Compression of 1,ω-Diammonio-oligo(ethylene glycol) Chains within the "Pyrene Box"

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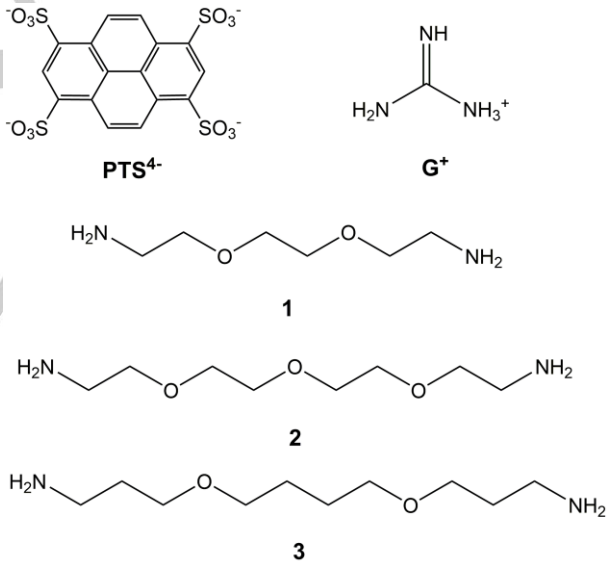
In memory of Prof. Silviu Teodor Balaban

Abstract: The compressed conformations and the coiling shapes extent of the 1,ω-diammonium-(oligo)ethyleneoxyde, OEG guests are determined within the internal space of the crystalline Pyrene Box host capsules. It was observed that the OEG chains have the tendency to fold in on themselves in random or S-shaped intermolecularly H-bonded conformations inside the Pyrene Box confined medium. The phenomenon was observed in solution through NMR spectroscopy and structural proof was provided by single crystal X-ray diffraction. The overall supramolecular spatial arrangement of the "Pyrene box" system present structural and dimensional variations/adaptations in order to accommodate the coiled OEG guests of different sizes and shapes.

Introduction

Molecular encapsulation is essential to life. The confinement of biological relevant molecules is a complex process that provides important insights in understanding the functional behaviors of important biological transformations under confined conditions.[1] We know that long flexible guests are dynamically folding in the small space of a capsule and several different and constitutionally confined conformers relevant to many biological occurrences may be observed. For example, the encapsulation of *n*-alkanes inside the artificial capsules with smaller dimensions than the total linear length of the alkane molecules is occurring with their compression inside a fixed chemical space. This field has been extensively described by Rebek Jr. et al.[2] and Gibb et al.[3] As in biological systems, the synergetic host-guest interactions and the flexibility of the host chains may induce variable bridge, loop and tail conformations stabilized inside the confined space of the capsules.

Our previous studies in the field concern the use of the supramolecular "Pyrene box", **PTSG** self-assembled from available commercial materials: 1,3,5,8 pyrene-tetrasulfonate anions, **PTS^{4-}** and guanidinium cations, **G^{+}** to encapsulate flexible guest alkanes or amino-acids.[4] The guests are anchored *via* H-bonding and electrostatic interactions of their ammonium/carboxylate terminal groups with the sulfonates of **PTS^{4-}** and guanidinium **G^{+}** platforms. Our conclusions based on NMR spectroscopy experiments in solution and single crystal X-ray diffraction experiments in solid state indicate that alkanes chains under compression are stabilized within "Pyrene box" by combined H-bonding, electrostatic interactions and van der Waals contacts with "Pyrene-Box" components. Moreover, subsequent work showed that by changing the shape and size of the encapsulating space, one can control the conformation of and several conformations of the alkane guest, adaptively folding within confined space of the cages.[5]



Scheme1. "Pyrene box" cages are self-assembled from 1,3,5,8 pyrene-tetrasulfonate anions, **PTS^{4-}** and the guanidinium, **G^{+},** 1,8-diammonium-3,6-dioxa-octane (**1**), 1,11-diammonium-3,6,9-trioxa-undecane (**2**) and 1,12-diammonium-4,9-dioxa-dodecane (**3**) cations.

