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Rim-functionalized cryptophane-111 derivatives *via* heterocapping, and their xenon complexes†

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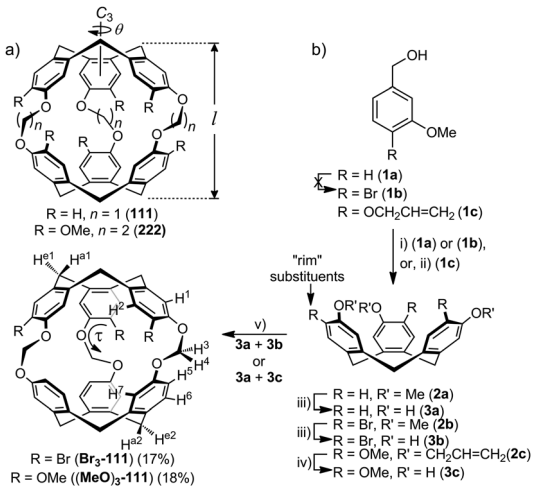
Capping of cyclotriphenolene (3a) by the more available cyclotriguaiacylene (3c) or trisbromocyclotriphenolene (3b) gives the first rim-functionalized cryptophane-111 derivatives. Crystal structures of the xenon complexes reveal high cavity packing coefficients and unprecedentedly short Xe···C contacts.

Cryptophanes (Scheme 1) are cage-like container molecules constructed by the covalent linking of two concave cyclotribenzylenes (**CTB**s), most commonly by alkyldioxy linkers.[1] They typically possess electron rich hydrophobic cavities that strongly and selectively bind complementary small molecules, gases, cations,[2] or even anions.[3] One of the most promising potential applications of cryptophanes is related to the smaller ones being the highest known affinity hosts for xenon, allowing development of as-low-as picomolar[4,5] detection limit ^{129}Xe NMR based indirect sensors or imaging/contrast agents.[6] To date, essentially all such sensors—*e.g.*, pH, temperature, protein, nucleotide, peptide, and Zn^{2+} ion sensors, to name a few—are derived from the (±)-cryptophane-222 core (**222**; R = OMe, n = 2). The **222** core features ethylenedioxy linkers that provide a flexible cavity ranging from ~85–119 Å^3 in volume (V_c)[7] and methoxy or other[8] substituents amenable to synthetic manipulation for the installment of water solubilizing and/or substrate binding sites for sensing applications. Although the parent **222** exhibits a high xenon binding constant in organic solvents ($K_a \approx 3000$ M^{-1} at 278 K in $(CDCl_2)_2$),[9] the core **222** cavity appears to be somewhat large for xenon (V_{Xe} = 42 Å^3), even in its most contracted conformation (V_c = 89 Å, for Xe@**222**). The smaller, also flexible, (±)-cryptophane-111 (**111**, R = H, n = 1, $V_c \approx$ 32–72 Å^3), however, is thought to possibly be a better core platform for xenon, at least in terms of its xenon affinity. The room temperature xenon binding constant of **111** is more than three times that of **222** in organic solvents under similar conditions ($K_a \approx 10^4$ M^{-1}).[10] The cage of the **111** core is also insusceptible to collapse.[11] To date, however, only a few derivatives of **111** have appeared, limited in part due to the low yield (6%) synthesis of the requisite cyclotriphenolene (**CTP**, Scheme 1a) precursor.[12,13] Nonetheless, the first water soluble **111** derivative, namely the pentamethylcyclopentadienyl ruthenium functionalized salt [(Cp*Ru)$_6$(**111**)]Cl$_6$,[12] was found to exhibit a high room temperature xenon binding constant (K_a = 2.9(2) × 10^4 M^{-1} in D_2O, by ^{129}Xe NMR) comparable to the best water soluble **222** derivatives.[8a] We report here the synthesis and xenon binding properties of two new rim-substituted cryptophane-111 derivatives achieved by a heterocapping synthetic approach that exploits the greater availability of methoxy or, ostensibly, bromine functionalized cyclotriphenols **3b** and **3c** (Scheme 1). The surprising crystal structures of their xenon



Scheme 1 (a) General cryptophane structure. (b) Synthesis of rim-substituted cryptophane-111 derivatives **(MeO)$_3$-111** and **Br$_3$-111** by the heterocapping method. (i) P_2O_5, Et_2O or CH_2Cl_2, reflux, (ii) 60% $HClO_4$, (iii) BBr_3, CH_2Cl_2, −78 °C, (iv) 10% Pd/C, 1,4-dioxane, (v) Cs_2CO_3, DMF, 80 °C, $BrCH_2Cl$. All chiral compounds are isolated as racemates.

