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A Water-Soluble Cryptophane Decorated with Aromatic Amine Groups

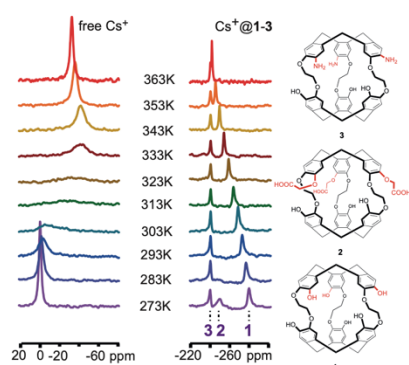
Shows High Affinity for Cesium and Thallium (I)

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TOC



ABSTRACT: An *anti*-cryptophane decorated with three aromatic amine and three phenol groups shows high affinity for the cesium and thallium cations in LiOH/H₂O (0.1 M). The formation of the complexes was studied by ¹³³Cs NMR and by ²⁰⁵Tl NMR spectroscopy at different temperatures. Characteristic signals for caged cesium and thallium were observed at high field with respect to the signals of the free cations present in the bulk. Isothermal Calorimetric Titration experiments performed in LiOH/H₂O (0.1 M) and NaOH/KCl buffer (pH = 13) allowed us to determine the parameter of complexation and to ascertain the high affinity of this cryptophane for cesium and thallium. A comparison with other cryptophanes that bind these two cations shows that the introduction of nitrogen atoms into the cryptophane backbone has an effect on the binding properties. The affinity for cesium and thallium(I) ions is in the

following order of substitution $\text{OH} > \text{NH}_2 > \text{OCH}_2\text{COOH}$. This study paves the way to the design of new efficient host molecules for the extraction of these two cations in aqueous solution.

Introduction

Among the various pollutants released into nature by human activities, heavy metals are particularly harmful, as they are responsible for the long-term pollution of soil and groundwater worldwide.^{1,2} For example, heavy metals such as arsenic, cadmium, lead and mercury are of great concern and well known to the public, but other metals such as cesium and thallium also pose a major threat to humans and mammals in general.³ For instance, ^{137}Cs (half-life: 30 years) is a highly toxic radioactive element that was released in large quantities during the two major nuclear accidents in 1986 (Tchernobyl) and 2011 (Fukushima).⁴ These two nuclear accidents have contaminated large areas that are not yet accessible to humans. On the other hand, thallium (mainly thallium(I)) is considered the most toxic metallic element, and an acute exposure to low concentrations of this metal can have a considerable impact on health.⁵ The ability of the thallium ions to mimic potassium ions in cells is the main reason of its toxicity.⁶ Thallium is now considered a priority pollutant by the US Environmental Protection Agency (EPA).⁷

Several solutions have been proposed to detect and/or extract these metals from soils and groundwater. Among the different approaches proposed, the synthesis of macrocyclic compounds represents an interesting approach to extract cesium and thallium dispersed in nature because the physical properties of these hosts can be adjusted to gain in selectivity or to increase the association constant for a specific metal.⁸ The nature of the substituents grafted onto their structure can also be modified to make these molecules soluble in water or organic solvents, depending on the desired applications. Despite the above-mentioned advantages, the synthesis of macrocyclic compounds however requires a multi-step synthesis, which makes

their utilization less convenient than the use of inorganic matrices, easier to prepare in large quantities.⁹ It is worth noting that, despite the harmful properties of thallium compounds, the radionuclide ^{201}Tl has an interesting application in single-photon emission computed tomography (SPECT) for the imaging and diagnosis of myocardial infarction. The synthesis of new chelators for ^{201}Tl imaging may therefore prove promising, even if it does represent a challenge.¹⁰

Among the various macrocyclic systems described in the literature, cryptophanes with a small internal cavity are shown to present high affinity for cesium and thallium(I) in aqueous solution.^{11,12,13} Cryptophanes are bowl-shaped molecules whose cavity size can be tuned by modifying the nature and the length of the linkers connecting the two cyclotribenzylene (CTB) units.¹⁴ Also, the presence of six aromatic rings in the structure of these compounds makes it possible to graft several substituents in order to fine-tune their chemical and physical properties. By combining these two properties, it becomes possible to build cage molecules effective to encapsulate cationic species and maximize their interaction with a specific cation.

In several articles, we have shown that the presence of phenol groups on such macrocyclic cages is favorable to bind cesium and thallium(I) ions in aqueous solution. For instance, to date cryptophane **1** (Chart 1) decorated with six phenol groups shows the highest affinity for Cs^+ and Tl^+ ions in aqueous solution. We have shown that a reduction of the number of phenol groups grafted on the cryptophane skeleton results in a decrease of the association constant for these two cationic species.¹⁵ For instance, compound **2** that possesses only three phenol groups binds cesium and thallium by several orders of magnitude less than compound **1** (chart 1). In addition, lowering the pH of the solution also leads to a decrease in the affinity constant for cesium and thallium(I).¹⁵

To date, all studies on cryptophane derivatives have been only carried out with phenol and aromatic ether-containing cage molecules. It is therefore interesting to extend the study to

other water-soluble cryptophanes that possess different substituents in order to assess their ability to bind cesium and thallium(I). Unfortunately, this study has often been delayed due to difficulties in introducing hetero-elements into the cryptophane skeleton. The recent synthesis of a cryptophane decorated with three aromatic amine groups offers the opportunity to prepare a new water-soluble cryptophane and to assess its ability to accommodate cesium and thallium(I) in basic solution.¹⁶ Interestingly, the physical properties of the new cryptophane **3** can be studied under the same conditions as those of compounds **1** and **2**, which facilitates a comparison of their binding affinities.

We firstly report in this article the synthesis of this water-soluble cryptophane **3** decorated with three aromatic amine substituents. The formation of the complex with cesium and thallium is then assessed at different temperatures by ¹³³Cs NMR and ²⁰⁵Tl NMR spectroscopy. Finally, Isothermal calorimetric titration experiments are carried out to determine the thermodynamic parameters of complexation under different conditions.

