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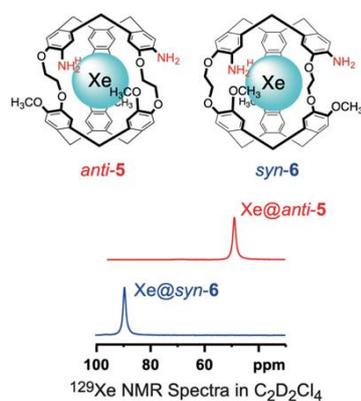
Study of *Syn* and *Anti* Xenon-Cryptophanes Complexes Decorated with Aromatic Amine Groups. Chemical Platforms for Accessing New Cryptophanes.

Martin Doll,[†] Patrick Berthault,[‡] Estelle Léonce,[‡] Céline Boutin,[‡] Erwann Jeanneau,^{!†} Thierry Brotin,^{*,†} Nicolas De Rycke^{*,†}

[†] Univ Lyon, ENS de Lyon, CNRS UMR 5182, Laboratoire de Chimie, F69342, Lyon, France.

[‡] NIMBE, CEA, CNRS, Université de Paris Saclay, CEA Saclay, 91191 Gif-sur-Yvette, France.

[!] Centre de Diffractométrie Henri Longchambon Université de Lyon 1, 5 rue la Doua 69100 Villeurbanne, France.



ABSTRACT:

We report the synthesis of C₃-symmetric cryptophanes decorated with three aromatic amine groups on the same CTB cap and their interaction with xenon. The relative stereochemistry of these two stereoisomers *syn* and *anti* was assessed thanks to the determination of the X-Ray structure of an intermediate compound. As previously observed with the tris-aza-cryptophanes analogs *anti-1* and *syn-2* (*J. Org. Chem.* **2021**, *86*, 11, 7648-7658), both compounds *anti-5* and *syn-6* show a slow in-out exchange dynamics of xenon at 11.7 T. Our work supports the idea that the presence of nitrogen atoms grafted directly onto the cryptophane backbone has a strong impact on the in-out exchange dynamics of the encapsulated xenon whatever their stereochemistry. This result contrasts with the case of other cryptophanes

decorated solely with methoxy substituents. Finally, we demonstrate that these new derivatives can be used to design new *anti/syn* cryptophanes bearing suitable ligands in order to constitute potent ^{129}Xe NMR-based sensors. An example is reported here with the synthesis of the tris-iodo derivatives *anti-13* and *syn-14* from compounds *anti-5* and *syn-6*.

INTRODUCTION:

For several decades, macrocyclic compounds with a high affinity for small guest molecules have attracted much attention. For instance, molecular containers capable of establishing specific interactions with gases such as methane or noble gases (xenon, krypton) are of great interest for gas detection, gas separation or biological applications.¹ Hollow molecules named *cryptophanes*, belong to this class of compounds, and are able to reversibly encapsulate in solution small molecules or atoms that do not interact strongly with their surrounding environment. Methane or xenon, are for instance, well recognized by cryptophanes with small internal cavities.² In most cases, the complex resulting from the guest-cryptophane association can be easily characterized via NMR through the shielding effect induced by the ring currents of the six benzene units. For instance, when xenon is used as a guest, the complexes can be identified by ^{129}Xe NMR spectroscopy as encapsulated xenon exhibits a specific spectral signature, resonating far away from xenon in the bulk. This property has been exploited for *in vitro* and *in cellulo* biosensing applications.³ Although much progress has been made in this area, much remains to be done to extend the use of these complexes to *in vivo* applications. Thus, the synthesis of novel cryptophane structures is highly desirable for this purpose and the synthesis of new cryptophane derivatives with optimized properties for biosensing applications is still being sought.

Our group has been actively working in this field for several years and the development of cryptophanes decorated with new functional groups in order to modify the properties of the

encapsulated xenon and to facilitate the functionalization of the host molecules is a major concern. Despite some progress in this field, the access to novel structures is not straightforward due to the difficulties to introduce, for instance, hetero-elements on the cryptophane skeleton. To do so, different parameters that have been summarized in a recent article have to be taken into account.⁴

We recently reported the synthesis of compounds **1** and **2** with a low yield.⁴ Compounds **1** and **2** are close analogs to cryptophanes A (**3**) and B (**4**), respectively.^{5,6} These compounds differed only by the replacement of three oxygens of the alkoxy linkers in compounds **3** and **4** by three nitrogen atoms (see Chart 1). The synthesis and purification of these two *syn* and *anti* aza-cryptophanes were tedious but, interestingly, the new xenon-cryptophane complexes showed unexpected properties. Indeed, we observed an important decrease of the xenon in-out exchange dynamics with these compounds. The ability of nitrogen atoms to establish hydrogen bonds with residual water molecules in tetrachloroethane was suggested to explain this effect. Thus, these results prompted us to further extend the synthesis of nitrogen-bearing cryptophanes and to study the behavior of these new derivatives in the presence of hyperpolarized ¹²⁹Xe.

Herein, we report the synthesis of cryptophanes **5** and **6** decorated with three aromatic amine groups positioned on the same CTB unit (see Chart 1). These compounds are again close analogs of cryptophanes A (**3**) and B (**4**), since the three methoxy groups present on the same CTB cap are replaced by three aromatic amine groups on compounds **5** and **6** (chart 1). Then, we study the new Xe@**5-6** complexes and compare these results with those previously reported for compounds **1-4**. Finally, we examine the opportunity to use these new derivatives as original platforms to prepare new compounds. Indeed, the aromatic amine groups can be exploited in a large series of reactions to access new derivatives. For instance, Sandmeyer-type

reactions are important pathways that can be used to give rise to new cryptophanes. An example is reported here with the synthesis of *anti/syn* iodo-cryptophanes.