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complexes reveal extremely compact xenon complexes with unprecedentedly short Xe···C contacts.

All reported **111** derivatives to date[12,13]—none of them rim-functionalized—were obtained by post-synthetic modification of **111**, which itself is best synthesized by the S_N2-mediated dimerization of two units of cyclotriphenolene **3a** using excess bromochloromethane (Scheme 1b, 46% optimized yield).[14] Unfortunately, despite recent progress,[15] the availability of **3a** remains limited by the low yield (6–14%) synthesis of its methylated cyclotrianisylene precursor (**2a**) from 3-methoxybenzylalcohol (**1a**). We reasoned that synthesis of rim-functionalized **111** derivatives might be achieved more directly by the heterocapping of **3a** with a pre-functionalized cyclotriphenolene, such as trisbromocyclotriphenolene (**3b**) or cyclotriguaiacylene (**3c**). Considering that homodimeric **111**-core cryptophanes of **3b** or **3c** should, at best, occur only in low yield due to steric crowding at opposing **CTB** rims,[16] the heterocapping approach could, in principal, alleviate up to half of the demand for precious **3a** while also directly providing functionalized **111** derivatives **(MeO)$_3$-111** or **Br$_3$-111**. Like **222**, which is rim-functionalized with methoxy (or other) substituents, the new rim-functionalized **111** derivatives ought to be amenable to further modification. Moreover, trisphenol **3c** is readily available in many-gram quantities and trisphenol **3b** is obtained from **1b** in two steps in reasonable yield.[17] Also, **3b** ought to be more accessible due to a somewhat recent report of the high yield, regioselective bromination of **1a** to give **1b**,[18] removing two steps from the overall synthesis of **3b**.

We also hypothesized that the introduction of substituents (*e.g.*, methoxy or bromo) on one of the inner rims of **111** might enhance the binding affinity of the cryptophane toward small gases due to: (i) increased host–guest dispersion interactions resulting from the introduction of heavy atoms—and, particularly, polarizable atoms like Br—at the surface of the binding site; (ii) the presence of a permanent dipole in the host, also thought to likely enhance host–guest dispersion interactions, and (iii) the bulk of the rim substituents prohibiting the **111** core from achieving the most contracted, small-cavity-volume conformation. It was thought that inhibiting contracted conformations may effectively pre-organize the cryptophane toward the more expanded, xenon-accommodating conformations and counter possible entropic consequences of substrate binding.

Reaction of **3a** with excess **3b** or **3c** under conditions similar to those used for synthesis of **111**,[14] was found to give the expected functionalized **111** derivatives **(MeO)$_3$-111** or **Br$_3$-111** in 18% and 17% yield based on **3a** (Scheme 1). The *anti*-stereochemistry of the products was confirmed by crystallography and there was no evidence for the presence of *syn* diastereomers in the products. Notably, as anticipated, only very small amounts of the homodimeric hexamethoxy- or hexabromo-**111** derivatives are observed. The latter (**Br$_6$-111**) remains as a minor impurity (<2%) in the **Br$_3$-111** product after purification. The results suggest that a heterocapping approach may also be successful if applied to a recent attempted synthesis of functionalized cryptophane-000 derivatives.[16] Unfortunately, the proposed shorter approach to **3b** did not proceed as intended; the previous report[18] of the regioselective bromination of **1a** to give the necessary **1b** was concluded to be erroneous, yielding instead the unproductive 2-bromo-5-methoxybenzyl alcohol regioisomer. **1b** was consequently synthesized from 3-hydroxybenzoic acid as reported in the literature.†[17]

