Pyrene-box capsules for adaptive encapsulation and structure determination of unstable or non-crystalline guest molecules

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"Pyrene-box" cages easily crystallize from aqueous solutions and readily encapsulate compounds of biological interest. These host–guest systems can be obtained under ambient conditions from 1,3,5,8-pyrenetetrasulfonate (PTS), guanidinium derivatives (G+) and biogenic guests bearing cationic groups. Out of the many examples of synthetic molecular capsules, Pyrene box cages are completely responding to the requirements of green chemistry: non-toxic, water soluble, cheap, commercially available compounds. The "Pyrene-Box" cages have been used for the in situ encapsulation of unstable or non-crystalline biogenic compounds, allowing the complete molecular structure determination of species that do not crystallize by themselves. The encapsulated guests have a reduced motional degrees of freedom which is obtained via their anchoring to the Pyrene box cages that allows at the same time to reduce a significant amount of disorder. In this highlight we discuss the recent developments of the encapsulation chemistry of the "Pyrene box" and the strategy behind its synthesis, together with further possible developments and the limitations of this biomimetic supramolecular cage system. The "Pyrene Box" shows great potential for future applications, ranging from fundamental studies of structure determination of unstable molecules to drug delivery vehicles.

Introduction

Molecular encapsulation is a fascinating domain as the interactions between the host molecules themselves or with the guest systems are generally different inside capsules than in the bulk solution.[1–5] The question as to how the encapsulation occurs, has been previously answered: the formation of host-depleted interiors is correlated with dominating interactional forces and favourable enthalpy/entropy changes.[6,7] Crossing the solution/capsule barrier, unexpected dynamic phenomena can be observed within an inner chemical space of the capsule, opening the door for a new emergent area of chemistry under confined conditions.

For example, the ability to encapsulate guests of biological interest offer possibilities to explore their behaviours very close to confined biological conditions.[2] The classical 'lock and key' analogy can be applied to the vast majority of capsule systems, where one or more guest molecules, *the key*, is encapsulated inside a discrete chemical space defined by a host molecule or a supramolecular assembly, *the lock*. However, not every key fits any lock and, to this extent, suitable hosts have been developed for almost every type of small molecular guest. These can be divided into two main categories: molecular or self-assembled supramolecular hosts. Molecular hosts are generally large organic molecules possessing accessible voids with an internal surface complementary to the guest binding: crown ethers,[8] cryptands,[9] cavitands,[10] cyclodextrins,[11] cucurbiturils[12] *etc.* The self-assembly of two or more molecular components into supramolecular capsules offer the advantages of collective and adaptive encapsulation of specific guests. More often than not, the latter is required to template the self-assembly process and to stabilize the host internal cavity. The main advantage of self-assembled capsules is their high availability, as they are usually obtained in only a few, if any, synthetic steps.[13] The drawbacks include in some cases the need of a templating guest, a low selectivity between guests, and their relatively low stability as compared to molecular hosts. In spite of these, the field has been steadily growing over the recent years, with

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notable examples including the Ward's organo-sulfonate guanidinium structures,[14] Rebek's 'tennis balls',[15] Fujita's crystalline sponges[16] *etc.*

Of practical interest, the host molecules need to be fixed within the cavity of the cage, thus practically limiting their molecular motions under confined conditions, but this is only possible if suitable anchoring functionalities are present, *e.g.* at the internal capsule walls.[5] If a crystal may be obtained in a solution containing a compound of interest, the compound is integrated into the cavity and the molecules could in principle self-assemble themselves with a variable probability depending on its own and capsule structural behaviours, in a fixed orientation. If this is then analysed by X-ray crystallography, the structure of the compound can be elucidated.

In this context, we developed the Pyrene box supramolecular capsules for biogenic guests encapsulation, from readily available cheap, benign and commercially available materials, containing the 1,3,5,8-pyrenetetrasulfonate anions, **PTS**, the guanidinium G^+ cations. Although this system was initially developed for the encapsulation and the study of the compression of long-chain ammonium-alkanes in aqueous solution, further studies showed the system to possess great flexibility towards the biogenic encapsulated guests and the final structure of the capsule. Herein we discuss the strategy behind the design of the Pyrene box supramolecular capsules, the recent developments, as well as the limitations of this system. Further possible avenues of development are also briefly highlighted.