With a long-term view aimed at the control and understanding of biomolecular functions under confinement, we continued our investigations on the encapsulation of other active molecules of biological significance within supramolecular "Pyrene box" in water. Among water-soluble active candidates, polyethyleneglycol (PEG) molecules are interesting examples as they are extensively used as interfaces in various PEGylation processes, resulting in the formation of well-defined bioconjugates.[6] Relevant studies on the encapsulation of oligo(ethylene glycol)s have been previously

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published by Ripmeester et al.[7a] and Rebek Jr. et al.[7b]

Herein, small/medium length 1,ω-diammonium (oligo) ethyleneglycol OEG compounds are encapsulated inside the "Pyrene box" cages in aqueous solutions and in the solid state. Their packing of longer confined OEG molecules is directed via intramolecular H-bonding which is responsible for their folding. It is squeezing longer springs inside a fixed chemical space of the "Pyrene box" host and is directing their confining *via* non-covalent interactions inside the cages.

Results and Discussion

Strategy: We know that relative spatial disposition of the **PTS**$^{4-}$ platforms is determining the precise length of the "Pyrene box", defined by terminal sulfonate moieties on **PTS**$^{4-}$ molecules. This geometrical behaviour is related to the presence/absence of the hydrated guanidinium or amino-guanidinium cations which bind the two **PTS**$^{4-}$ platforms together.

Three commercially available derivatives were chosen and used as dihydrochlorides: 1,8-diammonium-3,6-dioxa-octane (**1**), 1,11-diammonium-3,6,9-trioxa-undecane (**2**) and 1,12-diammonium-4,9-dioxa-dodecane (**3**). Compared to the known literature examples, the lengths of **1** correspond to the 1,8-diammonium-octane molecule, while **2** and **3** 1,11-diammonium-undecane and respectively 1,12-diammonium- dodecane molecules, previously encapsulated and fully characterized within PTS-OEG complexes. This is not simply a matter of size of the used OEG guest molecules, but it also brings important conformational changes of the OEG chains itself, due to their ability to act simultaneously both as H-bond acceptors via the oxygen atoms present in their backbones and as H-bond donors through their ammonium groups.

^{1}H-NMR spectroscopy studies: The host-guest proxy interactions between OEG guests **1-3** and **PTS**$^{4-}$ can be detected in aqueous solution. In order to ascertain the interaction between the encapsulated OEG guests and **PTSG** host components, several mixtures corresponding to the binary **PTS**$^{4-}$: **1-3** and to ternary **PTS**$^{4-}$: **G**$^+$: **1-3** mixtures, corresponding to variable molar ratios were measured in aqueous solution using ^{1}H-NMR spectroscopy.

The shielding of the protons of OEG-ylated backbones of **1-3** indicates their self-assembling with **PTSG** platforms in aqueous solution.

As a general rule and in accordance to literature data,[4,5] the shielding is progressively higher for the protons in the middle of the OEG chains, being positioned further inside the pyrene box cavity. The most deshielded protons in the case of 1,8-diammonium-3,6-dioxa-octane, **1** are H_a, vicinal to amino groups, with a chemical shift of 3.69 ppm. In the presence of **PTS**$^{4-}$ in a 1:0:2 molar ratio, the shift downfield to 3.44 ppm. Successive aliquots of **G**$^+$ decrease the shielding to 3.42 ppm for the 1:2:1 molar ratio and 3.47 ppm for 1:4:1 molar ratio and 3.53 ppm for the 1:10:1 molar ratio, respectively. The same trend is observed to the other protons, H_b and H_d. Their chemical shifts are 3.64 ppm and 3.13 ppm for 0:0:1 molar ratio, 3.30 ppm and 2.98 ppm for the 1:0:2 molar ratio, 3.22 ppm and 2.96 ppm for 1:2:1 and 1:4:1 molar ratio and 3.20 ppm and 2.94 ppm for the 1:10:1 molar ratio (Figure 1a)