Preliminary evidence for the binding of xenon by **(MeO)$_3$-111** and **Br$_3$-111** was obtained by room temperature ^{1}H and hyperpolarized (HP) ^{129}Xe NMR spectroscopy in $CDCl_3$ and nitrobenzene-d_5 (or CD_2Cl_2), respectively. The solvents are too large to enter the **111** cavity and essentially cannot compete with xenon. The degassed, xenon-free ^{1}H spectra (Fig. 1) are indicative of C_3 symmetric cryptophanes. After saturation of the solutions with xenon, the host resonances in the ^{1}H spectra of **(MeO)$_3$-111** and **Br$_3$-111** split into two signals. Under similar conditions, the HP ^{129}Xe spectra simultaneously show the appearance of resonances corresponding to Xe@**(MeO)$_3$-111** and Xe@**Br$_3$-111** (in CD_2Cl_2) at 39.3 and 80.7 ppm (Fig. S12 and S13, ESI†), respectively. The data demonstrate, as expected, slow exchange of the xenon between bound and free states on both spectral timescales, but time-averaged C_3-symmetry host conformations. The Xe@**(MeO)$_3$-111** resonance is significantly downfield from the Xe@**111** resonance (31.1 ppm)[10] and that of a hexaphenolic Xe@(OH)$_6$-**111** derivative (31 ppm);[13a] this may suggest there is less space available to xenon within this rim-functionalized **111** derivative. Preliminary data (not provided) also shows that guest in–out exchange is slower for **Br$_3$-111** and **(MeO)$_3$-111** than for **111**, reflecting the presence of substituents at the cavity windows. Though further study is needed to extract accurate binding constants, the K_a values are similar for both cryptophanes and are lower than expected ($K_a < 100$ M^{-1}, estimated). It is not yet known whether the lower xenon binding constants are due to entropic or enthalpic issues. In any case, xenon binding affinity is

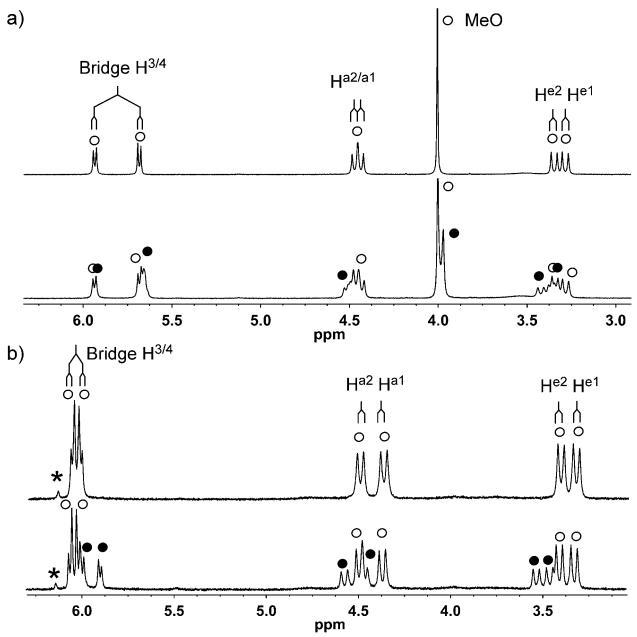

Fig. 1 Selected portions of room temperature ^{1}H spectra before (top) and after (bottom) saturation of the solvent with xenon. (a) **(MeO)$_3$-111** in $CDCl_3$, (b) **Br$_3$-111** in nitrobenzene-d_5. Open and filled circles represent signals of the free and xenon-occupied hosts, respectively. *Represents the homodimeric hexabromo derivative (**Br$_6$-111**), found as an impurity (~2%).

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expected to increase considerably in aqueous solution should these hosts be further modified to provide water soluble derivatives.

Single crystals of **(MeO)$_3$-111**·1.5DCE, the corresponding xenon complex, 0.92Xe@**(MeO)$_3$-111**·1.5DCE, **(MeO)$_3$-111**·2/3NO_2Me, **Br$_3$-111**, and its xenon complex, 0.96Xe@**Br$_3$-111**, were grown at room temperature from 1,2-dichloroethane (DCE), NO_2Me, and $NO_2C_6H_5$, respectively, and were analysed by X-ray diffraction (Fig. 2).† Crystals of the xenon complexes were obtained from vessels pressurized with xenon (14 or 17 bar), ensuring nearly 100% xenon occupancy.