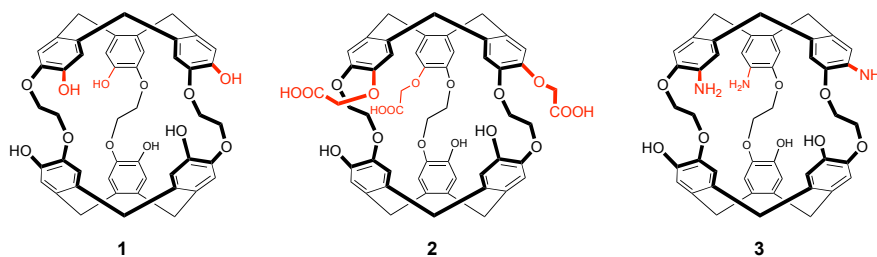
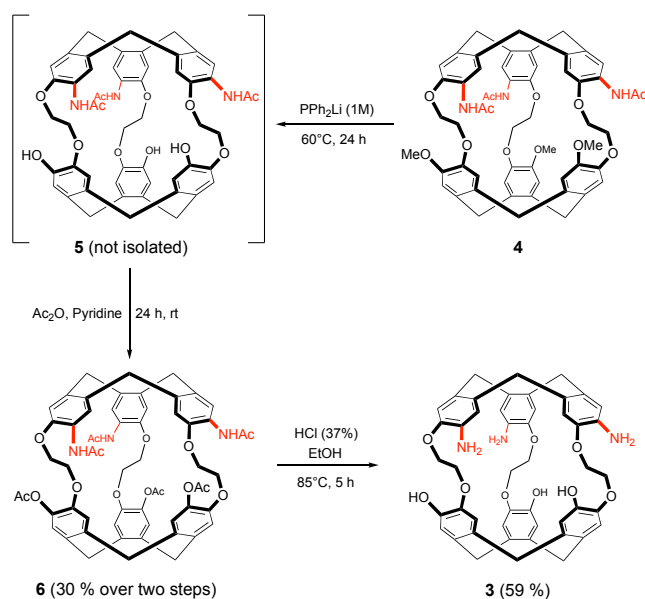


Chart 1. structures of *anti*-cryptophanes **1**, **2** and **3**.

RESULTS

Synthesis of cryptophane-3: *anti*-cryptophane **4** (see Scheme 1 and Figure S1) prepared according to a known procedure was used as a starting material to synthesize the triaminocryptophane **3**.¹⁶ Each cryptophane synthesized in the course of the study exhibits a *C*₃-symmetry and is present under the form of a racemic mixture. A Lewis base-promoted demethylation reaction of compound **4** in the presence of an excess of freshly prepared lithium

diphenylphosphide (1 M) in anhydrous THF at 60 °C allowed us to recover the cryptophane **5** as a crude compound. This compound was not isolated due to its low solubility, which also prevented direct conversion of compound **5** into **3**. Thus, a phenol acetylation reaction was then performed in a mixture of anhydrous pyridine and acetic anhydride at room temperature to facilitate its purification. The per-acetylated cryptophane **6** was obtained in a moderate 30% yield over two steps after purification on silica gel. Then, a Bronsted acid promoted-deprotection reaction of the three acetate and the three acetanilide functions was carried out in a mixture of concentrated hydrochloric acid and ethanol under reflux conditions to give compound **3** as a beige compound in a 59% yield (Scheme 1). Assignment of both ^1H and ^{13}C signals of compound **6** is reported (Figures S2-S3). Then, identification of compound **3** (Figures S4-S7) was performed thanks to ^1H , ^{13}C and 2D-NMR (HSQC and HMBC) spectroscopy in NaOD/D₂O (0.1 M). As expected for a compound of C_3 -symmetry, the ^1H NMR spectrum of cryptophane **3** shows four singlets in the aromatic region between 6.8 and 6.4 ppm. Four distinct doublets, corresponding to the two diastereotopic axial and equatorial protons pairs H_a and H_e of methylene bridges (H_a ; H_e ; $^2J_{\text{geminal H-H}} \sim 12\text{-}13$ Hz) of the two CTB units are also visible between 4.3 and 2.9 ppm. Cryptophane **3** is well soluble in basic LiOH/H₂O and NaOH/H₂O solutions at 0.1 M concentration, enabling us to perform NMR and ITC experiments under conditions similar to those used with cryptophanes **1** and **2**.



Scheme 1. Synthesis of *anti*-cryptophane-**3** (C_3 -symmetry) from *anti*-cryptophane **4**. Only one enantiomer is shown for each compound.

^{133}Cs and ^{205}Tl NMR spectroscopy:

The ability of compound **3** to bind a Cs^+ ion in $\text{NaOD}/\text{D}_2\text{O}$ was assessed by ^{133}Cs NMR spectroscopy. At 293.5 K, the ^{133}Cs NMR spectrum of compound **3** in the presence of a slight excess of CsCl shows a sharp signal located at $\delta = -3.0$ ppm (external reference: CsNO_3 at 0 ppm) that corresponds to cesium dissolved in the bulk. We also observe another signal at $\delta = -242.0$ ppm that starts to appear upon addition of **3** to the solution. This signal, previously observed at room temperature for cryptophanes with a high affinity for this cation, is characteristic of the $\text{Cs}^+@3$ complex.¹⁵

A series of ^{133}Cs NMR spectra was recorded using the same solution by changing the temperature from 276.8 K to 360.4 K (Figure 1). The change of the temperature has little effect on the chemical shift of the signal of encapsulated cesium. In contrast, while the ratio of the signal areas $\text{Cs}^+@3/\text{Cs}^+_{\text{free}}$ increases very slightly up to 293K, it decreases suddenly and very significantly above that (see Table S1 and Figure S8 in the Supp. Info).

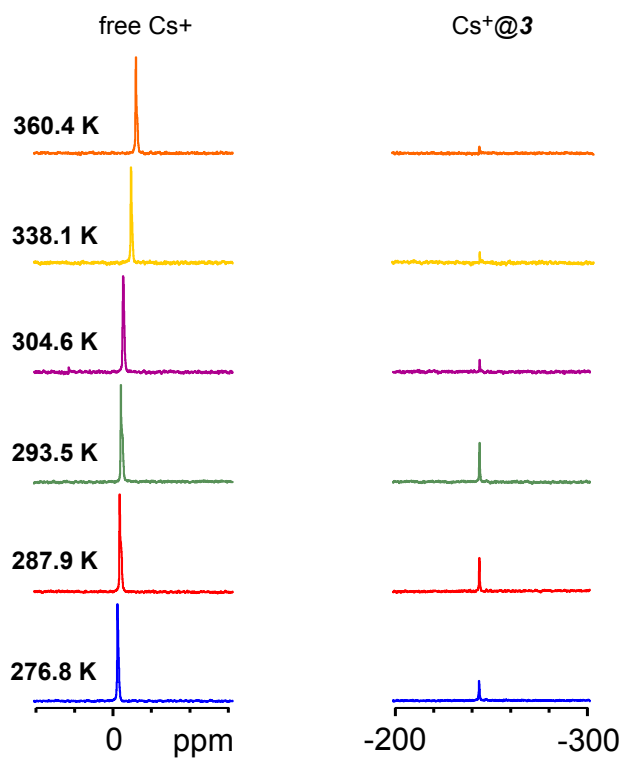


Figure 1. ^{133}Cs NMR spectra of compound **3** in NaOD/D₂O ($c = 4.5$ mM) recorded at different temperatures (276.8 K to 360.4 K) in the presence of five equivalents of cesium chloride.