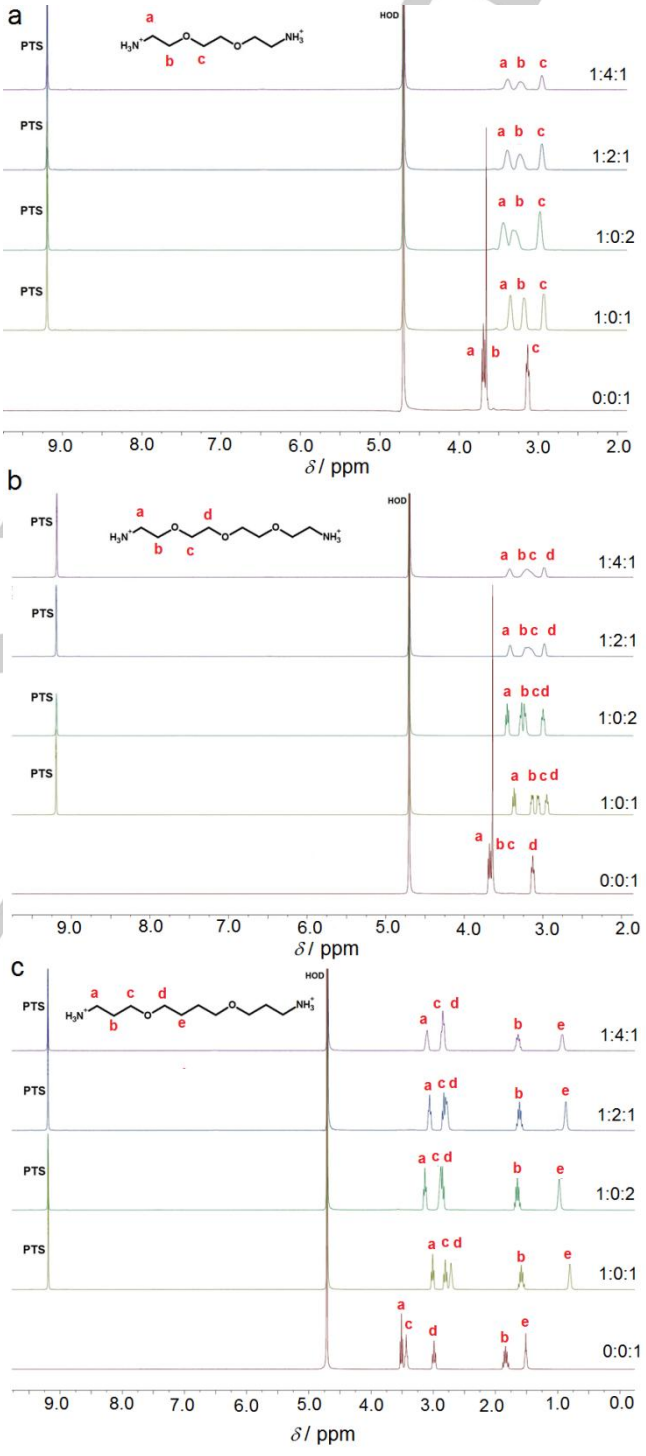


Figure 1. ^{1}H-NMR spectra in D_2O at 25 °C for mixtures of a) **PTS**$^{4-}$: **G**$^+$: **1**, b) **PTS**$^{4-}$: **G**$^+$: **2** and c) **PTS**$^{4-}$: **G**$^+$: **3**, at different molar ratios .