The conformation of **111** and its derivatives can be described by several structural parameters: the length of the cryptophane (l), defined by the CH_2 carbons of the **CTB** units, the relative twist angle between the CTB units (θ), and the torsion angles about the Ar–O bonds involving the methylenedioxy linkers (τ, defines in Scheme 1). The cryptophane cavity volume (V_c) can also be quantified and the reported crystal structures of 0.75H_2O@**111**·2$CHCl_3$ and metalated $[(Cp^*Ru)_6(\mathbf{111})][CF_3SO_3]_6\cdot x NO_2Me$ serve as useful comparisons (Fig. 2a and b).[12] In the former compound, **111** is found to have scavenged water from $CHCl_3$ solution and the cryptophane adopts a fully expanded conformation characterized by six *syn*periplanar conformations of the $ArOCH_2$ connections (τ = 4(4)°), an 8.6 Å end-to-end length (l), a minimal twist angle (θ = 18(1)°) and a cavity volume (V_c) that measures 69 Å^3. In contrast the conformation of the empty **111** core of $[(Cp^*Ru)_6(\mathbf{111})][CF_3SO_3]_6\cdot x NO_2Me$ is seemingly as-contracted-as-possible (l = 7.4 Å), being highly twisted (θ = 61°) with all six $ArOCH_2$ connections in an *anti*periplanar (τ = 177(2)°) arrangement and a minimized cavity volume ($V_c \approx 32$ Å^3). In the absence of xenon, **(MeO)$_3$-111** and **Br$_3$-111** are also found to be empty in the solid state.† Both **(MeO)$_3$-111** and **Br$_3$-111** exhibit conformations in between the fully contracted and fully expanded forms exhibited by empty and water-occupied **111**. In short, though there is some cryptophane conformational disorder in **(MeO)$_3$-111**·1.5DCE, 2.35 of the three crystallographically unique cryptophanes observed in the two crystal structures of empty **(MeO)$_3$-111** have only three of their six $ArOCH_2$ connections (τ) residing in the *anti*periplanar "closed" conformation (0.65/3 show four of the six connections in this conformation) whereas the remaining connections are all "*gauche*" (*syn*clinal or *anti*clinal). Similarly, in the structure of empty **Br$_3$-111**, only two of the six $ArOCH_2$ connections (τ) are *anti*periplanar while four are *gauche*. The net result of these linker conformations are less twisted (Fig. 2) cryptophane conformations and larger cavity volumes as compared to empty **111** core of $[(Cp^*Ru)_6(\mathbf{111})]^{6+}$ (V_c = 42 and 46 Å^3 for **(MeO)$_3$-111** and **Br$_3$-111**, respectively). The observation suggests that, as hypothesized, the steric bulk imposed by the rim substituents prevents the empty cryptophanes from contracting as much as is possible with **111**, and that the range of achievable conformations (and cavity volumes) is narrower for the rim-functionalized **111** derivatives. Further conformational details are available in the ESI† (Table S3, Fig. S14–S19).

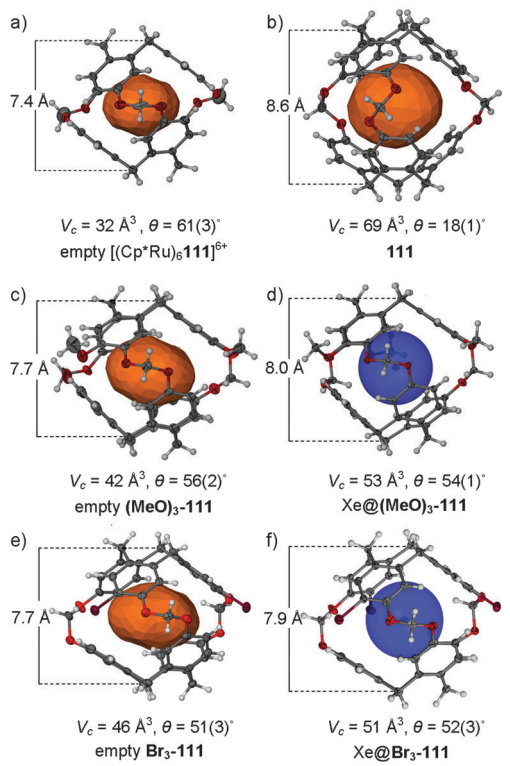

Fig. 2 Thermal ellipsoid plots of (a) the contracted **111** core of the reported empty $[(Cp^*Ru)_6\mathbf{111}]^{6+}$ cation,[12] (b) the expanded **111** conformation from the reported structure of 0.75H_2O@**111**·2$CHCl_3$,[12] (c) empty **(MeO)$_3$-111** from the crystal structure of **(MeO)$_3$-111**·1.5DCE, (d) the Xe@**(MeO)$_3$-111** complex from the crystal structure of Xe@**(MeO)$_3$-111**·1.5DCE, (e) empty **Br$_3$-111**, and (f) Xe@**Br$_3$-111**. The twist angles, θ, and cavity volumes (V_c, depicted in orange) are provided. Only the major occupancy positions of disordered species are shown. Xenon is depicted as semi-transparent blue spheres.

