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Synthesis of Cryptophane-223 Type Derivatives with dual functionalization

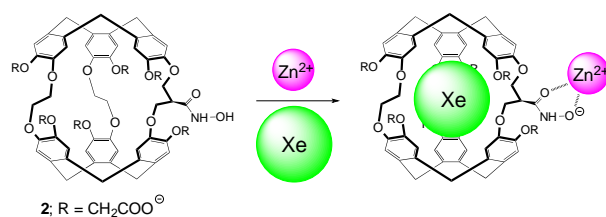
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TOC/Abstract graphic:



ABSTRACT: In this article, we present the synthesis of new cryptophane-type hosts capable of binding xenon in aqueous media and which may be useful for the development of xenon-based MRI derivatives. The synthetic route proposed was chosen in order to facilitate both the introduction of water-solubilizing substituents as well as the functionalization of the host with a single arm showing recognition properties that constitute two crucial steps. This was made possible by preparing new cryptophane-223 derivatives bearing two different chemical functions that can be easily modified at a later stage. Thus, subsequent reactions allowed the design of a new cryptophane host able to bind zinc or nickel cations. The ability of this molecule to bind cationic species was assessed by calorimetric titration experiments and hyperpolarized ¹²⁹Xe NMR. The advantages and inconveniences of this approach are discussed.

INTRODUCTION

Hyperpolarized xenon is considered a good candidate as an NMR probe because of its outstanding physical properties and ease of instillation.¹ It has been shown that, when caged in some molecular hosts, xenon atoms acquire a specific signature on the NMR spectrum that can be exploited to detect biological events at the molecular level.² In this domain, cryptophane derivatives are known to be excellent host molecules for xenon in aqueous solution.³ The targeting of biological receptors is made possible because these cryptophane derivatives can be chemically modified to attach a specific ligand. In recent years, different groups have benefited from both the properties of cryptophane and xenon to detect various biological targets *in vitro* or *in cellulo*.⁴

However, in order to be considered as efficient hosts for xenon imaging, cryptophane derivatives have to obey other specifications in addition to the clear spectral signature given to caged xenon. For instance, these hosts have to show a high specificity to xenon in physiological media. This condition is generally fulfilled for small cryptophane derivatives. Importantly, the in-out exchange of xenon has to be fast enough to allow a rapid replenishment of the cavity with new hyperpolarized xenon.¹ This condition is crucial for sensitive detection of the ^{129}Xe NMR signal via hyper-CEST approach. The host molecule must be soluble in aqueous media and must be easily functionalized with an appropriate chemical function showing a biological activity. This poses a challenging problem for chemists due to the high molecular symmetry of these hosts and their high lipophilicity. Toxicity and the bio-distribution of the cryptophane-biosensor are also principal parameters and have to be considered with care, but these properties can only be evaluated at the end of the synthesis.

Over the last ten years, many different cryptophane biosensors have been prepared for the construction of these xenon-based biosensors such as cryptophanol-A, a derivative bearing a single phenol group.⁵ However, its skeleton is rather lipophilic and suffers from a very low solubility in physiological media even at low concentration. Consequently, this compound is prone to interact with cellular membranes and its use cannot be extended to *in vivo* experiments. Also it may give rise to self-organized assemblies, as already shown for a cryptophane bearing a 20-mer oligonucleotide.⁶ On the other hand, hexacarboxylated cryptophane-222 shows a higher solubility in aqueous media but the functionalization and the purification of this derivative are tedious due to the high symmetry of this compound.⁷ Consequently, the elaboration of xenon-biosensors from this derivative leads to the formation of numerous by-products during the synthesis, which have to be separated from the main product. Despite the difficulties encountered to purify the desired biosensors, this cryptophane scaffold has been successfully used in its racemic or enantiopure forms to prepare xenon biosensors.^{4a,7a-b} Other cryptophane skeletons have been reported for xenon-biosensing but the same difficulties listed above have been encountered with these derivatives for the construction of xenon-biosensors.⁸

In 2015, our group proposed a new synthetic route aimed at facilitating the introduction of the water-soluble substituents and a linker bearing a recognition site.⁹ This strategy was based on the synthesis of a cryptophane with a low symmetry (C_1 -symmetry) possessing two reactive functions that could be functionalized at different stages of the synthesis. Among the different derivatives reported, a cryptophane derivative decorated with six carboxylic acid functions and a secondary alcohol group appeared a promising host molecule for the design of new biosensors (scheme 1). However, the synthesis of cryptophane **1** is not optimal since its functionalization is still difficult due to the steric hindrance of the central secondary alcohol.

In this article, we report the synthesis of a new molecular host of C_1 -symmetry whose secondary alcohol function has been replaced by a more accessible primary alcohol. We show that this new host can be modified in order to link water-soluble substituents and that the primary alcohol function can be modified in order to attach other chemical groups. As an example, we describe the synthesis of cryptophane **2** that possesses a terminal hydroxamic acid function capable of recognizing cationic species (chart 1). The capability of this host to recognize cationic species has been assessed by isothermal calorimetric titration experiments (ITC) and hyperpolarized ^{129}Xe NMR. The advantages and inconveniences of this approach are also discussed.

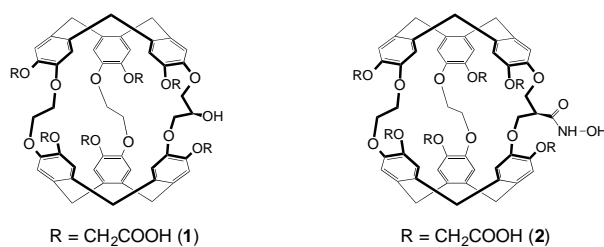
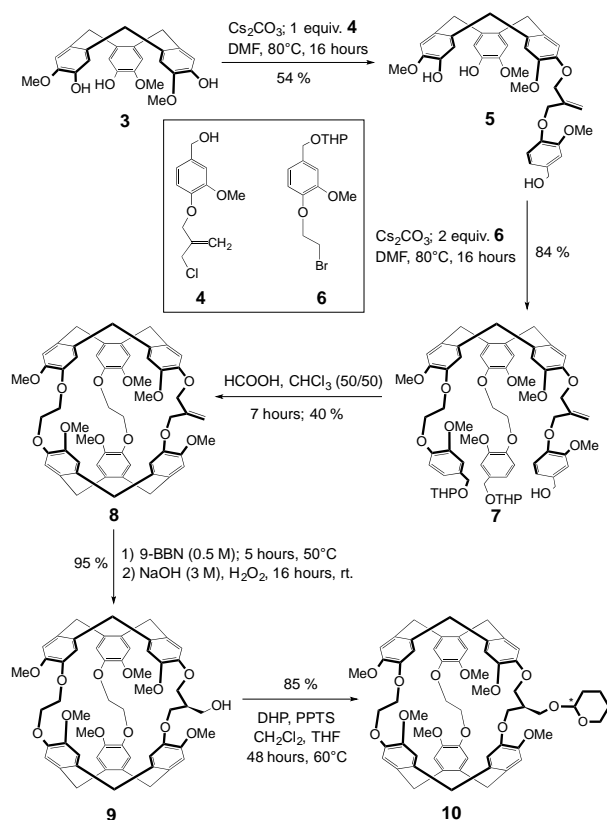


Chart 1: chemical structure of cryptophane **1** and cryptophane **2**

RESULT

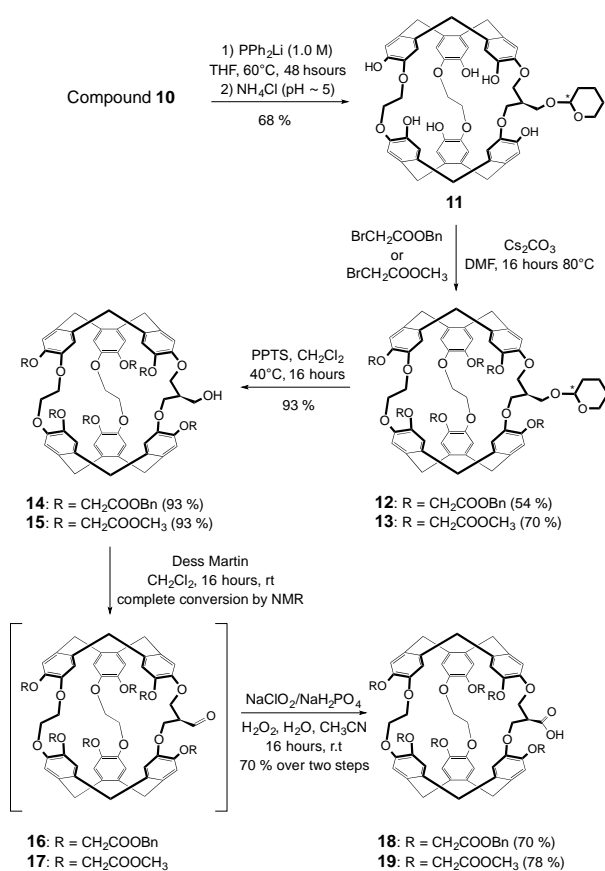
Synthesis of cryptophanes: cyclotriguiacylene (CTG; **3**) was used as a starting material to prepare compound **2** (scheme 1).¹⁰ It was allowed to react with compound **4** (Figures S1 and S2) to give the mono-substituted cyclotribenzylene **5** with a 54 % yield (Figures S3 and S4). Compound **4** was easily obtained in a single step with a 65 % yield by reacting the vanillic alcohol derivative with 3-chloro-2-chloromethyl-1-propene.