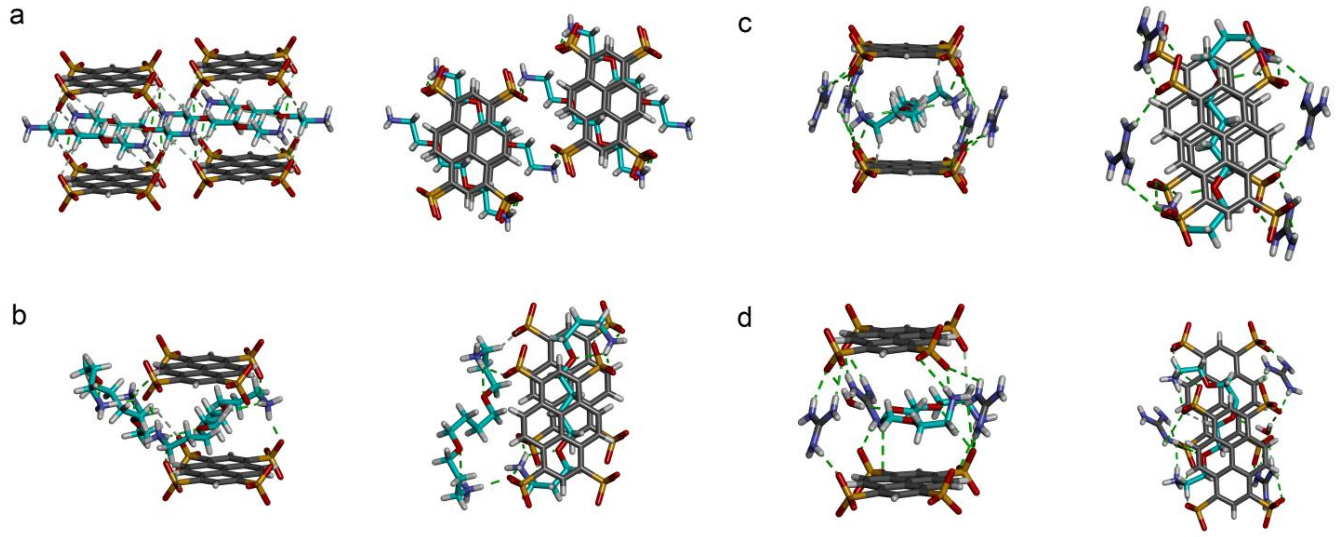


Figure 2. X-ray structures of a) **PTS(1)$_2$**, b) **PTS(3)$_2$(H$_2$O)$_3$,** c) **PTS(Gua)$_2$3** and d) **PTS(Gua)$_2$(H$_2$O)(2)** systems: Side (left) and top (right) views of the inclusion complexes highlighting the H-bonded matrices.

1,11-diammonium-3,6,9-trioxa-undecane **2,** has distinct signals, with the protons H_a appearing at 3.68 ppm, H_d at 3.13 ppm and H_b and H_c at 3.64 ppm. The presence of **PTS^{4-}** leads to a shielding of H_a to 3.46 ppm and H_d to 3.00 ppm. Interestingly, protons H_b and H_c are shielded differently, to 3.29 and 3.22 ppm, respectively. This difference between the signals is progressively decreasing with successive aliquots of **G$^+$**, from 3.26 ppm and 3.20 ppm for the 1:2:1 molar ratio, to 3.39 ppm and 3.38 ppm for the 1:10:1 molar ratio. The presence of **G$^+$** also decreases the shielding of the other protons. (Figure 1b)

The largest guest employed in the current study, 1,12-diammonium-4,9-dioxa-dodecane **3,** has five distinct signals in its ^{1}H-NMR spectrum at 3.51 ppm (H_a), 3.43 ppm (H_c), 2.99 ppm (H_d), 1.84 ppm (H_b) and 1.51 ppm (H_e), respectively. In a 1:0:2 molar ratio with the other components, most of the protons are shielded by about 0.5 ppm, with the smallest shift observed for H_d at 2.85 ppm and the highest for H_c at 2.88 ppm and He at 0.98 ppm. The presence of guanidinium produces relaxation of the system and the overall shielding is decreased. The largest shielding effects were observed for the 1:2:1 ratio, with H_a appearing at 3.06 ppm, H_b at 1.61 ppm, H_c at 2.78 ppm, H_d at 2.83 ppm and H_e at 0.87 ppm, respectively. However, increasing the **G$^+$** content has the same effect as in the previous two examples, a progressive decrease in the shielding of the protons (Figure 1c).