As this invariance of the chemical shift of caged cesium puzzled us, we prepared a nearly equimolar mixture of cryptophanes **1**, **2** and **3** in D₂O/NaOD at ca. 5.2 mM. Figure 2 emphasizes different cesium behaviors in the three cryptophanes at various temperatures.

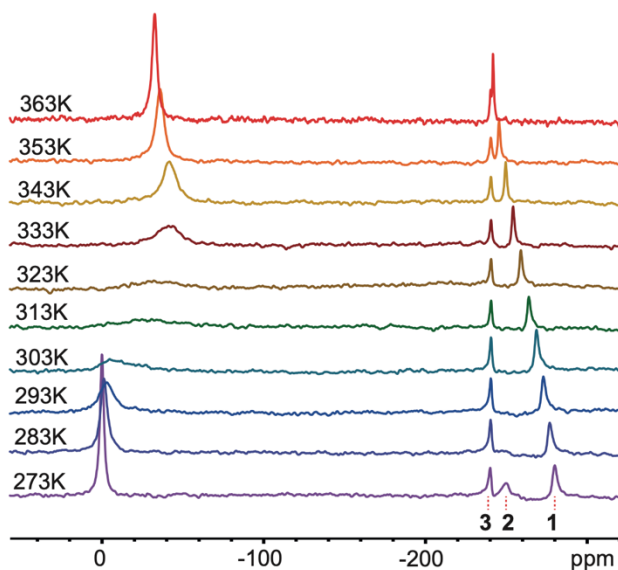


Figure 2. ^{133}Cs NMR spectra of Cs^+ in the presence of a nearly equimolar mixture of cryptophanes **1**, **2** and **3** ($[\mathbf{1}] = 5.3 \text{ mM}$; $[\mathbf{2}] = 5.1 \text{ mM}$; $[\mathbf{3}] = 5.4 \text{ mM}$) at various temperatures.

At the lowest temperature (273 K), three signals appear at high field, corresponding to cesium ions encapsulated in the cavity of each cryptophane. Signals of $\text{Cs}^+@1$ and $\text{Cs}^+@2$ complexes have been assigned from our previous work in references 11 and 15, respectively. We can immediately see that the $\text{Cs}^+@2$ signal is broader than the other two. As the temperature rises, this peak widens further until it disappears, while the free cesium peak also widens. A situation of coalescence appears at ca. 313 K. The two other high-field signals remain sharp, but their behavior as a function of temperature is not the same. While the chemical shift of $\text{Cs}^+@1$ increases with temperature (as already mentioned in Ref. 11), with a slope of $0.42 \text{ ppm}/^\circ$ ($R^2 = 0.996$), that of $\text{Cs}^+@3$ remains invariant. As also already reported in Ref. 11, the linewidth of the $\text{Cs}^+@1$ decreases with temperature. In contrast, the linewidth of the $\text{Cs}^+@3$ signal shows no significant variation. Note the unusual behavior of the free Cs^+ signal that shifts upfield and then downfield again with increasing temperature, due to the coalescence situation with cryptophane **2**.

In addition, ^{133}Cs T_1 experiments were recorded using the inversion-recovery method. The longitudinal relaxation time for the free cesium signal increases slowly from $837 \pm 16 \text{ ms}$ at 283 K to $1184 \pm 38 \text{ ms}$ at 313 K, stays on a plateau until 323 K, then decreases slightly to reach a value of $755 \pm 64 \text{ ms}$ at 363 K. The ^{133}Cs T_1 value of the $\text{Cs}^+@1$ signal passes from $38 \pm 2 \text{ ms}$ at 283 K to $146 \pm 7 \text{ ms}$ at 343 K (above this temperature the $\text{Cs}^+@1$ and $\text{Cs}^+@3$ frequencies are too close to enable safe measurement). The ^{133}Cs T_1 value of the $\text{Cs}^+@3$ signal is $27 \pm 4 \text{ ms}$ at 283 K, then it increases and fluctuates around 68 ms with a deviation of 15 ms. Here again, for **3** the dependence of this NMR parameter with temperature is not as important as for the other two cryptophanes. It should also be noted that very slow cesium complexation kinetics

(timescale of hours) appeared with the mixture of cryptophanes, since the first day's experiments (in particular T_1 measurements) had to be redone to give results more in line with the others. This is probably due to the formation of molecular assemblies with the cesium salt used, which gradually break up; in any case, we checked that the sample was no longer evolving before repeating the experiments.

We have also studied the ability of cryptophane **3** to bind Tl^+ ions using ^{205}Tl NMR spectroscopy. Although the thallium nucleus has a half-spin and a fairly high gyromagnetic ratio, recording ^{205}Tl NMR spectra is not straightforward on commercial NMR probes and requires a special setup. Its spectrum can cover several thousands ppm and the signal of the complexed cation can be difficult to find, in particular due to the limited bandwidth covered by the excitation pulse. The other difficulty comes from the appearance of precipitates when thallium salts are introduced in solution, which prevents quantitative interpretation of the ^{205}Tl NMR spectra.

