermal Titration Calorimetry (ITC) experiments were performed at 298 K. In a typical experiment, the host solution ($\sim 0.1 \text{ mM}$) in LiOH (0.1 M), NaOH (0.1 M) or KOH (0.1 M) was placed in the calorimeter cell (1.4 mL) and 28 successive aliquots (10 μL) of guest solution (10 times more concentrated) were added via a computer-automated injector at 3 min intervals. Heat changes were recorded after each addition. Heats of dilution were measured by a blank experiment (in the absence of host) under the same conditions, and they were subtracted from the titration data prior to curve fitting. The first injection was discarded from each data set to remove the effect of guest diffusion across the syringe tip during the equilibration process. Titrations curves were fitted with the one binding site model. Additional ITC experiments were performed at higher LiOH/H₂O, NaOH/H₂O or KOH/H₂O (1 M) concentrations under the same conditions.

NMR Experiments. ¹³³Cs NMR spectra (65.587 MHz) were recorded on a 11.7 T Bruker Avance spectrometer using a 5 mm probehead. A solution of cesium nitrate was used as the chemical shift reference (0 ppm). A delay time of 1 s was applied between each pulse. At 298 K the delay time was 5 s. The ²⁰⁵Tl NMR experiments were performed on a Bruker DMX300 spectrometer (7 T) equipped with a 5 mm BB Nalorac probehead recovered from an 11.7 T spectrometer. First, a solution of thallium nitrate was used as a chemical shift reference (0 ppm). Then, the other spectra were recorded by part. The interscan delay was 0.9 s. For all the displayed ²⁰⁵Tl NMR spectra the FIDs were apodized by an exponential window of 200 Hz before Fourier transformation.

■ RESULTS

UV–Vis and ECD Spectroscopy of Compound *MM*-2. The complexation of the cesium and thallium cations by enantiopure cryptophane *MM*-2 has been investigated by UV–vis and ECD spectroscopy in NaOH/H₂O and KOH/H₂O

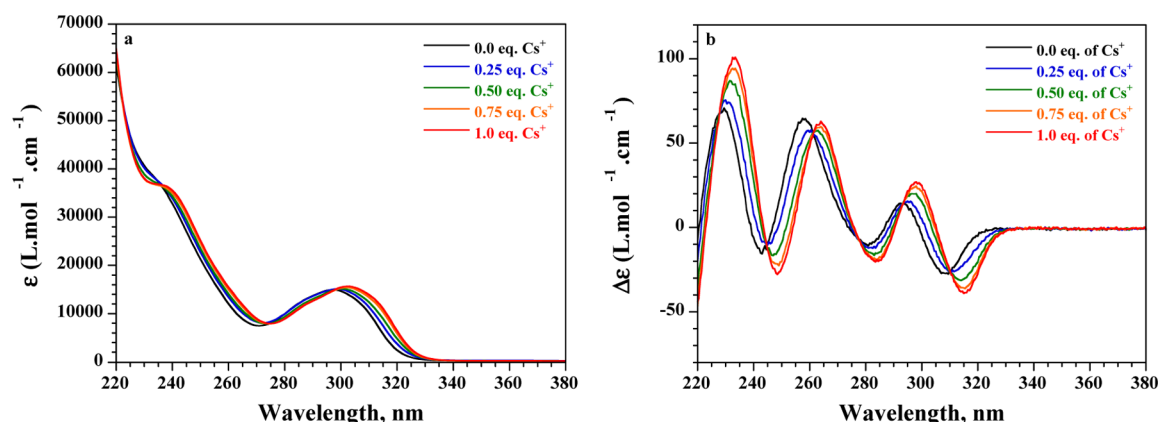


Figure 1. (a) UV-vis spectra recorded at 293 K of MM-2 ([host] 2.9×10^{-5} M, path length of 1 cm) in NaOH/H₂O solution (0.1 M) in the presence of different amounts of cesium hydroxide solution. (b) ECD spectra recorded at 293 K of MM-2 ([host] 1.55×10^{-5} M, path length of 1 cm) in NaOH/H₂O solution (0.1 M) in the presence of different amounts of cesium hydroxide solution. ECD spectra for higher [Cs⁺] are identical to that recorded for 1 equiv of Cs⁺.