Scheme 1: Synthesis of cryptophane **10**

Then, an $\text{S}_\text{N}2$ reaction between compounds **5** and **6** gave the cryptophane precursor **7** in a good yield (84 %; Figures S5 and S6). Like the large majority of these compounds, derivatives **5** and **7** were isolated as glassy products. The second ring closing reaction was then performed under acidic conditions by using a mixture of formic acid and chloroform (50/50). This allowed us to isolate the cryptophane **8** (C_2 -symmetry) in 40 % yield (Figures S7 and S8). The transformation of the double bond into the primary alcohol function was then carried out with 9-BBN in the presence of H_2O_2 and NaOH (3M). The reaction gave rise exclusively to the formation of the *anti*-cryptophane **9** in 95 % yield (Figures S9 and S10). An X-ray structure of the derivative **9** allows us to ascertain the *anti*-configuration of this derivative. The primary alcohol function was then protected with a tetrahydropyranyl group in the presence of dihydropyran and PPTS to give derivative **10** in 85 % yield after purification (Figures S11 and S12). Due to the presence of a stereogenic center on the THP group,

compound **10** has been isolated as a mixture of diastereomers that could not be separated on silica gel. The removal of the six methoxy groups was achieved in a single step by reacting derivative **10** with an excess of freshly prepared lithium diphenylphosphide (1 M) in THF (scheme 2). Then, a smooth acidification of the aqueous solution with a saturated solution of ammonium chloride allowed us to leave unreacted the THP group and to collect compound **11** in 68 % yield as a mixture of diastereomers (Figures S13 and S14).

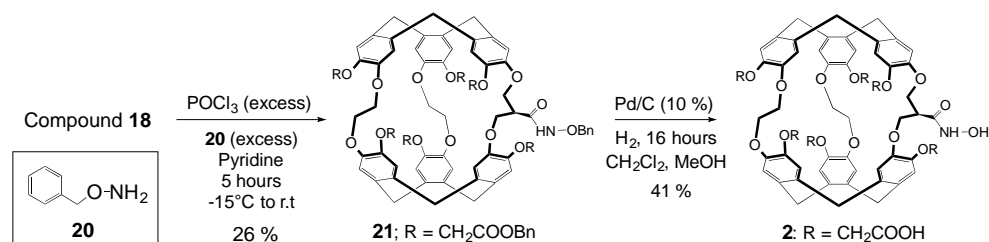


Scheme 2: Synthesis of the chemical platforms **18** and **19**.

The six phenol functions can then be used to introduce water-solubilizing substituents. This was achieved by reacting compound **11** with benzyl bromoacetate and methyl bromoacetate in the presence of cesium carbonate. Thus, compounds **12** and **13** decorated with six protected ester groups were obtained in 54 % and 70 % yields, respectively. These two compounds

could not be fully characterized due to their high lipophilicity that prevent us to remove solvents. The THP protecting groups were then removed under smooth acidic conditions to give derivative **14** and **15** in almost quantitative yields (93 %) after purification (Figures S15 – S20). Then, the oxidation reaction of the primary alcohol function was successfully achieved with the Dess-Martin reagent in CH₂Cl₂ to give rise to compounds **16** and **17**. An NMR analysis of the crude products showed that the reaction has gone to completion in both cases. Unfortunately, we also observed that these two compounds rapidly decompose on silica gel and could not be isolated. Thus, compounds **16** and **17** were used directly for the next step without further purification. An over-oxidation step using NaClO₂ and NaH₂PO₄ allowed us to transform the aldehyde function into a carboxylic acid group and to obtain compounds **18** and **19** in 70 % and 78 % yields, respectively (Figures S21 - S26). Interestingly, the free carboxylic acid moiety can be used for subsequent reactions (scheme 3). As an example, derivative **18** was allowed to react with O-benzylhydroxylamine **20** by a phosphorous oxychloride assisted amide coupling, to give rise to compound **21** with a moderate 26 % yield after purification on silica gel (Figures S27 and S29). Finally, a hydrogenolysis step using a palladium catalyst in a CH₂Cl₂/MeOH mixture allowed the removal of the seven benzyl groups at the same time to give rise compound **2** in 41 % yield after purification (Figures S30 and S33). It is worth mentioning that compounds **18** and **19** can be used to introduce a large range of sensing units. For instance, another protected chelating group such as the O-aminophenol-N,N,O-triacetic ester (APTRA) derivative (N-[4-amino-2-(2-methoxy-2-oxoethoxy)phenyl]-N-(2-methoxy-2-oxoethyl)-, methyl ester Glycine) was successfully reacted with compound **19** to give cryptophane **23** with a 35 % yield (Figures S34 and S36). Hydrolysis of this calcium sensor under basic conditions (0.3 M KOH) offered the water-soluble sensor in a good yield (70 %). Although synthetically interesting, the obtained compound was not stable enough to conduct calcium chelation studies due to the APTRA

derivative. Nevertheless, this compound assures that our strategy to introduce a sensing unit is reliable and extendable to attach even the least reactive aniline derivatives.



Scheme 3: synthesis of the cations chelating derivative **2**

X-ray crystallography of compound **9**:

Several attempts have been made to grow crystals with compounds **8-19** but only compound **9** gave X-ray quality crystals. The ORTEP representation of **9** is reported in figure 1 (see also Figures S37 and Table S1). This structure allows us to ascertain that compound **2** and **8-21** possess the anti-conformation. Compound **9** crystallizes in the cubic system, space-group $I2_13$ with twenty four molecules per unit-cell. The volume of the internal cryptophane cavity was calculated using the SQUEEZE procedure with a probe size of 1.2 Å.¹¹ It was found to be 108 Å³ with an electron count of 30, which is compatible with the presence of an ethanol molecule. However, the ethanol molecule could not be modeled due to heavy disorder. An inter-molecular void of 9831 Å³ filled with disorder solvent molecules was also observed. The contributions of both inter and intra-molecular residual electronic density were then removed from the observed data.

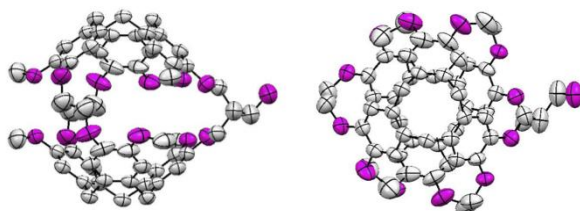


Figure 1: ORTEP representation of compound **9**. Two different views are shown. Hydrogen atoms have been removed for clarity. The cavity is filled with an ethanol molecule (not shown). The displacement ellipsoids were plotted at 30 % probability level.