Several conclusions can be drawn from the ^{1}H-NMR data. First, it is clear that ion-pairing always occurs between **PTS^{4-}** platforms and the 1,ω-diammonium-polyethyleneglycol guests, resulting in a complex changes in both NMR patterns of both host and guest components. In all three cases, successive aliquots of **G$^+$** cations lead to a slight incremental decrease in the shielding of the protons. This is consistent with the interaction of the guest molecules **1**-**3** with the **PTS^{4-}** platforms within the formation of oligomers system in aqueous solution.

X-ray single crystal structures: The previous ^{1}H-NMR results reminiscent with the encapsulation of the guests in aqueous solution, are backed up by four single crystal X-ray structures, two corresponding to the binary mixtures **PTS(1)$_2$** and **PTS(3)$_2$(H$_2$O)$_3$**, and two to "Pyrene box" **PTS(Gua)$_2$(H$_2$O)(2)** and **PTS(Gua)$_2$(3)**, respectively. Unfortunately, suitable crystals of **PTS(2)$_2$** and **PTS(Gua)$_2$(1)** could not be obtained.

Overall, these structures show interesting encapsulation behaviours and the compression of the larger OEG chains of **2** and **3**, mainly driven by strong intermolecular H-bonding and assisted by simultaneous binding of their terminal nitrogen atoms to the sulfonate oxygens of two opposite **PTS^{4-}** platforms, $d_{H\text{-}O}$ = 2.10-2.14 Å (Figure 2).

In the **PTS(1)$_2$** structure the two encapsulated guest molecules of 1,8-diammonium-3,6-dioxa-octane, **1** are equivalent and adopt a linear arrangement with a N_1 – N_8 distance of $d_{N1\text{-}N8}$ = 10.71 Å. The chain of the guest is tethered to three distinct **PTS^{4-}** platforms at each end *via* hydrogen bonds (Figure 2a). The overall packing consists of columns of alternating molecules of **PTS^{4-}** and **1** which are offset in order to facilitate hydrogen bonding.

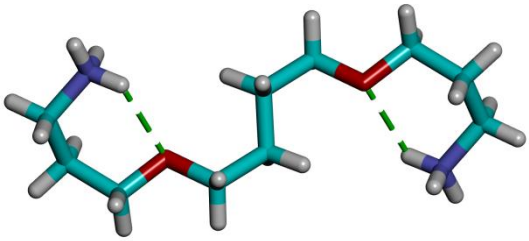
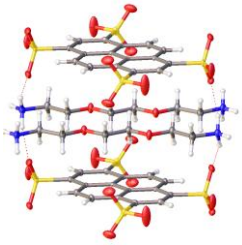
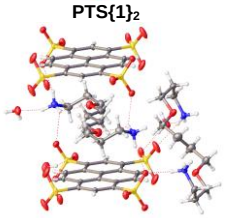
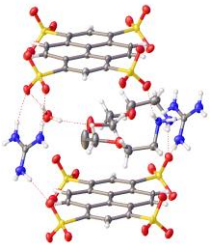
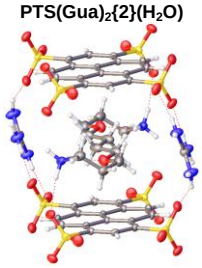


Figure 3. X-ray structures of the S"-shaped conformation of 1,12-diammonium-4,9-dioxa-dodecane **3,** stabilized *via* internal hydrogen bonding ($d_{O\text{-}H}$= 2.40 Å) between the ammonium group and the oxygen atoms in the 4 and 9 positions

Table 1. Overview of the structures obtained together with relevant lengths.

