COMMUNICATION

Tight Xenon Confinement in Crystalline Sandwich-like Hydrogen Bonded-Dimeric Capsule of Cyclic Peptides

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Dedication ((optional))

Abstract: A cyclic hexapeptide containing three pyridyl moieties connected to its backbone forms hydrogen-bonded dimers, which encapsulate tightly a single xenon atom, like a pearl in its shell. Supramolecular capsules self-assemble hierarchically forming a porous supramolecular architecture whose cavities are filled by small molecules and gases. The dimers imprint their shape and symmetry to the captured xenon, as demonstrated by ^{129}Xe NMR, X-Ray diffraction, and computational studies.

Recently, the interest for the investigation of heavy noble gases has grown given their importance in lightening, medical imaging, sensing, and neuro-protection.[1] Most of these gases are dispersed in very low amounts in the atmosphere and lithosphere, but high purity is needed for technological applications.[2] Cryogenic methods are used industrially to extract these gases from air, although the separation is costly because of the low concentration. Efficient sequestration under mild conditions of room temperature and low pressure would be competitive with the current energy-demanding technologies. In principle, greater energy efficiency in the separation can be achieved by using porous materials with tailored binding properties for the noble gases in a mixture. Indeed, in the last few years task-specific porous materials have been prepared for capturing noble gases,[3] although the specificity is still a challenge for their scarce polarity or polarizability. The limited size-difference of noble gases with respect to other important gases and the spherical shape do not provide handles for shape-selective recognition. To accomplish specific encapsulation, recently, host/guest chemistry of cryptophanes and molecular cages has been shown as a new promising alternative for gas separation.[4] Several hollow macromolecular structures have been designed for encapsulation of Xe *versus* other noble gases with good selectivity.[5] In fact, cryptophane-111 has shown a good Xe selectivity and implemented in high-contrast molecular imaging using hyperpolarized ^{129}Xe NMR spectroscopy.[6] More biocompatible derivatives, such those derived from peptides, are required to this end.

Peptide nanotubes are tubular structures made by the assembly of low molecular weight peptides.[7] One of the approaches for the preparation of nanotubes with controlled pore diameter is based on cyclic peptides that adopt a flat-ring conformation. The self-assembly of cyclic peptides containing γ-amino acids (α,γ-CPs) leads to the formation of tubular structures of piled rings with tunable cavity properties.[8] During the last years, we have been working with simple α,γ-dimeric units that have been evaluated for a variety of applications ranging from molecular capsules to electron transfer systems.[9] These dimers entrap guest molecules in their internal cavities.[10-12] In this work, we show novel pyridyl-substituted cyclic α,γ-hexapeptides that self-assemble in a hierarchical controlled fashion, to fabricate porous molecular crystals of dimeric units stabilized by multiple hydrogen bonds with docking recognition.[13] These dimers retail specific spaces for entrapping tightly individual chloroform and xenon atoms. The crystalline structure shows additional inter-capsular cavities that ensure gas diffusivity and accessibility. The confinement in the dimers and the partitioning of guests in the distinct pores were investigated by the use of multiple recognition techniques for solid- and gas-phase, encompassing single-crystal XRD, ^{129}Xe NMR, and DFT calculations. Xenon descriptors highlight the imprint of the anisotropic shape of the niche, wherein xenon is nested.

To carry out these studies, cyclic peptides **CP1** and **CP2** (Scheme 1) were prepared, as illustrated in Scheme S1. These compounds consist of three 3-aminocyclopentanecarboxylic acids alternated with proteogenic α-amino acids[11,12] wherein the γ-residues bear propynyl and 3-pyridylpropynyl moieties (R^2), respectively, We envisage that the self-assembly of peptides bearing reactive moieties attached to the peptide backbone would not interfere in the formation of supramolecular dimers (**D1**

