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Design and Synthesis of New Cryptophanes with Intermediate Cavity Sizes

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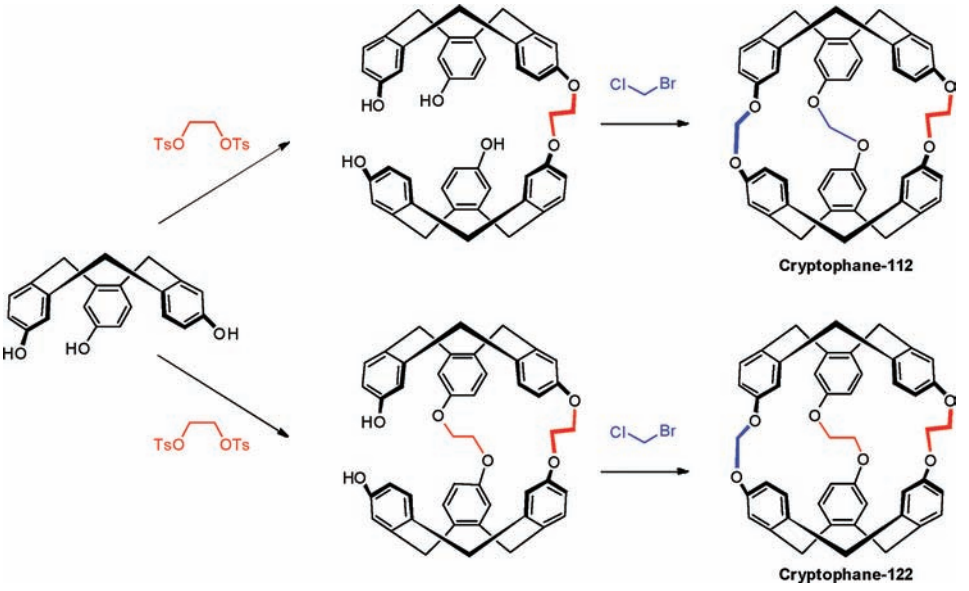
ABSTRACT



The development of molecular imaging using hyperpolarized xenon MRI needs highly optimized biosensors. Cryptophane-111 and cryptophane-222 are promising candidates that show complementary encapsulation properties although they only differ by the length of the three alkane linkers joining two cyclotriphenolene units. Cryptophanes containing both methoxy and ethoxy linkers have never been synthesized. Here we synthesize two new cages with intermediate internal volumes, in two steps from cyclotriphenolene.

The use of hyperpolarized ^{129}Xe in magnetic resonance imaging is highly attractive for *in vitro* and *in vivo* applications. Indeed, thanks to an NMR signal enhanced by 4 or 5 orders of magnitude through optical pumping, small amounts of gas dissolved in biological tissues can be rapidly detected with excellent sensitivity. However, xenon partitions in a nonspecific manner in most biological environments. Detection of particular biomolecules can be achieved by xenon biosensors, which trap xenon atoms in cage molecules that can bind the desired targets. Cryptophane cages have shown excellent affinity for xenon and constitute good candidates for biosensing.[1]

Small structural differences in the cage lead to important modifications of the encapsulation properties.[1c,2] For example, cryptophane-111 and cryptophane-222 only differ by the length of the three alkane linkers (methylene versus ethylene). Cryptophane-111 has a stronger binding constant

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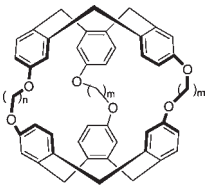
for xenon, but cryptophane-222 has a higher in−out xenon exchange rate which allows continuous refilling of the cages with polarized xenon[2b] (Table 1).

Table 1. Relevant Data for Cryptophanes-111 and -222[2b]

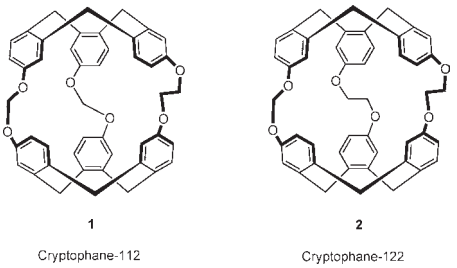


Cryptophane-111 n=m=1
Cryptophane-222 n=m=2

	cryptophane-111	cryptophane-222
binding constant (278 K)	28000 M^{-1}	1400 M^{-1}
exchange rate (293 K)	2.4 Hz	~8000 Hz

Cryptophanes containing both methylene and ethylene linkers have never been synthesized, although they could combine the advantages of both cryptophane-111 and cryptophane-222. In this paper, we present the synthesis of cryptophanes-112 (**1**) and -122 (**2**) of intermediate cavity sizes (Figure 1).