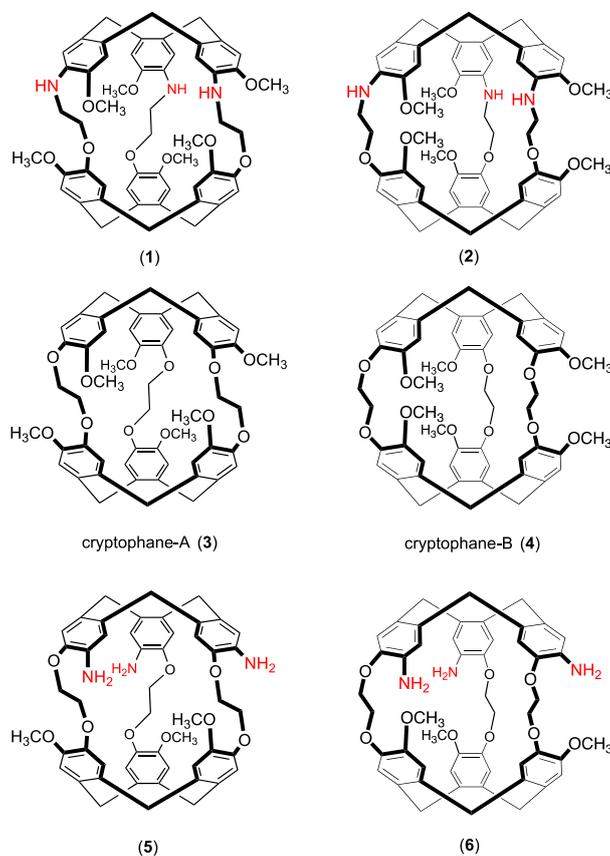


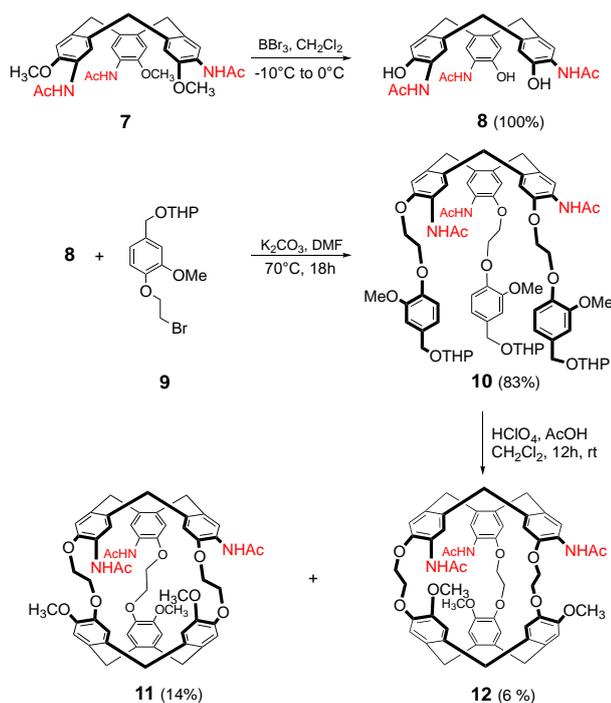
Chart 1: Chemical structures of *anti*-tris-aza-cryptophane **1** (C_3 -symmetry), *syn*-tris-aza-cryptophane **2** (C_3 -symmetry); cryptophane-A (**3**; D_3 -symmetry) and cryptophane-B (**4**; C_{3h} symmetry); *anti*-tris-aza-cryptophane **5** (C_3 -symmetry), *syn*-tris-aza-cryptophane **6** (C_3 -symmetry).

RESULTS:

Synthesis and characterization of cryptophanes **5**, **6**, **11**, **12**, **13** and **14**.

The known CTB **7** bearing three protected amine functions was used as a starting material for the preparation of cryptophanes **5-6**.⁷ A Lewis acid-promoted demethoxylation reaction of compound **7** in the presence of an excess of boron tribromide in CH_2Cl_2 afforded the CTB **8** with three phenol functions in quantitative yield (Figures S1-S2). Then, an alkylation reaction of compound **8** in the presence of an excess of 2-[[4-(2-Bromoethoxy)-3

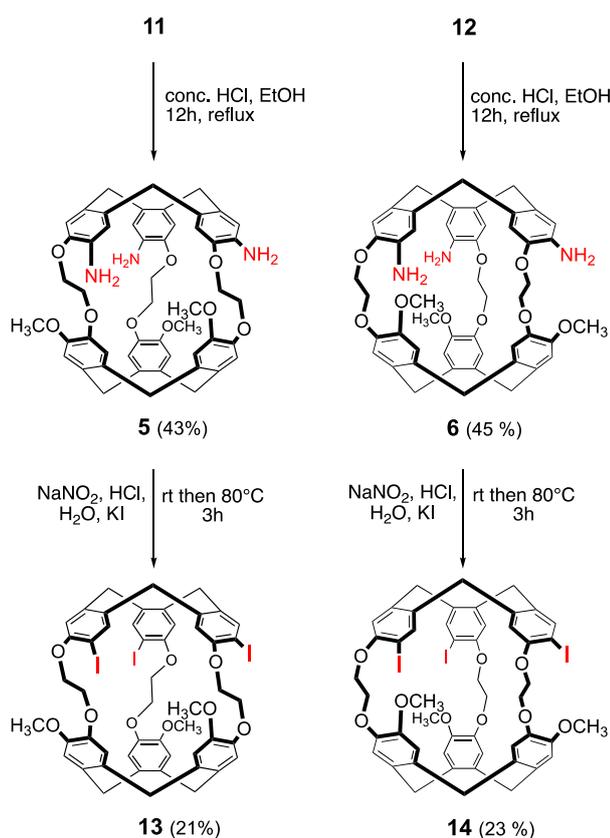
methoxyphenyl]-methoxy]-tetrahydro-2*H*-pyran **9** and potassium carbonate in DMF gave rise to the cryptophane precursor **10** in 83 % yield (Figures S3-S4).⁸ Finally, the second ring-closing reaction was achieved in the presence of perchloric acid and acetic acid at room temperature to promote the formation of two compounds that were isolated with 14 % and 6% on silica gel. Thanks to HR-mass spectroscopy these two compounds were easily identified as the *syn*- and *anti*-cryptophane diastereomers **11** and **12**. At this stage, the relative *syn*- and *anti*-configuration of these two compounds was still not known and additional characterizations are needed to attribute the stereochemistry of these two compounds. Indeed, the ¹H and ¹³C NMR spectra of these two compounds are very similar and do not allow to attribute with confidence their relative configuration (Figures S5-S8). Both ¹H NMR spectra of these two compounds display four proton signals in the aromatic region as expected for cryptophanes made of two different CTB units. Compared to the cryptophane congeners **1-2**, the aromatic protons of these new derivatives resonate on a wider frequency range due to the presence of the three protected aromatic amine groups. For instance, the aromatic protons nearby the acetamide unit shows resonance signals above 8.0 ppm for both compounds. Protons directly attached to nitrogen atoms also appear in the same region. As previously noticed for compounds **1-2**, the other spectral regions of the ¹H NMR spectra are not very useful to discriminate between the two structures and to establish with a high degree of confidence their relative configuration. However, thanks to the use of 2D NMR spectroscopy (COSY, HSQC and HMBC) a complete assignment of protons was achieved for these two compounds (Figures S9-S11 and S12-S14). Finally, the determination of the relative *syn*- and *anti*-configuration of these two cryptophanes could be resolved by the use of the X-ray crystallography (Figure S15 and Table S1). The structure obtained allows the assignment of the relative *syn* configuration to the second eluted compound (**12**) on silica gel. Consequently, the *anti*-relative configuration could be confidently assigned to the first eluted compound on silica gel (compound **11**) as depicted in scheme 1.