General design and overview

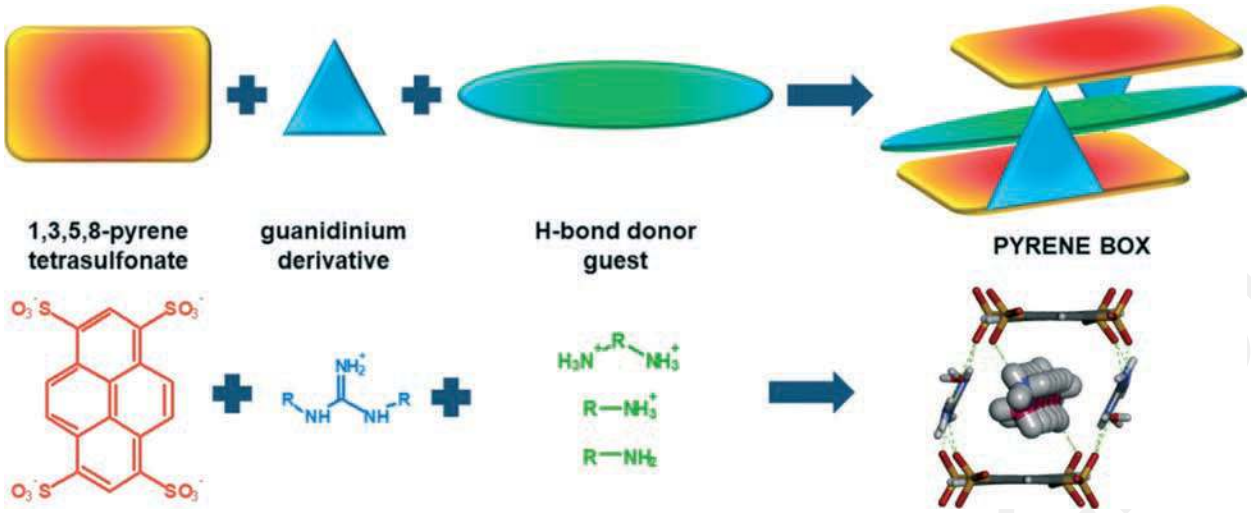
The inspiration for the Pyrene box came from similar H-bonded guanidinium–organosulfonate systems developed by Ward *et al.*[14] In this case, the geometric and chemical complementarity between a G^+ cation and a organosulfonate anion leads to the formation of a highly robust hydrogen bond networks, comprised of $R_2^2(8)$ rings, merged into larger $R_6^6(12)$. In the voids, guests of a suitable length are encapsulated, depending on the size and shape of the organosulfonate pillar. As such, several guests have been encapsulated, starting from small molecules, such as acetonitrile, to larger aromatic ones. In particular, 1,5- or 2,6-naphthalene disulfonates and calix[4]arene tetrasulfonate caught our attention and led directly to the development of the Pyrene box. The first two form pillared structures, with the two sulfonates involved in opposite H-bonded networks and the guest molecules between the pillars.[14]

Calix[4]arene tetrasulfonate tetraguanidinium salt has proven to be a very useful supramolecular system, being able not only to encapsulate solvent molecules,[17a] but also acting as a molecular flask by stabilizing unstable molecules.[17b] This system has been used for the photochemical formation of highly unstable chemical species like 4,6-dimethyl-Dewar-β-lactone and 1,3-dimethyl-cyclobutadiene, that are sufficiently stable under the confined conditions at 175 K to allow a conventional structure determination by X-ray diffraction.[5a] It is important to note that during the irradiation the guanidinium–calixarene–sulfonate matrix remains unchanged, while the structure of the confined phoactive 4,6-dimethyl-α-pyrone host has been modified along the successive series of irradiations. Considering the electron density map which can be connected in a reasonable manner, we may argue that the crystal structure is not really associated with a local disorder but with the superpositions of encapsulated 4,6-dimethyl-Dewar-β-lactone and 1,3-dimethyl-cyclobutadiene structures presenting an amazing similarity of the bond lengths and angles as those predicted by theory. Due to a cage and H-bonding effects the CO_2 fragment remains close to CBD and its elimination results in the destruction of the crystal, unfortunately not useful for a total transformation of 4,6-dimethyl-Dewar-β-lactone in 1,3-dimethyl-cyclobutadiene.[5b]

Taking into account these examples, an ideal organosulfonate for constructing a discrete supramolecular capsule should have at least four sulfonate groups in order to prevent channel formation, while having a planar rigid structure for conformational stability. 1,3,5,8-Pyrenetetrasulfonate is the ideal candidate which should satisfy all these conditions, while also being cheap, non-toxic and commercially available as a fluorescent marker for water reservoirs.[18]

The "Pyrene box" is comprised of two 1,3,5,8-pyrenetetrasulfonate anionic platforms, which for the top and bottom of the box and two, G^+ cations which act as the side platforms. The remaining two sides of the 'box' are empty in order to allow for a cationic guest, a H-bond donor, to be tethered to one of the sulfonate groups belonging to the top and/or bottom **PTS** platform (Scheme 1).

The supramolecular self-assembly process of the Pyrene box formation is rather flexible, the structure being able to incorporate water molecules or use different un/symmetrical guanidinium derivatives into its H-bond network in order to accommodate larger guests. The facile synthesis under ambient conditions, of the "Pyrene box" systems implies mixing all the



Scheme 1 Pyrene box self-assembly from 1,3,5,8-pyrenetetrasulfonate (**PTS**), guanidinium cations (G^+) and biogenic guests bearing cationic ammonium groups.

