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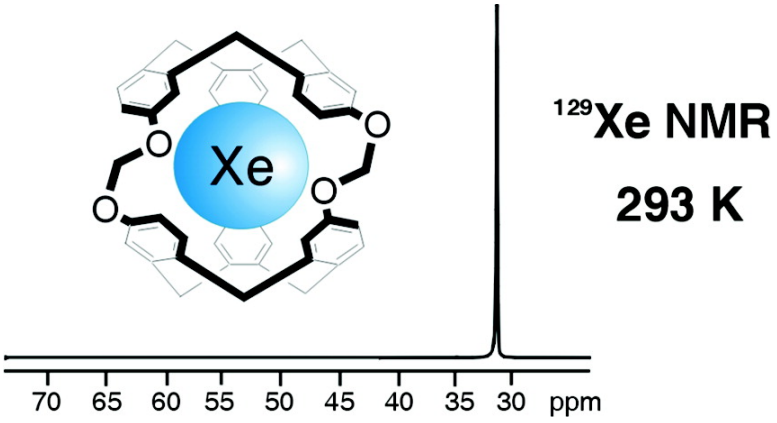

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A Cryptophane Core Optimized for Xenon Encapsulation

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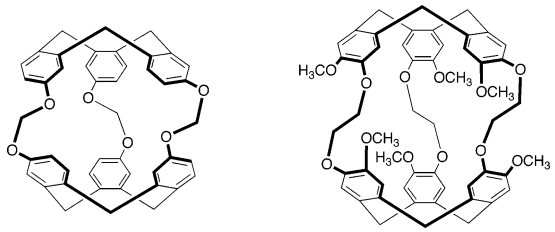
In this study we present the smallest cryptophane synthesized, cryptophane-1.1.1 (compound **1** in Chart 1), which exhibits the highest binding constant to date, 10000 M^{-1} at 293 K, for xenon encapsulation in organic solvent and very slow decomplexation kinetics resulting in an extremely sharp, low-frequency shifted ^{129}Xe NMR signal. Cryptophanes are molecular hosts of primary importance for the transport of apolar guests as well as for understanding the interactions that exist between a host and a neutral guest in solution. For instance, cryptophane-A (**2**) and its congeners have demonstrated their ability to trap a large range of neutral molecules and exhibit a large affinity for Xe solely based on van der Waals forces.[1,2] The molecular host **2** efficiently encapsulates Xe in 1,1,2,2-tetrachloroethane-d_2 (binding constant $K = 3900$ M^{-1} at 278 K). A congener of **2**, where carboxylic groups replace the methoxy groups, exhibits an even greater binding constant ($K =$ 6900 M^{-1} at 293 K) in water.[3] In both cases, the ^{129}Xe NMR spectra display a chemical shift of approximately 65 ppm for encapsulated Xe, vastly different from the signal of free Xe in solution (appearing between 190 and 230 ppm). These characteristics make **2** the core of potent supramolecular biosensors for future MRI applications based on laser-polarized (LP) Xe.[4,5] Recent papers from the Pines group[6−8] have clearly demonstrated the feasibility of combining the exceptional sensitivity of LP Xe NMR with a clear spectral discrimination between bound and free Xe signals, opening access to chemical-shift imaging for biological applications. The calculated internal volume of **2** ($V = 95$ Å^3) suggests however that it is not fully optimized for Xe ($V = 42$ Å^3) encapsulation and that it is possible to design even more efficient molecular hosts by reducing the cavity size. A cavity of ideal size would maximize the van der Waals interactions between the host and the Xe atom.