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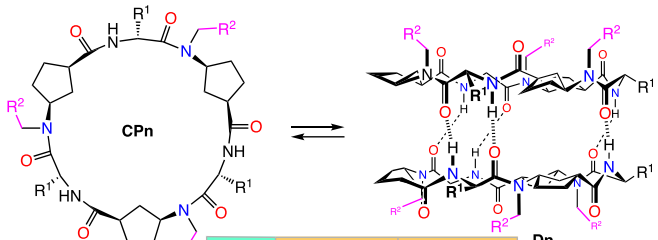
and **D2)** and would project these moieties towards both-faces of the dimeric assembly. The semi-rigid group with the *meta*-substituted pyridine in **CP2** was incorporated with the aim of increasing the inter-dimer contacts and interactions (*i.e.*, halogen or hydrogen bonds) and elongating the tubular length.[14,15]



CPn	R^1	R^2
CP1	$CH_2CH(CH_3)_2$	H
CP2	$CH_2CH(CH_3)_2$	N
CP3	CH_3	H

Scheme 1. Structure of cyclic peptides (**CP1**, **CP2** and **CP3**) and their corresponding dimers (**D1**, **D2** and **D3**).

The resulting peptides were studied by different techniques. ^{1}H NMR experiments confirmed that both CPs form the corresponding dimers, characterized by the down-field shift of amide protons involved in the hydrogen bonds due to the dimer formation (δ= 8.11 and 8.62 ppm for **CP1** and **CP2**, respectively, Fig. S1). FTIR with bands at 3301 (Amide A), 1665 (amide I_{II}), 1620 (amide $I_{\perp}$) and 1533 (amide II) for **CP1** and 3307 (Amide A) 1665 (amide I_{II}), 1627 (amide I) and 1530 (amide II) for **CP2**, also confirmed the proposed β-sheet-like structure characteristic of the dimeric form (Fig. S2).

Crystals of the cyclic peptide **CP2** suitable for single crystal X-ray diffraction were grown from a chloroform solution by slow vapour diffusion, using hexane as anti-solvent. The crystal structure of the resulting needle-shaped crystals was solved by synchrotron X-ray radiation diffraction in order to obtain high-resolution diffractograms (Figure 1). The **CP2** crystallizes in the tetragonal $P4_22_12$ space group with the unit cell parameters of *a*=35.52 Å and *c*=11.22 Å. The cyclic peptide forms dimers in which the two flat rings self-assemble in an antiparallel β-sheet-like arrangement through six hydrogen bonds involving the amide moieties and the amidic C=O (N···O distances of 2.83-2.98 Å, Fig. 1a). The body-centered structure of the crystal forms tubular channels by stacking the dimers along the crystallographic *c* axis. Each dimer interacts with the next neighbour by a series of weak C···O contacts (C···O distances of 3.06 - 3.22 Å) between the amidic oxygens and the linker chains (both -CH_2 and acetylenic carbons) connecting the pyridine moieties (Fig. S3a). Additional van der Waals contacts involving the Leu side chains further stabilize the tubular channels. The tubular channels show parallel packing, stabilized by short contacts involving the pyridine moieties of nearby rings. Further stabilization of the lateral self-assembly is provided by the interactions between the pyridine residues and the peptide backbone of adjacent tubes (Fig. S3b). The drum-shaped dimer has an approximate van der Waals internal equatorial diameter of 5.4 Å and a height proper for hosting a maximum size sphere of 4.5 Å diameter, as previously reported for similar compounds.[16] The tubular channels are filled with two chloroform molecules per dimer, both showing partial site occupancy (60% and 50%, respectively). The first lies within the cavity;[16] the second one occupies the site between adjacent dimers in the tubular motif along the *c*-axis. The guest molecules are stabilized in the channels through a network of Cl···O contacts involving the amidic oxygens of the peptide rings (Fig. S3c). In addition, another chloroform molecule lies externally to the channel, filling the inter-tubular spaces (25% occupancy).