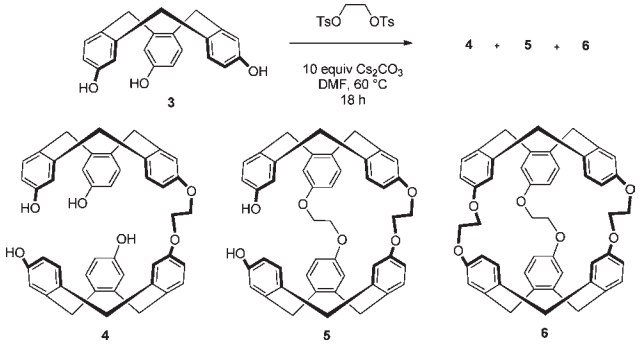
Our synthesis requires acid-free conditions owing to the presence of one or two methylenedioxy bridges on the target molecules. Therefore, neither the template method nor the direct method reported in the literature for cryptophane syntheses can be applied.[1o] Recently, cryptophane-111 was efficiently synthesized by a direct coupling of two cyclotriphenolene units with bromochloromethane.[2c,1q] We anticipated that such a reaction could be applied to obtain cryptophane-112 and -122 from open intermediates. We therefore decided to isolate compounds **4** and **5**, which are intermediates leading to cryptophane-222 (**6**) (Table 2).



1 Cryptophane-112 **2** Cryptophane-122

Figure 1. Structures of cryptophane-112 (**1**) and -122 (**2**).

Table 2. Yields of Compounds **4**, **5**, and **6** Depending on the Ratio of Ethylene Glycol Bis(Tosylate) to Cyclotriphenolene, Calculated from LC/MS Spectra



equiv of linker	yield of **4** (%)	yield of **5** (%)	yield of **6** (%)
0.5	40	7	0
1	16	8	0
1.2	17	9	13
1.4	0	6	18
1.5	0	0	26

Cyclotriphenolene **3** was obtained in 4 steps in 30% overall yield following a described procedure[1q] elaborated by our group.

We then investigated the optimized ratio of ethylene glycol bis(tosylate) to cyclotriphenolene in order to maximize the yields of products **4** and **5**. Reactions employing different ratios were carried out for 18 h in DMF at 60 °C in the presence of 10 equiv of base. The mixture was analyzed by LC/MS, and measured yields are reported in Table 2. We observed that 0.5 equiv of ethylene glycol

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bis(tosylate) is necessary to selectively form the intermediate **4**, whereas 1.2 equiv maximizes the yield of **5**. Cryptophane-222 **6** can be observed at up to 26% yield in the presence of 1.5 equiv of linker. When more than 1.5 equiv of linker is used, the formation of polymers is observed without improvement in the yield of compound **6**.

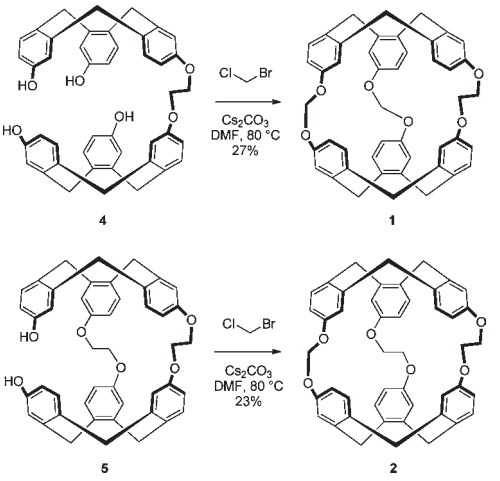
Then, we isolated the intermediates using the optimized ratio of linker. Compound **4** was obtained in 30% yield from the reaction of cyclotriphenolene **3** with 0.5 equiv of linker after purification by reversed phase chromatography. The same reaction with 1.2 equiv of bis(tosylate) gave 6% of compound **5** after purification by normal phase chromatography. We also managed to isolate compound **6** from the reaction of **3** with 1.5 equiv of linker, with a very poor yield (1.5%) after column chromatography and several extractions, which were necessary to remove secondary products of the same polarity. Surprisingly, only the anti- cryptophane **6** was formed. The same observation was made concerning the syntheses of cryptophane-111[2c] and cryptophane-A.[1o]

Finally, compounds **4** and **5** were reacted with an excess of $ClCH_2Br$ in DMF at 80 °C in the presence of 10 equiv of Cs_2CO_3 for 18 h to give cryptophane-112 (**1**) and -122 (**2**) in modest yields of 27% and 23%, respectively (Scheme 1) along with polymerized material.

Chiral HPLC was used to determine the stereochemistry (syn or anti) of the products. Under UV detection, compounds **1** and **2** showed two peaks of equal intensity that can only be attributed to the two enantiomers of the chiral *D*3-symmetry (anti) form. The two peaks appeared to be of opposite signs when product **2** was further analyzed by chiral HPLC using CD detection.

Interaction of xenon with these new cages is under study by hyperpolarized ^{129}Xe NMR. Preliminary NMR experiments show that the cryptophane precursors **4** and **5** do not bind xenon. As expected, cryptophanes **1** and **2** effectively encapsulate xenon. The signals of Xe@**1** and Xe@**2** appear at specific chemical shifts (respectively 52 and 63 ppm in tetrachloroethane at 278 K). These new cages could therefore be the precursors of biosensors used in multiplexed ^{129}Xe MRI experiments.

Scheme 1. Synthesis of Cryptophanes **1** and **2** by Closure of Open Precursors



In conclusion, we have synthesized two new cryptophanes in two steps from cyclotriphenolene. These cages show promising encapsulation properties. In addition, our approach has provided open precursors that can be engaged in the synthesis of new asymmetric cages with functionalized linkers.

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Supporting Information Available. Detailed experimental procedures, full characterization, and copies of ^{1}H, ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.