Titration experiments: in order to assess the ability of compound **2** to bind cationic species in water, isothermal calorimetric titration experiments (ITC) have been performed by adding Zn^{2+} or Ni^{2+} cations to a solution of **2**. A buffer has been added to the solution to avoid large pH modification upon addition of the analyte. Several buffers have been tested for our experiments but only the 2-amino-2-hydroxymethyl-1,3-propanediol (TRIS) gave satisfactory results in our case. The other buffers tested (HEPES, MOPS, PBS) gave rise to cloudy solution due to zinc or nickel precipitation. This seems surprising since some titration experiments have been previously reported with Ni^{2+} in HEPES.¹² Our results show that in these conditions (Figure 2) efficient binding takes place between host **2** and Zn^{2+} . The results are consistent with a 1:1 complex and the affinity constant is consistent with the values reported in the literature for the hydroxamic group and Zn^{2+} . Upon addition of Zn^{2+} to the solution we observe an exothermic process and the thermodynamic parameters are $\Delta H^0 = -4.27 \pm 0.08 \text{ kcal mol}^{-1}$ and $K = 4.44 \pm 0.22 \cdot 10^4 \text{ M}^{-1}$. Thus, this leads to $T\Delta S^0 \sim 0.63 \text{ kcal mol}^{-1} \text{ K}^{-1}$ and $\Delta G^0 = -6.3 \text{ kcal mol}^{-1}$ at 298 K. Similar results have been obtained in the presence of Ni^{2+} at 298 K: $K = 3.64 \pm 0.14 \cdot 10^4 \text{ M}^{-1}$; $\Delta H^0 = -5.75 \pm 0.10 \text{ kcal mol}^{-1}$ (Figure S38). This leads to a free enthalpy of complexation ΔG^0 and entropy of complexation $T\Delta S^0$ of $-5.6 \text{ kcal mol}^{-1}$ and $0.15 \text{ kcal mol}^{-1} \text{ K}^{-1}$, respectively. The data collected for this system are also consistent with a 1:1 complex. To ascertain that the zinc cation interacts only with the hydroxamic moiety another ITC experiment has been performed with the cryptophane-222 hexacarboxylate that possesses only six carboxylate moieties. The ITC experiment (Figure S39) performed under the same conditions (TRIS Buffer 20 mM; pH = 7.0) displays very

weak endothermic signals (the enthalpogram in Figure S39 is reported at the same scale as in Figure 2) whereas the binding process with zinc and compound **2** is strongly exothermic. Thus, we can conclude that the interaction between compound **2** and zinc originates solely from the zinc cation and the hydroxamic moiety.

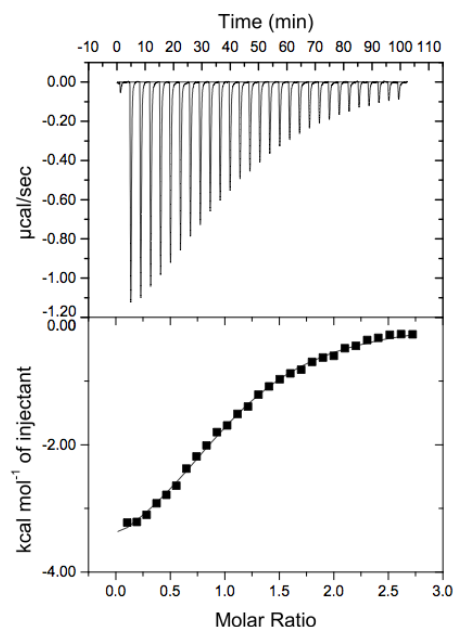


Figure 2: representative plot of the raw ITC data for the titration of **2** with Zn^{2+} . Titrations were carried out at 298 K in TRIS buffer (20 mM, pH = 7.6) with **2** (0.08 mM) in the sample cell and 1mM of Zn^{2+} in the syringe.

¹²⁹Xe NMR spectroscopy

Compound **2** has been also studied by ¹²⁹Xe NMR using laser-polarized noble gas. As it possesses seven ionisable groups, it is worth to study the effect of pH. Figure 3 displays the ¹²⁹Xe NMR spectrum of a 0.2 mM D₂O solution at three different pH values: 9.9 (top), 8.2 (middle) and 3.3 (bottom). The signal located at low field corresponds to xenon dissolved in the bulk. It has been deliberately fixed at 196 ppm. A second signal is also visible at higher field and corresponds to the encapsulated xenon in host **2**. At pH 9.9, 8.2 and 3.3 the encapsulated xenon peaks are located at 58.4, 59.4 and 61.3 ppm, respectively. A downfield chemical shift variation occurs with decreasing pH, with a chemical shift difference of almost 3 ppm.

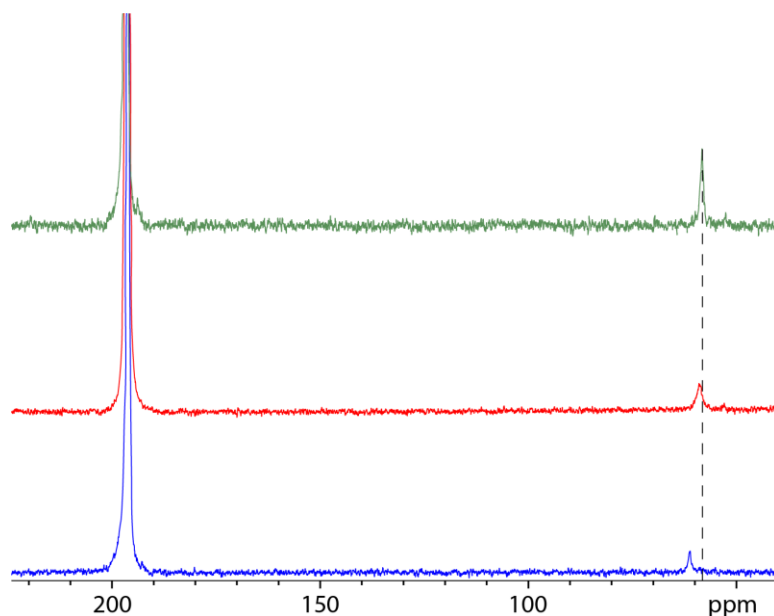


Figure 3: One-scan ^{129}Xe NMR spectra recorded at 298 K of compound **2** (0.2 mM) in D_2O at pH = 9.9 (green), pH = 8.9 (red) and pH = 3.3 (blue).

Because hydroxamic function is known to effectively chelate Zn^{2+} ions, ^{129}Xe NMR spectra have been recorded in the absence and presence of Zn^{2+} . As the zinc chloride solution renders cryptophane's solution acidic, a buffer is needed to run these experiments. Upon addition of Zn^{2+} (1 equiv. and 5 equiv.) into a buffered (TRIS 20 mM, pH 7.5) solution of **2**, the signal of the encapsulated xenon is not strongly modified (Figure S40).

DISCUSSION

Synthesis: A cryptophane decorated with a hydroxamic acid function for Ni^{2+} and Zn^{2+} chelation has been prepared in 11 steps from compound **3** in order to illustrate the advantages of our approach. The naturally occurring hydroxamic acid serves as a metal chelator in a number of metallo-enzymes showing inhibition or transport properties.^{13,14,15}

These ligands possess good affinity to different transition metals and they are used in several analytical applications.^{16,17} In addition this chelating group is structurally simple and can be easily added to our platform. Because of its short length, grafting the hydroxamic acid at the cryptophane propylenedioxy linker is especially important to increase our chances to get a smart xenon biosensor.^{1a} Moreover, the interesting ability to bind different metal cations makes hydroxamic acid a good candidate to perform multiplexing experiments. Introducing such a sensing unit allows us also to compare our approach with the one used in the NTA bearing sensor. Synthetically speaking, even though the preparation of compound **2** looks tedious, the synthesis of this cage has brought new advances in cryptophane development and presents many advantages over other synthetic routes reported in the literature. Cryptophane **2** has two different functionalities, six water solubilizing carboxylic acids moieties and a unique hydroxamic acid unit for metal chelation. The strategy followed to elaborate these cages is based on the template method, which allows us to prepare cryptophane with C₂-symmetry such as compound **8**. The oxidation of the alkene chain with 9-BBN allows us to easily introduce a primary alcohol function that can be subjected to subsequent reactions. Other methods have been tested to carry this reaction like peroxide-based oxidation (oxone) but this reaction resulted in a degradation of the starting material. Another approach to get compound **9** was to immediately introduce a primary alcohol or an acid substituted vanillic alcohol on CTG **3**. This could be achieved, for instance, by performing an S_N2 reaction type reaction of 4-Hydroxy-3-methoxybenzyl alcohol on 3-bromo-2-(bromomethyl)-1-propanol or 3-bromo-2-(bromomethyl)-propionic acid, respectively. Unfortunately, these attempts failed and mainly degradation or elimination by-products were obtained. The demethylation step of compound **10** with LiPPh₂ represents a crucial step for the elaboration of our chemical platforms and it is worth noting that great care has to be done to keep the tetrahydropyranyl group unreacted. This was successfully achieved by a careful acidification of compound **11** under mild