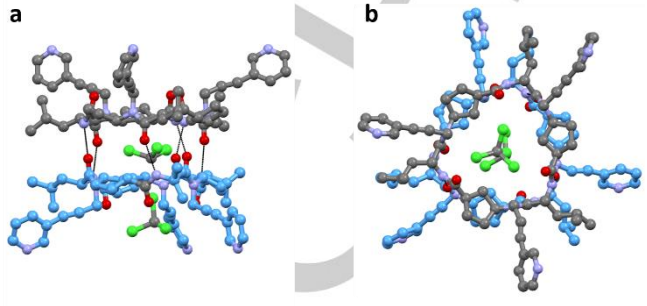


Figure 1. Side view a) and top view b) of tubular channel formed by **CP2**, containing chloroform molecules in the intra- and inter-cavities. Color code: carbon, grey and light blue; oxygen, red; nitrogen, violet; chlorine, green. Hydrogen atoms have been omitted for clarity.

The permanent porosity of the crystalline compound, after guest removal under vacuum, was demonstrated by CO_2 isotherm at 273 K and up to 5 bar (Fig. S4). Additionally, after exposure of single crystals to Xe under pressure of 5 bars (see SI for details), synchrotron radiation SCXRD at 100 K revealed carefully Xe atom location owing to its high electron density. The space group and unit cell parameters did not change after Xe adsorption, indicating the robustness of the structure (*a*=34.87 Å and *c*=11.89 Å). A single Xe atom is tightly confined in the intra dimer cavity with an occupancy factor of 0.4 (Fig. 2); an additional Xe atom having very low occupancy (5%) fills the inter-cavity of the same tubular channel (Fig. S5). As previously, the cyclic peptide forms antiparallel β-sheet like structure, forming hydrogen bonds with N···O distances in the range 2.89-2.93 Å (Fig. S5).

The direct observation of Xe confinement in intra-dimer cavities was provided by ^{129}Xe NMR on a polycrystalline sample (Figure 3). For this purpose, the sample was evacuated and exposed to Xe gas at the pressure of 10 bar and room temperature. ^{129}Xe NMR spectrum, collected under static conditions at 298 K, showed a signal with a remarkable downfield shift with respect to Xe in the gas phase at 0 ppm. Remarkably, the line-shape exhibits a large chemical shift anisotropy (CSA) with the following parameters: $\delta_{//}$ = 171 ppm, $\delta_{\perp}$ = 211 and 216 ppm. The virtual coincidence of $\delta_{\perp}$ indicates an axial symmetry. The value of calculated isotropic chemical shift (δ_{iso}=199 ppm) demonstrates a tight Xe confinement in the restricted space of comparable size to that of Xe atom (4.3 Å). ^{129}Xe chemical shift values as high as 200 ppm have been rarely observed in narrow cages of cucurbituryls and cyclodextrins in solution.[17] Additionally, in the present case, ^{129}Xe CSA can report about the geometry of the cavity. In fact, xenon atoms receive the imprint of the cavity shape, wherein confinement is more effective along the channel *c*-axis than in the *a*/*b* plane.[3e,f] Thus, the space available for Xe within the dimeric capsule is described as a disc-like space, where CP rings clamp individual Xe atom, squeezing it along the *c*-axis. ^{129}Xe NMR spectrum was also collected at 233 K showing a similar anisotropy although slightly shifted at higher ppm values

(Fig. S7), indicating that xenon retains an equally high degree of confinement over a wide temperature range and explores a virtually identical cavity. This is a rare example of complexation of a bare non-polar noble gas with a supramolecular size-fitting cavity that offers close Van der Waals contacts and favours the encapsulation in the solid state.[3a,d,h]