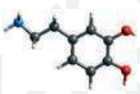
components as their corresponding salts in water. This not only has the advantage of increasing the solubility of all of the components, but also helps in the self-assembly process, as sodium or other counterions can participate if necessary in the structure. By using this strategy, all possible combinations of the host–guest components and **PTS** and **G** counterions are stoichiometrically possible.

Encapsulated guests

The interplay between the surfaces of the hydrophobic flat pyrene plateau and those of the hydrophilic polar sulfonate moieties dictates the type and size of the guest. As such, the Pyrene box system has a preference for amphiphilic molecules possessing a hydrophobic core central component and one or two polar, hydrophilic ends. An overview of all the guests studied so far is presented is Table 1 and every series will be discussed in detail in the order of increasing chemical complexity of each type of guest. The known examples of molecules successfully encapsulated in the system fall into two main categories: flexible ammonium terminated aliphatic or ethylene glycol chains and ammonium aromatic derivatives, respectively.

The Pyrene box was initially developed to encapsulate *n*-alkanes and, by encapsulating progressively larger molecules, to stabilize unstable conformations under chain compression. In the series starting from 1,10-diammonium decane (V = 297.83 Å^3) to 1,11-diammonium undecane (V = 312.21 Å^3) and 1,12-diammonium dodecane (V = 318.23 Å^3), the structure of the Pyrene box remains almost isomorphic, with only a slight increase in unit cell volume (953.907 Å^3 to 983.188 Å^3 and 976.919 Å^3).[19] In spite of the larger volume of 1,12-diammonium dodecane compared to that of the 1,11-undecane derivative, the volume of its unit cell is smaller due to the compressed conformation adopted by the first. These *gauche* conformations are stabilized in the discrete space of the box through weak attractive dihydrogen contacts. This, combined with the 'steric ambiguity' between the elongated 1,10-diammonium decane and the compressed 1,12-diammonium dodecane derivatives results in the formation of a mixed structure containing both molecules in a 2 : 1 molar ratio.[16] Two water molecules are also included in the H-bond network. Smaller molecules, such as 1,9-diammonium nonane, result in the formation of precipitates. One way of increasing the chemical complexity of the guest is by formally substituting the carbon atoms in the alkane chains with oxygen, in polyethyleneglycol PEG ammonium terminated compounds. In this case, the long chains lose the ability to form dihydrogen contacts, but can adopt compressed conformations. Three guests were studied: 1,8-di ammonium-3,6-dioxa-octane, 1,11-diammonium-3,6,9-trioxa-undecane and 1,12-diammonium-4,9-dioxadodecane.[20] The first molecule proved to be a too small guest, while the larger two could be encapsulated into Pyrene box. Compared to the previously *n*-alkane guests, in which series the structures are isomorphic and the compression of the chains proceeds through a predictable increase in the number of *gauche* conformations, the PEG–guests adopt different and unusual arrangements. 1,11-diammonium-3,6,9-trioxa-undecane is compressed to an unsymmetrical conformation as its chain is not stabilized though any intramolecular interaction. This asymmetry is transferred to the Pyrene box, with the two G^+ cations being non-equivalent and only one water molecule included in the structure. On the other hand, the longer, but symmetrical, 1,12-diammonium-4,9-dodecane forms an almost typical Pyrene box assembly, with two equivalent G^+ cations on each side of the box. Interestingly, under compression this chain adopts an S-shaped conformation, stabilized by two internal H-bonds between the terminal ammonium groups and the chain oxygen atoms. The overall crystalline structure is puckered compared to the alkane guests examples and no water molecules are included in the structure (Fig. 1a).

Table 1 Overview of the guest molecules confined so far inside the Pyrene box. Guest Hirschfield volumes were calculated using Crystal Explorer and are the values discussed in the text. The packing coefficient (%) was calculated using Olex2 using a 1.2 Å probe on a 0.1 Å grid

