JOC The Journal of Organic Chemistry

Note

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High Affinity of Water-Soluble Cryptophanes for Cesium Cations

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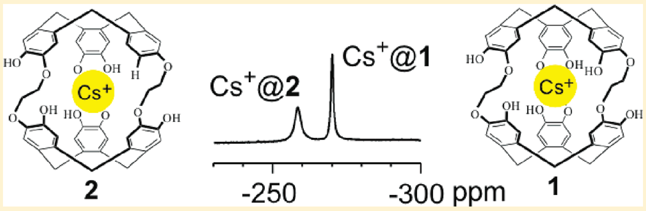
Supporting Information

ABSTRACT: Exceptionally high affinity for cesium cations was achieved in aqueous solution using two enantiopure cryptophanes. Complexation of cesium was evidenced by ^{133}Cs NMR spectroscopy and by electronic circular dichroism (ECD). Binding constants as high as 6×10^9 M^{-1} have been measured by isothermal titration calorimetry (ITC). Very strong complexation of rubidium cations ($K \sim 10^6$ M^{-1}) has also been measured. Chiral hosts allowed the detection of the two cations at low concentrations (μM) using ECD.

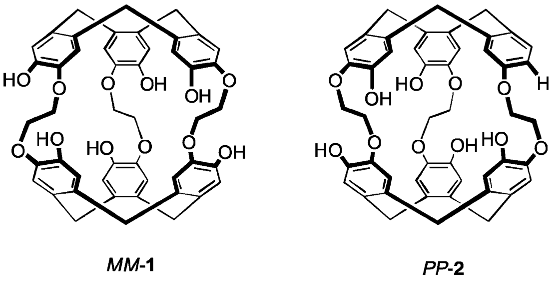


Since the pioneering work of Pedersen,[1] the synthesis of molecular hosts showing good affinity for ionic species has represented an important field of research in today's chemistry. Besides the fundamental interest in understanding host−guest interactions, the encapsulation of cations is strongly motivated by applications in analytical chemistry, biology, biotoxicity and environmental chemistry.[2] For instance, supramolecular hosts able to detect toxic species at low concentration (such as Pb^{2+} and Cd^{2+}) or to encapsulate radioactive elements (mainly $^{137}Cs^+$) are highly desirable.

Cesium is of major concern in environmental chemistry since it is one of the most important radioactive elements found in nuclear waste and the long half-life of ^{137}Cs (30 years) requires its sequestration to avoid air or soil contamination. Thus, it is important that chemists synthesize host molecules for the recognition of ionic species such as Cs^+. So far, numerous supramolecular systems have been described in the literature for the sequestration of Cs^+ in organic solvents or in water, and calixarene derivatives appeared to be the most successful class of compounds for cesium complexation.[3] For instance, Reinhoudt and co-workers have synthesized calixarene derivatives showing strong affinity for Cs^+ in MeOH or in $CHCl_3$ and exhibiting a good selectivity toward Na^+.[4] On the other hand, Valeur and co-workers have reported the synthesis of a water-soluble calixarene showing excellent selectivity for Cs^+.[5] In the latter case, the complexation of Cs^+ can be easily detected by fluorescence in the μM range.

Abrahams et al. have also reported the encapsulation of the cesium cation by hydrogen-bonded pairs of cyclotricatechylene in the solid state.[6] Cryptophane derivatives are another class of compounds able to bind small molecules or atoms.[7] For instance, Akabori et al. and Weber et al. have reported the encapsulation of Cs^+ by cryptophane derivatives in organic solvents.[8] In Akabori's cryptophanes, cesium encapsulation is made possible by the three diethyleneoxy bridges surrounding the cation, whereas in Weber's cryptophanes, the encapsulation of Cs^+ is made possible thanks to the presence of three carboxylic acid groups pointing toward the cavity of the host. In this note, we show that, even in absence of such functionalities, the cryptophanes **1** and **2** (scheme 1) are able to bind cesium cations in water at pH > 12. Basic conditions are necessary to allow the solubilization of these two hosts in water. The synthesis of these water-soluble cryptophanes has been

Scheme 1. Structure of Water-Soluble Cryptophanes 1 and 2[a]



[a]A single enantiomer is shown for each compound.