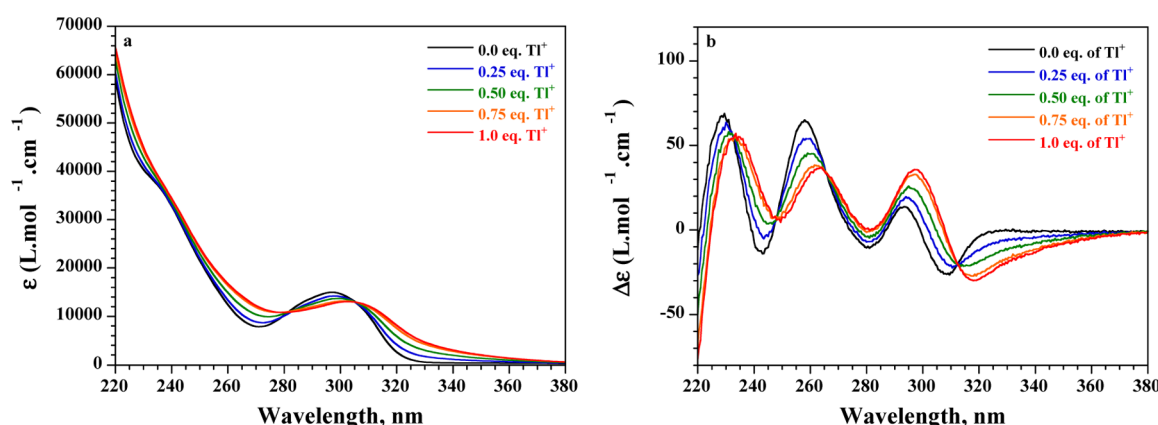


Figure 2. (a) UV-vis spectra recorded at 293 K of MM-2 ([host] 2.54×10^{-5} M, path length of 1 cm) in NaOH/H₂O solution (0.1 M) in the presence of different amounts of thallium acetate solution. (b) ECD spectra recorded at 293 K of MM-2 ([host] 1.64×10^{-5} M, path length of 1 cm) in NaOH/H₂O solution (0.1 M) in the presence of different amounts of thallium acetate solution. ECD spectra for higher [Tl⁺] are identical to that recorded for 1 equiv of Tl⁺.

solutions of various concentrations (0.1, 1 and 3 M) at 293 K. The UV-vis and ECD spectra of empty MM-2 and MM-2 in the presence of cesium hydroxide are reported in Figure 1 in the 220–380 nm spectral range. The UV-vis spectra (Figure 1a) exhibit strong absorption below 220 nm corresponding to the allowed ¹B_g transition (Platt's notation) of the benzene rings and two absorption bands of medium intensity around 240 and 300 nm corresponding to the two forbidden ¹L_a and ¹L_b transitions of the benzene rings, respectively. The UV-vis spectrum of empty MM-2 is slightly modified by the addition of cesium hydroxide, involving a bathochromic shift of the ¹L_a and ¹L_b transitions. On the other hand, Figure 1b shows that the addition of various quantities of a cesium hydroxide solution (from 0 to 1 equiv) to the NaOH/H₂O solution of guest free host 2 gives rise to a significant change of the overall ECD spectrum in the 220–380 nm region. A bathochromic shift of the whole spectrum is observed and the presence of six isosbestic points indicates the formation of a new species upon addition of Cs⁺. This new species can be attributed to the formation of the Cs⁺@MM-2 complex. Replacing the Cs⁺ cation by the more polarizable Tl⁺ cation leads to more marked modifications of the UV-vis and ECD spectra of MM-2 (Figures 2a,b). These spectral changes mainly occur for the

ECD bands of the ¹L_b transition (280–320 nm) for which addition of one equivalent of Tl⁺ result in a significant bathochromic shift (Figure 2b). As observed with Cs⁺, the ECD spectra also reveal the presence of several isosbestic points indicating the formation of the Tl⁺@MM-2 complex. The ECD spectra of MM-2 in the presence of Cs⁺ or Tl⁺ cations have also been found very dependent on the experimental conditions. For instance, the presence of a competitor (CHCl₃) inside the cavity of MM-2 significantly affects the overall ECD spectrum of compound MM-2. The replacement of the chloroform molecule by the Cs⁺ or the Tl⁺ cations has a dramatic effect on the global shape of the ECD spectrum of MM-2, especially for the ECD bands of the allowed ¹B_g transition located at short wavelength (close to 220 nm). Indeed, a strong decrease in intensity is observed upon addition of Cs⁺ or Tl⁺ cations into the solution (Supporting Information, S5a and S5b). The presence of isosbestic points indicates that both the Cs⁺@MM-2 and Tl⁺@MM-2 complexes are efficiently formed and that these two cations can successfully expel the CHCl₃ molecule from the inner cavity of the hosts. Moreover, it can be noticed that the addition of more than one equivalent of cations (Cs⁺, Tl⁺) into the solution does not produce any further spectral changes. A similar behavior had been observed with host-1 in LiOH/H₂O solution.^{4b}

The replacement of NaOH/H₂O by a KOH/H₂O solution reveals different behavior in the ECD spectra of MM-2 upon addition of Cs⁺ or Tl⁺ cations. In the presence of cesium hydroxide solution, very small modifications of the ECD spectra of MM-2 are observed, whereas the spectral changes are more pronounced when a thallium acetate solution was added (Supporting Information, S6a and S6b). The effect of the concentration of the basic solution (NaOH/H₂O and KOH/H₂O) on the global shape of the ECD spectra of MM-2 has also been investigated. Increasing the concentration of NaOH/H₂O and KOH/H₂O (1 and 3 M) leads to a significant change of the ECD spectra of MM-2. For instance, the ECD spectrum of MM-2 in NaOH/H₂O (1 M) is still affected upon addition of a CsOH/H₂O solution (Supporting Information, S7a). As previously observed at lower NaOH/H₂O concentration, the ECD bands corresponding to the forbidden ¹L_b transition and the allowed ¹B_b transitions are significantly modified. Interestingly, no further spectral changes are observed when more than 1 equiv of Cs⁺ is added. The replacement of the CsOH/H₂O by TlOAc/H₂O also results in stronger spectral modifications (Supporting Information, S7b). The replacement of the NaOH/H₂O solution by KOH/H₂O (1 M) reveals spectral changes, upon addition of a TlOAc/H₂O solution, only at wavelengths lower than 240 nm and higher than 310 nm (Supporting Information, S8). Further increasing the concentration of the basic solutions (NaOH/H₂O and KOH/H₂O 3 M) leads to similar spectral changes (Supporting Information, S9a and S9b), suggesting that complexation still occurs efficiently. However, when such harsh conditions are used, the ECD spectrum of MM-2 is modified upon addition of more than 1 equiv of TlOAc/H₂O solution.