Pyrene box	Guest	Guest Hirschfield volume (Å^3)	Packing coefficient (V_{guest}/V_{cavity})
PTSG{C10}G$_2$(H$_2$O)$_2$	 1,10-Diammonium decane (C10)	297.83	51.9%
PTSG{C11}G$_2$(H$_2$>O)$_2$	 1,11-Diammonium undecane (C11)	312.21	50.1%
PTSG{C12}G$_2$(H$_2$O)$_2$	 1,12-Diammonium dodecane (C12)	318.23	62.3%
PTSG{C10/C12}G$_2$(H$_2$O)$_2$	1,10-Diammonium decane (67%)/1,12-diammonium dodecane (33%)	—	63.5%
PTSG{C11COOH}G$_2$(H$_2$O)$_3$	 11-Ammonium undecanoic acid (C11COOH)	307.31	47.9%
PTSG{C6COOH}G$_2$(H$_2$O)$_2$	 6-Ammonium hexanoic acid (C6COOH)	170.68	31.0%
PTSG{C11O3}G$_3$(H$_2$O)	 1,11-Diammonium-3,6,9-trioxa-undecane (C11O3)	269.98	51.4%
PTSG{C12O2}G$_2$	 1,12-Diammonium-4,9-dioxa-dodecane (C12O2)	323.61	46.5%
PTSG{HISH$^+$}G$_3$(H$_2$O)$_2$	 Protonated histamine (HISH$^+$)	143.84	55.8%
PTSG{SERH$^+$}G$_3$(H$_2$O)$_4$	 Protonated serotonine (SERH$^+$)	218.01	58.2%
PTSG{DOPH$^+$}G$_3$(H$_2$O)$_6$	 Protonated dopamine (DOPH$^+$)	197.31	53.9%
PTSG{NP}G$_4$(H$_2$O)$_2$	 *p*-Nitrophenol (NP)	145.55	62.8%

Another way of increasing the chemical complexity of the long-chain guests is to vary the terminal groups, while taking into account the need of having a H-bond donor as a tether to the **PTS** molecules. Since it is desirable to have tethering points at each end of the chain, preferably at least one ammonium groups in order to promote charge assisted hydrogen bonding, 6-ammonium-hexanoic acid and 11-ammonium-undecanoic acid were tested as guests. In spite of it being a weak H-bond donor, the carboxyl group can still contribute to the H-bond network and stabilizes the Pyrene box.[21]

This is probably due to the small size of the guest molecule, rather than to the different chemical structure. In this case, the protonated amino acid chains are arranged in infinite columns in a head to tail manner sandwiched between **PTS** platforms. For each **PTS** molecule two protonated amino acid function as guests. Guanidinium cations act as binders

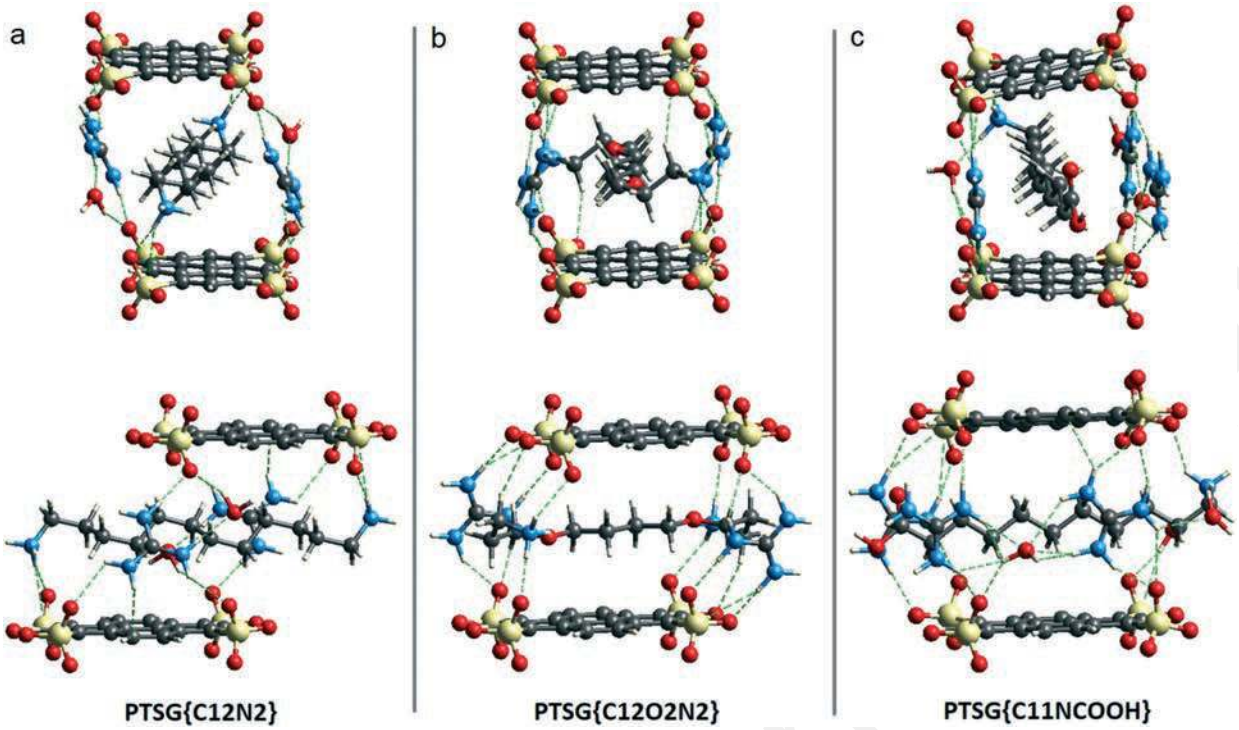


Fig. 1 Comparison between three different Pyrene boxes with three guests of very similar lengths: a) 1,12-diammonium dodecane, inside the structure **PTSG{C12N2}** b), 1,12-diammonium-4,9-dioxo dodecane, inside the structure **PTSG{C12O2N2}** and c) 11-ammonium undecanoic acid, inside the structure **PTSG{C11NCOOH}**, respectively. The shape and size of the Pyrene box adapts to the chemical and steric requirements of each individual guest.