Received: November 14, 2011
Published: December 22, 2011

previously reported both in their racemic and enantiopure forms.[9]

We have recently described the unusual chiroptical properties of the water-soluble cryptophanes **1** and **2** under basic condition ($pH \geq 12$).[9] We have shown that these two hosts exhibit very peculiar behavior with respect to cryptophanes studied in organic solvents. Indeed, the chiroptical properties of **1** and **2** strongly depend on the nature of the counterions surrounding the host molecules. For instance, in $LiOH/H_2O$ and $NaOH/H_2O$ solutions, the electronic circular dichroism (ECD) spectra of **1** and **2** are very sensitive to the encapsulation of neutral molecules (such as $CHCl_3$ or CH_2Cl_2) and lead to significant changes of the ECD spectra, especially in the ^1L_b and ^1B_b regions. In contrast, in $CsOH/H_2O$ and to a lesser extent in KOH/H_2O, the ECD spectra remain unchanged. In a preliminary study,[9a] this result had been interpreted as a consequence of the steric effects induced by K^+ or Cs^+ counterions surrounding cryptophane **1**, preventing the guest molecules to access the cavity of the host. However, thanks to molecular dynamics (MD) calculations, it has been recently shown that cesium cations can easily enter the cavity of hosts **1** and **2**.[9b] In contrast, lithium and sodium cations are not well recognized by hosts **1** and **2**. This result prompted us to investigate in more details the binding of alkali cations by these two cryptophanes.

First, the encapsulation of cesium cations by enantiopure hosts **1** (*MM*-**1** and *PP*-**1**) and **2** (*MM*-**2** and *PP*-**2**) was investigated by ECD spectroscopy with and without a competitor ($CHCl_3$) using a $LiOH/H_2O$ solution at an arbitrary concentration of 0.1 M. Figure 1a shows that even the addition of a very small amount of Cs^+ cations (0.2 equiv [host]) to the solution is sufficient to induce a significant change of the ECD spectra of host **2**. The presence of the isosbestic points in Figure 1a is due to the apparition of a new species which can be attributed to the Cs^+@**2** complex. Interestingly, a similar behavior occurs in presence of a large excess of a competitor guest molecule (saturated solution of $CHCl_3$ in $LiOH/H_2O$). The spectral changes (Figure 1b) are in this case more pronounced in the ^1B_b region (around 220 nm), because of the large conformational changes of the three ethylenedioxy linkers induced by the replacement of $CHCl_3$ molecules by cesium cations. Indeed, we have previously shown that the ECD and vibrational circular dichroism (VCD) spectra are very sensitive to the conformation of the three linkers, which is directly related to the size of the guest molecule.[10] Thus, the guest-free cryptophane favors the *gauche* conformation of the bridges in order to reduce the size of the cavity (hydrophobic effect), whereas the filled cryptophane favors the *trans* conformation of the linkers when large guest molecules, such as $CHCl_3$ (guest volume of 72 Å^3) enter its cavity. Consequently, subtle conformational modifications of the linkers occur during the encapsulation process to maximize the host–guest interactions. Figure 1 shows that ECD spectra are very sensitive to these subtle conformational modifications of the linkers, allowing an accurate investigation of the host–guest interactions. Thus, the ECD spectroscopy can be a powerful technique for the detection of guest molecules and in particular for the detection of cesium cations. Indeed, we have been able to detect Cs^+ in the μM range or below when a competitor ($CHCl_3$) is used (Supporting Information, Figures 1–2). Similar behavior has been obtained for host **1** in presence of cesium cations (Supporting Information, Figures 3 and 4). These ECD results clearly show that both hosts **1** and **2** exhibit a very high affinity for cesium cations. Rubidium cations also bind hosts **1** and **2**, producing similar effect on the ECD spectra of Rb^+@**1** and Rb^+@**2** complexes (Supporting Information, Figures 5–8).