Scheme 1: synthesis of compounds *anti*-11 and *syn*-12.

The deprotection step of the three acetanilide functions of compounds *anti*-11 and *syn*-12 was successfully performed by using an excess of hydrochloric acid in ethanol under reflux conditions. Purification on silica gel gave rise to the two cryptophanes *anti*-5 and *syn*-6 in 43% and 45 % yield, respectively. Due to the presence of substituents of different nature on the two CTB caps of compounds *anti*-5 and *syn*-6, all the proton signals could be easily identified and a complete assignment of the proton signals of these two compounds was performed thanks to the use of ^1H , ^{13}C and 2D-NMR spectroscopy experiments (Figures S16-S25). In addition, these two derivatives showed four de-shielded singlet signals between 6.9 and 6.4 ppm and four distinct doublets, corresponding to the methylene bridges (H_{axial} , $\text{H}_{\text{equatorial}}$) of the two CTB units. These signals confirmed the C_3 molecular symmetry of the *anti*-5 and *syn*-6 compounds. Finally, we took advantage of the unprotected aromatic amine functions present in compounds *anti*-5 and *syn*-6 to prepare new cryptophane derivatives. As an example, we introduced via a Sandmeyer-type reaction three iodine atoms. The reaction was carried out by reacting

separately compounds *anti*-**5** and *syn*-**6** with sodium nitrite and potassium iodide in the presence of hydrochloric acid.⁹ These experimental conditions gave rise to the new derivatives *anti*-**13** and *syn*-**14** in 21 and 23 % yield, respectively (see scheme 2 and Figures S26-S35). Compound **13** was obtained as a mixture of two conformations as revealed by ¹H NMR spectroscopy (Figure S36). Indeed, the ¹H NMR spectrum of **13** reveals in the aromatic region twelve proton signals with the same intensity, which is characteristic of the presence of the imploded form (C₁-symmetry). Additional resonance signals at low frequencies confirm this. Dissolving compound **13** in CHCl₃ and using reflux conditions for 16 h allows the recovery of **13** with the unique globular form (C₃-symmetry). No imploded form was detected during the purification of the *syn*-**14** diastereomer.



Scheme 2: Synthesis of cryptophane **5-6** (C₃-symmetry) and **13-14** (C₃-symmetry).

X-Ray Crystallographic Structure of Compound 12. Rectangular shaped single crystals suitable for x-ray diffraction were obtained in a mixture of CH₂Cl₂/EtOH. Views of

compound **12** with displacement ellipsoids plotted at the 30% probability level are shown in Figure 1. Compound **12** crystallizes in a monoclinic $P2_1/n$ space group with four molecules per unit cell. Residual electronic density was observed both inside and outside the inner cavity of the molecule. This density could not be modeled by disorder solvent molecules and was thus taken into account by using the SQUEEZE procedure.¹⁰ As previously observed in the structure of compound the cryptophane congener *syn-4*, the two CTB unit are slightly tilted with respect to each other. The three linkers display a gauche conformation with different torsion angles. Two linkers possess a negative torsion angle - 63.6 ° and -70.4 °, whereas the third one is twisted oppositely with a torsion angle of + 49.7 °. The three amide groups are located out of the plane of the benzene rings and form angles of 45.6°, 46.6° and 62.5°, respectively. The inner cavity for this compound has been measured to be $V_{vdw} = 99 \text{ \AA}^3$.

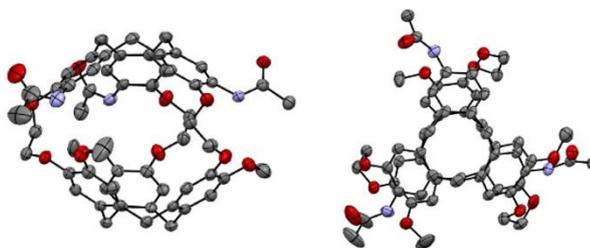


Figure 1: Molecular view of cryptophane-**12** (Hydrogen atoms were omitted for clarity. Displacement ellipsoids plotted at the 30% probability level. Colors: Carbon/grey; Oxygen/red; Nitrogen/blue).

¹²⁹Xe NMR spectroscopy of new xenon@cryptophane complexes: The ability of these new derivatives to reversibly encapsulate xenon in 1,1,2,2-tetrachloroethane-*d*₂ at 293 K was then investigated. The experimental conditions are similar to those used to study cryptophanes **1-2** and cryptophanes A (**3**) and B (**4**) whose ¹²⁹Xe NMR spectra were reported in distinct articles.⁴ As previously reported, hyperpolarized xenon produced by Spin Exchange Optical Pumping was used in these experiments (see details in the experimental section). This

technique not only provides the rapid acquisition of the ^{129}Xe NMR spectra with an improvement of the signal to noise ratio, but also it enables to use smaller quantities of dissolved xenon (mM range), making the signal intensities of free and caged xenon more balanced. Furthermore, a too large xenon concentration in solution would broaden the caged xenon signal, as it has already been shown and studied.¹¹

The ^{129}Xe NMR spectra of the noble gas in compounds *anti-5* and *syn-6* at 293 K revealed two well resolved signals located far away from each other. The low field signal could be assigned to xenon free in solution ($\delta = 223$ ppm) and was used as a reference to calibrate the spectra. The spectra also revealed an additional well-resolved signal upfield shifted by 173 ppm for the *anti-5* derivative ($\delta_{\text{Xe}@5} = 50$ ppm) and 134 ppm for the *syn-6* derivative ($\delta_{\text{Xe}@6} = 89$ ppm), respectively (Figure 2). These two signals correspond to the spectral signatures of the two complexes $\text{Xe}@anti\text{-}5$ and $\text{Xe}@syn\text{-}6$. It is noteworthy that the difference of chemical shift between xenon encapsulated in one or the other cryptophane is significantly larger $\Delta\delta = 39$ ppm than the difference observed for xenon in the compounds **1-2** ($\Delta\delta = 22$ ppm).