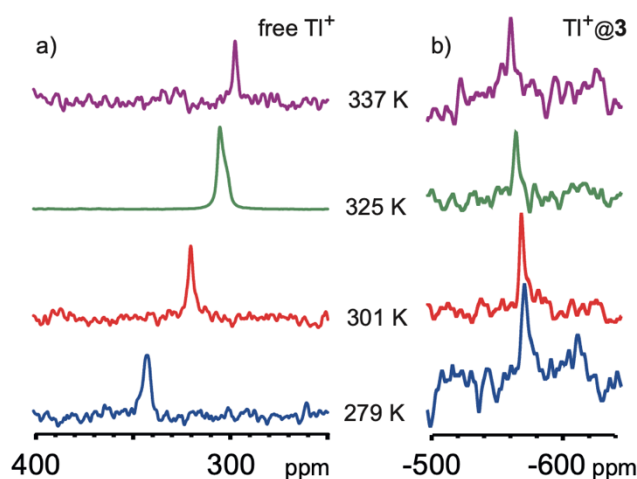


Figure 3. ^{205}Tl NMR spectra of compound **3** ($c = 16$ mM) dissolved in NaOD/D₂O (0.1 M) at four different temperatures in the presence of an excess of thallium acetate. a) low-field signal acquired with the rf carrier frequency at 320 ppm; b) high-field signal acquired with the rf carrier frequency at -560 ppm. The spectra have been recorded with different numbers of scans.

Figure 3 displays the low- and high-field regions of the ^{205}Tl NMR spectrum of cryptophane **3** in the presence of thallium acetate (TlOAc) at four temperatures from 279 to 337 K. The splitting between the free Tl^+ signal and that of the complexed cation ranges from 858 ppm (at 337 K) to 913 ppm (at 279 K), with a slope of $-0.94 \text{ ppm}/^\circ$ ($R^2 = 0.997$). This variation of 55 ppm in a temperature window of 58 degrees is small for an element with such a polarizable electron cloud, noting in particular that it is mainly the frequency of the free thallium signal that varies with temperature.

The ability of the Rb^+ , Cs^+ and Tl^+ cations to form complexes with compound **3** was also assessed by HRMS spectroscopy (Figure S9). In each cases a 1:1 complex was detected. For instance, the $\{\text{Rb}^+@[\mathbf{3} - 2\text{H}]\}^-$, $\{\text{Cs}^+@[\mathbf{3} - 2\text{H}]\}^-$, $\{\text{Tl}^+@[\mathbf{3} - 2\text{H}]\}^-$ pics have been identified with $m/z = 891.2121$; 938.2048 and $1010, 2771$, respectively.

Isothermal Calorimetric Titration Experiments: ITC experiments is the method of choice to assess the binding properties of cryptophane derivatives in aqueous solution. The method provides a complete description of the binding process and gives in a single experiment the stoichiometry of the complex the association constant K and the enthalpy of complexation ΔH^0 . In this way, the entropy of complexation ΔS^0 and the free enthalpy of complexation ΔG^0 can be easily calculated from these experiments, providing a comprehensive overview of the host-guest binding process.

ITC experiments have been carried out with compound **3** in $\text{LiOH}/\text{H}_2\text{O}$ (0.1 M) at 298 K in the presence of alkali cations (K^+ , Rb^+ , Cs^+) and Tl^+ . The binding constants and thermodynamic parameters for these cations are given in Table 1.

Table 1: Thermodynamic parameters of complexation K , ΔH^0 , $T\Delta S^0$ and ΔG^0 for the $\text{M}^+@[\mathbf{3}]$ ($\text{M} = \text{Rb}, \text{Cs}, \text{Tl}$) complexes obtained by Isothermal Titration Calorimetry experiments. ITC

recorded at 298 K in LiOH/H₂O (0.1 M). [a] competition experiments (competitor Rb⁺). K⁺ is not recognized by host **3** in the same conditions.

M ⁺ @ 3	K (M ⁻¹)	ΔH ⁰ (kcal.mol ⁻¹)	TΔS ⁰ (kcal.mol ⁻¹)	ΔG ⁰ (kcal.mol ⁻¹)
Rb ⁺	3.4 ± 1.2 x10 ⁴	-10.1 ± 0.5	-3.9 ± 0.5	-6.2 ± 0.3
Cs ⁺	3.8 ± 0.6 x10 ⁷	-15.5 ± 0.2	-5.2 ± 0.6	-10.3 ± 0.2
Tl ⁺ [a]	8.0 ± 3.0 x10 ⁸	- 16.9 ± 0.9	- 4.8 ± 0.8	-12.1 ± 0.3

In LiOH/H₂O (0.1 M) compound **3** does not show any affinity for K⁺ at 298 K. In contrast, this receptor shows good affinity for Rb⁺ with a binding constant $K = 3.4 \times 10^4 \text{ M}^{-1}$ ($\Delta G^0 = -6.2 \text{ kcal mol}^{-1}$) in the same solvent (Figure S10). An increase of the binding constant $K = 3.8 \times 10^7 \text{ M}^{-1}$ has been measured with Cs⁺ in the same conditions (Figure 4 and Figure S11). As the binding constant observed with Cs⁺ is close to the maximum value that can be accurately measured by ITC (direct measurement), we considered it preferable, in the case of Tl⁺, to use a competitor (Rb⁺) in order to obtain a good fit of the experimental data (see Figure 4). This procedure allowed us to measure a binding constant $K = 8.0 \pm 3.0 \times 10^8 \text{ M}^{-1}$ ($\Delta G^0 = -12.1 \pm 0.3 \text{ kcal mol}^{-1}$) for the Tl⁺@**3** complex (Figure 4 and Figure S12). Despite the presence of a competitor (RbCl; c = 0.4 mM), the slope of the ITC curve at the inflection point remains high, allowing a rough estimate of the binding constant. Attempt to improve the accuracy of the measurements by increasing the concentration of the competitor (RbCl; c = 0.8 mM) resulted in partial precipitation of the complex in the cell. It should be noted that for such a high binding constant, the error on the free enthalpy of complexation ΔG^0 remains limited.

Compound **3** has been isolated from precipitation in water during the work-up step. Although this derivative has been subsequently washed by organic solvents (*i.e.* ethanol and diethyl ether) it is still expected that compound **3** is solvated by water molecules. Here, drying compound **3** in vacuo (with heating) is not recommended, as even cryptophanes with small cavities can

collapse.¹⁷ Before carrying out ITC experiments, and in order to determine more precisely the actual mass of **3** introduced into the ITC cell, a calibration based on a ¹H NMR experiment was performed. A known quantity of a reference (maleic acid; $\delta_{(\text{CH}=\text{CH})} = 5.96$ ppm in LiOH/H₂O (0.1 M)) was added to compound **3** in a solution of LiOH/H₂O (0.1 M). The ratio between the aromatic protons of **3** and those of maleic acid was used to estimate the corrective factor (0.65 ± 0.05).