The chiroptical properties of cryptophanes 3 and 4 have not been investigated in this Article since the two enantiomers of these compounds have not been isolated yet. Nevertheless, the UV-vis spectra of their racemic forms have been recorded in the presence of various amounts of cesium hydroxide and thallium acetate solutions (Supporting Information, S10–S11). The spectral changes observed upon addition of Cs⁺ (or Tl⁺) are very similar to those reported for compound 2.

¹³³Cs and ²⁰⁵Tl NMR Spectroscopy. ¹³³Cs NMR experiments have been performed at 298 K in NaOD/D₂O (0.1 M) to study the complexation of cesium by cryptophanes 3 and 4 (Figure 3). ¹³³Cs NMR experiments of compound 2 are not discussed here, since the ¹³³Cs NMR spectrum has been previously published.^{4a} The ¹³³Cs NMR spectrum of compound 3 reveals two signals with different intensities. An intense signal is observed close to 0 ppm (reference CsNO₃ in D₂O), corresponding to dissolved Cs⁺, whereas a broader signal is located at −270 ppm, which is assigned to the Cs⁺@3 complex. Similarly, the same experiment conducted with compound 4 reveals two signals. It is noteworthy that the signal corresponding to the Cs⁺@4 complex is even further shifted toward low frequencies (δ = −288 ppm). Interestingly, the behavior of ¹³³Cs NMR spectra as a function of the temperature (from 278 to 333 K) is different for the two complexes. Indeed, the signal of the Cs⁺@3 complex becomes sharper as the temperature increases, as previously reported for compounds 1 and 2.^{4a} In contrast, the intensity of the ¹³³Cs NMR signal of the Cs⁺@4 complex decreases upon increasing the temperature.

To complete this study, the ¹³³Cs NMR spectrum of cryptophane 5 has been also recorded under the same experimental conditions. This compound possesses three propylenedioxy linkers and exhibits a larger cavity (*V*_{vdw} =

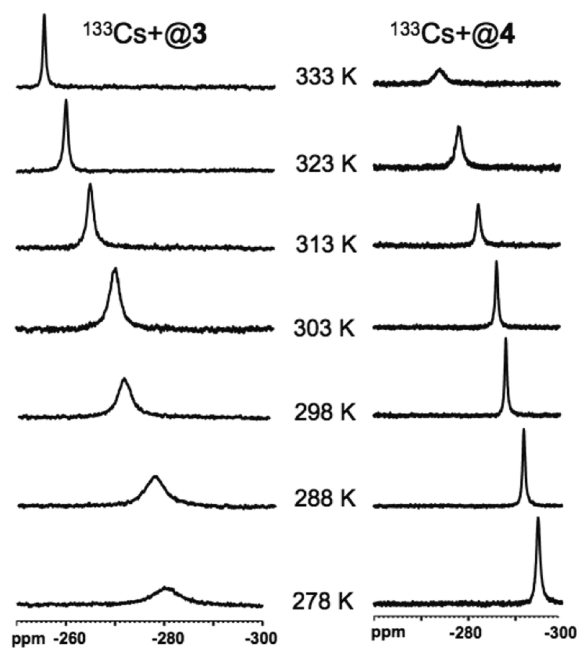


Figure 3. ¹³³Cs NMR spectra of cryptophanes 3 and 4 in NaOD/D₂O (0.1 M) at various temperatures.

120 Å³). The ¹³³Cs NMR spectrum of cryptophane 5 in LiOD/D₂O solution reveals a fast exchange, at the resonance frequency time-scale, characterized by a unique signal located at −1.25 ppm (Supporting Information, S12). Since compound 5 is sparingly soluble in LiOD/D₂O (the solution appears cloudy even in the presence of Cs⁺) and presents poor binding properties, it has not been further investigated. Nevertheless, the fast-exchange dynamics observed with compound 5 demonstrates that cryptophane 4 possesses the optimal cavity size to bind efficiently Cs⁺ under basic conditions.

²⁰⁵Tl NMR spectroscopy has also been used to characterize the Tl⁺@2–4 complexes. The ²⁰⁵Tl NMR spectrum of 2 in NaOD/D₂O (0.1 M) solution in the presence of a trace of thallium acetate reveals a slow exchange on the NMR time-scale at 293 K, characterized by the presence of two signals associated with the free and complexed ²⁰⁵Tl⁺ cation (Supporting Information, S13). These two signals are separated by a huge chemical shift difference (Δδ = 900 ppm), as already observed for the Tl⁺@1 complex in NaOD/D₂O (0.1 M) solution.^{4b} The signal at low field (δ = 340 ppm, reference TlNO₃ in D₂O) corresponds to dissolved Tl⁺. Shifting the transmitter frequency reveals the second, broad, ²⁰⁵Tl NMR signal at high field (δ = −560 ppm), which is assigned to the ²⁰⁵Tl⁺@2 complex. Similar results are obtained for the ²⁰⁵Tl⁺@3 and ²⁰⁵Tl⁺@4 complexes, and chemical shifts of δ = −575 ppm and δ = −485 ppm have been measured for ²⁰⁵Tl⁺@3 and ²⁰⁵Tl⁺@4 complexes, respectively (Supporting Information, S14). A change of the temperature has led to the same behavior as previously reported for the Cs⁺@3 and Cs⁺@4 complexes (not shown). For instance, the ²⁰⁵Tl NMR spectra of the ²⁰⁵Tl⁺@2 and ²⁰⁵Tl⁺@3 complexes display an increased intensity of the signals as the temperature increases. In contrast, the ²⁰⁵Tl NMR signal of the ²⁰⁵Tl⁺@4 complex shows a strong decrease of its intensity as the temperature increases. Finally, the ²⁰⁵Tl NMR spectrum at 335 K of a mixture of cryptophanes 1, 2 and 3 in NaOD/D₂O (0.1 M) in the presence of a small

amount of thallium acetate shows in Figure 4 that the three complexes can be easily detected.