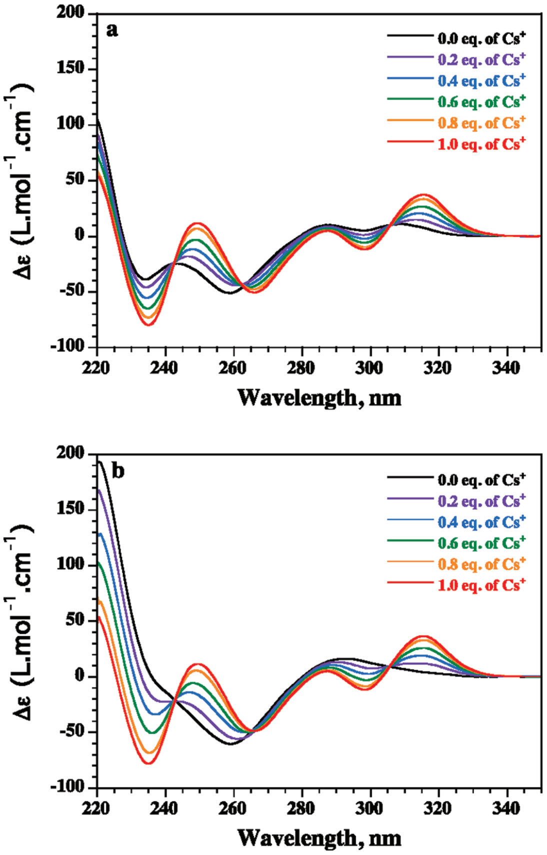


Figure 1. ECD spectra recorded at 293 K of *PP*-**2** ([host] from 6.5 to 8.5×10^{-5} M): (a) in $LiOH/H_2O$ solution (0.1 M) in the presence of different amounts of a $CsOH/H_2O$ solution; (b) in a saturated solution of $CHCl_3$ in $LiOH/H_2O$ in presence of different amounts of a $CsOH/H_2O$ solution. ECD spectra for higher [Cs^+] are identical to that recorded for 1 equiv of Cs^+.

Second, ^{133}Cs NMR experiments have been performed to study the Cs^+@**1** and Cs^+@**2** complexes. ^{133}Cs NMR spectroscopy has been previously used by different authors to investigate the formation of various cesium complexes in solution.[11] In $LiOD/D_2O$ solution, the ^{133}Cs NMR spectrum of host **1** in presence of small amount of CsOH reveals two signals (Supporting Information, Figure 9). A first signal is observed at 5 ppm, ascribed to free Cs^+ dissolved in solution, and a second sharp signal is located at −275 ppm (reference $CsNO_3$), which is assigned to the cesium atom present in the cavity of the host. Similarly, host **2** reveals a signal located at −263 ppm (Supporting Information, Figure 10). The chemical shift of the encapsulated cesium in host **1** and **2** varies only slightly with the nature of the counterions surrounding the host molecule (Supporting Information, Figure 11). The chemical shift difference observed between free Cs^+ in solution and Cs^+@**1** or Cs^+@**2** complexes reflects the high sensitivity of the Cs^+ cation to its surrounding environment. It is noteworthy that some similarities exist between Cs^+ trapped in hosts **1** and **2** and xenon encapsulation with cryptophanes.[12] Indeed, Cs^+ is isoelectronic with monatomic xenon and is, therefore, highly polarizable. The strong shielding by the six aromatic rings of cryptophanes produces similar effects with these two species, allowing the easy detection of the corresponding complexes by ^{133}Cs NMR and ^{129}Xe NMR spectroscopy.

As shown in Figure 2, a competition experiment between an equimolar amount of hosts **1** and **2** in LiOD/D_2O solution in presence of CsOD/D_2O reveals that the Cs^+ cation has a better affinity with pentahydroxy derivative **2** than with penta-hydroxy derivative **2**. The relative area of the two NMR peaks associated with the encapsulated cesium gives [Cs^+@**1**]/[Cs^+@**2**] = 1.3 at 298 K. This selectivity has been found slightly dependent on the temperature, since the NMR spectra change with the temperature (Supporting Information, Figure 12). Indeed, the width of the ^{133}Cs NMR signal of the Cs^+@**2** complex is strongly broadened as the temperature decreases, in contrast to that observed for the Cs^+@**1** complex. The broadening of the NMR peak is certainly associated with the lower symmetry of host **2** and the dynamics of the cesium cation, which explores different regions of the cavity during its long residence time within the cryptophane's cavity.

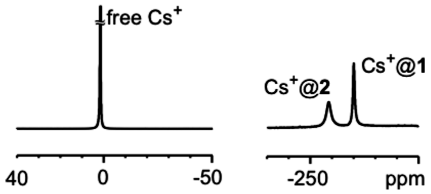


Figure 2. ^{133}Cs NMR spectra recorded at 298 K of hosts **1** and **2** in LiOD/D_2O solution (0.1 M) in the presence of a small amount of CsOH.