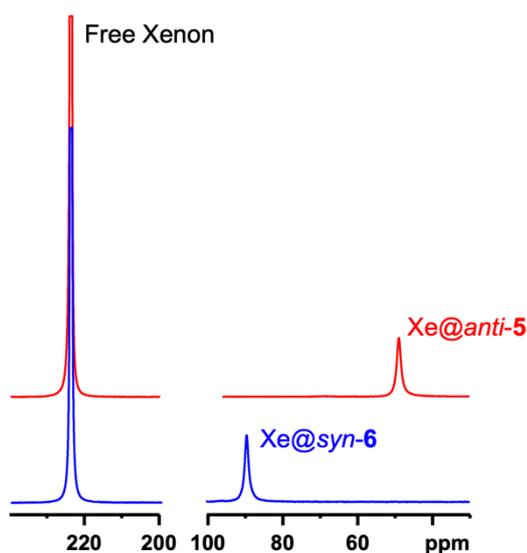


Figure 2: one-scan ^{129}Xe NMR spectra (11.7 T) of solutions containing *anti*-**5** at 1.8 mM (red spectrum) and *syn*-**6** at 1.8 mM (blue spectrum), both in 1,1,2,2-tetrachloroethane- d_2 in the presence of ca. 1 atm of xenon. Temperature: 293K.

Compound **11** and **12** whose aromatic amine groups are protected by acetate moiety also exhibit characteristic ^{129}Xe NMR signals corresponding to the $\text{Xe}@anti\text{-11}$ and $\text{Xe}@syn\text{-12}$ complexes. Indeed, ^{129}Xe NMR spectra recorded in the same conditions revealed two different behaviors for these complexes. A broad signal centered at $\delta = 79$ ppm was observed for the $\text{Xe}@syn\text{-12}$ complex whereas the $\text{Xe}@anti\text{-11}$ complex exhibited a sharper signal with two shoulders with a maximum at $\delta = 60$ ppm (Figure S37).

From a general point of view, it can be noticed that $\text{Xe}@syn\text{-cryptophane}$ complexes resonate systematically at higher frequencies than the corresponding $\text{Xe}@anti\text{-diastereomer}$ complexes. For instance, xenon in *syn*-cryptophane-D, a cryptophane with C_3 -symmetry and decorated with only three methoxy groups on the same cyclotribenzylene (CTB) cap seems to behave similarly and resonates at a higher frequency than xenon in the *anti*-cryptophane-C.^{11b} However, it should be noted that the number of *anti/syn*-cryptophane pairs showing good affinity for xenon and exhibiting a slow exchange regime at the NMR time scale is rather limited. Thus, it is difficult to state that this rule applies for other *syn/anti*-systems.

The replacement of aromatic amine groups by larger atoms such as iodine has a strong impact on the ^{129}Xe NMR spectra. The ^{129}Xe NMR spectrum of the $\text{Xe}@anti\text{-13}$ complex reveals a slow in-out exchange dynamics of xenon at 11.7 T and 293 K ($\delta_{\text{Xe}@13} = 72$ ppm). This result was expected since the overwhelming majority of *anti*-cryptophane-222 congeners exhibits this behavior. More surprisingly, the ^{129}Xe NMR spectrum of compound **14** appears significantly different from those obtained for the $\text{Xe}@syn\text{-6}$ and $^{129}\text{Xe}@syn\text{-2}$ complexes since no separate signal corresponding to the $\text{Xe}@syn\text{-14}$ complex was observed in this case. Instead,

a broad signal corresponding to free xenon in solution was observed suggesting that a fast regime takes place in these conditions with the Xe@*syn*-**14** complex. Overall, these experiments performed with the new cryptophanes **5**, **6** and **11-14** illustrate that both the nature of the substituents and the relative stereochemistry of the cryptophanes have a strong impact on the physical properties of these complexes. In turn, the combined effects of these two parameters make it difficult to predict how their complexes with xenon behave in solution especially for compounds with the *syn* stereochemistry (Figure 3).

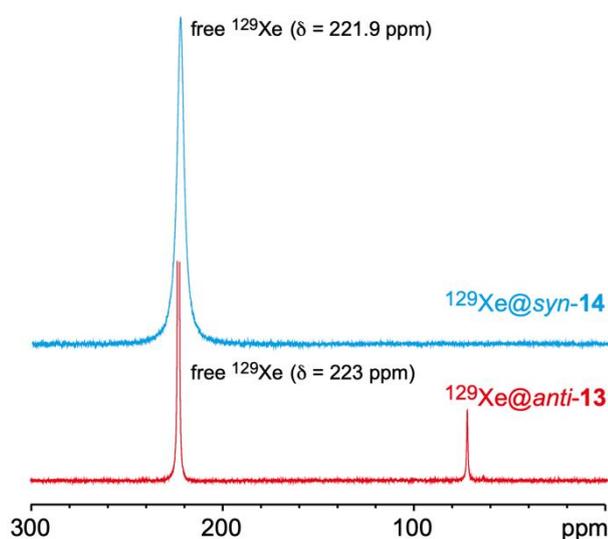


Figure 3: one-scan ^{129}Xe NMR spectra (11.5 T) of solutions containing *anti*-**13** at 2.1 mM (red spectrum) and *syn*-**14** at 1.8 mM (blue spectrum), both in 1,1,2,2-tetrachloroethane- d_2 in the presence of ca. 1 atm of xenon. Temperature: 293K.

DISCUSSION:

Unlike cryptophane-A (**3**) and B (**4**), the new cryptophanes *anti*-**5** and *syn*-**6** have been obtained simultaneously in a single step from the cryptophane precursor **10**. These two compounds have been obtained with better yields than the cryptophane congeners *anti*-**1** and *syn*-**2** but with significant lower yields than cryptophane-A (**3**) that presents a similar structure. At first sight, this result seems surprising since the amide functions are not supposed to play

any role in the formation of the second ring closure reaction. However, we can assume that the amide function is a larger group than a methoxy group and that it can therefore interfere more easily with nearby linkers. This may lead to a population of conformations different from that observed with the cryptophane-A precursor in solution, which in turn may make cyclization of the second CTB cap more difficult. Even though this assumption seems reasonable it cannot be generalized since some cryptophane precursors decorated with bulky substituents give rise to the corresponding cryptophane in good yield.¹² For instance, when the second ring-closure reaction takes place with cryptophane precursors bearing long PEG functions or benzyl groups to give the corresponding cryptophane in good yields. Nevertheless, it should be noted that the experimental conditions used for the preparation of the latter compounds are different from those used for the preparation of *anti-2* and *syn-3*.