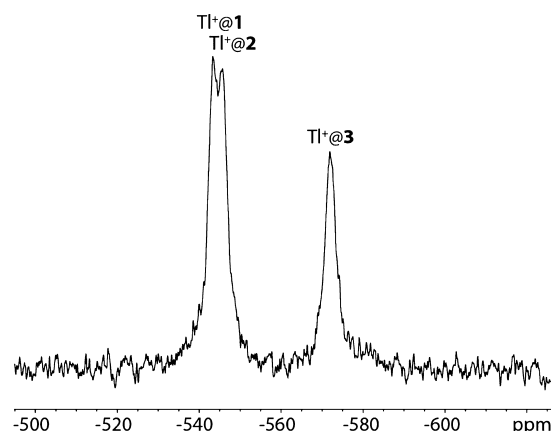


Figure 4. ^{205}Tl NMR spectrum of a mixture of cryptophanes **1**, **2**, and **3** recorded at 335 K in NaOD/D₂O (0.1 M) in the presence of a small amount of thallium acetate. [host-**1**] = 6.2×10^{-3} M, [host-**2**] = 8.0×10^{-3} M, [host-**3**] = 8.3×10^{-3} M. The number of scans was 2490.

ITC Experiments. Isothermal titration calorimetry (ITC) experiments have been carried out to obtain quantitative information about the host–guest complexation process between hosts **2–4** and various cations (Rb^+ , Cs^+ and Tl^+). ITC experiments have been performed at 298 K by varying the nature and the concentration of the basic solution. As mentioned previously,^{4a,b} the measurement of the binding constant (K) for the Cs^+ @cryptophanes and Tl^+ @cryptophanes complexes in basic solutions cannot be determined accurately from direct ITC measurements. Indeed, the high affinity of Cs^+ or Tl^+ cations for water-soluble cryptophanes sometimes requires the determination of K from competition experiments, using another cation having a lower affinity. In this study, the Rb^+ cation has been used as the competitor.

In a first series of experiments, the binding constants between Rb^+ and hosts **2–4** have been measured in LiOH/H₂O, NaOH/H₂O and KOH/H₂O for two different cation concentrations (0.1 and 1 M). These titration measurements and the thermodynamic parameters of complexation (K , ΔH , ΔS and ΔG) extracted from these ITC experiments are reported in the Supporting Information (S15–S18).⁸ The results show that compound **2** complexes the Rb^+ cation quite well. Binding constants as large as $1.4 \times 10^6 \text{ M}^{-1}$ and $9.2 \times 10^5 \text{ M}^{-1}$ were measured in NaOH/H₂O and LiOH/H₂O (0.1 M), respectively. A decrease of the binding constant by 2 orders of magnitude is observed in KOH/H₂O. Increasing the concentration of the basic solution (1 M) leads to a similar effect, whereas no binding is observed in KOH/H₂O (1 M). The replacement of host **2** by **3** having a larger inner cavity, results in a decrease of the binding constants. For LiOH/H₂O and NaOH/H₂O (0.1 M) solutions, efficient complexation of Rb^+ is still observed with binding constants $K = 3.7 \times 10^5 \text{ M}^{-1}$ and $6.7 \times 10^5 \text{ M}^{-1}$, respectively. A significant decrease of the binding constants is observed at higher concentration (1 M) of the basic solutions ($K = 3.7 \times 10^3 \text{ M}^{-1}$ and $4.9 \times 10^3 \text{ M}^{-1}$ for LiOH/H₂O and NaOH/H₂O solutions, respectively). Replacing LiOH/H₂O or NaOH/H₂O by KOH/H₂O strongly affects the results since no binding was observed under these conditions. Host **4**, having the largest inner cavity, shows moderate complexation of the Rb^+ cation only in LiOH/H₂O and NaOH/H₂O at a concentration of 0.1 M.

The data collected for the Rb^+ @**2–4** complexes can now be used to measure the binding constants of Cs^+ @**2–4** and Tl^+ @**2–4** complexes from competition experiments. ITC experiments for Cs^+ @**2–4** and Tl^+ @**2–4** complexes in LiOH/H₂O (0.1 and 1 M), NaOH/H₂O (0.1 and 1 M), and KOH/H₂O (0.1 and 1 M) solutions are reported in the Supporting Information (S19–S24), and the thermodynamic parameters of complexation are summarized in Tables 1 and 2. Cryptophane **2** shows a very high affinity for these two cationic species. For instance, in NaOH/H₂O (0.1 M) binding constants $K = 4.4 \times$