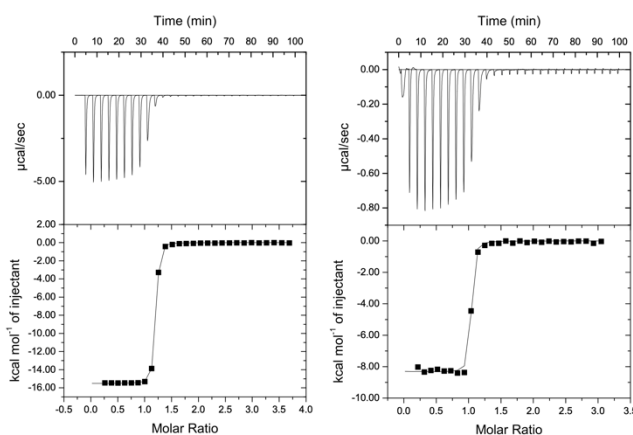


Figure 4: (Left) Isothermal calorimetric titration data of compound **3** in LiOH (0.1 M)/H₂O at 298 K. The host solution ($c = 0.06$ mM) was placed into the calorimeter cell (1.4 mL), and 28 successive aliquots (10 μL) of CsCl ($c = 1.0$ mM) were added at 3 min intervals ($n = 1.15 \pm 0.10$; $K = 3.8 \pm 0.6 \times 10^7 \text{ M}^{-1}$; $\Delta H^0 = -15.5 \pm 0.2 \text{ cal.mol}^{-1}$; $T\Delta S^0 = -5.2 \text{ kcal.mol}^{-1}$; $\Delta G^0 = -10.3 \pm 0.2 \text{ cal.mol}^{-1}$). (Right) Isothermal calorimetric titration data of compound **3** recorded under the same conditions. The host solution ($c = 0.08$ mM) was placed into the calorimeter cell (1.4 mL), and 28 successive aliquots (10 μL) of TlOAc ($c = 0.299$ mM) were added at 3 min intervals ($n = 1.16 \pm 0.10$; $K = 8.0 \pm 3.0 \times 10^8 \text{ M}^{-1}$; $\Delta H^0 = -16.9 \pm 0.9 \text{ cal.mol}^{-1}$; $T\Delta S^0 = -4.8 \pm 0.8 \text{ kcal.mol}^{-1}$; $\Delta G^0 = -12.1 \pm 0.3 \text{ kcal.mol}^{-1}$).

As compound **3** possesses both basic and acidic functions, it should be noted that the pH of the cell containing compound **3** may not be constant after each injection. Thus, to ensure that the

pH of the solution is not changed during these experiments, we have conducted at 298 K a new series of ITC experiments in a NaOH/KCl buffer that allows us to work at pH = 13.0. The results are gathered in Table 2 (see also Figures S13-S15). Using these conditions similar results have been obtained. For instance, in this solvent, the Rb⁺@**3** and the Cs⁺@**3** complexes shows binding constants $K = 1.7 \pm 0.3 \times 10^7 \text{ M}^{-1}$ ($\Delta G^0 = -5.7.0 \pm 0.1 \text{ kcal mol}^{-1}$) and $K = 2.4 \pm 1.0 \times 10^4 \text{ M}^{-1}$ ($\Delta G^0 = -10.0 \pm 0.5 \text{ kcal mol}^{-1}$), respectively. As previously observed, higher affinity was found with Tl⁺ and a binding constant $K = 9.0 \pm 5.0 \times 10^8 \text{ M}^{-1}$ ($\Delta G^0 = -11.8 \pm 0.7 \text{ kcal mol}^{-1}$) was measured in this solvent. Note that despite the high concentration of K⁺ cations in the NaOH/KCl buffer, similar results are obtained for both sets of experiments, confirming that K⁺ has no affinity for cryptophane **3**.

Table 2. Thermodynamic parameters of complexation K , ΔH^0 , $T\Delta S^0$ and ΔG^0 for the cation@**3** complexes recorded in aqueous solutions of sodium hydroxide (0.1 M) – potassium chloride (0.049 M) at 298 K. The values reported were obtained from isothermal titration (ITC) experiments. [a] from competition experiments (competitor Rb⁺).

M ⁺ @ 3	$K \text{ (M}^{-1}\text{)}$	$\Delta H^0 \text{ (kcal.mol}^{-1}\text{)}$	$T\Delta S^0 \text{ (kcal.mol}^{-1}\text{)}$	$\Delta G^0 \text{ (kcal.mol}^{-1}\text{)}$
Rb ⁺	$1.7 \pm 0.3 \times 10^4$	-7.3 ± 1.3	-1.5 ± 1.4	-5.7 ± 0.1
Cs ⁺	$2.4 \pm 1.0 \times 10^7$	-14.4 ± 0.5	-4.4 ± 0.5	-10.0 ± 0.5
Tl ⁺ [a]	$9.0 \pm 5.0 \times 10^8$	-15.7 ± 0.5	-3.9 ± 0.3	-12.0 ± 0.5

DISCUSSION

Grafting hetero-elements onto the aromatic rings of cryptophanes is a difficult task, and only a few examples have been reported so far. In this context, the groups of Hardie and Chambron independently described the preparation of sulfur-containing cryptophane

derivatives.¹⁸ Interestingly, the key step of these syntheses involves disulfide bridge formation via oxidative dimerization conditions. Also, the first synthesis of C_3 -symmetric aromatic amine-containing cryptophane on CTB unit was recently published by our group.^{19a} A year later, Vigier et al. performed the synthesis of a C_1 -symmetric aromatic amine-containing cryptophane where nitrogen atom replaces one of the three methylene bridges of a CTB unit.^{19b} With few exceptions, we found challenging to introduce hetero-elements directly onto the cryptophane backbone. It is easier to graft these hetero-elements on CTB rings and then to build the cryptophane scaffold. This is the strategy which has been used to prepare compound **4**, the cryptophane precursor of **3**. However, in the case of compound **4**, the grafting of three nitrogen atoms leads to difficulties in purifying intermediates. For example, compound **5** could not be isolated due to its low solubility and high retention time on silica gel. Lithium diphenylphosphide used in excess to promote the demethoxylation reaction also complicated the purification of this intermediate because the complete removal of this reactant can not be achieved. Nevertheless, PPh_2Li was the only reactant that successfully provides the desired cryptophane **6**. For example, the use boron tribromide or boron trichloride at -78°C to remove the three methyl groups results in a complex mixture of compounds, and the desired product could not be identified from the crude. The acetylation step of both the phenol and aromatic functions presents the advantage to increase the solubility of compound **6** in organic solvents and to facilitate its purification through silica gel. Then, this approach also allows us to remove in a single step the six acetate groups under acidic conditions to give rise to the expected cryptophane **3** in moderate yield. The presence of NH_2 and OH groups on compound **3** suggests that this compound could act as an amphoteric compound since, depending on the experimental conditions, it can act as either a base or an acid. Unfortunately, at lower pH values, the solubility of **3** decreases significantly and the solutions formed become cloudy, making it impossible to study the physical properties of **3** over a wide pH range under the right conditions. For instance,