Host **1** bears three methylenedioxy bridges that connect two identical C_3-symmetry substituted cyclotribenzylene units and possesses a small internal cavity estimated at 81 Å^3 from GRASP.[9] The volume ratio, *r*, calculated between Xe and the cavity of host **1** ($r = 0.52$) is close to the optimal value of 0.55 predicted by J. Rebek.[10] Also, the average internuclear distance between opposite aromatic rings of **1** (7.78 Å, as determined by MM3 modeling, Supporting Information), when filled by a Xe atom, is very close to twice the most stabilizing aromatic ring−Xe distance (3.75 Å).[11] These results suggest that the cavity size of **1** is optimized for Xe encapsulation. The synthesis of **1** requires acid-free conditions owing to the presence of the three methylenedioxy bridges and was thus isolated in low yield (11%) from the coupling reaction of 2 equiv of C_3-symmetric tris-hydroxy-substituted cyclotribenzylene derivative[11] in the presence of Cs_2CO_3 and $BrClCH_2$ in DMF. The reaction leads almost exclusively to the chiral D_3-symmetry (anti) form, as observed by chiral HPLC, and a trace amount of a compound that we believe to be the C_3-symmetry syn form, which has been detected only by LP ^{129}Xe NMR spectroscopy under conditions allowing sub-micromolar detection limits (Figure S6).[3]

Chart 1. Structures of **1** and **2** (D_3-Symmetry, Anti Forms). A Single Enantiomer Is Shown for Each Compound



1 **2**

The ^{1}H NMR spectrum at room-temperature exhibits a single signal at approximately 5.7 ppm characteristic of the magnetically equivalent bridge methylene protons. In 1,1,2,2-tetrachloroethane-d_2, $CDCl_3$, or even CD_2Cl_2, the aromatic protons exhibit signals that are not significantly modified upon solution degassing, suggesting that these solvents are unable to enter the cavity of **1** because of their size.[1] In contrast, the introduction of Xe gas into the solution leads to sharpening of these signals (Figure S5), indicating that Xe enters the cavity of this new cryptophane. It is noteworthy that in entering **1**, a rather rigid host, Xe crosses portals whose static dimensions (opposing H−H internuclear distances of 2.9−4.5 Å, Table S2) are smaller than the van der Waals diameter of Xe ($d = 4.3$ Å). The transport of Xe through 4 Å wide channels in gramicidin has been shown, in which the transport of the noble gas was mostly related to the flexibility of the channels.[13] Thus, dynamic deformations of the portals of **1** likely affect the energy barrier for the movement of Xe across the portals.

The thermodynamic and kinetic parameters of the complex were obtained from ^{129}Xe NMR measurements of either thermal or LP gas. The spectrum of LP ^{129}Xe dissolved in a 1,1,2,2-tetrachloroethane-d_2 solution containing host **1** (Figure 1) displays two very sharp signals with a chemical shift difference of 194 ppm at 293 K. The upfield peak, at 31.1 ppm, corresponding to bound Xe, exhibits a significant reduction of line width compared to Xe encapsulated in **2**, indicating a strong decrease of the exchange dynamics between the two environments with respect to the case of host **2**. The Xe@**1** signal also exhibits an unexpected upfield shift of ∼36 ppm with respect to Xe@**2** indicating that the chemical shift of encapsulated Xe is governed by factors whose relative importance is currently difficult to predict: the size of the cavity,[3,14] the steric effects of the phenyl substituents, and the electronic density of the six aromatic rings surrounding the Xe atom.

The binding constant between Xe and **1** was estimated by a competition experiment between hosts **1** and **2** in 1,1,2,2-tetrachloroethane-d_2 at 293 K. A binding constant 3.5 times larger than that

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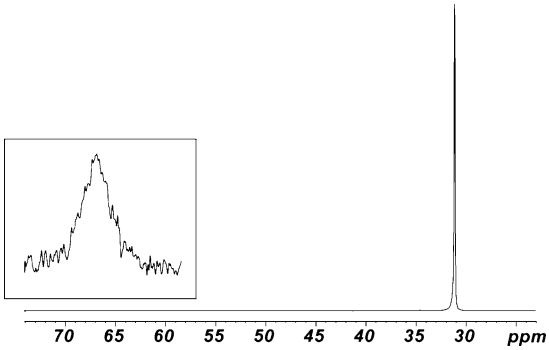