Table 1. Thermodynamic Parameters of Complexation for Cs^+ @2–4** Complexes in LiOH/H₂O, NaOH/H₂O, and KOH/H₂O Solutions (0.1 and 1 M) at 298 K: Binding Constant K (M^{-1}), Enthalpy ΔH (kcal mol^{-1}), Entropy ΔS ($\text{cal mol}^{-1} \text{ deg}^{-1}$), and ΔG (kcal mol^{-1}) of Complexation**

host	solvent	K (mol^{-1})	ΔH (kcal mol^{-1})	ΔS ($\text{cal mol}^{-1} \text{ deg}^{-1}$)	ΔG (kcal mol^{-1})
2	LiOH (0.1 M) ^a	2.7×10^9	−13.3	−1.4	−12.9
2	NaOH (0.1 M) ^a	4.4×10^9	−13.6	−1.3	−13.2
2	KOH (0.1 M) ^a	2.9×10^7	−10.1	+0.2	−10.2
2	LiOH (1 M) ^a	7.9×10^7	−13.4	−8.8	−10.8
2	NaOH (1 M) ^a	2.2×10^8	−12.2	−2.8	−11.4
2	KOH (1 M) ^b	1.3×10^6	−9.1	−2.6	−8.3
3	LiOH (0.1 M) ^a	1.2×10^9	−12.7	−1.5	−12.3
3	NaOH (0.1 M) ^a	5.0×10^9	−12.2	+3.3	−13.2
3	KOH (0.1 M) ^b	1.3×10^7	−6.5	+10.8	−9.7
3	LiOH (1 M) ^b	1.2×10^7	−10.5	−3.0	−9.7
3	NaOH (1 M) ^b	1.7×10^7	−8.4	+4.8	−9.9
3	KOH (1 M) ^b	9.3×10^4	−3.8	+9.9	−6.8
4	LiOH (0.1 M) ^b	4.1×10^7	−11.7	−4.5	−10.4
4	NaOH (0.1 M) ^b	4.3×10^7	−11.6	−4.0	−10.4
4	KOH (0.1 M) ^b	2.2×10^6	−5.9	+9.2	−8.6
4	LiOH (1 M) ^b	1.5×10^5	−6.6	+1.5	−7.1
4	NaOH (1 M) ^b	6.1×10^5	−4.6	+11.2	−7.9
4	KOH (1 M)	–	–	–	–

^aFrom competition experiments. ^bFrom direct measurements.

Table 2. Thermodynamic Parameters of Complexation for $\text{Ti}^+@2-4$ Complexes in $\text{LiOH}/\text{H}_2\text{O}$, $\text{NaOH}/\text{H}_2\text{O}$ and $\text{KOH}/\text{H}_2\text{O}$ Solutions (0.1 and 1 M) at 298 K: Binding Constant K (M^{-1}), Enthalpy ΔH (kcal mol^{-1}), Entropy ΔS ($\text{cal mol}^{-1} \text{ deg}^{-1}$), and ΔG (kcal mol^{-1}) of Complexation

host	solvent	K (mol^{-1})	ΔH (kcal mol^{-1})	ΔS ($\text{cal mol}^{-1} \text{ deg}^{-1}$)	ΔG (kcal mol^{-1})
2	LiOH (0.1 M) ^a	5.0×10^{10}	−12.8	+6.0	−14.6
2	NaOH (0.1 M) ^a	6.2×10^{10}	−12.3	+8.1	−14.7
2	KOH (0.1 M) ^a	2.5×10^8	−8.9	+8.5	−11.5
2	LiOH (1 M) ^a	3.5×10^8	−11.0	+2.0	−11.6
2	NaOH (1 M) ^a	6.8×10^8	−9.7	+8.0	−12.1
2	KOH (1 M) ^b	6.2×10^6	−6.5	+9.2	−9.3
3	LiOH (0.1 M) ^a	6.6×10^9	−12.1	+4.4	−13.4
3	NaOH (0.1 M) ^a	2.2×10^{10}	−10.8	+11.3	−14.1
3	KOH (0.1 M) ^b	6.3×10^7	−5.9	+15.9	−10.6
3	LiOH (1 M) ^a	4.9×10^7	−10.0	+1.6	−10.5
3	NaOH (1 M) ^b	4.6×10^7	−7.9	+8.5	−10.5
3	KOH (1 M) ^b	4.4×10^5	−3.2	+15.0	−7.7
4	LiOH (0.1 M) ^a	3.7×10^8	−12.4	−2.3	−11.7
4	NaOH (0.1 M) ^a	6.9×10^8	−11.9	+0.7	−12.1
4	KOH (0.1 M) ^b	1.2×10^7	−6.6	+10.2	−9.7
4	LiOH (1 M) ^b	1.1×10^6	−8.8	−1.8	−8.2
4	NaOH (1 M) ^b	3.9×10^6	−6.5	+8.4	−9.0
4	KOH (1 M)	–	–	–	–

^aFrom competition experiments. ^bFrom direct measurements.