compound **3** dissolved in a diluted aqueous HCl solution gives a suspension, despite the presence of three ammonium chloride units onto the cryptophane skeleton. Cryptophane **3** shows in its neutral form high solubility in DMSO but it is only sparingly soluble in CHCl₃ and CH₂Cl₂.

The interaction with cesium and thallium(I) ions was first investigated by NMR spectroscopy. NMR is well-suited to study cryptophane complexes in solution due to the strong ring current effects that affect the chemical shift of the caged ion or molecule. Hence, the guest species experience a strong shielding that results in a significant change of the chemical shift for the complex of interest. For hydrogen-containing guest molecules, the chemical shifts observed by ¹H NMR spectroscopy are moderate and are typically of few ppm.²⁰ However, large ions with highly polarizable electron cloud, such as cesium and thallium, exhibit significant chemical shift variations. A change in their environment induced by the encapsulation process results in an important variation of the NMR parameters.

Despite some similarities observed in their ¹³³Cs NMR spectra, the Cs⁺@Cryptophane complexes **1-3** behave differently as a function of the temperature. Previously, two main behaviors had been observed for Cs⁺@Cryptophane complexes as a function of temperature. For instance, cryptophane **1** and one of its congeners, which is decorated with five phenol groups shows a sharpening of the ¹³³Cs NMR signal as the temperature increases. A cryptophane-223(OH)₆ whose CTB units are connected together with two -O-CH₂CH₂-O and one O-CH₂CH₂CH₂-O linkers shows a similar behavior.^{13,21} The second trend is an opposite effect where a broadening of the ¹³³Cs NMR signal occurs when the temperature rises. This is the case for instance, for cryptophane **2** and a compound with a larger inner cavity.^{13,15} Actually, four phenomena can affect the variation in the ¹³³Cs relaxation time of the encapsulated cation: quadrupolar relaxation, sensitive to electric field gradients, chemical shift anisotropy (CSA), dipolar cross-relaxation with protons from the host molecule, and in-out

exchange of the cation (and undoubtedly the interferences between these phenomena.). Except for the last two, for which temperature increase is expected to lead to a lengthening of T_1 and T_2 , the effect of temperature on the other two mechanisms is more difficult to predict. However, cesium-133 has a small quadrupole moment $Q = -3 \times 10^{-31} \text{ m}^2$ and quadrupolar relaxation is unlikely to change drastically with temperature. Only the ^{133}Cs CSA must have a significant effect on the variation of NMR parameters as a function of temperature (T_1 , T_2 , chemical shift). Solid-state ^{133}Cs NMR on complexes with macrocyclic ligands have already evidenced a wide range of isotropic chemical shift and shielding constants, according to the macrocycle shapes.²² The puzzling behavior difference of the ^{133}Cs signals between these three complexes as a function of temperature - variation of the $\text{Cs}^+@$ Cryptophane chemical shift, T_1 , and T_2 estimated through the linewidth could be explained taking into account the ITC data recorded in LiOH/H₂O. Indeed, ITC experiments shows in LiOH/H₂O high binding constants $K = 3.8 \times 10^7 \text{ M}^{-1}$ for the $\text{Cs}^+@$ **3**. This binding constant measured between **3** and the Cs^+ cation is intermediate between those measured with hosts **1-2**. However, it can be noticed that the binding constant obtained with host **3** is very close to that obtained with host **1**. For instance, a binding constant have been previously measured to be $K = 2.9 \times 10^9 \text{ M}^{-1}$ for the $\text{Cs}^+@$ **1** in the same conditions. In contrast, a lower binding constants $K = 11 \times 10^3 \text{ M}^{-1}$ have been measured previously for the $\text{Cs}^+@$ **2** complex. Dealing with the evolution of the ^{133}Cs linewidth as a function of temperature, it has to be noted that it seems related to the free enthalpy of the complex. For cesium complexes with cryptophanes **1**, **3** and cryptophane-223-(OH)₆ that exhibit favorable free enthalpy ($\Delta H^\circ < -12 \text{ kcal.mol}^{-1}$), the linewidth diminishes when temperature rises.^{11,13} In addition, it should be also noted that in the absence of exchange of intermediate kinetics (*i.e.* when the exchange rate is far lower than the frequency difference between free and caged cesium), the caged cesium chemical shift experiences a linear variation as a function of temperature, which seems related to the complexation entropy. For cryptophane

1 (as well as for cryptophane-223-(OH)₆ and cryptophane-233-(OH)₆, see ref. 13), the slope is important, while for cryptophanes **2** and **3**, it is very shallow. For the first three, the TΔS° values are lower than -0.5 kcal.mol⁻¹.

A large chemical shift splitting ($\Delta\delta = 890$ ppm) is observed between the ²⁰⁵Tl NMR signals of the free Tl⁺ ion in solution and the Tl⁺@**3** complex at 301 K. The chemical shift difference observed with compound **3** is of the same order of magnitude as those previously observed with other water-soluble cryptophanes, except compound **2** for which the Tl⁺ ions are in fast exchange between the free and caged forms. For example, the chemical shift difference observed with compound **1** was measured at $\delta = 880$ ppm at 335 K.¹³ The large chemical shifts observed in the case of cryptophanes are a consequence of the highly polarizable nature of the electronic cloud that makes thallium as one of the most sensitive nuclei to its surrounding environment. This is also a consequence of the strong interaction that thallium can establish with the two CTB rings. A DFT calculation performed on a cryptophane-223 molecule revealed a more negative total binding energy for thallium than for cesium.²³ In addition, a theoretical approach based on the decomposition of the total binding energy into different contributions reveals that the Pauli repulsion term is strongly positive for thallium and contributes significantly to the destabilization of the complex.²³ However, this contribution is largely offset by the strongly negative electrostatic and orbital interaction terms, with non-negligible charge-transfer between Tl⁺ and the host molecule.