Contrary to the synthesis of cryptophane-A derivative that can be obtained under different experimental conditions, the formation of compounds *anti-11* and *syn-12* takes place under specific conditions. Indeed, only a mixture of perchloric acid and acetic acid in CH₂Cl₂ was able to produce these two derivatives in low yields. Other conditions used to prepare cryptophanes failed to produce the new compounds **11-12**. For instance, a mixture of HCOOH and CHCl₃ (50/50) gave only traces of the expected cryptophanes and no isolated compounds were obtained by this way.¹³ Scandium triflate, an efficient Lewis acid to promote the formation of cyclotribenzylenes, cryptophanes and hemi-cryptophanes derivatives bearing electron donating substituents, did not give satisfactory results in our case and the formation of *anti-5* and *syn-6* was not detected in the crude product.^{14,15,16,17}

Compounds **5-6** and **11-12** possess an inherent chiral structure and like cryptophanes **1** and **2** they belong to the point group C₃. In the case of compounds **1** and **2**, this property has been successfully exploited to determine their relative configuration through the combined use of vibrational circular dichroism spectroscopy and DFT calculations. It is noteworthy that, like

compounds **1**, **2**, new derivatives **5** and **6** also show similar ^1H NMR spectra that make difficult their structural determination. Thus, a strategy similar to that used for compounds **1** and **2** could be envisaged to determine their relative configuration even though this approach appears to be time consuming. Fortunately, an approach based on the optical resolution of compounds **5-6** was not necessary here because we were able to obtain X-ray quality crystals of intermediate **12**, thus allowing its stereochemistry to be determined easily. In turn, the relative configuration of cryptophanes **5-6** compounds as well as the stereochemistry of compounds **13** and **14** could be easily determined from this analysis.

These cage molecules also represent interesting precursors to synthesize new cryptophanes thanks to the presence of the three aromatic amine functions grafted on the cryptophane skeleton of *anti-5* and *syn-6*. Indeed, the three amine functions can be engaged in subsequent chemical reactions. For instance, Sandmeyer-type transformations can be envisaged with compounds *anti-5* and *syn-6* to introduce a wide variety of functional groups. Indeed, the diazonium salts can react with various nucleophiles to promote the formation of carbon-halogen, carbon-carbon and carbon-heteroatom bond formation.¹⁸ Thus, this approach appears as an efficient way to obtain new functionalized cryptophanes from a single *anti* or *syn* cryptophane skeleton. To illustrate this approach, compounds **13** and **14** have been prepared in moderate yields by using a classical Sandmeyer iodination reaction. The ^1H NMR spectrum of *anti-13* reveals the presence of twelve additional signals in the aromatic region that could be attributed to the imploded conformation. This particular conformation results from the presence of a methylene group of a CTB cap inside the cavity of the cryptophane.¹⁹ This conformation breaks the molecular symmetry of the cryptophane and has been also detected by ^1H NMR spectroscopy with different cryptophane-A congeners when no guest can enter their cavities. In the case of the *anti-13*, the imploded-globular conformer is reversible. Indeed, the globular shape can be restored at higher temperature by using a guest (solvent CHCl_3) that can enter its

cavity. Note that the ^1H spectrum of compound *syn*-**14**, which has a stiffer skeleton due to the arrangement of the linkers, does not indicate the presence of the imploded form under the same conditions.

Introduction of hetero-substituents like nitrogen atoms on a cryptophane skeleton present several advantages. For instance, these new compounds represent interesting chemical platform to build-up new derivatives with interesting properties. This approach seems to be particularly interesting for introducing electron-withdrawing substituents on the cryptophane backbone by taking advantages of the numerous chemical reactions that it is possible to achieve. Such compounds are expected to show an interesting behavior in presence of xenon.

It is noteworthy that *anti*-**11** and *syn*-**12** compounds are obtained simultaneously from the precursor **10**. Cryptophane precursors that give rise simultaneously to *syn*- and *anti*-cryptophane are rare and difficult to functionalize. For instance, *anti*-cryptophane-A and *syn*-cryptophane-B have to be prepared by two different approaches. Thus, due to the presence of the three aromatic amine groups that can be engaged in a wide range of reactions, the compound *syn*-**6** offers the possibility to prepare many *syn*-cryptophanes. This represents a major asset for developing new derivatives of this type. Finally, these chemical transformations can be started once the two *syn*- and *anti*-cryptophane derivatives have been isolated separately. This can also be an advantage, since *syn*- and *anti*-cryptophanes can be sometimes difficult to separate.

Cryptophanes **5-6** and **11-14** constitute interesting systems to be studied by ^{129}Xe NMR spectroscopy as it has been shown that cryptophanes with small cavities can accommodate xenon under various conditions. Our results reveal that xenon in all the nitrogen-containing cryptophanes synthesized so far exhibit slow exchange regime at 11.7 T. Even though this behavior has been observed many times with the *anti*-cryptophane stereoisomers, *syn*-cryptophane stereoisomers with slow exchange dynamics of xenon are rare. Previous results suggest that there exists a strong correlation between the nature of the substituents grafted on

the benzene rings and the exchange dynamics of xenon. For instance, the one-scan ^{129}Xe NMR spectrum of the *syn*-cryptophane-B (**4**) decorated with six methoxy moieties show a fast-exchange regime at 11.7 T and its spectrum is characterized by a single signal corresponding to free xenon in $\text{C}_2\text{D}_2\text{Cl}_4$ at $\delta = 223$ ppm. Contrary to compound **4**, a slow exchange regime takes place in the same conditions at 11.7 T with the *syn*-cryptophane-**2** whose cavity size is similar to that of **4**. The ^{129}Xe NMR spectrum of the xenon@*syn*-**2** complex reveals a very sharp signal at $\delta = 51.9$ ppm in $\text{C}_2\text{D}_2\text{Cl}_4$ at 293 K. In this example, a clear slowing-down of the in-out exchange dynamics is noticed compared to cryptophane-A (**3**) and its congeners. To explain the difference of behavior observed between these two cryptophanes, the formation of cluster of water molecules near the three portals of *syn*-**2** was hypothesized. This assumption seems to be confirmed by 2D-EXSY experiments that show that water molecules can exchange between two distinct different sites. Thus, contrary to compound *syn*-**4** devoid of nitrogen atoms, compound *syn*-**2** can establish hydrogen-bonds with water molecules present in $\text{C}_2\text{D}_2\text{Cl}_4$ thanks to the presence of the three nitrogen atoms. Such a behavior has also been observed with other systems. The same assumption seems to be valid for the new compounds **5-6** and **13-14**. In all cases, independently of the *anti* or *syn* stereochemistry of cryptophanes, we observed a slow exchange regime at 11.7 T for all these derivatives. Thus, in these examples, we can point out that aromatic amine groups or amide functions, unlike methoxy groups, can also establish hydrogen bonds both as hydrogen bond donor and acceptor with water molecules. In turn, the presence of these water clusters near the cryptophane portals may reduce the xenon exchange dynamics. This hypothesis seems to be confirmed by the study of the ^{129}Xe NMR spectra of the tris-iodo derivatives *anti*-**13** and *syn*-**14** derivatives. Contrary to the ^{129}Xe @*anti*-**13** complex, the chemical exchange of the ^{129}Xe @*syn*-**14** complex takes place in a fast regime at 11.7 T despite the fact that iodine is much larger than a nitrogen atom. This result can be explained by the fact that iodine atoms cannot establish hydrogen bonds unlike amino groups.