10^9 M^{-1} and $K = 6.2 \times 10^{10} \text{ M}^{-1}$ were measured for the $\text{Cs}^+@2$ and $\text{Ti}^+@2$, respectively. The replacement of the $\text{NaOH}/\text{H}_2\text{O}$ solution by $\text{KOH}/\text{H}_2\text{O}$ results in a decrease of the binding constants ($K = 2.9 \times 10^7 \text{ M}^{-1}$ and $2.5 \times 10^8 \text{ M}^{-1}$ for $\text{Cs}^+@2$ and $\text{Ti}^+@2$, respectively). Increasing the concentration of the basic solution results also in a decrease of the binding constants. The cryptophane 3 having a larger inner cavity reveals a good affinity for both the cesium and thallium cations as well. In $\text{NaOH}/\text{H}_2\text{O}$ (0.1 M), the binding constants are $K = 5.0 \times 10^9 \text{ M}^{-1}$ and $K = 2.2 \times 10^{10} \text{ M}^{-1}$ for the $\text{Cs}^+@3$ and $\text{Ti}^+@3$ complexes, respectively. Increasing the concentration of the $\text{LiOH}/\text{H}_2\text{O}$ and $\text{NaOH}/\text{H}_2\text{O}$ solutions results in a decrease of the binding constants by, at least, 2 orders of magnitude ($K = 1.7 \times 10^7 \text{ M}^{-1}$ and $4.6 \times 10^7 \text{ M}^{-1}$ for $\text{Cs}^+@3$ and $\text{Ti}^+@3$ in $\text{NaOH}/\text{H}_2\text{O}$ solution, respectively). As observed for host 2, smaller binding constants were measured in $\text{KOH}/\text{H}_2\text{O}$ solution. Finally, the study of the cryptophane 4 under the same experimental conditions, reveals that this host binds cesium and thallium cations fairly well. Indeed, binding constants as high as $K = 4.3 \times 10^7 \text{ M}^{-1}$ and $K = 6.9 \times 10^8 \text{ M}^{-1}$ were measured in $\text{NaOH}/\text{H}_2\text{O}$ (0.1 M) for cesium and thallium cations, respectively. In $\text{KOH}/\text{H}_2\text{O}$ (0.1 M) solution, the decrease of the K values is about 1 order of magnitude, which is lower than that observed for cryptophanes 2 and 3. In contrast, at higher $\text{KOH}/\text{H}_2\text{O}$ concentration (1 M), no binding was observed between host 4 and the two cations.

In order to estimate the experimental error on the determination of the ΔG values, the synthesis of host 3 was achieved three times and the ITC experiments in the presence of Rb^+ and Cs^+ cations were performed on these three independent samples in $\text{NaOH}/\text{H}_2\text{O}$ (0.1 M) solution. An absolute uncertainty of $0.5 \text{ kcal mol}^{-1}$ has been measured for the ΔG value (Supporting Information, S25).

DISCUSSION

Complexation of Cesium and Thallium Cations by Water-Soluble Cryptophanes. In previous Articles, we showed that ECD spectroscopy is a very valuable and sensitive

technique to investigate the complexation of cesium and thallium cations by water-soluble cryptophanes.^{4a,b} The study of enantiopure cryptophane 1 revealed that this host exhibits very different ECD spectra depending on the experimental conditions used (solvent, concentration, temperature) and the presence (or not) of the Cs^+ or Ti^+ cations inside its cavity. The spectral modifications were directly correlated to the conformational changes adopted by the host molecule to maximize its interactions with cationic species.

Similarly, the ECD spectra of *MM-2* provides important information about the complexation process of cesium and thallium cations. For instance, in the presence of a competitor (CHCl_3), important spectral changes are observed in the ECD spectra of *MM-2*, upon addition of a $\text{CsOH}/\text{H}_2\text{O}$ or $\text{TlOAc}/\text{H}_2\text{O}$ solution (Supporting Information, S5). This behavior can be related to conformational changes of the three linkers of host 2, occurring during the complexation of these two cationic species. Indeed, upon encapsulation with a chloroform molecule ($V_{\text{vdw}} = 72 \text{ \AA}^3$) the three ethylenedioxy linkers of *MM-2* preferentially adopt an *all-trans* conformation to accommodate this guest.⁹ The replacement of the chloroform molecule by a cesium ($V_{\text{vdw}} = 19.5 \text{ \AA}^3$) or a thallium ($V_{\text{vdw}} = 14.1 \text{ \AA}^3$) cation constrains host *MM-2* to reduce the size of its cavity in order to maximize host–guest interactions. Thus, upon encapsulation of Cs^+ (or Ti^+) cation, the ethylenedioxy linkers of *MM-2* preferentially adopt an *all-gauche* conformation. This effect is particularly visible for the Ti^+ cation, where a strong modification of the ECD spectrum of *MM-2* occurs, especially for the ECD bands of the forbidden $^1\text{L}_b$ transition (280–340 nm) and the allowed $^1\text{B}_b$ transition (around 220 nm). The absence of any further spectral changes upon addition of more than one equivalent of cesium or thallium cations suggests that these spectral modifications are exclusively due to the host–guest interactions and not to an effect of the bulk solution. In the absence of competitor, the spectral changes are less intense since the guest-free cryptophane favors the *gauche* conformations of the ethylenedioxy linkers due to solvophobic effect.

The different behavior observed in the 1L_b region of the UV–vis and ECD spectra for the $Cs^+@MM-2$ and $Tl^+@MM-2$ complexes, reveals that these two cations interact differently with the cavity of host 2. The more pronounced spectral changes observed for the $Tl^+@MM-2$ complex suggest a stronger interaction between the Tl^+ and the host molecule, as previously reported by Canet and co-workers for calixarene hosts.¹⁵ The stronger affinity of host *MM-2* for the thallium cation is also confirmed by ITC experiments. Binding constants about ten times greater for Tl^+ than for the Cs^+ cations are determined in $LiOH/H_2O$, $NaOH/H_2O$ and KOH/H_2O solutions. The better affinity of *MM-2* for the thallium cation is probably due to its higher polarizability, which is about twice that of the cesium cation. Another interesting point comes from the comparison of the binding constants of host 2 and those reported previously for host 1.^{4b} Indeed, the higher affinity of host 2 for both the cesium and thallium cations suggests that the number of phenolate moieties play a key role in the stabilization of these complexes. An increase of the values of the binding constants by 1 order of magnitude has been found for host 2 (6 phenolate groups) with respect to host 1 (5 phenolate groups). This feature suggests that Coulombic interactions between the phenolate moieties and the two cations are very important in the stabilization of these complexes. The higher values of the free enthalpy of complexation ΔG by 2 kcal mol^{−1} for host 2 with respect to host 1, using identical experimental conditions, support this conclusion.