conditions (pH ~ 5.0). Attempt to achieve the same reaction with HCl at 0° C resulted in a mixture of protected and unprotected products. Compound **11** represents a particularly interesting derivative due to the fact that it bears two different functions, six phenol moieties that can be easily alkylated with different electrophilic substituents and a protected primary alcohol. In our case we grafted two types of acid precursors, benzyl and methyl protected bromo acetate derivatives to increase the solubility of the cryptophane skeleton in water. On the other hands, the free alcohol function obtained upon smooth acidification of the tetrahydropyranyl group can be subjected to subsequent reactions. In our case, we have chosen to oxidise compounds **14** and **15** into carboxylic acid because this chemical group is widely used in biochemistry to graft chemical functions via amide bond formation. Direct oxidation of the alcohol to an acid by using cyanuric chloride failed, so a step-wise oxidation to aldehyde then to acid was done instead. The conversion to aldehyde using Dess-Martin periodinane was successful showing a complete conversion of the starting material by ¹H NMR. Then, a second oxidation to carboxylic acid was made possible with sodium chlorite. It is noteworthy that compounds **18** and **19** constitute important platforms since they satisfy most of the specifications required for xenon-based biosensors.² Importantly these two compounds possess a unique reactive function that can be exploited to introduce more easily a chemical function with a biological activity. Consequently, the use of **18** and **19** strongly reduce the formation of side-products, which are often encountered during the grafting of the biological active site.⁷ These two compounds can be produced in fair quantities (~500 mg) in a relatively short period of time (one and a half month). The most time demanding step in this synthesis is the preparation of compound **8** that has to be performed under diluted conditions (mM range) and repeated several times to obtain enough material. The ease of functionalization of derivatives **18** and **19** has been illustrated by adding two different sensing units, a hydroxylamine and an APTRA derivative via its aniline group, respectively. The

unique properties, from selective functionalization and solubility of compounds **18** and **19**, make them leading molecular hosts for rapid development of cryptophane-based biosensors.

Isothermal Titration Calorimetry experiments show that efficient binding occurs between host **2** and Zn^{2+} or Ni^{2+} at neutral pH (20 mmol TRIS, pH = 7.6 at 25° C). We notice that the association constant $K = 3.64 \cdot 10^4 \text{ M}^{-1}$ reported between host **2** and Ni^{2+} is the same order of magnitude than the one reported between Ni^{2+} and the benzohydroxamate chelator. However, in the case of the benzohydroxamate chelator the experimental conditions are slightly different since the experiments have been conducted in HEPES buffer (0.1 M, pH = 7.5). In addition, in their example, the proposed binding model fits better with a two-site sequential model ($K_1 = 1.5 \cdot 10^4 \text{ M}^{-1}$ and $K_2 = 850 \text{ M}^{-1}$). Similarly, a 1:1 complex is observed for Zn^{2+} and compound **2**, with a binding constant $K = 4.44 \cdot 10^4 \text{ M}^{-1}$. The observed value however is slightly lower than that with 1:1 Zn^{2+} -acetohydroxamic acid complex $K = 2.8 \cdot 10^5 \text{ M}^{-1}$. Zinc complexation with acetohydroxamic acid also showed a 1:2 sequential binding of association constant $K = 4.3 \cdot 10^9 \text{ M}^{-1}$ and $K = 1.5 \cdot 10^4 \text{ M}^{-1}$ obtained at different conditions.^{18,19} The latter values indicate that the association constants are strongly dependent on the experimental conditions. In our case, the formation of a 1:2 with Ni^{2+} and Zn^{2+} complex appears less probable due to the presence of the bulky cryptophane skeleton.^{14,15}

The ability of the cryptophane-223 type molecules to bind xenon in water has been studied in the past. In aqueous solvents and at room temperature, xenon exchange in and out of these compounds is slow with respect to the difference of resonance frequency between the free and encapsulated forms, which allows us to easily identify the ^{129}Xe NMR signals of these complexes. Indeed, these signals appear far away and are high field shifted with respect to the ^{129}Xe NMR signal of xenon dissolved in the bulk. Our results show that host **2** behaves similarly since the bound signal is detected in the same spectral region (50 - 60 ppm).

The fact that compound **2** bears seven ionizable groups triggered us to study the effect of pH. A similar study was previously conducted with two different cryptophanes, cryptophane-222 hexacarboxylate and cryptophane-222 tricarboxylate-triphenolate, which show in both cases a significant variation of the xenon chemical shift as a function of pH.^{20,21} Between pH 8.9 and 9.9, not much change is observed although the pK_a of the hydroxamic acid function is expected to be in the range 8.0 and 9.0, indicating that the ionization of the hydroxamic group is not seen by encapsulated xenon.²² This is probably because the change in the ionization state of this group does not modify the ring current of the aromatic cycles bordering the cavity. At acidic pH, however, a downfield chemical shift change of about 3 ppm is detected. As similar effect is also observed with cryptophane hexacarboxylate it can reasonably be assigned to an ionization change of the carboxylate groups.²⁰ However, compared to the latter, compound **2** revealed less enhanced change, which can be explained by its larger cavity (xenon is more distant from the aromatic rings; thus the ring current effects are smaller).

Despite its proximity with the cavity of host **2**, the hydroxamic group only induces a moderate change of the chemical shift upon binding with Zn²⁺ or Ni²⁺. The ¹²⁹Xe chemical shift differences observed with host **2** in 20 mM TRIS buffer (pH 7.5) upon addition of 1.0 and 5.0 equiv. of Zn²⁺ are small. These results may appear disappointing considering that other systems studied in the past by our group have shown a better responsiveness to zinc chelation.²³ However, It is worth mentioning that these two systems are quite different since the two functionalities are not grafted on the same position. In the first example reported by our group, the NTA functionality was grafted, via a small spacer, on the benzene ring.^{7c} The chelation of Zn²⁺ is likely to induce a variation of the orientation of the aromatic ring current on which the NTA moiety is grafted, and thereby modifies the magnetic environment of the encapsulated xenon via a different ring current effect on it. This effect appears much less

effective when the hydroxamic function is grafted on one of the bridges. This lack of sensitivity of these probes can also be exemplified by studying the ^{129}Xe NMR spectrum of cryptophane **10** in $\text{C}_2\text{D}_2\text{Cl}_4$. Compound **10** is present as a mixture of diastereomers but gives rise to a single ^{129}Xe NMR peak (Figure S41). This contrasts with previous results that showed that diastereomeric mixtures could be easily distinguished by ^{129}Xe NMR spectroscopy.²⁴ In these examples, it should be noted that all the stereogenic centers were grafted on the benzene rings via different spacers.

The fact that compound **2**, particularly, is poorly responsive by ^{129}Xe NMR, does not prevent its employment as an MRI tracer as long as the recognition site shows a very high affinity and selectivity for the biological target of interest. The first xenon-cryptophane biosensor reported in 2001 by Pines and co-workers enters in this category.^{4f} Another family of xenon-cryptophane biosensors can be categorized as “smart” biosensors and they respond very well to a slight change of their surrounding environment, which in turn is characterized by a significant shift of the ^{129}Xe NMR tracer.^{1a}

Conclusion

We report in this article the synthesis of new chemical platforms for ^{129}Xe NMR-based probes, based on a modification of the cryptophane-223 scaffold. A unique primary alcohol function has been introduced on the cryptophane skeleton in order to facilitate the introduction of a biologically active functionality. We have shown that this function could be subjected to subsequent transformations in order to add active groups such as a hydroxamic acid moiety. Moreover, additional chemical transformations allow us to easily introduce hydrophilic substituents on the cryptophane scaffold in order to facilitate the solubilisation of the xenon-cryptophane complex at neutral pH. Thus, we have been able to prepare new

platforms that possess most of the specificities required for biosensing application. For instance, compounds **18** and **19** are believed to be extremely useful in the future to prepare new ^{129}Xe NMR-based sensors. The originality of these compounds lies in the presence of a unique carboxylic acid moiety that is expected to facilitate the grafting of a chemical function with a biological activity. To illustrate this approach, we have reported the synthesis of compound **2** that contains a hydroxamic function and which is able to bind Zn^{2+} or Ni^{2+} in aqueous solution. The efficient binding of Zn^{2+} and Ni^{2+} has been clearly demonstrated by using isothermal titration experiments. Our results show a moderate effect of the complexation on the ^{129}Xe NMR spectra due probably to the position of the chelator on the cryptophane skeleton. Bioconjugation of these derivatives is under way to investigate their efficiency as MRI tracers.