Structure	$d_{PTS-PTS}$ (Å)[a]	$d_{N1-N\omega}$ (Å)[b]	d_{N-O} (Å)[c]	$d_{Gua-Gua}$ (Å)[d]
 **PTS{1}$_2$**	7.29	10.71	-	-
 **PTS{3}$_2$(H$_2$O)$_3$**	7.36	8.91, 10.21	-	-
 **PTS(Gua)$_2${2}(H$_2$O)**	7.66	7.90	2.99	8.07
 **PTS(Gua)$_2${3}**	7.48	9.94	2.69	9.02

[a] $d_{PTS-PTS}$= centroid-centroid distance between the PTS aromatic planes

[b] $d_{N1-N\omega}$ = distance between the terminal N_1 and N_ω nitrogen atoms of OEG guests **1**-**3**

[c] d_{N-O} = distance between the the guanidinium nitrogen and sulfonate O of the PTS platforms

[d] $d_{Gua-Gua}$= C-C distance between the guanidinium molecular planes

The longest molecule in used in this study, 1,12-diammonium-4,9-dioxa-dodecane **3,** is adaptively shortened during encapsulation, adopting a "S"-shaped conformation, stabilized *via* internal hydrogen-bonding between the ammonium group and the oxygen atoms in the 4 and 9 positions and those belonging to the sulfonates of the **PTS^{4-}** platforms (Figure 3).

This is proof of the adaptability of the supramolecular system and of the stability of the intramolecular hydrogen bonds of the OEG chain, as the environment of the two molecules is quite different. One molecule is sandwiched between **PTS^{4-}** anions with some short contacts between the H-atoms of the sandwiched chain and the aromatic units on top and bottom, while the second one occupies the space between the stacked columns.

Although belonging to "Pyrene box" class of structures, **PTS(Gua)$_2$(3) (**Figure 2c) and **PTS(Gua)$_2$(H$_2$O)(2)** (Figure 2d) differ significantly from the known literature examples for alkane type congeners 1,11-diammonium-undecane and 1,12-diammonium-dodecane.[4] The S-shaped conformation of **3** is preserved in the **PTS(Gua)$_2$(3)** structure, with a $N_1 - N_\omega$ distance $d_{N1-N\omega}$ = 9.94 Å between the terminal nitrogen atoms of the guest **3**. The S-shaped conformation is stabilized *via* internal H-bonding: the ammonium groups anchored to the oxygen atoms of the sulfonates of the top and bottom **PTS^{4-}** platforms, form supplementary internal hydrogen bonds with the oxygen atoms of the OEG chains in positions 4 and 9 (Figure 2c). Two **G$^+$** cations act as the sides of the "Pyrene box" and are hydrogen bonded to the opposing **PTS^{4-}** anions, the distance between guanidinium nitrogen and sulfonate oxygen or the **PTS^{4-}** is d_{N-O} =2.69 Å. No water molecules are included in the structure, compared to literature examples.[4,5]

The individual "pyrene boxes" are not arranged in the usual columnar fashion and in the crystal packing have a zig-zag arrangement.

The positions of the oxygen atoms in 1,11-diammonium-3,6,9-trioxa-undecane **2,** are not favourable for the formation of an intramolecular hydrogen bond, as in the case of **3**. The encapsulated molecule of **2** adopts a highly unsymmetrical conformation in order to fit inside the "Pyrene box" (Figure 2d). Due to this unusual folding, the terminal ammonium groups($d_{N-N\omega}$ = 7.90 Å), no longer bind together the top and bottom of the **PTS^{4-}** platforms, but are each hydrogen bonded to the three distinct **PTS^{4-}** platforms from the top, and the other from bottom, respectively. In this structure both **G$^+$** cations are on the same side of the Pyrene box, the other side being empty. The non-symmetrical conformation of **2** is stabilized by two intermolecular hydrogen bonds. The first is provided by the water molecule present in the structure and H-bonded to sulfonate of the **PTS^{4-}**, d_{o-o} = 2.82 Å, and the second by a **G$^+$** cation from an adjacent pyrene box, d_{N-O} =2.99 Å. The overall packing of **PTS(Gua)$_2$(H$_2$O)(2)** consists of alternating layers of **PTS^{4-}** anions and **2** and **G$^+$** cations, this being the first such example of the Pyrene Box structures.