Influence of the Cavity Size. Our study reveals the strong affinity of hosts 3 and 4 for cesium and thallium cations in $LiOH/H_2O$ and $NaOH/H_2O$ (0.1 M) solutions. This result may appear surprising since the cavity sizes of host 3 and 4 are supposed to be higher than the one of host 2. Moreover, the ITC experiments indicate that only a single cesium or thallium cation is encapsulated inside the cavity of hosts 3 and 4.¹⁰ The most remarkable result comes from host 3, which has its cavity estimated to be $V_{vdw} = 102 \text{ \AA}^3$, slightly greater than those calculated for hosts 1 and 2 ($V_{vdw} = 95 \text{ \AA}^3$).¹¹ Values of binding constants as high as those obtained for host 2 have been measured. Interestingly, these binding constants are also higher than those previously obtained with host 1, having a smaller cavity ($V_{vdw} = 95 \text{ \AA}^3$) but bearing only five phenolate moieties. This feature suggests that the number of phenolate moieties appears to be the main parameter in the stabilization of the complexes and that the “real” size of the cavity is certainly reduced by conformational changes of the linkers when the complexes are formed. Indeed, as it has been clearly demonstrated by studying the ECD spectra of host 1 and 2, cryptophane derivatives are flexible and tiny changes in the conformation of the linkers are sufficient to reduce significantly the cavity size. This phenomenon probably occurs with host 3 and 4, and the calculated cavity size, given for an *all-trans* conformation of the linkers, does not necessarily correspond to the real size of the cavity once the cesium or thallium cation is encapsulated.

The lowest binding constants are measured for host 4, which has the biggest cavity size ($V_{vdw} = 117 \text{ \AA}^3$). Nevertheless, the decrease in the complexation process is moderate since significant binding constants are still measured, especially with thallium as guest. These results are confirmed by the study of the ^{133}Cs and ^{205}Tl NMR spectra of host 4. However, the dependence in temperature of the ^{133}Cs and ^{205}Tl NMR spectra of host 4 is different to the one observed for host 1–3. The

intensity decrease of the NMR signal observed for host 4 upon heating the solution suggests that it is governed by the exchange dynamics in contrast to that is observed with host 1–3. Thus, it can be stated that host 3 behaves like cryptophanes 1–2, whereas host 4 behaves differently, probably because this host has the maximum cavity size possible to bind efficiently these two cations. Finally, the lack of efficient encapsulation by host 5, bearing three propylenedioxy linkers, supports this assumption.

In KOH/H_2O (0.1 M) solution, the binding is less efficient since the potassium cation competes with both the cesium and the thallium cations.¹² This explains why a significant decrease of the binding constants is observed with Rb^+ , Cs^+ and Tl^+ . This effect is more pronounced for cryptophanes 3 and 4 than for cryptophane 2. It is noteworthy that the encapsulation of the potassium cation by cryptophanes 2–4 forces the host molecules to adopt a preferential *gauche* conformation of the linkers, which is very close to that observed upon encapsulation of the cesium and thallium cations. Thus, no conformational changes of the host are expected by replacing K^+ with Cs^+ (or Tl^+). This assumption is confirmed since no significant change of the ECD spectra of *MM-2* is observed in KOH/H_2O (0.1 M) upon addition of different amounts of cesium hydroxide solution (Supporting Information, S6a). However, spectral modifications appear for the complexation of the Tl^+ cation (Supporting Information, S6b), as a consequence of the stronger interaction between this cation and the host molecule (confirmed by ITC experiments).

The affinity of cryptophanes 2–4 for Cs^+ and Tl^+ is also modified by increasing the concentration of the basic solution. ITC experiments show that the values of the binding constants decrease by about 2 orders of magnitude, changing the concentration of the basic solution from 0.1 to 1 M. Moreover, the ECD spectra of *MM-2* reveal significant spectral changes in $NaOH/H_2O$ solution at 0.1 M (Figures 1b and 2b) and at 1 M (Supporting Information, S7). Spectral changes had been previously observed for host 1,^{4b} and had been interpreted as conformational modifications of the linkers by changing the concentration of the basic solutions. Thus, at lower concentration the hydrophobic effect dominates and the cryptophanes tend to reduce the size of their cavity by favoring a preferential *all-gauche* conformation of the linkers. In contrast, at higher concentration, the linkers adopt a preferential *all-trans* conformation due to the strong interactions between the cationic species present in solution and the oxygen of the bridges. This feature tends to increase the cavity size of the hosts but it is reversed upon encapsulation of Cs^+ or Tl^+ cations, which favors the *all-gauche* conformation of the linkers to maximize the interactions between these cations and the cryptophane. This opposite effect on the cavity size may explain the decrease of the values of the binding constant at higher concentration. This effect is particularly important for KOH/H_2O (1 M) solution since the potassium is, additionally, a competitor for Cs^+ and Tl^+ cations. Nevertheless, ITC experiments show that efficient binding occurs for hosts 2 and 3 in $LiOH/H_2O$ (1 M), $NaOH/H_2O$ (1 M) and even in KOH/H_2O (1 M) solutions. The situation is somewhat different for host 4 in KOH/H_2O (1 M) solution. Indeed, in this case the interaction between the cesium or thallium cations and the cryptophane is not sufficient to counteract both the conformational changes of the linkers and the competition with K^+ cations.