The stabilization of the Cs⁺@**3** and the Tl⁺@**3** complexes can be interpreted by the greater electron-donating effect of the nitrogen atom, which increases the electron density of the aromatic ring. As a result, the basicity of the cavity of host **3** is enhanced and it can more easily accommodate both Cs⁺ and Tl⁺. Since compound **1** exhibits higher binding constants upon Cs⁺ and Tl⁺ complexation, the introduction of three aromatic amine substituents grafted on the same CTB unit does not seem to fully replace the ability of three phenolate moieties to

stabilize the corresponding host-cation complexes. Nevertheless, the effect is very positive since triamino-cryptophane **3** is a much more potent receptor than compound **2** for the encapsulation of these cationic species under the same experimental conditions. Eventually, these host-guest properties come up with very promising perspective for the design of new nitrogen containing cryptophanes for the complexation of cesium and thallium(I) cations in aqueous solutions. It would have been interesting to take advantages of the amphoteric properties of **3** since a large pH dependence is expected with host. Unfortunately, the formation of a precipitate at neutral pH or in acidic solution hampered this study.

CONCLUSION

A C_3 -symmetrical *anti*-cryptophane **3** decorated with three primary amine groups located on the same CTB ring and three phenol groups positioned on the second CTB ring has been synthesized, and its interaction with Cs^+ and Tl^+ ions has been studied. Whereas this compound possesses amphoteric properties, its solubility is insufficient to investigate its complexation properties at neutral pH and in acidic solution. Nevertheless, cryptophane **3** exhibits a very high solubility in water under basic conditions. Compound **3** binds rubidium, cesium and thallium cations but not potassium in $\text{LiOH}/\text{H}_2\text{O}$ (0.1 M). ^{133}Cs and ^{205}Tl NMR spectroscopy allowed us to identify NMR characteristic signals of the cesium and thallium complexes with **3**, respectively. These signals are high-field shifted by several hundreds of ppm with respect to that of the cations dissolved in the bulk. Thanks to the ITC experiments, a complete description of the binding process could be achieved and the thermodynamic parameters K , ΔH^0 , ΔS^0 and ΔG^0 have been determined. These data shows that compound **3** binds very well cesium and thallium in these conditions and that the binding properties are close to those obtained with compound **1** that represents, to date, the best cryptophane for

encapsulating these two cationic species in aqueous solution. Our results suggest that the introduction of heteroatoms such as nitrogen atoms onto the cryptophane backbone has a positive effect on the binding properties of these hosts, probably due to an enhancement of the electron density of the CTB ring and a possible participation of the nitrogen lone pair in the stabilization of the complex. Chemical engineering shall be carried out on the design of future nitrogen-containing cryptophanes in order to investigate their binding properties in the full pH range of aqueous solutions. This work paves the way for the synthesis of efficient molecular hosts for thallium extraction in aqueous solution, and for the preparation of new molecular chelators for the radionuclide ^{201}Tl .

Experimental Section

Synthesis of cryptophane *anti*-6: Excess of a freshly prepared lithium diphenylphosphide solution (1 M; 6 mL in THF) was added to a suspension of *anti*-cryptophane **4** (300 mg, 0.31 mmol) in THF (3 mL) under argon. The dark red mixture was then heated (oil bath) at 60°C for 24 hours. At the end we notice that the mixture keeps its red color. The mixture was poured into water (30 mL). Then, the aqueous layer was washed three times (20 mL) with CH_2Cl_2 . Then, a conc. HCl solution (12 M, 5.0 mL) was added to give rise to compound **5** as a precipitate, which was collected on a frit. Compound **5** was engaged without further purification in the next reaction. Thus, crude compound **5** was dissolved in pyridine (20 mL) and the mixture was cooled to 0°C under argon. Then, acetic anhydride (1.5 mL; 15.0 mmol) was added slowly via a syringe. The mixture was stirred for 5 hrs at room temperature. Pyridine was removed under reduced pressure. The crude was taken up in dichloromethane and washed with a solution of sodium hydroxide (1 M, 2 x 20 mL) to remove phosphine. The crude was purified by column chromatography on silica gel (eluent: CH_2Cl_2 / acetone: 70/30) to give rise to *anti*-cryptophane

6 as a colorless solid (98 mg, 30% over two steps). ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 8.22 (s, 3H), 7.57 (s, 3H), 6.84 (s, 3H), 6.83 (s, 3H), 6.81 (s, 3H), 4.62 (d, 3H, $J = 13.9$ Hz), 4.58 (d, 3H, $J = 14.3$ Hz), 4.40-4.31 (m, 3H), 4.31-4.17 (m, 3H), 4.03-3.98 (m, 6H), 3.49 (d, 3H, $J = 13.3$ Hz), 3.47 (d, 3H, $J = 13.9$ Hz), 2.39 (s, 9H), 2.24 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3 , 25 °C): δ 169.1 (3C), 167.4 (3C), 148.6 (3C), 146.1 (3C), 140.2 (3C), 137.9 (3C), 134.9 (3C), 134.0 (3C), 132.8 (3C), 128.3 (3C), 124.3 (3C), 122.7 (3C), 121.2 (3C), 116.2 (3C), 69.9 (3C), 68.6 (3C), 36.5 (3C), 36.3 (3C), 25.1 (3C), 20.9 (3C). HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{60}\text{H}_{57}\text{N}_3\text{NaO}_{15}^+$ 1082.3682; found 1082.3687.