This work illustrates the important role played by nitrogen atoms in modulating the in-out exchange dynamics of xenon. Their introduction inside a cryptophane backbone appears as a way to modify the in-out regime of xenon without changing the size of the inner cavity. It is now well recognized that the in-out exchange dynamics of xenon is a crucial parameter to detect the ^{129}Xe @cryptophanes complexes in physiological media. Knowledge and control of structural parameters that can impact the in-out xenon kinetics are therefore of great importance to design efficient molecular hosts for xenon biosensing.

CONCLUSION:

We report the synthesis of new cryptophane *anti-5* and *syn-6* decorated with three aromatic amine groups. These two compounds have been obtained by a multi-step procedure in low yields from the tris-amino CTB **7**. Compound *anti-5* and *syn-6* have been fully characterized by classical spectroscopic techniques and their stereochemistry have been determined thanks to the X-ray crystallographic structure of the cryptophane intermediate *syn-12*. As previously observed with cryptophane *anti-2* and *syn-3*, all the xenon-aza-cryptophane complexes reported in this article exhibit a slow in-out exchange dynamics of xenon at 11.7 T. Thus, all the complexes of xenon with cryptophanes *anti-5*, *syn-6*, *anti-11* and *syn-12* are characterized in ^{129}Xe NMR by a specific high field chemical shift. This behavior differs from those observed with cryptophanes decorated solely with methoxy groups such as the cryptophane-B (**3**) whose ^{129}Xe NMR spectrum presents a fast in-out exchange dynamics of xenon in the same conditions. In order to explain this difference in behavior, the formation of water clusters located near the portals of the *anti-5*, *syn-6*, *anti-11* and *syn-12* cryptophanes and connected to the nitrogen atoms by hydrogen bonds has been proposed. This assumption seems to be supported by the study of compound *syn-15* whose aromatic amine groups have been

replaced by iodine atoms that cannot establish hydrogen bonds. In this example, the ^{129}Xe NMR spectrum of *syn-15* is characterized by fast exchange dynamics of xenon at 11.7 T. Thus, introduction of nitrogen atoms in cryptophane skeletons appears as a way to decrease the exchange dynamics of xenon.

Besides these observations, compounds *anti-5* and *syn-6* represent interesting chemical platform to design new cryptophanes. In the future, these *anti/syn* platforms should be able to give rise to a wide range of new cryptophane structures thanks to the possibilities offered by the presence of the three amine functions which can be engaged in numerous reactions thus allowing the introduction of different functionalities. For instance, cryptophanes decorated with electron-withdrawing substituent are expected to give interesting results in the presence of xenon. The possibility offered by cryptophane *syn-6* to prepare new derivatives that possess this stereochemistry represents also an asset. Indeed, *syn*-cryptophanes with small cavities are usually difficult to obtain and they have not been studied in great details. Finally, *anti/syn*-cryptophanes possessing amphoteric properties can now be envisaged thanks to the acido-basic properties of the aromatic amine group.

EXPERIMENTAL DETAILS:

Materials

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 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 CH_2Cl_2 from CaH_2 and THF from Na/benzophenone.

^{129}Xe NMR spectroscopy. Xenon enriched at 83% in isotope 129 was hyperpolarized via Spin Exchange Optical Pumping (SEOP) in the batch mode, using our home-built setup previously described.²⁰ The cryptophanes were solubilized in tetrachloroethane- d_2 and placed in 5-mm NMR tubes capped with J. Young's valves. The transfer of hyperpolarized xenon into these tubes previously evacuated was made through a vacuum line in the fringe field of the NMR magnet to preserve polarization. All the ^{129}Xe NMR experiments were run at 11.7 T (^{129}Xe Larmor frequency 138.36 MHz) and 293 K.

Single-Crystal X-ray diffraction

A suitable single-crystal was selected and mounted on an Xcalibur Gemini kappa-geometry diffractometer equipped with an Atlas CCD and a Molybdenum X-ray source ($\lambda = 0.71073 \text{ \AA}$). Intensities were collected by means of the CrysAlisPro software.²¹ Reflection indexing, unit-cell parameters refinement, Lorentz-polarization correction, peak integration and background determination were carried out with the CrysAlisPro software.²¹ An analytical absorption correction was applied using the modeled faces of the crystal.²² The resulting set of hkl was used for structure solution and refinement. The structures were solved with the ShelXT structure solution program using the intrinsic phasing solution method and by using

Olex2 as the graphical interface.^{23,24} The model was refined with version 2018/3 of ShelXL using least-squares minimization.²⁵

CCDC 2111771 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

EXPERIMENTAL PROCEDURE:

Compound 8: Derivative **7** (1.00 g, 1.88 mmol), was suspended in dry CH₂Cl₂ (50 mL). The suspension was cooled down to -10 °C and boron tribromide (1M) in CH₂Cl₂ (7.0 mL, 7.0 mmol) was added dropwise.⁵ After complete addition, the reaction mixture was allowed to warm to room temperature and was stirred overnight at room temperature. Then, water (50 mL) was added to quench the solution. The precipitate was filtered on a frit and washed with water (2 x 20 mL), ethanol (2 x 20 mL) and diethyl ether (2 x 20 mL). It was then dried under reduced pressure to give compound **8** (915 mg, 100%) as a brown solid. Mp: 253-254 °C. ¹H NMR (400 MHz, DMSO-*d*₆, 25 °C): δ 9.39 (s, 3H), 7.55 (s, 3H), 6.78 (s, 3H), 4.65 (d, 3H, *J* = 13.3 Hz), 3.36 (d, 3H, *J* = 13.3 Hz), 2.07 (s, 9H). ¹³C{¹H} NMR (101 MHz, DMSO-*d*₆, 25 °C): δ 169.1 (3C), 146.6 (3C), 130.1 (3C), 124.8 (3C), 123.6 (3C), 117.2 (3C), 35.3 (3C), 23.4 (3C). HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₂₇H₂₇N₃NaO₆ 512.1792; Found 512.1796.