CONCLUSION

In this Article, the binding properties of cesium and thallium cations by cryptophanes 2–4 have been thoroughly investigated in basic aqueous solution. These host molecules have different cavity sizes, going from 95 Å³ (2) to 117 Å³ (4). We have shown that these hosts are able to bind these two cationic species under a large range of experimental conditions. To demonstrate the efficient binding of Cs⁺ and Tl⁺ by water-soluble cryptophanes 2–4, several spectroscopic techniques such as ECD, ¹³³Cs and ²⁰⁵Tl NMR have been used. ITC experiments have been performed to quantify the complexation process. Cryptophane 2, which possesses the smallest cavity, exhibits the highest binding constants toward cesium and thallium cations, whatever the experimental conditions used. Surprisingly, cryptophane 3 shows binding properties, which are very similar to those observed for host 2, even though its cavity is assumed to be greater. Cryptophane 3 even presents a better affinity for these two cations than host 1, bearing five hydroxyl groups. Finally, cryptophane 4 shows a good affinity for Cs⁺ and Tl⁺ cations at low concentration in LiOH/H₂O, NaOH/H₂O and KOH/H₂O solutions but its binding properties are strongly affected by increasing the concentration of the basic solution.

The ensemble of these results demonstrate that the cavity size of the cryptophane is not the predominant factor that governs cesium or thallium complexation by these molecular hosts. This is due to the flexibility of these water-soluble cryptophanes, which can easily modify the conformation of the three linkers in order to optimize their cavity size and, consequently, maximize the interactions with the two cations. In contrast, the number of phenolate groups seems to be pivotal for the binding efficiency since higher binding constants are measured with host 3 than with host 1. Interestingly, a very high selectivity has been observed since efficient binding occurs in the presence of a high concentration of Li⁺, Na⁺, and even K⁺ cations. As previously observed with host 1, cryptophanes 2–4 present a better affinity for the thallium cation. This is probably due to the high polarizability of this cation, which is about twice that of the cesium cation.

ASSOCIATED CONTENT

Supporting Information

¹H NMR spectrum of compounds (2–5) in DMSO-*d*₆ solution at 298 K. ECD spectra recorded at 293 K of MM-2 in NaOH/H₂O and KOH/H₂O (0.1 M) solutions in the presence of different amounts of cesium hydroxide solutions. ECD spectra of MM-2 in NaOH/H₂O and KOH/H₂O (0.1 M, 1 M and 3M) solutions, in the presence of different amounts thallium acetate solutions. UV–vis spectra recorded at 293 K of compounds 3 and 4 in NaOH/H₂O solution (0.1 M) in the presence of different amounts of cesium hydroxide and thallium acetate solutions. ¹³³Cs NMR spectrum of compound (5) in LiOD/D₂O solution at 298 K. ²⁰⁵Tl NMR spectrum of cryptophanes 2 recorded at 293K in NaOD/D₂O (0.1 M) in the presence of a small amount of thallium acetate. Calorimetric titration of compounds 2–4 at 298 K in LiOH/H₂O, NaOH/H₂O, and KOH/H₂O (0.1 and 1 M) solutions with rubidium chloride, cesium hydroxide and thallium acetate solutions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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ABBREVIATIONS

Cs, cesium; CsOH, cesium hydroxide; ECD, electronic circular dichroism; ITC, isothermal titration calorimetry; NMR, nuclear magnetic resonance; RbCl, rubidium chloride; Tl, Thallium; TlOAc, thallium acetate; TlNO₃, thallium nitrate; VCD, vibrational circular dichroism

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(8) The symbol ΔG is used in this Article for free enthalpy of complexation. It is also noted ΔG^0 or ΔG_{comp} in the literature. Idem for the enthalpy of complexation ΔH and the entropy of complexation ΔS .

(9) The terms “preferentially *all-trans*” and “preferentially *all-gauche*” are used in the text for simplicity. It is most likely that replacing a chloroform molecule by a cesium (or a thallium) cation modifies the distribution of conformation adopted by the three linkers. Thus, the proportion of *gauche* conformation is higher when a small cation (such as cesium) enters the cavity whereas the *trans* conformation dominates when a large guest (such as chloroform) fills the cavity of cryptophane.

(10) The stoichiometry found by ITC experiments gives values slightly smaller than $N = 1$. This arises from the presence of purification solvents (including water), which can be present in compounds **2–4**. This overestimates the mass of cryptophanes **2–4** used for the ITC experiments. Attempts to remove these solvents by heating the sample under vacuum is not recommended, since it has been observed that an imploded conformation is formed during the process, even for the cryptophane derivatives having smallest cavities.

(11) The cavity size of cryptophanes **2–4** was calculated by using the GRASP program: Brotin, T.; Dutasta, J.-P. *Eur. J. Org. Chem.* **2003**, 973–984.

(12) A binding constant of $K = 1100 \text{ M}^{-1}$ was measured for the K^+ @**3** complex in $\text{LiOH}/\text{H}_2\text{O}$ (0.1 M) at 298 K.