Synthesis of cryptophane *anti*-3: Cryptophane *anti*-6 (110 mg, 0,104 mmol) was suspended in ethanol (18 mL) and HCl (37% aqueous, 2 mL) was added to the mixture. The mixture was heated (oil bath) to 90 °C. After 5 hours, no solid remained in the mixture. The solution was then cooled down to room temperature and the solvent was removed under reduced pressure. A saturated solution of sodium hydrogenocarbonate (5 mL) was added to the crude and the resulting solid residue was filtered on a frit. The solid was washed with water, diethyl ether and dichloromethane to give rise to **3** as a beige solid (49 mg, 59%); ^1H NMR (400 MHz, NaOD/ D_2O ; 0.1 M), 25 °C): δ 6.60 (s, 3H), 6.54 (s, 3H), 6.52 (s, 3H), 6.29 (s, 3H), 4.29 (d, 3H, $J = 13.2$ Hz), 4.18 (d, 3H, $J = 11,6$ Hz), 4.10 (s, 12 H), 3.11 (d, 3H, $J = 13.8$ Hz), 2.98 (d, 3H, $J = 13.0$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, D_2O (NaOD 0.1 M), 25 °C): δ 158.5 (3C), 149.5 (3C), 147.1 (3C), 138.4 (3C), 137.3 (3C), 136.2 (3C), 133.3 (3C), 127.2 (3C), 123.1 (6C), 120.4 (3C), 118.5 (3C), 71.6 (3C), 70.2 (3C), 37.7 (3C), 37.1 (3C). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{48}\text{H}_{46}\text{N}_3\text{O}_9^+$ 808.3229; found 808.3220.

GENERAL METHODS:

Characterization of the samples: Mass spectra (HRMS) were performed by the Centre de Spectrométrie de Masse, University of Lyon. Analyses were performed with a hybrid

quadrupole-time-of-flight mass spectrometer, microToF QII equipped with an electrospray ion source. Data Analysis 4.0 was used for instrument control, data collection, and data treatment. HRMS analyses were performed in full scan MS with a mass range from 50 to 2000 Da at an acquisition rate of 1 Hz. Transfer parameters were as follows: RF Funnel 1, 200 V; RF Funnel 2, 200 V; hexapole, 50 V; transfer time, 70 μ s; and PrePulse storage time, 1 μ s. Before each acquisition batch, external calibration of the instrument was performed with a sodium formate clusters solution. ^1H and ^{13}C NMR spectra were recorded at 400.0 and 100.6 MHz, respectively. Chemical shifts (ppm) are referenced to Me_4Si (^1H , ^{13}C). Structural assignment of compound **3** were made with additional information from HSQC and HMBC experiments.

Column chromatographic separations were carried out over Merck silica gel 60 (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel TLC plates, F-254. The solvents were distilled prior to use: DMF and CH_2Cl_2 from CaH_2 and THF from Na/benzophenone.

Isothermal Titration Calorimetry: The ITC instrument used was VP-ITC 200 (TA Instruments, New Castle, DE), which operated at constant temperature (293K). To carry out a binding experiment, a stock solution was prepared by dissolving LiOH or NaOH/KCl in water. The sample solution was then prepared by diluting the cryptophane **3** to the desired concentration using the stock solution. The cryptophane **3** solution was then placed in the sample cell (1.4 mL) and the reference cell was filled with the stock solution. Both cells are mounted in an adiabatic chamber held at a constant temperature during the measurement. A long-needle syringe with a twisted paddle fastened to its end was filled with the metal-ion solution. **CAUTION!** The acute toxic thallium(I) acetate constitutes significant safety hazards and must be handled with extreme care. During the experiment, the syringe needle was placed inside the sample cell, and the entire needle was rotated at constant speed (307 RPM). Once thermal equilibrium has been reached, the metal ion solution is automatically injected again.

Due to possible dilution of the first measurement, the first injection (and sometimes the second) is omitted from the data analysis. The first 2- μ L injection was followed by a series of 42, 10 μ L injections. The time interval between two consecutive injections was 210 s to ensure that equilibrium was reached before each injection. Nonlinear least-squares curve fitting was conducted using the Origin program given by the manufacturer. The heats of dilution (baseline) were achieved by replacing the host molecule with the stock solution. Data are then subtracted before curve fitting.

^{133}Cs NMR. ^{133}Cs NMR spectra (65.59 MHz) were recorded on a 11.7 T Bruker Avance II spectrometer using a 5 mm broadband inverse probehead. The ^{133}Cs 90° pulse was measured at 44 μ s at 40 W. A solution of CsNO_3 was used as a chemical shift reference (0 ppm). Except otherwise specified, an interscan delay of 2.5 s was applied. The FIDs were apodized by an exponential window of 10 Hz before Fourier transformation.

^{205}Tl NMR (CAUTION HIGHLY TOXIC). For reasons of variable capacitance bandwidth, the broadband channel of commercial NMR probes generally ranges from ^{15}N (50.7 MHz at 11.7 T) to ^{31}P (202.4 MHz at 11.7T). However, ^{205}Tl resonates at 288.5 MHz at 11.7 T, *i.e.* above the latter value, but far from the frequency of ^{19}F . We therefore had to adapt a probe to reach this frequency. As a result, the ^{205}Tl NMR experiments were performed on a narrow bore Bruker Avance II spectrometer equipped with a 5 mm broadband (BB) triple axis gradient Nalorac probe. On the BB channel a homemade inductive tuning rod was built to reach the ^{205}Tl Larmor frequency. The ^{205}Tl 90° pulse with this setup was measured at 21 μ s at 75 W. Note that this only allows an excitation range of around 165 ppm (considering the first lobe of the sinc function which is the Fourier transform of the square pulse), and therefore free thallium and complexed thallium can only be observed with two separate experiments (which is advantageous for taking advantage of the in-out exchange). Except otherwise specified, an interscan delay of 1.5 s was applied. A solution of thallium nitrate was used as a chemical shift

reference (0 ppm). The FIDs were apodized by an exponential window of 400 Hz before Fourier transformation.

ASSOCIATED CONTENT

Data availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information.

^1H NMR spectrum of **4**. ^1H and ^{13}C NMR spectra of compounds **3** and **6**. Integral ratio between the $\text{Cs}^+@3$ complex and the Cs^+ free. Theoretical and experimental High Resolution Mass Spectra of complexes $\{\text{Rb}^+@[\mathbf{3} - 2\text{H}]\}^-$, $\{\text{Cs}^+@[\mathbf{3} - 2\text{H}]\}^-$ and $\{\text{Tl}^+@[\mathbf{3} - 2\text{H}]\}^-$. HMBC and HSQC spectra of **3**. Isothermal Calorimetric Titration data of the $\text{Rb}^+@3$, $\text{Cs}^+@3$, $\text{Tl}^+@3$ in $\text{LiOH}/\text{H}_2\text{O}$ and NaOH/KCl .

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Notes

The authors declare no competing financial interest.

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