EXPERIMENTAL DETAILS

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: RF Funnel 1, 200 V; RF Funnel 2, 200 V; hexapole, 50 V; transfer time, 70 μs and PrePulse storage time, 1 μs 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 and 100.6 MHz, respectively. Chemical shifts are referenced to Me_4Si (^1H , ^{13}C). 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 CH₂Cl₂ from CaH₂, THF from Na/benzophenone and pyridine from KOH.

Production of hyperpolarized xenon. Hyperpolarized xenon was produced in the batch mode via SEOP (Spin Exchange Optical Pumping) using a home-built setup.²⁵ Rubidium is used as the alkali metal, and five minutes suffice to produce five millilitres of xenon at a polarization ranging from 15 to 20%. Frozen hyperpolarized xenon immersed in a bath of liquid nitrogen and subjected to a magnetic field of 0.3 T provided by a solenoid is transported near the NMR magnet. There it is sublimated in the fringe field of the magnet and transferred thanks to a vacuum line to the NMR tube. A hollow spinner enabled us to condense it in the upper part of the NMR tube (screw capped Wilmad PP-528) without cooling the solution. The hyperpolarized ¹²⁹Xe NMR experiments were performed at 11.7 T (¹²⁹Xe resonance frequency 138.35 MHz) using a 5mm-broadband inverse probehead.

Crystallography: A suitable crystal of Cryptophane **9** was selected and mounted on a Gemini kappa-geometry diffractometer (Agilent Technologies UK Ltd) equipped with an Atlas CCD detector and using Cu radiation ($\lambda = 1.5418 \text{ \AA}$). Intensities were collected at 150 K by means of the CrysAlisPro software.²⁶ Reflection indexing, unit-cell parameters refinement, Lorentz-polarization correction, peak integration and background determination were carried out with the CrysAlisPro software. An analytical absorption correction was applied using the modeled faces of the crystals.²⁷ The resulting set of *hkl* was used for structure solution and refinement. The structures were solved by direct methods with SIR97 and the least-square refinement on F² was achieved with the CRYSTALS software.^{28, 29} All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft

restraints on the bond lengths and angles to regularize their geometry (C--H in the range 0.93--0.98 Å, O--H = 0.82 Å) and $U_{\text{iso}}(\text{H})$ (in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints. Residual electronic density inside and in between the cryptophane cages was located but could not be modeled. The contribution of the disordered solvent molecules was removed using the SQUEEZE algorithm. The volume of the cryptophane cage was calculated to be 108 Å³ using the VOID algorithm within the PLATON software.³⁰ CCDC 1900550 contains the supplementary crystallographic data for cryptophane **9**. These data can be obtained free of charge from the Cambridge Crystallographic data Centre via [www.ccdc.cam.ac.uk/data request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

EXPERIMENTAL PROCEDURE

Synthesis of (4-(((2-(bromomethyl)allyl)oxy)methyl)-3-methoxyphenyl)methanol 4: 3-chloro-2-chloromethyl-1-propene (4.49ml, 64.8 mmol) was added under argon to a mixture of K₂CO₃ (4.48 g, 32.4 mmol) and vanillic alcohol (5 g, 32.4 mmol) in acetone 60 mL). The reaction mixture was heated for 16 hours at 80 °C (oil bath) under an argon atmosphere. Then, the solvent was evaporated under reduced pressure. The solid residue was then dissolved in ethyl acetate (200 mL). The organic layer was washed three times with 0.1 M NaOH solution and finally washed with water. The organic layer was dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude was then subjected to column chromatography on silica gel (CH₂Cl₂/ethyl acetate: 80/20). After evaporating the solvents, compound **4** was collected as a white solid (5.1g, 65 %). Mp: 60 °C. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 6.91-6.83 (m, 3H), 5.34 (m, 2H), 4.65 (s, 2H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.18 (s, 2H), 3.84 (s, 3H), 1.65 (t, *J* = 5.8 Hz, 1H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 149.8, 147.4, 140.7, 134.5, 119.3, 117.5, 114.2, 111.06, 69.4, 65.2, 55.9, 45.08 HRMS (ESI): *m/z* [M+Na]⁺ calcd. for C₁₂H₁₅NaClO₃ 265.0607 found 265.0602.

Synthesis of CTB 5: Derivative **4** (2.0 g, 8.2 mmol) was added under an argon atmosphere to a stirred mixture of Cs_2CO_3 (5.4 g, 16.4 mmol, 2 equiv.) and cyclotriguacylene **3** (3.5 g, 8.6 mmol) in DMF (120 mL). The mixture was heated up to 80°C (oil bath) for 16 hours under an argon atmosphere. Then, the dark-brown mixture was poured in water (200 mL) and extracted 5 times with ethyl acetate (800 mL). The combined organic layer was then washed 5 times with water (500 mL) and dried over Na_2SO_4 . Evaporation of the solvent under reduced pressure left an oily residue, which was purified on silica gel (AcOEt/petroleum ether: 90/10). Evaporation of the fractions gave rise to compound **5** (2.7 g, 54 %) as a glassy product. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 6.92 (s, 1H), 6.87 (s, 1H), 6.84 (s, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 6.73 (s, 1H), 6.69 (s, 1H), 6.67 (s, 1H), 6.58 (m, 1H), 5.40 (s, 1H), 5.37 (s, 1H), 5.29 (m, 2H), 4.71 (s, 3H), 4.67-4.62 (m, 4H), 4.52 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.65 (s, 3H), 3.52-3.46 (m, 3H), 1.54 (t, $J = 5.6$ Hz, 1H). ^{13}C { ^1H } NMR: δ (100.6 MHz, CDCl_3) 149.3, 147.8, 147.1, 146.1, 144.9, 144.8, 143.7, 143.6, 140.2, 133.8, 132.1 (2C), 131.9, 131.5, 130.9, 118.96, 115.6, 115.2, 115.0, 114.8, 113.3, 113.2, 112.0, 111.8, 110.5, 69.6, 69.4, 64.9, 55.75, 55.7, 55.5, 55.3, 36-35.9 (3C). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{36}\text{H}_{38}\text{NaO}_9$ 637.2413 found 637.2408.

Synthesis of CTB 7: 2-((4-(2-bromoethoxy)-3-methoxybenzyl)-oxy)tetrahydro-2H-pyran (4.106 g, 11 mmol; 2 equiv.) was added under an argon atmosphere to a stirring mixture of Cs_2CO_3 (7.69 g, 23 mmol) and CTB **5** (3.65 g, 5.94 mmol) in DMF (140 mL). The reaction mixture was heated to 80°C (oil bath) for 16 hours under an argon atmosphere. Then, the yellowish mixture was poured in water (200 mL) and ethyl acetate (200 mL). The aqueous layer was extracted 5 times with ethyl acetate (500 mL). The combined organic layer was then washed 5 times with water (500 mL) and dried over Na_2SO_4 . The solvent was removed under

reduced pressure to leave a glassy solid, which was purified on silica gel (AcOEt/petroleum ether: 90/10) gives rise to compound **7** (5.63 g, 84 %) as a white glassy solid. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 7.01-6.65 (15s, 15H), 5.30 (s, 1H), 5.29 (s, 1H), 4.63-4.73 (m, 10H), 4.53 (m, 2H), 4.43-4.32 (m, 8H), 3.90 (m, 2H), 3.86 (2s, 6H), 3.74-3.71 (3s, 9H), 3.61 (s, 3H), 3.48-3.53 (m, 5H), 1.85-1.59 (m, 12H). ^{13}C $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3), δ : 149.8, 149.7 (2C), 148.6, 148.5, 148.3, 147.6 (2C), 147.5, 146.9 (2C), 146.8, 147.5, 140.6, 134.5, 133.1 (2C), 132.5, 131.9 (2C), 131.8 (3C), 120.5 (3C), 119.2, 117.0, 116.9, 116.1, 115.1, 113.8-114.3 (8C), 112.1 (2C), 111.0, 97.7 (3C), 70.1, 69.9, 68.6 (2C), 68.4, 67.93, 65.1, 62.2 (2C), 55.7-56.2 (6C), 36.3 (2C), 30.5 (2C), 25.4 (2C), 19.4 (2C). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{66}\text{H}_{78}\text{NaO}_{17}$ 1165.5136 found 1165.5131.