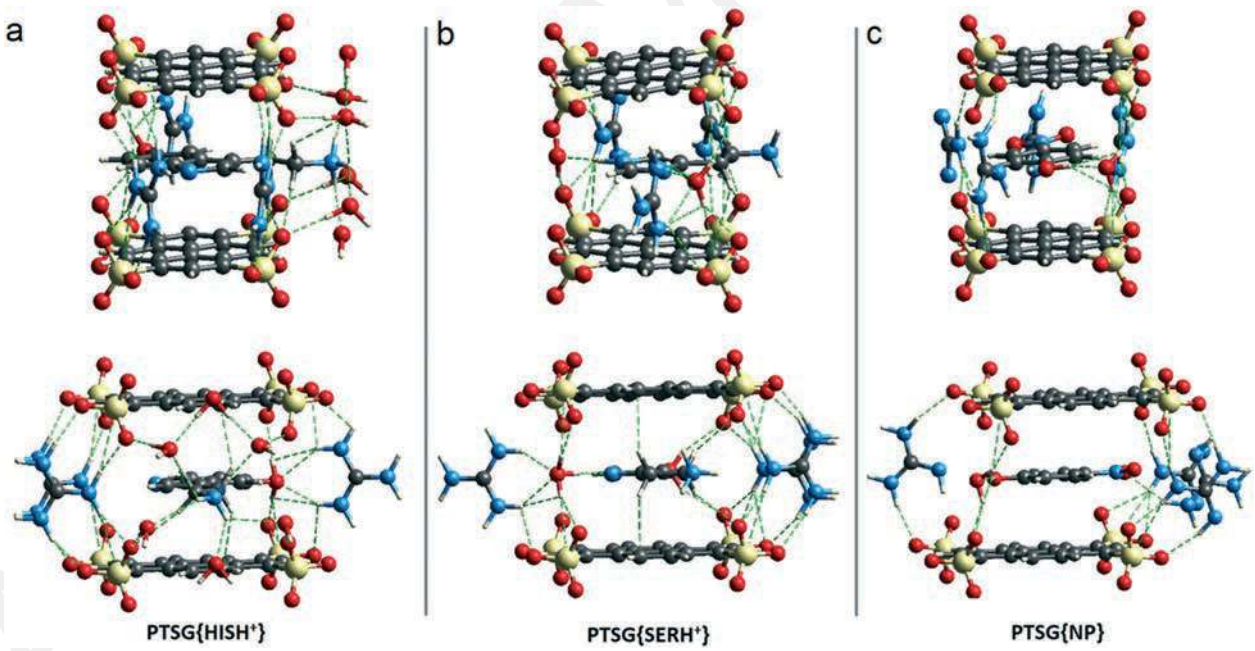


Fig. 2 Comparison between the Pyrene box structures, binding aromatic guests: a) protonated histamine **PTSG{HISH$^+$}** b), protonated serotonin **PTSG{SERH$^+$}** and c) *p*-nitrophenol **PTSG{NP}**. In the first two cases, the guest is oriented width-wise to the PTS molecules, while the smaller, uncharged nitrophenol is oriented along the box length.

between adjacent columnar assemblies and also as tether for the carboxylic groups.

The ammonium group is connected directly to sulfonates of different **PTS** platforms, while the carboxyl group is indirectly hydrogen bonded through a G^+ cation and two water molecules. By using the longer 11-ammonium undecanoic acid, whose chain length is comparable to that of 1,12-diammonium dodecane or 1,12-diammonium-4,9-dioxa-

dodecane, an at first sight Pyrene box structure is obtained (Fig. 1b and c). On closer inspection, several differences between this and the classical structure are visible. In order to balance the charges, an additional G^+ cation is encapsulated into the structure. At one end the guest molecule is bound through the ammonium group to PTS platforms in the expected fashion. The other end of the chain, containing the carboxylic group, protrudes outside of the Pyrene box and is indirectly connected through G^+ and water molecules to the Pyrene box.