Surprisingly, the crystal structures of the xenon-occupied cryptophanes—0.92Xe@**(MeO)$_3$-111**·1.5DCE and 0.96Xe@**Br$_3$-111**—are isostructural and nearly identical to their empty crystal forms, except that xenon is found within the cryptophane cavities at nearly 100% occupancy. The unit cell volume of 0.96Xe@**Br$_3$-111**, for instance, is only 24 Å^3 greater than **Br$_3$-111**—almost completely attributable to the slight (5 Å^3, 11%) expansion of the **Br$_3$-111** cavities—despite the introduction of 4 × 42 Å^3 of atomic xenon. The xenon atom is centered within the **Br$_3$-111** cavity (Fig. S21, ESI†) and the 36 closest heavy atoms to the xenon are the arene carbon atoms of the host. In fact, several of the Xe···C(arene) distances are the shortest ever measured for a complex of atomic xenon,[19] ranging from 3.66–4.20 Å (avg. = 3.89(16) Å), with more than 15 contacts being shorter than the sum of the van der Waals radii (3.86 Å). The Xe···centroid(arene) distances average 3.63(4) Å, considerably shorter than that measured for the Xe···C_6H_6 complex in the gas phase (3.77 Å).[20] The result is clearly a very tightly enshrouded xenon atom; the packing coefficient (PC, V_{Xe}/V_c) of xenon within the **Br$_3$-111** cavity measures 0.82, extremely high for supramolecular complexes governed by dispersion forces (typically 0.55 ± 0.09) and particularly so for gas complexes.[21] Notably, this is the highest PC reported to date for any structurally characterized neutral guest@cryptophane complex.[22] In comparison, the Xe@**111** complex exhibits a cavity volume of 70 Å^3 (PC = 0.62) and significantly longer, likely more optimal, Xe···C(arene) contacts, with Xe···C(arene) distances averaging 4.01(9) Å (range: 3.86–4.20 Å)

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and Xe···centroid(arene) distances measuring 3.77(3) Å.[23] The xenon thermal parameters (at 100 K) are also noticeably larger for the Xe@**111** complex than for Xe@**Br$_3$-111**. Similarly, the xenon atoms of the Xe@**222** complex is even less crowded, exhibiting longer Xe···C(arene) contacts and a packing coefficient of 0.47. Interestingly, single crystals of 0.96Xe@**Br$_3$-111** appear to be indefinitely stable under ambient conditions; over a period of months, no loss of xenon can be detected by X-ray diffraction, despite the otherwise volatile nature of the guest. We note that gas-encapsulating molecules such as these may have materials applications related to gas confinement or separations.[24]

Crystals of 0.92Xe@**(MeO)$_3$-111**·1.5DCE are similarly isostructural to the empty crystal form **(MeO)$_3$-111**·1.5DCE, except that the (65 : 35) conformational disorder of the cryptophane observed in the empty structure is not present in 0.92Xe@**(MeO)$_3$-111**·1.5DCE. Only the more open of the two conformers is observed (Fig. S14 and S20, ESI†), yet, like Xe@**Br$_3$-111**, the xenon is centered and highly crowded within an intermediate cryptophane-111 core conformation (PC = 0.79, V_c = 53 Å^3). Similarly also, close Xe···C(arene) intermolecular contacts are observed for the Xe@**(MeO)$_3$-111** complex, ranging from 3.64–4.35 Å (avg. = 3.91(19) Å) and exhibiting Xe···centroid(arene) distances averaging 3.65(14) Å.

The first rim-functionalized derivatives of cryptophane-111 were synthesized by a heterocapping synthetic approach. As observed by crystallography and ^{1}H and ^{129}Xe NMR spectroscopy, **(MeO)$_3$-111** and **Br$_3$-111** bind xenon in organic solvents, albeit more weakly than expected. The crystallographically characterized xenon complexes exhibit the shortest known Xe···C intermolecular contacts. At this time, we do not have a definitive explanation for the crowded xenon complexes. It is possible that crystal packing forces dictate that the complexes maintain somewhat contracted conformations. It is more likely, however, that the rim-positioned functional groups may prevent the cryptophanes from adopting the *syn*periplanar ArOCH$_2$ conformations (τ) characteristic of the most expanded **111** core conformation. Rim-functionalization thus appears to significantly limit the range of achievable conformations of the **111** core and suggests that such **111** derivatives may be better hosts than **111** for smaller gases such as N$_2$, O$_2$, *etc.*

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