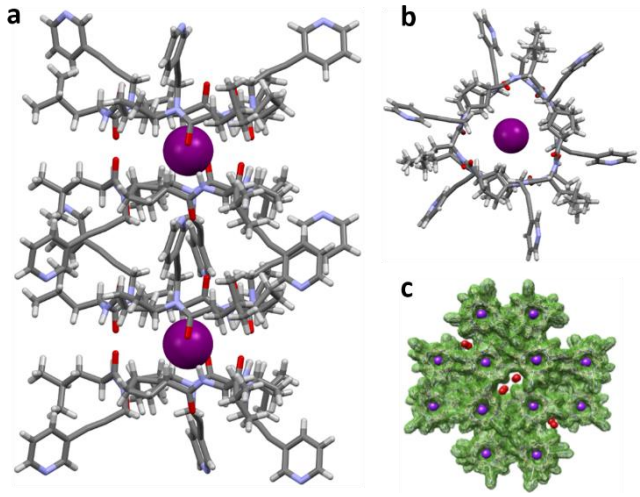


Figure 2. Side view a) and top view b) of a channel-forming structure by the stacking of **CP2** dimers. c) Packing of the resulting nanotubes in the crystal structure. Color code: carbon, grey; oxygen, red; nitrogen, violet; xenon, purple.

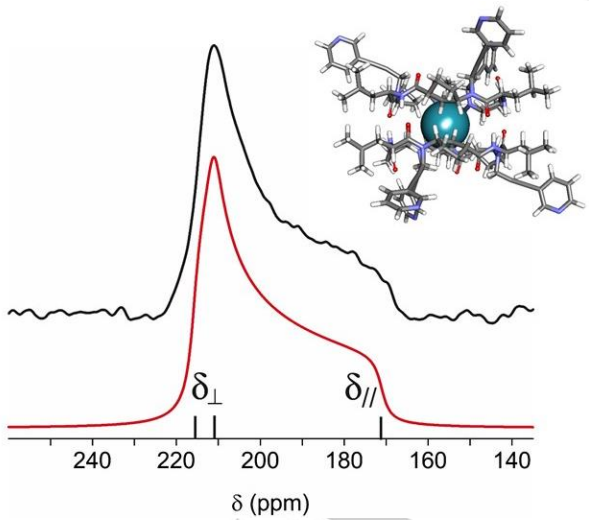


Figure 3. ^{29}Xe static NMR spectrum at 293 K under a gas pressure of 10 bar (black line) compared to the simulated lineshape (red line). The main components of the chemical shift tensor are reported (black line). The chemical shifts are referred to the xenon in the gas phase at 0 ppm. Xe confined (blue sphere) in the dimer **D2** is reported in the inset.

DFT calculations were carried out to understand the cyclic peptide dimer cavity affinity for different noble gases (Xe, Kr and Rn) and chloroform molecule (see Computational Methods in SI). The dimeric model from cyclic peptide *c*-{[(1*R*,3*S*)-^{Me}*N*-Acp-*D*-Ala-]$_3$}, (**D3**) (Scheme 1) was employed to reduce conformational variants related to Leu side chain and pyrididyl pendant. The optimized geometries for **CHCl$_3$⊂D$_3$** and **Xe⊂D$_3$** suggest that the complexes are stable in both cases. The cyclic peptides adopt a slightly distorted flat conformation that forms hydrogen bonds with a wider range of N···O distances, 2.85–2.93 Å in the case of **CHCl$_3$⊂D$_3$** and 2.86–2.89 Å in the case of **Xe⊂D$_3$** (Fig. 4).

The calculations (Table S1) confirmed the stability of the xenon confinement with an interaction energy of -6.4 Kcal/mol. These results suggest that Xe could be entrapped in the pore of the dimeric structure although the larger affinity was found for chloroform (-14.1 Kcal/mol). The computational studies showed the ability of the supramolecular host to modify the conformation for a better fit to the specific guest, going from 125 Å^3 for hosting Xe to 138 Å^3 for chloroform molecule. This volume is even bigger than the previously crystallized dimer of *c*-{[(1*R*,3*S*)-^{Me}*N*-Acp-*D*-Leu-]$_3$} that incorporated a chloroform molecule in its cavity.[16] It is worth noting that also Kr and Rn can be favourably encapsulated in the dimer cavity and the binding energy increases with the augment of the atom volume, suggesting that this is a promising system for the capture of noble gases.