The second class of possible guests consists of biogenic amine derivatives. To date, only four structures are described in the literature.[22] These correspond to protonated histamine, dopamine and serotonin, as well as unprotonated/protonated serotonin mixed structure.[20] Histamine, dopamine and serotonin are the smallest guests encapsulated into the Pyrene box system, with a volumes of only ~140 $Å^3$, ~197 $Å^3$ and ~218 $Å^3$, respectively. All three structures share similar features, but are not isomorphic. For example, three G^+ cations for each guest molecule are included in the H-bond network of each of the structures and the guests have the same relative orientation compared to the **PTS** molecules. The number of water molecules included in the structure is however different, with two water molecules in the histamine structure, six for dopamine and four for serotonin, respectively. The overall H-bonded network of the Pyrene box adapts to compensate for the small volume of the guests and is quite similar to that of **PTSG{C6NCOOH}**. Interestingly, in all three cases the guest molecules are arranged width-wise to the **PTS** platforms into infinite columnar assemblies. These in turn are bound together by the G^+ cations. The structures are reminiscent of the pillared architectures described by Ward, with continuous parallel channels sandwiched between highly puckered guanidinium-sulfonate H-bond networks.[14]

Another very interesting aspect is the manner in which these biogenic amines are H-bonded to the Pyrene box structures (Fig. 2). In neither of the three cases discussed above the guest molecule is H-bonded directly to the top or bottom PTS platforms. Only in the case of **PTSG{HIS}** are the ammonium groups from the histamine moiety directly H-bonded to sulfonates from different boxes. In the other two examples, **PTSG{DOPH$^+$}** and **PTSG{SER}**, the guest dopamine or serotonin are only hydrogen bonded to water molecules, without a single charge assisted hydrogen bond to strengthen the encapsulation process. A direct consequence of this is the unusually high number of water molecules included in the structure, which mediate the hydrogen bonding between the guest and host.

An interesting example is the mixed structure **PTSG{SER/SER$^+$}**, in which both a protonated and an unprotonated serotonin molecules are present in a 1 : 1 molar ratio. In order to have charge balance, for every two PTS anions, seven G^+ cations are included in the crystal structure together with a charged $SERH^+$ and an uncharged SER. Both serotonin molecules are encapsulated into Pyrene box and, surprisingly, adopt relatively similar conformations. In both cases, the hydroxyl group contributes to the binding of the guest through an H-bond with one of the sulfonate groups. The flexible ethylammonium and ethylamine residues adopt different conformations, with the protonated one in the same plane as the indole ring. The unprotonated one is out of planed and rotated in order to be able to hydrogen bond to one of the sulfonates.

The guanidinium cations act both as a Pyrene box component and also link these discrete assemblies through a cationic layer. The only example to be published in a next paper so far of a completely unprotonated guest being encapsulated inside a Pyrene box structure, is that of *p*-nitrophenol. This is a very particular case, with 4 G^+ cations included in the structure for each **PTS** and guest molecule. The orientation of the guest inside the capsule is more reminiscent of that of long chain molecules, rather than the ones bearing an aromatic residue.

Salt structures of PTS anion and cationic ammonium or guanidinium guests

The structure comprising only of **PTS** and the cationic guest molecules were denoted here as 'salt' structures, and in some cases, were also isolated and characterized. It should be noted that such structures are fewer in number than the Pyrene box type assemblies, probably due to the more restrictive steric requirements in the absence of guanidinium.

From list of guests presented in Table 1, only the following were could be obtained in their corresponding salt structure: 1,10-diammonium decane, 1,12-diammoniumdodecane, 1,12-diammonium-4,9-dioxadodecane and 1,8-diammonium-3,6-dioxaoctane (Fig. 3). Interestingly, when attempting to obtain the Pyrene box structures of 6-ammonium hexanoic acid, 11-ammonium undecanoic acid with aminoguanidinium, the carboxylic groups reacted with the free amino group, resulting the corresponding amides.[21] Considering that the guanidinium group is now part of the guest, the structures obtained can be considered 'salt' structures.

Guanidinium is not the only component which can act as a Pyrene box component, but also its derivatives. In the case of 1,12-diammonium dodecane as guest, a series of three structures was obtained, corresponding to guanidinium, aminoguanidinium and diaminoguanidinium as Pyrene box sides, respectively.[23] As expected, such a major change in the number of H-bond donors and acceptors results in significantly different supramolecular architectures. While in the case of the **PTSG{C12N2}** the structure is very well defined and symmetrical, **PTSGN{C12N2}** has a much larger internal cavity, encapsulating two 1,12-diammonium dodecane molecules (Fig. 4). By using diaminoguanidinium, the Pyrene box cavity returns back to normal dimensions, with only one guest encapsulated inside, albeit with an increase in