Synthesis of cryptophane 8: CTB **7** (0.700 g, 0.62 mmol) was dissolved in a mixture of chloroform (300 ml) and formic acid (300 ml). The solution was then stirred for 6 hours at 55 - 60 °C (water bath). The solvent was then evaporated under reduced pressure to leave a yellow residue. It was then purified by column chromatography on silica gel (CH_2Cl_2 /Acetone: gradient 97/3 up to 95/5). The white solid was then crystallized in a mixture of CH_2Cl_2 and ethanol. The crystals were collected on a frit and washed with diethyl ether. Compound **8** (0.230 g, 40 %) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 6.77 (s, 2H), 6.72 (s, 2H), 6.65 (s, 2H), 6.655 (s, 2H), 6.64 (s, 2H), 6.62 (s, 2H), 5.58 (s, 2H), 4.63-4.56 (m, 6H), 4.46 (d, $J=10.7$ Hz, 2H), 4.35 (d, $J=10.7$ Hz, 2H), 4.29-4.09 (m, 8H), 3.80 (s, 6 H), 3.79 (s, 6H), 3.75 (s, 6H), 3.43-3.36 (m, 6H). ^{13}C $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3), δ : 149.4 (2C), 149.4 (2C), 147.7 (2C), 147.3(2C), 146.6 (2C), 146.4 (2C), 140.0 (1C), 133.8 (4C), 132.2 (2C), 131.9 (2C), 131.3 (2C), 130.6 (2C), 120.7, 120.4 (2C), 120.3 (2C), 113.9 (2C), 113.3 (2C), 113.2 (2C), 112.2 (2C), 69.6 (2C), 68.9 (2C), 68.8

(2C), 56.1 (2C), 55.5 (2C), 55.4 (2C), 36.4 (2C), 36.08 (2C), 36.04 (2C). HRMS (ESI): m/z $[M+Na]^+$ calcd. for $C_{56}H_{56}NaO_{12}$ 943.3669 found 943.3664.

Synthesis of cryptophane 9: Derivative **8** (0.280 g, 0.304 mmol) was dissolved in a mixture of THF (20 mL) and CH_2Cl_2 (5 mL) under an argon atmosphere. Then, 9-BBN (1.81 mL, 0.5M, 0.9 mmol, 3 equiv.) was added dropwise at 0 °C. The solution was stirred at 50 °C (oil bath) for 5 hours. The mixture was then quenched at 0 °C by a dropwise addition of a NaOH solution (0.56 mL, 3M) and then by addition of H_2O_2 (1.7 mL, 15 %). The reaction was stirred overnight at room temperature for 16 hours. Then, the reaction was quenched by a dropwise addition of 20 ml of $Na_2S_2O_3$ solution at 0 °C. The reaction mixture was poured in CH_2Cl_2 (50 ml) and the aqueous layer was washed 5 times with CH_2Cl_2 (each time 50 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography using silica gel (CH_2Cl_2 /acetone: gradient 90/10 up to 80/20). Compound **9** (0.27 g, 95 %) was then isolated as a white solid and washed on a frit with diethyl ether. 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.79-6.61 (m, 10 H), 6.51 (s, 2H), 4.62-4.53 (m, 6H), 4.25-3.93 (m, 14 H), 3.87-3.77 (4s, 12 H), 3.74 (s, 3H), 3.71 (s, 3H), 3.43-3.34 (m, 6H), 2.40 (m, 1H). ^{13}C $\{^1H\}$ NMR (100.6 MHz, $CDCl_3$), δ : 149.6, 149.5 (2C), 149.4, 147.5, 147.4, 147.3, 146.7, 146.6 (2C), 146.63, 146.3, 134 (2C), 133.8 (2C), 132.5, 132.3, 132.1, 131.5, 131.3, 131.1, 130.8, 130.6, 120.5, 120.4, 120.2, 120.0, 114.3, 114.2, 113.6, 113.2, 112.7, 112.3, 112.1, 111.8, 69.8, 69.5, 68.9, 68.7, 68.5, 67.0, 64.3, 56.3 (2C), 55.5 (2C), 55.4, 55.3, 40.2, 36.4 (2C), 36.1 (3C), 36. HRMS (ESI): m/z $[M+Na]^+$ calcd. for $C_{56}H_{58}NaO_{13}$ 961.3775 found 961.3770.

Synthesis of cryptophane 10: A solution of PPTS (0.12 g, 0.47 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **9** (0.3 g, 0.31 mmol) and 3,4-dihydropyran (0.1 mL, 1.09 mmol) in

THF (8 mL). The solution was heated up to 60 °C (oil bath) for 48 hours. Then, the solvent was evaporated under reduced pressure. The oily residue was subjected to column chromatography on silica gel (CH₂Cl₂/acetone: 90/10) to give rise to compound **10** as a white solid (0.27 g, 85 %) was collected on a frit and washed with diethyl ether. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 6.76-6.55 (12s, 12H), 4.69 (m, 1H), 4.60-4.55 (m, 6H), 4.20-3.97 (13H), 3.88 (m, 2H), 3.78 (3s, 9H), 3.76-3.74 (3s, 9H), 3.59 (m, 1H), 3.38-3.35 (m, 6H), 2.60 (m, 1H), 1.82-1.50 (m, 6H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 149.4 (3C), 147.9, 147.6, 147.4, 147.3, 147.2, 146.8, 146.7, 146.5 (2C), 134.0, 133.95, 133.9, 133.8, 132.4 (2C), 131.4 (4C), 130.6 (2C), 120.5 (4C), 114 (2C), 113.7, 113.5, 113.0, 112.8, 112.4 (2C), 112.3, 98.4, 69.7, 69.0, 65.5, 65.4, 64.7, 62.6, 61.8, 56.2, 55.8, 55.6 (2C), 55.5, 55.4, 40.5, 36.4 (2C), 36.0 (4C), 30.7, 25.5, 19.71, 19.2. HRMS (ESI): *m/z* [M+Na]⁺ calcd. For C₆₁H₆₆NaO₁₄ 1045.4350 found 1045.4344.

Synthesis of cryptophane 11: 4 mL (4.1 mmol, 20 equiv.) of Lithium diphenylphosphide (1M) was added dropwise to a solution of **10** (0.21 g, 0.21 mmol) in THF (3 mL) under an argon atmosphere. The red solution was heated up to 60 °C (oil bath) for 48 hours. Then, the mixture was poured in 20 mL of water and then extracted 5 times with CH₂Cl₂. The aqueous solution was acidified at 0 °C with an ammonium chloride solution (10 mL, pH ~ 5). The resulting precipitate was collected on a frit and washed with water. The dried solid was then washed several times with diethyl ether to give a beige solid. The solid was then purified on column chromatography (silica gel, acetone/DMF: 96/4) to give clean compound **11** (0.13 g, 68 %). ¹H NMR (400 MHz, DMSO *d*₆, 25 °C): δ 8.42-8.22 (6s, 3 H), 7.95-7.74 (6s, 3H), 6.65-6.48 (m, 12H), 4.66 (m, 1H), 4.47-4.39 (m, 6H), 4.13-3.87 (m, 13H), 3.72 (m, 1H), 3.34 (m, 2H), 3.22-3.17 (m, 6H), 2.33 (m, 1H), 1.67-1.49 (m, 6H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 146.8, 146.7, 146.3, 146.2, 146, 145.9, 145.6, 145.4, 145.06, 145.0, 144.8, 144.7,

134.3, 134.1, 134.0, 133.9, 132.9, 132.8, 131.4, 131.2, 130.9, 130.8, 129.7, 129.6, 120.5, 120.3, 119.3 (2C), 118.7, 118.5, 118.02 (2C), 117.4, 116.9, 115.6, 115.5, 98.9, 69, 68.7 (2C), 67.6, 66.5, 65.9, 62.2, 35.6 (2C), 35.2 (4C), 30.8, 25.5, 19.8, 19.7. HRMS (ESI): m/z [M+Na]⁺ calcd. for C₅₅H₅₄O₁₄Na for 961.3411 found 961.3405.