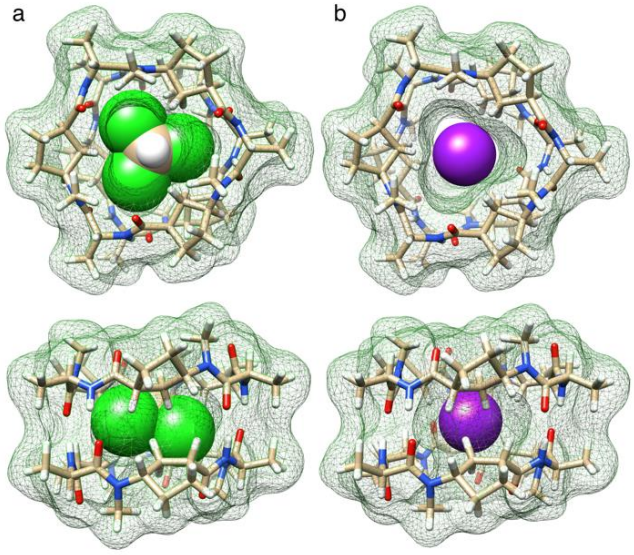


Figure 4. Top and side view of computer minimized [**B3LYP/6-31G(d),** and **aug-cc-pVTZ-PP** for Xe] models of α,γ-CP dimers (**D3**) with their cavity filled with (a) a chloroform molecule (**CHCl$_3$⊂D$_3$**) and (b) Xe (**Xe⊂D$_3$**).

In conclusion, cyclic hexapeptides, opportunely substituted by pyridyl groups, constituted a building block that recognizes its twin and self-assembled at the first hierarchical level into dimeric capsules. It was demonstrated that these capsules contain void spaces, which are favourably occupied by xenon, although notoriously a poorly interacting noble element. The molecular crystals of peptide rings with absorbed xenon can be manipulated at the open air and room temperature without gas release. Synchrotron-radiation single-crystal XRD shows that the gas atom is located precisely in periodic positions at the centre of the shells. Xenon receives the anisotropic imprint from the sandwich-like clamping dimers, as perceived by static ^{129}Xe NMR spectroscopy. Indeed, the anisotropic line-shape reflects the axial symmetry of the sandwich cavity and defines the most effective directions of the confinement. The practical consequence of the present design is to provide a tool to construct supramolecular structures by exploiting the constraints of cyclic rings and their directional interactions to build up customized porous crystals. In

the case realized here, the specificity is directed towards elusive rare gas. In general, the suggested strategy is especially attractive because of the use of cyclic oligopeptides based partly on amino-acids of biological origin, which do not consume unrenewable mineral resources.

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Keywords: Xenon • host-guest • cyclic peptide • self-assembly • gas confinement

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Layout 2:

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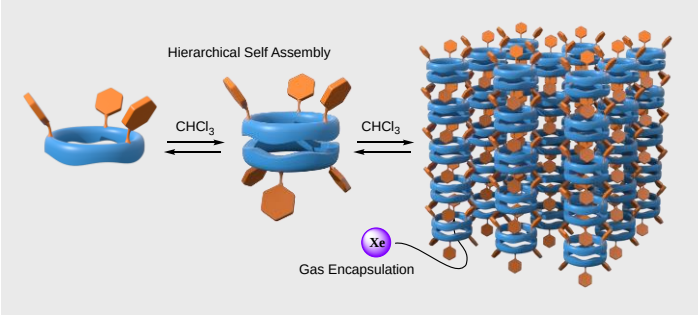

Peptide-based supramolecular capsules hierarchically form supramolecular porous materials able to encapsulate Xe atoms in their internal cavity.

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Tight Xenon Confinement in Crystalline Sandwich-like Hydrogen Bonded-Dimeric Capsules of Cyclic Peptide

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