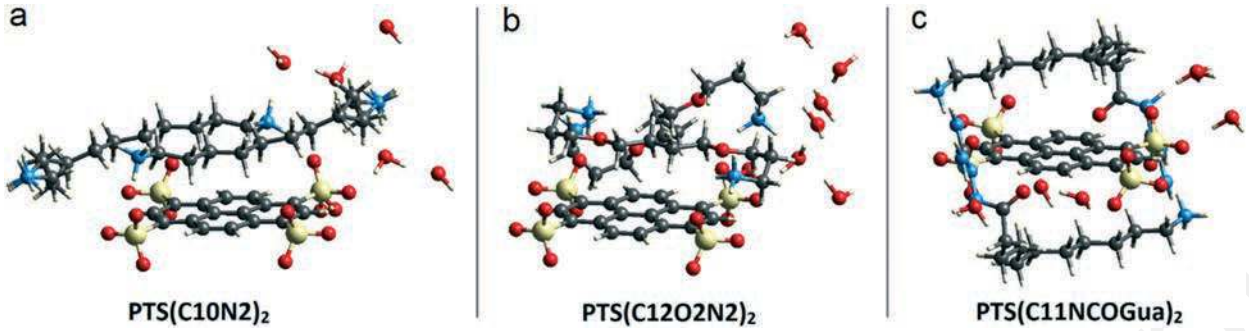


Fig. 3 Representative salt structures, corresponding to a) 1,10-diammonium decane, b) 1,12-diammonium-4,9-dioxadodecane and c) 11-ammonium undecanoic acid aminoguanidinium amide counter cationic guests.

disorder. Although no linear correlation between the type of the guanidinium counterion used and the compression of the diammonium dodecane guest was observed, properly compressed chains could only be observed in the case of the classic example **PTSG{C12N2}**.

Comparison with other capsule hosts

Several types of hosts have been developed for the encapsulation of guests of this size and shape. The discrete chemical space provided by the host is markedly different though. Calixarenes offer a bowl-shaped hydrophobic cavity with, in some cases, a polar rim. Similarly, cyclodextrins have a tubular hydrophobic inner surface, with polar hydroxyl groups on the outside. On the other hand, the cavity of cucurbiturils has a high affinity for cationic species and other hydrophilic species. Compared to these, the box shaped interior space of the Pyrene box is more similar to the first two. It shows an almost complete preference toward amphiphilic molecules, as the hydrophobic part, *i.e.* the alkyl chain, can be accommodated by the PTS aromatic residue, while the polar end can bind to the sulfonate groups through hydrogen bonds, ionic interactions, or a combination of the two.

In order to compare the binding energy of a guest to the Pyrene box, we chose *p*-nitrophenol (**NP**) as a representative molecule and searched the CCDC for similar host–guest compounds.

Two cryptand-like isomeric host molecules were found, both of which complex **NP**.[24] By using Crystal Explorer,[25a,b] we were able to calculate a rough estimate of the binding energy for all three cases. (Table 2) It is interesting to note that the binding energy of *p*-nitrophenol in Pyrene box is in between those observed for the two isomeric hosts.

A useful way of visualizing intermolecular interactions is by using Hirshfeld surfaces.[25c,26a] In these, blue coloured surfaces indicate weak interactions, white no interactions, while red denotes strong directional forces such as hydrogen bonds. The analysis of the three examples discussed above is presented in Fig. 5. For the sake of clarity, all three **NP** molecules are shown in the same orientation.

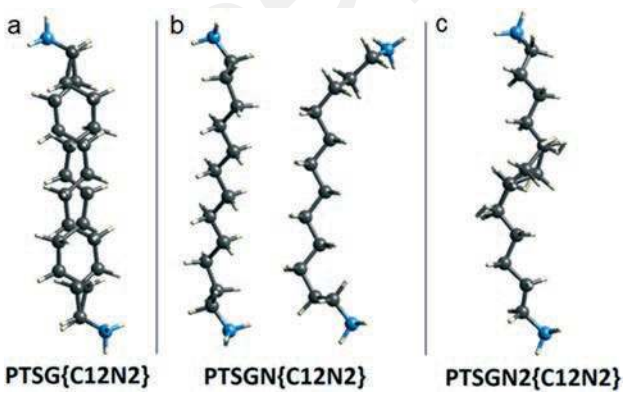


Fig. 4 Comparison between the compression of 1,12-diammonium dodecane inside pyrene box capsules formed with a) **Gua**$^+$ (J), b) **GuaNH$_2$**$^+$ (K) and c) **Gua(NH$_2$)$_2$**$^+$ (L).

Limitations

One of the main limitations of the Pyrene box is that the size of the guest molecule(s) has to be in a certain range. The smallest guest encapsulated to date is protonated histamine (**HISH**$^+$), with a volume of 143.84 Å^3, and the largest 1,12-diammonium-4,9-dioxo-dodecane, having a volume of 323.61 Å^3. The length of the chain-like molecules is not such a relevant factor though, as these can adopt compressed conformations stabilized by the encapsulation process. Another limitation is the chemical nature of the guest. In our studies, all guest molecules had an amphiphilic character, with a hydrophobic middle, either an aliphatic chain or aromatic residue, connected to one, or preferably two, hydrophilic ends. All guest had at least a hydrogen bond donor, but ammonium groups were far more common, as the resulting charge-

Table 2 Calculated energies for the three complexes using Crystal Explorer software. All energies are in kJ mol^{-1} and are corrected for CE-B3LYP basis set[25]