Figure 1. High-field region of the ^{129}Xe NMR spectrum of the LP gas dissolved in a 10 mM solution of **1** in 1,1,2,2-tetrachloroethane-d_2 at 293 K. The Xe@**1** complex resonates at 31.1 ppm. Inset shows the ^{129}Xe NMR signal of the Xe@**2** complex under the same conditions with the same horizontal scale given for comparison. Xe chemical shifts are given with respect to Xe gas extrapolated to zero pressure.

for **2** was found for **1**, which gives a value close to 10000 M^{-1}.[15] The in−out exchange is characterized by $k_{out} = 2.4\ s^{-1}$ at this temperature, for a cryptophane concentration of 15 mM and a Xe pressure of 1 bar. The mean residence time of 0.4 s deduced from the k_{out} value is significantly longer than that observed for host **2**. As already noted for all Xe@cryptophane complexes, an increase of the temperature leads to a shift of the bound signal toward higher frequency, as a consequence of the internal dynamics of the host. However, the Xe line width for Xe@**1** is much less dependent on temperature than in other Xe@cryptophane complexes (Figure S9, Table S1). Monitoring of the ^{129}Xe line width as a function of temperature in the range 293−354 K gave the following values for the activation energy terms using Eyring's equation: $\Delta H^{\ddagger}_{out} = 43.2 \pm 1.6$ kJ mol^{-1}; $\Delta S^{\ddagger}_{out} = -74 \pm 3$ J mol^{-1} K^{-1}. This leads to $\Delta G^{\ddagger}_{out} = 64.9 \pm 3$ kJ mol^{-1} at 293 K. The high value of the activation enthalpy term indicates, as expected, that the energy barrier for Xe to escape from the host cavity is important. These values can be compared to the corresponding ones for Xe@**2** in the same solvent: $\Delta H^{\ddagger}_{out} = 35.5$ (33.6) kJ mol^{-1}; $\Delta S^{\ddagger}_{out} = -60$ (−70) J mol^{-1} K^{-1}.[14,16] The difference between the energy barriers is thus mainly due to the enthalpic terms, as the entropic contributions are of the same magnitude. The Xe longitudinal relaxation time T_1 of the bound state was found to be 12.1 ± 0.7 s at 293 K. This is significantly lower than the T_1 measured for **2** (18.8 ± 5.0 s) in similar experimental conditions.[17] This is not surprising as (i) each aromatic ring of **1** possesses one hydrogen in place of the methoxy groups in **2**, (ii) the higher rigidity of the complex increases the Xe-proton correlation times, and (iii) the average xenon−proton distance is shorter.

Host **1** shows remarkable binding properties toward Xe atoms in organic solution: (i) the highest binding constant ever found between a host molecule and Xe, due solely to van der Waals interactions, (ii) a long calculated residence time for the Xe@**1** complex, and (iii) a surprising large highfield shift of the Xe@**1** signal relative to those of other Xe@cryptophane complexes.[14] Previous results reported for the water-soluble congener of **2** suggest that an even larger binding constant can be expected for future water-soluble congeners of **1**.[3] Thus these new supramolecular systems are excellent candidates for future *in vivo* MRI experiments after suitable chemical transformation aimed to improve the solubility and stability in biological media. For such applications, the Xe T_1 value of the bound state could be lengthened by deuteration of the aromatic rings and the methylene bridges.[3] The measured in−out exchange rate could be adapted to MRI biosensing applications where the frequency difference between Xe signals of the bound and free states enables multishot experiments based on the replenishment of the cage with LP Xe between two scans.[3,18] This parameter is of key importance for a gain in sensitivity. The most important property of this host may be its selectivity for Xe, which makes **1** a molecular receptor of reference for the design of new Xe complexing systems for sensing applications.

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Supporting Information Available: Experimental details for the synthesis, NMR experiments and modeling, the chiral HPLC chromatogram, UV−vis spectrum of **1**, ^{1}H NMR spectra of **1** in various solvents, ^{129}Xe NMR spectra of Xe@**1** at various temperatures, and the Eyring plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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