Compound 10: 2-[[4-(2-Bromoethoxy)-3 methoxyphenyl]-methoxy]-tetrahydro-2*H*-pyran **9** (350 mg, 0.716 mmol) was added to a solution of CTB **8** (860 mg, 2.49 mmol) and potassium carbonate (500 mg, 3.62 mmol) in DMF (20 mL). The mixture was heated to 70 °C (oil bath) for 18 hours under an argon atmosphere. Then, the mixture was poured in water (80 mL) and the resulting precipitate was filtered on a frit. The solid was washed with water (3 x 20 mL) and then purified on silica gel (eluent: CH₂Cl₂/MeOH (96:4)) to give rise to compound **10** as a

slightly yellow glassy solid (760 mg, 83%). ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 8.37 (s, 3H), 7.83 (s, 3H), 7.00 (s, 3H), 6.91-6.88 (m, 9H), 4.75-4.65 (m, 9H), 4.44-4.30 (m, 15H), 3.95-3.87 (m, 1H), 3.82 (s, 9H), 3.62-3.52 (m, 6H), 2.01 (s, 9H), 1.84-1.56 (m, 18H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3 , 25 °C): δ 168.4 (3C), 149.9 (3C), 147.8 (3C), 145.6 (3C), 135.0 (3C), 132.8 (3C), 132.2 (3C), 127.8 (3C), 121.1 (3C), 120.7 (3C), 114.9 (3C), 114.6 (3C), 112.2 (3C), 97.8 (3C), 69.0 (3C), 68.8 (3C), 68.1 (3C), 62.4 (3C), 56.0 (3C), 36.6 (3C), 30.7 (3C), 25.6 (3C), 24.8 (3C), 19.6 (3C). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{72}\text{H}_{87}\text{N}_3\text{NaO}_{18}$ 1304.5877; Found 1304.5881.

Cryptophanes *anti*-11 and *syn*-12: Compound **10** (14.00 g, 10.9 mmol) in CH_2Cl_2 (280 mL) was added dropwise (using a syringe pusher) to a mixture of acetic acid (840 mL) and perchloric acid (280 mL). The reaction mixture was then stirred at room temperature for three further hours. The mixture was poured in water (2 L) and was extracted with CH_2Cl_2 (2 x 1 L). The organic layer was washed with water and a saturated solution of Na_2CO_3 . It was dried over sodium sulfate and the solvent was removed under reduced pressure by rotary evaporation. The resulting crude product was purified on silica gel (CH_2Cl_2 /acetone (6:4) then CH_2Cl_2 /acetone (4:6)) to separate the diastereomers *anti*-**11** and *syn*-**12**. Each diastereomer was then purified by precipitation in diethyl ether to give rise to cryptophane **11** (1.49 g, 14%) and cryptophane **12** (630 mg, 6%) as beige powders. First eluted (compound *anti*-**11**): ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 8.24 (s, 3H), 7.57 (s, 3H), 6.76 (s, 3H), 6.70 (s, 3H), 6.65 (s, 3H), 4.63 (d, 3H, $J = 13.7$ Hz), 4.55 (d, 3H, $J = 13.8$ Hz), 4.43-4.28 (m, 9H), 4.14-4.08 (m, 3H), 3.71 (s, 9H), 3.47 (d, 3H, $J = 13.4$ Hz), 3.38 (d, 3H, $J = 13.9$ Hz), 2.18 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3 , 25 °C) δ 167.6 (3C), 149.5 (3C), 145.8 (3C), 145.6 (3C), 135.2 (3C), 134.1 (3C), 132.5 (3C), 132.0 (3C), 127.4 (3C), 123.0 (3C), 120.7 (3C), 115.6 (3C), 114.7 (3C), 70.0 (3C), 68.6 (3C), 56.0 (3C), 53.6 (3C), 36.6 (3C), 36.1 (3C), 25.1 (3C). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for

$C_{57}H_{57}N_3NaO_{12}$ 998.3834; Found 998.3842. Second eluted (compound *syn-12*): 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.04 (s, 3H), 7.90 (s, 3H), 6.75 (s, 3H), 6.66 (s, 3H), 6.62 (s, 3H), 4.62 (d, 3H, $J = 13.9$ Hz), 4.61 (d, 3H, $J = 13.9$ Hz), 4.42-4.19 (m, 9H), 3.87-3.80 (m, 3H), 3.73 (s, 9H), 3.50 (d, 3H, $J = 13.9$ Hz), 3.39 (d, 3H, $J = 13.9$ Hz), 2.29 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 25 °C): δ 168.8 (3C), 149.1 (3C), 147.4 (3C), 145.9 (3C), 135.5 (3C), 133.4 (3C), 132.9 (3C), 132.1 (3C), 128.7 (3C), 123.6 (3C), 118.6 (3C), 115.8 (3C), 115.1 (3C), 69.1 (3C), 67.0 (3C), 56.7 (3C), 36.7 (3C), 36.6 (3C), 25.0 (3C). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{57}H_{57}N_3NaO_{12}$ 998.3834; found 998.3841.

Cryptophane *anti-5*: Cryptophane *anti-11* (400 mg, 410 μ mol) was suspended in a mixture of EtOH (5 mL) and HCl (37% in water, 5 mL). The mixture was heated to reflux (oil bath) for 16 hours. Water was added to the mixture and the resulting solid was filtered and then washed with a saturated aqueous solution of K_2CO_3 . The crude product was purified on silica gel (CH_2Cl_2 /acetone: 85/15) to give rise to compound *anti-5* (150 mg, 43%) as a beige powder. 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.83 (s, 3H), 6.68 (s, 3H), 6.58 (s, 3H), 6.51 (s, 3H), 4.60 (d, 3H, $J = 13.8$ Hz), 4.49 (d, 3H, $J = 13.8$ Hz), 4.38-4.23 (m, 6H), 4.14-4.08 (m, 3H), 4.01-3.95 (m, 3H), 3.78 (s, 9H), 3.42 (d, 3H, $J = 13.8$ Hz), 3.27 (d, 3H, $J = 13.8$ Hz). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, 25 °C): δ 149.8 (3C), 146.7 (3C), 145.4 (3C), 136.5 (3C), 134.4 (3C), 134.2 (3C), 131.8 (3C), 129.8 (3C), 122.0 (3C), 117.5 (3C), 116.9 (3C), 114.0 (3C), 70.3 (3C), 68.9 (3C), 55.9 (3C), 36.3 (3C), 36.1 (3C). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{51}H_{51}N_3NaO_9$ 872.3518; Found 872.3524.