	$E_{electrostatic}$	$E_{polarization}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}
Correction factors	1.057	0.74	0.871	0.618	
PTSG{NP}	−8	−27.3	−127.6	67.8	**−97.8**
1-D{NP}	−97.9	−27.1	−146.8	171.9	**−145.3**
1-P{NP}	−19.4	−13	−137.4	127.6	**−71**

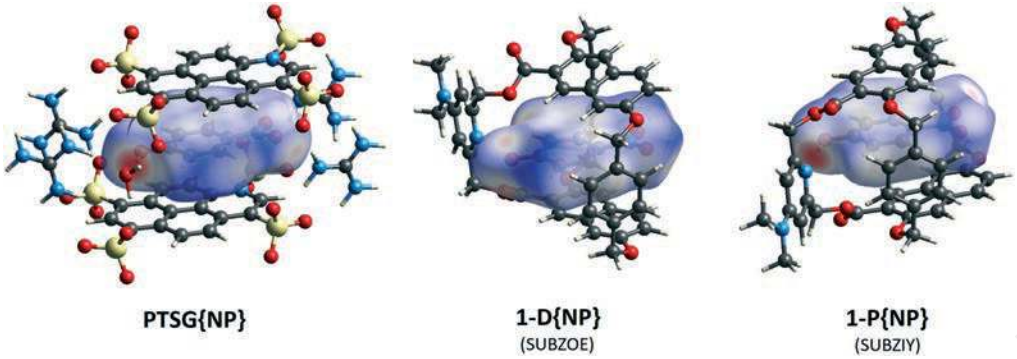


Fig. 5 Hirshfeld surfaces for *p*-nitrophenol in different guests, **PTSG{NP}**, **1-D{NP}** and **1-P{NP}**, respectively.

assisted hydrogen bond between it and the **PTS** sulfonates stabilizes the supramolecular complex.

The Pyrene box structure is very adaptive and can change in order to accommodate various guests, of variable size and chemical make-up. Although in some ways this is an advantage, one cannot be completely sure about the final box structure. Therefore, the compartmentalization of the chemical space is not fixed, as it is in the case of cyclodextrins for example. This, coupled with the ability of the system to incorporate water molecules in its H-bond network, means it is almost impossible to accurately predict the PB structure for a new potential guest molecule.

Further developments

The Pyrene box system shows great promise for further developments. The propensity with which such systems are formed and crystallize is quite astonishing. Furthermore, given the relatively large range of encapsulated guests, the total number of potential structures is huge. Several avenues of research remain open.

The first is to try to encapsulate other types of molecules, not limited to ammonium compounds. Although having at least one positive charge on the guest helps in the encapsulation process, this is not a necessarily a requirement. As such, a large number of amino or hydroxy group bearing small molecule drugs could also be targets for encapsulation.

The second is to change the 'sides' of the Pyrene box from guanidinium cations to other species. The data obtained to date indicates that other guanidinium derivatives should work in almost the same manner, by binding the top and bottom PTS molecules. Other examples shows it is possible to substitute guanidinium altogether with sodium ions.

The Pyrene box is especially suited to constrain very flexible chains and, as such, can be used as a platform for the study of unstable conformations or as a crystalline sponge. The benign nature of 1,3,5,8-pyrenetetrasulfonate makes the system very promising as a drug delivery vehicle, with a production cost far lower than that of cyclodextrins.

Conclusions

The Pyrene box is one of the most readily available encapsulation supramolecular systems, both from a synthetic point of view and also from a cost perspective. To date over 15 examples have been obtained and characterized both in solution using NMR spectroscopy and also in the solid state using single crystal X-ray diffraction. The inclusion phenomenon was observed in both cases, implying that the discrete nature of the encapsulation compound is preserved.

Although one limitation is the requirement of the guests to possess H-bond donors, such as the amino or ammonium groups, from a steric point of view the Pyrene box system is quite adaptable, being able to adopt various spatial arrangements or incorporate water molecules in its structure.

In all literature examples to date, the corresponding Pyrene box was readily obtained from water using commercially available materials. Per gram, this system is cheaper than are cyclodextrins to obtain. In some cases, the crystallization process is so fast and reliable that it could be even used as a classroom experiment. Correlations between the Pyrene box capsules and the well-studied functional protein cavities, might allow designing novel mechanisms that parallel to natural encapsulating processes. Interestingly, the dynamical yet slow molecular-scale hydrodynamics of confined guests is of crucial relevance for understanding complex biological functions and scenarios.

It can be concluded that the Pyrene box is an interesting system for the compartmentalization of the chemical space, and for the encapsulation of a large number of guests of biological interest. This Highlight Article is not a comprehensive treatise, but is a timely objective snapshot of the Pyrene box systems from which all readers can get an insight into this and hopefully a future source of inspiration, toward further sustained effort in this area.

Conflicts of interest

There are no conflicts to declare.

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