Several features are common in all structures presented before, such as all of them are packing in the alternating stacking of **PTS^{4-}** platforms and 1,ω-diammonium-polyethylene glycol guest molecules. The distance between two successive **PTS^{4-}** platforms is higher in the case of the "Pyrene box" structures including the **G$^+$** cations, compared to that in the binary mixtures in the absence of **G$^+$** cations (Table 1). This is consistent with the NMR spectroscopy results, where a lower shielding was interpreted as an increase of the internal volume. As expected, this distance is larger in the case of **PTS(3)$_2$** than in the case of **PTS(1)$_2$**, with the distance between the pyrene planes of $d_{PTS-PTS}$ = 7.36 Å and $d_{PTS-PTS}$ = 7.29 Å, respectively. The order is inversed in the case of the "Pyrene box"structures, with $d_{PTS-PTS}$ = 7.66 Å in the case of **PTS(Gua)$_2$(H$_2$O)(2)** and $d_{PTS-PTS}$ = 7.48 Å in the case of **PTS(Gua)$_2$3.** These distances

are probably not correlated with the chain length but the presence of H-bondes water molecules seems to influence the relative position of the pyrene units with respect to each other.

Conclusions

In this study it was shown that the 'Pyrene box' cages can encapsulate not only hydrophobic alkane chains, but also hydrophilic linear OEG-like compounds. To this extent, 1,8-diammonium-3,6-dioxa-octane, **1** 1,11-diammonium-3,6,9-trioxa-undecane, **2** and 1,12-diammonium-4,9-dioxa-dodecane, **3** of different lengths and binding patterns, were tested as OEG-type guest molecules. Only the later two resulted in the guest templated self-assembly of the 'Pyrene box' that could be isolated and characterized in the solid state.

However, a strong interaction was observed in the case of the shorter 1,8-diammonium-3,6-dioxa-octane, **1**, hinting towards $\mathbf{PTS^{4-}}$: **1** supramolecular assemblies in the solid state. Inclusion of the OEG chains inside the confined space promotes a constrained conformation and very interestingly stabilized via internal H-bonds, which represents the main novelty with respect to the previously studied hydrocarbon equivalents.[4] They adaptively stabilize an S-shape conformation for 1,12-diammonium-4,9-dioxa-dodecane **3,** while 1,11- diammonium-3,6,9-trioxa-undecane **2** adopts a random conformation.

Molecular encapsulation of flexible OEG chains is an adaptive process in which constitutionally different confined conformers may be observed depending on the length and structure of the OEG molecules used. The guest molecule disorder under confinement is sufficiently low to allow a conventional structure determination by X-ray diffraction. These results generalize the concept of the adaptive chemistry encapsulation of flexible chains. It offers interesting perspectives on understanding their chemical structures of interacting guests in a small space, relevant for many biological occurrences. [8]

Experimental Section

All the compounds were purchased from Sigma-Aldrich and were used without further purification. Suitable crystals for all the structures were readily obtained in large quantities by slow evaporation from aqueous solutions stoichiometric mixtures of the components.

^{1}H NMR spectroscopy experiments were performed on an AVANCE 300 MHz Bruker spectrometer in D_2O with the use of the residual solvent peak as reference. Samples were analysed in 5 mm NMR tubes and the chemical shifts are reported in ppm. Typical ^{1}H-NMR spectra consisted of 16 scans with delay time 1 s. The FID was not processed prior to Fourier transformation. The average acquisition time of the ^{1}H NMR spectra was approximately 3 min.

^{1}H NMR titration experiments were performed by adding successive aliquots of 0.1 M guanidinium or 1,ω-diammonium-PEG dihydrochloride D_2O solutions to 0.5 mL $1{,}67\times10^{-2}$ M of 1,3,5,8-pyrenetetrasulfonate tetrasodium salt D_2O solution. The samples were left to equilibrate for 2-3 minutes at ambient temperature before each measurement.