Third, isothermal titration calorimetry (ITC) experiments have been performed at 278 K to provide quantitative information about the encapsulation of alkali cations by hosts **1** and **2** in LiOH/H_2O solution. The binding strongly depends on the nature of the cation encapsulated within the cavity (Table 1). For instance, the recognition of sodium cations by hosts **1** and **2** is very low, giving rise to binding constant values, *K*, lower than 80 M^{-1} (Supporting Information, Figure 13). This result is consistent with ECD experiments performed in a saturated solution of CH_2Cl_2 or $CHCl_3$ in NaOD/D_2O previously published,[9] showing that the guest molecules can easily fill the cavity of **1** and **2** and that Na^+ cations do not compete with these guests. In addition, MD calculations have revealed a preferential affinity of the sodium cations for the oxygen atoms surrounding the cavity of the hosts. For potassium cations, the ITC experiments reveal a moderate affinity of K^+ for the cryptophane cavity, with binding constants of 1790 M^{-1} and 350 M^{-1} for hosts **1** and **2**, respectively (Supporting Information, Figure 14). This affinity becomes more pronounced for Rb^+ and very important for Cs^+, indicating that the value of the binding constant is correlated with the size of the cation. Thus, Rb^+ cation exhibits a high affinity for hosts **1** and **2** with binding constants of 1.9 × 10^6 M^{-1} and 4.2 × 10^5 M^{-1}, respectively (Supporting Information, Figure 15). For Cs^+ cations, the direct measure of the binding constant leads to inaccurate value of K since the detection limit of the ITC device was reached. Experiments involving competition between Rb^+ and Cs^+ have been performed to estimate more precisely the binding constants of Cs^+ with cryptophanes **1** and **2** (Supporting Information, Figure 16).[13] Binding constant values of 5.9 × 10^9 M^{-1} and 2.1 × 10^9 M^{-1} have been obtained for the Cs^+@**1** and Cs^+@**2** complexes, respectively. These values represent the highest binding constants ever found between a guest and a cryptophane derivative.

Table 1. Thermodynamic Parameters of Complexation of K^+, Rb^+, and Cs^+ by Hosts 1 and 2 in LiOH/H_2O Solution at 278 K: Binding Constant K (M^{-1}), Enthalpy ΔH (kcal mol^{-1}), Entropy ΔS (cal mol^{-1} deg^{-1}), and ΔG (kcal mol^{-1}) of Complexation

host	cation	K	ΔH^b	ΔS	ΔG
1	K^+	1790	−3.5	+2.5	−4.2
1	Rb^+	1.9 × 10^6	−5.3	+9.6	−8.0
1	Cs^{+a}	5.9 × 10^9	−11.9	−0.1	−11.9
2	K^+	350	−4.4	−4.1	−3.3
2	Rb^+	4.2 × 10^5	−5.4	6.4	−7.2
2	Cs^{+a}	2.1 × 10^9	−12.1	−0.8	−11.9

[a] From competition experiments. [b] ±5% errors were estimated.

On the other hand, ITC experiments show that the Cs^+-cryptophane interaction is enthalpically controlled for the two hosts. Indeed the $T\Delta S$ term is very low (<0.2 kcal mol^{-1}) and is certainly associated with the preorganized structure of the cryptophane backbone. The high value of the enthalpy of complexation (ΔH ~ −12 kcal mol^{-1}) can be explained in terms of strong Coulombic interactions between Cs^+ and phenolate moieties as well as in terms of electrostatic interactions between the cationic species and the π-donor cavity of the hosts. Finally, our results reveal that a single cation is encapsulated in the cavity, despite the small volume of Rb^+ (V = 13.3 Å^3) and Cs^+ (V = 19.5 Å^3) with respect to the size of the cavity of hosts **1** and **2** (V_{vdw} ~ 95 Å^3).

To better understand the origin of the high affinity of Cs^+ cation with hosts **1** and **2**, we have investigated the binding of Cs^+ by an other water-soluble host molecule, in which the six phenolate moieties have been replaced by six OCH_2COOH functions. A recent study of ^{1}H NMR[14] and ^{133}Cs NMR experiments (Supporting Information, Figure 17) shows that this hexaacid cryptophane **3** does not have any affinity for Cs^+ cations. The lack of affinity of cesium cation for **3** suggests that the presence of the phenolate moieties is pivotal to observe cesium complexation by cryptophanes and that Coulombic interactions between Cs^+ and the phenolate moieties play a key role in the stabilization of the complexes.