Cryptophane *syn-6*: Cryptophane *syn-12* (300 mg, 0,307 mmol) was suspended in a mixture of EtOH (5 mL) and HCl (37% in water, 5 mL). The mixture was heated to reflux (oil bath) for 16 hours and cooled down to room temperature. Water was added and the mixture was filtered,

washed with a saturated aqueous solution of K_2CO_3 . The crude was purified on silica gel ($\text{CH}_2\text{Cl}_2/\text{acetone}$: 7/3) to give compound *syn-6* (117 mg, 45%) as a beige powder. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 6.69 (s, 3H), 6.66 (s, 3H), 6.60 (s, 3H), 6.47 (s, 3H), 4.66 (d, 3H, $J = 13.8$ Hz), 4.45 (d, 3H, $J = 13.8$ Hz), 4.42-4.35 (m, 3H), 4.28-4.21 (m, 6H), 3.83-3.76 (m, 3H), 3.75 (s, 9H), 3.41 (d, 3H, $J = 13.8$ Hz), 3.25 (d, 3H, $J = 13.8$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3 , 25 °C): δ 149.0 (3C), 145.9 (3C), 145.3 (3C), 138.4 (3C), 134.8 (3C), 133.2 (3C), 132.4 (3C), 129.0 (3C), 119.1 (3C), 117.4 (3C), 116.9 (3C), 114.8 (3C), 69.5 (3C), 67.5 (3C), 56.4 (3C), 36.8 (3C), 36.0 (3C). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{51}\text{H}_{51}\text{N}_3\text{NaO}_9$ 872.3518; found 872.3531.

Cryptophane *anti-13*: Cryptophane *anti-5* (70 mg, 0.082 mmol) was added to a solution of hydrochloric acid (1% in water, 5 mL). Then, sodium nitrite (30 mg, 0.44 mmol) was added. Five minutes were necessary for the complete solubilization of the cryptophane. The mixture was cooled down to 0 °C and KI (300 mg, 1.81 mmol) was added. The red mixture was heated to reflux for 3 hours. Then, the product was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over sodium sulfate, filtered and evaporated by rotary evaporation. The crude product was purified on silica gel ($\text{CH}_2\text{Cl}_2/\text{acetone}$: 99/1) to give compound *anti-13* (20 mg, 21%) as a white glassy solid. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ 7.58 (s, 3H), 6.88 (s, 3H), 6.73 (s, 3H), 6.64 (s, 3H), 4.62 (d, 3H, $J = 13.8$ Hz), 4.52 (d, 3H, $J = 13.8$ Hz), 4.48-4.33 (m, 6H), 4.27-4.19 (m, 3H), 3.99-3.91 (m, 3H), 3.87 (s, 9H), 3.44 (d, 6H, $J = 13.8$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3 , 25 °C): δ 157.3 (3C), 150.0 (3C), 146.4 (3C), 141.2 (3C), 140.0 (3C), 134.7 (3C), 134.1 (3C), 131.2 (3C), 122.5 (3C), 118.1 (3C), 114.0 (3C), 87.2 (3C), 70.2 (3C), 70.1 (3C), 56.7 (3C), 36.4 (3C), 36.1 (3C). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{51}\text{H}_{45}\text{I}_3\text{NaO}_9$ 1205.0090; Found 1205.0075.

Cryptophane *syn*-14: Cryptophane *syn*-6 (70 mg, 0.082 mmol) was suspended in a solution of hydrochloric acid (1% in water, 5 mL). Sodium nitrite (30 mg, 0.44 mmol) was added and caused the suspension to turn orange. The mixture was cooled down to 0 °C and KI (300 mg, 1.81 mmol) was added. The mixture turned immediately dark red. It was heated to reflux for 3 hours, then cooled down. The product was extracted with CH₂Cl₂ (2 x 10 mL). The organic layer was dried over sodium sulfate and evaporated. The crude was purified on silica gel (CH₂Cl₂/acetone: 98/2) to give compound *anti*-14 (22 mg, 23%) as a white glassy solid. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 7.61 (s, 3H), 6.73 (s, 3H), 6.72 (s, 3H), 6.70 (s, 3H), 4.60 (d, 3H, *J* = 13.9 Hz), 4.52 (d, 3H, *J* = 13.4 Hz), 4.54-4.50 (m, 3H), 4.27-4.25 (m, 3H), 4.08-4.05 (m, 3H), 3.94-3.91 (m, 3H), 3.85 (s, 9H), 3.43 (d, 3H, *J* = 13.4 Hz), 3.40 (d, 3H, *J* = 13.9 Hz). ¹³C{¹H} NMR (101 MHz, CDCl₃, 25 °C): δ 157.3 (3C), 149.9 (3C), 146.1 (3C), 140.7 (3C), 140.7 (3C), 135.5 (3C), 134.1 (3C), 131.1 (3C), 121.0 (3C), 120.7 (3C), 114.1 (3C), 87.8 (3C), 70.7 (3C), 68.9 (3C), 56.4 (3C), 36.6 (3C), 36.3 (3C). HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₅₁H₄₅I₃NaO₉ 1205.0090; found 1205.0094.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C spectra of compounds **5**, **6**, **8** and **10-14**. One scan ¹²⁹Xe NMR spectra of compounds **11** and **12** in TCE-*d*₂. ORTEP representation of cryptophane *syn*-**12**. Crystallographic data of cryptophane *syn*-**12**.

X-ray crystallographic data of **12** (CIF).

AUTHOR INFORMATION

Corresponding author

*E-mail: thierry.brotin@ens-lyon.fr; nicolas.de-rycke@ens-lyon.fr

ORCID

Thierry Brotin: 0000-0001-9746-4706

Nicolas De Rycke: 0000-0001-6487-1030

Patrick Berthault: 0000-0003-4008-2912

Martin Doll: 0000-0001-9254-1821

Estelle Léonce: 0000-0002-0882-8297

Notes

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