Synthesis of cryptophane 14: Benzyl bromoacetate (0.88 mL, 5.5 mmol, 12 equiv.) was added under an argon atmosphere to a solution of compound **11** (0.44 g, 0.46 mmol, 1 equiv.) and Cs₂CO₃ (1.83 g, 5.5 mmol, 12 equiv.) in DMF (8 mL). The mixture was heated for 16 hours at 60 °C (oil bath) under argon. The mixture was poured in water and then extracted 5 times with AcOEt. The combined organic layers were then washed 5 times with water, dried over Na₂SO₄. Filtration and evaporation of the solvent under reduced pressure gave an oily residue, which was subjected to column chromatography on silica gel (CHCl₃/acetone: 95/5). Compound **12** was collected as viscous oil (0.47 g, 58 %). This compound was used without further purification for the next step. Thus, PPTS (0.3 g, 1.3 mmol, 5 equiv.) in methanol (2 mL) was added in one portion to cryptophane **12** (0.47 g, 0.25 mmol) in CH₂Cl₂ (6 mL). The solution was heated to 40 °C for 48 hours. Then, the solvents were evaporated under reduced pressure and the residue was purified on silica gel (CH₂Cl₂/acetone: 96/4). Compound **14** (0.4 g, 93 %) was obtained as white solid. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 7.42-7.30 (m, 30H), 6.58-6.39 (12s, 12H), 5.31-5.00 (m, 12H), 4.60-4.36 (m, 18 H), 4.18-3.83 (m, 14H), 3.26-3.05 (m, 6 H), 3.02 (m, 1 H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 169.5, 169.3, 169.2 (2C), 169, 168.8, 148.4, 147.9, 147.6, 147.5 (2C), 147.4, 147.2 (4C), 146.0 (3C), 135.6 (2C), 135.5, 135.4 (3C), 134.7, 134.3, 133.8, 133.5, 133.4, 133.37, 133.2 (2C), 132.9, 132.0, 131.6, 131.3, 128.5-128.8 (30 C), 121.1, 120.7, 120.6, 119.7, 119.4, 119.2, 119.1, 118.8, 118.1, 115.5, 113.5, 113.1, 69.7, 69.1, 68.8, 68.6, 68.1, 68.0, 67.9, 67.9, 67.8, 67.7, 67.2, 67 (2C),

66.9 (2C), 66.8, 66.7, 66.6, 66.3, 63.4, 41.1, 36.2, 35.9, 35.7 (3C). HRMS (ESI): m/z $[M+Na]^+$ calcd. for For $C_{104}H_{94}NaO_{25}$ 1765.5981 found 1765.5976.

Synthesis of cryptophane 15: Methyl bromoacetate (0.2 mL, 2.28 mmol, 24 equiv.) was added under an argon atmosphere to a mixture of cryptophane **11** (0.090 g, 0.095 mmol) and Cs_2CO_3 (0.37 g, 1.13 mmol, 12 equiv.) in DMF (3 mL) and CH_2Cl_2 (1 mL). The mixture was heated up to 50 °C (oil bath) for 16 hours under argon. Then, the mixture was poured in water and extracted 5 times with AcOEt. The combined organic layers were then washed 5 times with water and dried over Na_2SO_4 . Evaporation of the solvent gave rise to an oily residue, which was subjected to column chromatography on silica gel ($CHCl_3$ /acetone: gradient 90/10 to 85/15). Compound **13** was isolated as a white solid (0.090 g, 70 %) and used without further purification for the next step. Thus, PPTS (0.050 g, 0.2 mmol) in methanol (3 mL) was added under an argon atmosphere to a solution of **13** (0.17 g, 0.12 mmol) in CH_2Cl_2 (5 mL). The solution was stirred under argon at 40 °C. The solvents were evaporated under reduced pressure and the oily residue was subjected to column chromatography on silica gel (CH_2Cl_2 /acetone: 80/20). After evaporating the solvents, compound **15** (0.14 g, 93 %) was collected on a frit as a white solid and was washed with a small volume of diethyl ether. 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.82-6.55 (12s, 12 H), 4.66-4.46 (m, 18 H), 4.34-3.78 (m, 32 H), 3.40-3.34 (m, 6H), 2.29 (m, 1H). ^{13}C $\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 170.0, 169.8, 169.7 (2C), 169.6, 169.2, 148.3, 147.9, 147.6 (3C), 147.4, 147.2, 147.1 (2C), 147.0, 145.9 (2C), 134.9, 134.8, 134.4, 133.8, 133.5, 133.48, 133.3, 133.2, 133.1, 132.9, 131.8, 131.7, 121.0, 120.8, 120.3, 119.7, 119.3, 119.2, 118.9, 118.4, 118.1, 114.7, 113.5, 113.1, 69.6, 69.2, 68.8 (2C), 68.6, 68.3, 67.7 (2C), 67.5, 67.3, 67.0, 66.5, 66.3, 51.8-52.1 (6C), 41.0, 35.7-36.2 (6C). HRMS (ESI): m/z $[M+Na]^+$ calcd. For $C_{68}H_{70}NaO_{25}$ 1309.4103 found 1309.4098.

Synthesis of cryptophane 18: Dess martin periodinate reagent (15% wt solution in DCM, 0.9 mL; 0.37 mmol) was added at room temperature to a solution of **14** (0.1 g, 0.057 mmol) in freshly distilled CH₂Cl₂ (13 mL). The solution was stirred at room temperature for 16 hours. Then, the solution was filtered on a frit. The filtrate solution was collected and the solvent was removed under reduced pressure to leave a solid residue. Dissolution in a minimum of CH₂Cl₂ and precipitation with diethyl ether gave rise to compound **16** as white solid. This compound decomposes on silica gel. Thus, **16** was used without further purification for the next step. A HRMS spectrum allows us to ascertain the structure of **16**. HRMS (ESI): *m/z* [M+Na]⁺ calcd. For C₁₀₄H₉₂NaO₂₅ 1763.5825 found 1763.5819. Then, sodium chlorite (0.01 g in 0.1 ml water, 0.16 mmol; 3 equiv.) was added along with sodium monobasic phosphate (99.45 μg in 0.01 ml water, 0.0083 mmol) and H₂O₂ (1.59 μl) to a solution of compound **16** (0.1 g, 0.06 mmol), CH₃CN (1.5 mL), H₂O (0.15 mL) under an argon atmosphere at room temperature. The, solution was stirred for 16 hours at room temperature and the solvent was removed under reduced pressure. The resulting residue was subjected to column chromatography on silica gel (CH₂Cl₂/acetone: 75/25). After evaporation of the solvents, compound **18** (70 mg, 70 %) was collected as white solid. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 7.44-7.30 (m, 30H), 6.62-6.36 (12s, 12H), 5.31-5.09 (s, 12H), 4.55-4.37 (m, 18 H), 4.15-3.95 (m, 12H), 3.19-3.15 (m, 6H), 3.07 (m, 1H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 172.5, 169.6, 169.4, 169.3, 169.2 (2C), 169.1, 147.8, 147.7 (2C), 147.6 (2C), 147.4 (2C), 147.3, 147.2 (2C), 146.2, 145.9, 135.2,-135.5 (6C), 134.4 (2C), 133.6 (2C), 133.3, 133.2 (2C), 133.1 (2C), 133.0, 132.4, 132.0, 128.6-128.8 (30C), 120.9 (2C), 120.6, 120.27 (2C), 119.1 (2C), 118.8, 118.3, 117.5, 114.5, 114.2, 69.4, 69.3, 68.8 (2C), 68.1, 68.0, 67.9 (2C), 67.2 (2C), 67.0-66.9 (6C), 64.8 (2C), 62.8, 45.6, 36.1 (2C), 35.7 (4C). HRMS (ESI): *m/z* [M+Na]⁺ calcd.For C₁₀₄H₉₂NaO₂₆ 1779.5774 found 1779.5769.