We have shown in this paper that hosts **1** and **2** bind alkali cations in the order $Cs^+ \gg Rb^+ \gg K^+ > Na^+$. Thus, the greater the polarizability of the cation,[15] the stronger the binding constant. The encapsulation of cesium by hosts **1** and **2** has been characterized by a high-field shifted ^{133}Cs NMR signal (250−270 ppm) and by very high binding constants (2−6 × 10^9 M^{-1}) as determined from ITC experiments. This study shows also that the presence of phenolate groups on the cryptophane backbone is essential to ensure cesium and rubidium sequestration. In contrast to what is observed for the complexation of neutral molecules by cryptophanes, the guest/host molecular volume ratio is not the preponderant factor in the binding process. Indeed, the dimension of ionic volume of Rb^+ and Cs^+ is small with respect to the cavity of the two hosts (V ~ 95 Å^3), with a ratio of 14% and 21% for Rb^+ and Cs^+, respectively, whereas it is in the range of 55−60% for neutral molecules. Instead, strong Coulombic interactions between Cs^+ and phenolate moieties as well as electrostatic interactions between the cationic species and the π-donor cavity of the hosts are responsible of this very good binding.

In summary, the high binding of Cs^+ by host **1** and **2** is unusual, considering that the association occurs in water in presence of a large excess of other cationic species (Li^+, Na^+, K^+). Very low concentrations of Cs^+ ($<\mu M$) can thus be detected by ECD, using an enantiopure host. The results reported in this note prompt us to investigate other polarizable cations that can play an important role in the environmental chemistry (Tl^+, Sr^{2+}).

■ EXPERIMENTAL SECTION

Synthesis of Enantiopure Hexahydroxy and Pentahydroxy Cryptophanes 1. The synthetic route used to obtain water-soluble hexahydroxy cryptophane, *rac*-**1**, and pentahydroxy cryptophane, *rac*-**2** as well as their two enantiomers *MM*-**1**, *PP*-**1**, *MM*-**2** and *PP*-**2** from cryptophanol *rac*-**4** and its two enantiomers *MM*-**4** and *PP*-**4** has been previously reported.[9]

ECD Measurements. ECD spectra were recorded at 293 K using a 0.2 or 1 cm path length quartz cell. The concentration of *MM*-**1** and *PP*-**2** was in the range $6-9 \times 10^{-5}$ M in basic H_2O solutions (0.1 M solution of LiOH). Additional spectra were recorded at lower concentration to evaluate the detection limit. Spectra were recorded in the 220–400 nm wavelength range with a 0.5 nm increment and a 1 s integration time. Spectra were processed with standard spectrometer software.

ITC Experiments. Isothermal titration calorimetry (ITC) experiments were performed at 278 K. In a standard experiment, the host solution (~0.1 mM) in LiOH (0.1 M) was placed into the calorimeter cell (200 μL) and 19 successive aliquots (2 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 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.

NMR Measurements. ^{133}Cs NMR spectroscopy (65.58726 MHz) was recorded on a 500 MHz using a 5 mm probehead (with spinning). A 90° pulse of 10 μs (for a $Pl_1 = 3$ dB) was applied. A delay time of 1s was applied between each pulse. At 298 K the delay time was 5 s.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

ECD spectra recorded at 293 K of *MM*-**1** and *PP*-**2** in LiOH/H_2O solution (0.1 M, saturated or not with $CHCl_3$) in the presence of different amounts of a CsOH/H_2O solution. ECD spectra recorded at 293 K of *MM*-**1** and *PP*-**2** in LiOH/H_2O solution (0.1 M, saturated or not with $CHCl_3$) in the presence of different amounts of a RbCl/H_2O solution. ^{133}Cs NMR spectrum recorded at 298 K of *MM*-**1** and *MM*-**2** in LiOD/D_2O, NaOD/D_2O and KOD/D_2O solutions (0.1 M) in the presence of CsOH and in CsOD/D_2O solution (0.1 M). Calorimetric titration of *MM*-**1** (left) and *MM*-**2** (right) in LiOH/H_2O solution (0.1 M) with NaOH/H_2O, KOH/H_2O, RbCl/H_2O, and CsOH/H_2O solutions. ^{133}Cs NMR spectrum recorded at 298 K of *PP*-**3** in LiOD/D_2O solution (0.1 M) in the presence of CsOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

T.B. thanks S. Denis-Quanquin for the implementation of the ^{133}Cs NMR sequence, J.-P. Dutasta for fruitful discussions, and O. Thorn-Seshold for critical reading of this manuscript. ECD experiments were performed on the PAP platform of SFR Biosciences Gerland-Lyon Sud UMS344.

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