$\mathbf{PTS\{1\}_2}$ (300 MHz, D_2O) *δ,* ppm: 9.19 (4H, s, H_{PTS}), 3.44 (8H, bs, H_a), 3.37-3.19 (8H, bs, H_b), 2.98 (8H, bs, H_c). see Fig 1 for the proton attribution.

$\mathbf{PTS\{3\}_2(H_2O)_3}$ (300 MHz, D_2O) *δ,* ppm: 9.19 (4H, s, H_{PTS}), 3.13 (8H, q, *J*= 6.0Hz, H_a), 2.85 (16H, m, H_c, H_d), 1.65 (8H, c, *J*= 6.3 Hz, H_b), 0.98 (8H, bs, H_e).

$\mathbf{PTS(Gua)_2\{2\}(H_2O)}$ (300 MHz, D_2O) *δ,* ppm: 9.19 (4H, s, H_{PTS}), 3.42 (4H, bs, H_a), 3.27-3.08 (8H, bs, H_b, H_c), 2.98 (4H, bs, H_d).

$\mathbf{PTS(Gua)_2\{3\}}$ (300 MHz, D_2O) *δ*, ppm: 9.19 (4H, s, H_{PTS}), 3.06 (4H, t, *J*= 5.8 Hz, H_a), 2.82 (8H, m, H_c, H_d), 1.61 (4H, c, *J*= 6.3 Hz, H_b), 0.87 (4H, bs, H_e).

X-ray diffraction data of the structures have been measured on a Rigaku Oxford Diffraction Gemini-S four circle diffractometer using Mo-K□ radiation (λ = 0.71073 Å) equipped with a Sapphire3 detector at 175 K at the joint X-ray scattering facility of the Pôle Balard at the University of Montpellier, France. The structures have been solved using the ab-initio charge flipping method as implemented in SUPERFLIP[9] Hydrogen atom positions were determined using Fourier differential maps in the case of **$\mathbf{PTS(1)_2}$** and the low temperature structure of **$\mathbf{PTS(Gua)_2\{2\}(H2O)}$**. Hydrogens in the case of **$\mathbf{PTS(Gua)_2\{3\}}$** were added geometrically. It should be noted that in all cases the ammonium hydrogens were found using Fourier maps. All structures were initially refined using non-linear least-squares methods as implemented in CRYSTALS[10], in which the hydrogen atoms were treated as riding on their parent atoms and with Uiso(H) constrained to in general 1.2-1.5 times Ueq(H) that of the parent atom. The positions of hydrogen atoms involved in classical hydrogen bonds were refined using geometrical restraints. The final difference Fourier maps showed in many cases residual peaks due to bonding effects, because of the in general very good resolution of the experimental data (mostly around 0.75 Å or better, except in the case of **PTS(Gua)2{2}(H2O)**, where the experimental resolution is defined according to Dauter.[11] The crystal data is summed up in Table 1S- see Supporting information. CCDC 1524141-1524144 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

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Keywords: Molecular encapsulation • H-bonding • self-assembly • molecular contraction • biomimetics

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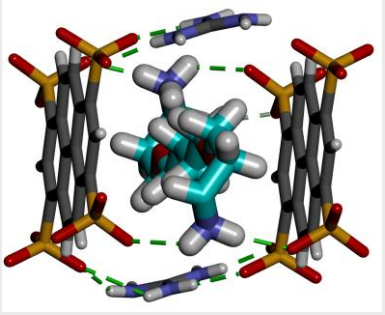
FULL PAPER

We present encapsulation and compression mechanisms of 1,ω-diammonium-polyethyleneglycols, confined within a Pyrene Box. The exact coiling behaviours, determined from atomic resolution X-ray diffraction shows intramolecular H-bonded S-shaped conformations of the OEG chains in the compressed states.



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Compression of 1,ω-diammonium-(oligo)ethyleneglycol chains within the "Pyrene box"

Key topic: molecular encapsulation