Synthesis of cryptophane 19 : Dess martin periodinate reagent (0.4 mL; 0.16 mmol) was added at room temperature to a solution of **15** (0.15 g, 0.11 mmol) in freshly distilled CH₂Cl₂ (4 mL). The solution was stirred at room temperature for 16 hours under an argon atmosphere. Then, the solution was filtered on a frit. The filtrate solution was collected and the solvent was removed under reduced pressure to leave a solid residue. Dissolution in a minimum of CH₂Cl₂ and precipitation with diethyl ether gives rise to compound **17** as white solid. This compound also decomposes on silica gel. Thus, compound **17** was used without further purification for the next step. A HRMS spectrum allows us to ascertain the structure of **17**. HRMS (ESI): *m/z* [M+Na]⁺ calcd. For C₆₈H₆₈NaO₂₅ 1307.3947 found 1307.3942. Then, sodium chlorite (0.035 g in 0.35 mL water, 0.38 mmol; 2 equiv.) was added along with sodium monobasic phosphate (0.01g in 0.017 mL water, 0.07 mmol) and H₂O₂ (0.53 mL) to a solution of compound **17** (0.25 g, 0.19 mmol), CH₃CN (5.3 mL), H₂O (0.15 mL) under an argon atmosphere at room temperature. The, solution was stirred for 16 hours at room temperature and then quenched with sodium thiosulfate (2 mL) at 0°C. The solvent was then removed under reduced pressure. Then, the crude was recrystallized from CH₂Cl₂ and diethyl ether to give a white precipitate. Filtration on a frit allows us to collected compound **19** (0.19 g, 78 %) as a white solid. This solid was washed several times with diethyl ether and dried in air. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 6.81-6.60 (12s, 12 H), 4.66-4.42 (m, 18 H), 4.38-4.13 (m, 12 H), 3.83-3.76 (6s, 18 H), 3.39-3.36 (m, 6 H), 3.24 (m, 1H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 172.6, 170, 169.9 (4C), 169.8, 147.8, 147.7, 147.7 (2C), 147.6, 147.5 (2C), 147.4, 147.3 (2C), 146.4, 146.2, 134.5 (2C), 133.7, 133.6, 133.5, 133.4 (4C), 133.3, 133.2, 132.9, 132.3, 121.0 (2C), 120.1 (2C), 119.7, 119.3 (2C), 118.2 (2C), 117.4, 115.4, 115.0, 69.5 (2C), 68.8 (2C), 67.7 (2C), 67.6 (2C), 67.2, 67.0, 65.6, 65.2, 52.0-52.2 (6C), 45.9, 36.3 (3C), 35.9 (3C). HRMS (ESI): *m/z* [M+H]⁺ calcd. For C₆₈H₆₉O₂₆ 1301.4077 found 1301.4072.

Synthesis of cryptophane 21 : Excess of POCl₃ (0.013 mmol) was slowly added at -15 °C to a solution of **18** (0.14 g, 0.08 mmol) and O-benzyl hydroxylamine (0.020 mL) in pyridine (3 mL). The solution was stirred for 30 minutes at this temperature hours and then stirred for further 5 hours at room temperature. The solution was quenched by addition of a mixture of ice/water/NaHCO₃ at 0 °C. The obtained mixture was washed 5 times with CH₂Cl₂. Then the combined organic layers were dried over Na₂SO₄. The solution was filtered and the solvent was removed under pressure to leave a residue. Purification on silica gel (CH₂Cl₂/acetone: 95/5) gave rise to compound **21** (0.04 g; 26 %) as a white solid. This solid was collected on a frit and washed several times with diethyl ether. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 9.63 (s, 1H), 7.43-7.26 (m, 35H), 6.59-6.26 (12s, 12H), 5.35-4.94 (m, 14H), 4.65-4.34 (m, 18H), 4.05-3.68 (m, 12H), 3.27-3.19 (m, 6H), 2.89 (m, 1H). ¹³C {¹H} NMR (100.6 MHz, CDCl₃): δ 169.5, 169.4, 169.3, 169.2, 169.1, 168.7, 168.6, 147.9, 147.7, 147.6, 147.66, 147.5, 147.3 (2C), 147.2 (2C), 146.5, 146.4, 146.3, 135.3-135.7 (6C), 134.6, 134.2, 133.7, 133.6, 133.4 (2C), 133.3, 133.2, 133.1 (2C), 132.6, 132.1, 129.5-129.5 (35C), 121.0, 120.7, 120.0, 119.6, 119.5, 119.1, 118.8, 118 (2C), 115.5 (3C), 115.2, 78.1, 69.7, 69.1, 68.7, 68.4, 68.1, 67.9, 67.8 (2C), 67.3, 66.8-66.9 (6C), 66.5, 66.0, 64.7, 47.3, 36.0, 35.9, 35.7 (4C). HRMS (ESI): *m/z* [M+Na]⁺ calcd. For C₁₁₁H₉₉NNaO₂₆ 1884.6353 found 1884.6347.

Synthesis of cryptophane 2 : Hydrogen gas was bubbled into a solution of cryptophane **21** (0.057 g; 0.03 mmol) and Pd/C (10 %) (5 mg) in a mixture of CH₂Cl₂ (2 mL) and methanol (1 mL). The solution was kept under hydrogen atmosphere for 2 nights at room temperature. Then, the mixture was filtered on celite and washed CH₂Cl₂ and methanol. The solvents were evaporated under reduced pressure to leave a residue. It was then dissolved in aqueous NaOH (0.3 M) and the aqueous layer was washed 3 times with CH₂Cl₂. Acidification with few drops of conc. HCl at 0 °C gave rise to a precipitate which was collected on a frit and washed

several times with diethyl ether. Compound **2** (15 mg, 41 %) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 9.69 (s, 1H), 6.94-6.69 (12s, 12H), 4.79-4.29 (m, 30 H), 3.98-3.84 (m, 7H). ^{13}C $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ 171.5, 170.4 (3C), 170.1, 170.0, 168.3, 148.5, 148.2, 147.5, 147.4, 146.3 (2C), 146.2, 146.1, 146.0, 145.9, 145.4, 144.8, 134.9, 133.8, 133.7, 132.9, 132.8 (3C), 132.7, 132.6, 132.3, 132.2, 132.0, 123.9, 120.2, 118.8 (2C), 118.6, 118.4, 117.8, 117.4, 117.1, 115.7 (2C), 115.3, 68.9, 68.2, 67.9 (2C), 67.8, 67.2, 66.9, 66.8, 66.0, 65.6, 65.4, 65.1, 43.3, 35.4-35.0 (6C). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd. For $\text{C}_{62}\text{H}_{57}\text{NNaO}_{26}$ 1254.3066 found 1254.3061.

Synthesis of cryptophane 23 : Compound **19** (0.13g, 0.09 mmol, 1equiv.) was introduced and then dissolved in freshly distilled pyridine (1 mL). Then compound **22** was added (0.033 g, 0.09 mmol, 1equiv.). The mixture was stirred at -15 °C, then POCl_3 (0.010 mL, 0.1 mmol, 1.2 equiv.) was added dropwisely and the mixture turned red upon addition. The solution was stirred for 30 minutes at -15 °C then stirred for 5 hours at room temperature where it turned orange. The solution was then poured carefully on a mixture of ice/water/ NaHCO_3 . The obtained solution was extracted 5 times with DCM, then dried over Na_2SO_4 , filtered and the solvent was evaporated under reduced pressure. The brownish crude was subjected to column chromatography using silica gel (CHCl_3 / Acetone, 65:35) the desired product as white powder (50 mg) with 31 % yield. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 9.07 (s, 1H), 7.44 (m, 1H), 7.04 (m, 1H), 6.84 (m, 1H), 6.82-6.52 (12s, 12H), 4.69-4.45 (m, 20 H), 4.26-4.15 (m, 18 H), 3.84-3.64 (9s, 27H), 3.46-3.34 (m, 6H), 3.12 (m, 1H). ^{13}C $\{^1\text{H}\}$ NMR (100.6 MHz, CDCl_3): δ 171.6 (2C), 170, 169.9, 169.89, 169.8 (2C), 169.5, 169.3, 169.2, 149.8, 147.9, 147.8, 147.7 (3C), 147.5, 147.44, 147.41, 147.2, 147.0, 146.6 (2C), 135.6, 134.9, 134.4, 133.9, 133.6, 133.57, 133.5 (2C), 133.4 (3C), 133.1 (2C), 132.3, 132.2, 121.1, 120.6, 120.4, 120.2, 119.7, 119.4, 118.9, 118.5, 118.0, 116.3, 115.7, 115.4, 1114.0, 107.6, 69.9,69.21, 68.7, 68.5, 67.9,

67.6, 67.5, 67.4, 67.2, 67.8, 66.0 (2C), 53.6 (2C), 52.1, 52.09, 52.05 (2C), 52.026 (2C), 51.9, 51.7 (2C), 49.1, 36.2 (3C), 35.9 (3C). HRMS (ESI): m/z $[M+Na]^+$ calcd. For $C_{83}H_{86}N_2NaO_{32}$ 1645.5061 found 1645.5056.

ASSOCIATED CONTENT

Supporting Information: 1H and ^{13}C NMR spectra of compounds **2**, **4**, **5**, **7-11**, **14**, **15**, **18**, **19**, **21**, **23**, ORTEP representation of compound **9**, calorimetric titration experiment of the $Ni^{2+}@2$ complex, calorimetric titration experiment of the cryptophane-222 hexacarboxylate with Zn^{2+} . (HP) ^{129}Xe NMR spectra of **2** and the $Zn^{2+}@2$ complex in TRIS Buffer, (HP) ^{129}Xe NMR spectrum of compound **10** and crystallographic data of compound **9**.

X-ray crystallographic data of **9** (CIF).

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Notes

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