Adaptive Encapsulation of 1,ω-Amino-Acids within the "Pyrene Box"

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Shao-Ping Zheng,[a, b] Wei-Xu Feng,[c] Ji-Jun Jiang,[a] Dawei Wang,[a] Arie van der Lee,[b] and Mihail Barboiu*[a, b]

Abstract: Pyrene boxes, self-assembled from 1,3,5,8-pyrenetetrasulfonate anions, $\mathbf{PTS^{4-}}$ and Guanidinium $\mathbf{G^{+}}$, aminoguanidinium $\mathbf{AG^{+}}$ and hydrated alkali counter cations have been used for the encapsulation of 1,ω-amino-acids of variable lengths. The NMR spectroscopy illustrates that these systems are stable in aqueous solution and encapsulation process involves dynamic or fixed guest molecules within Pyrene box, depending of the nature of the counter-cations. The amide bond coupling between the amino-guanidinium $\mathbf{AG^{+}}$ and encapsulated 1,ω-amino-acid guests occur in water in the absence of coupling catalysts. The variable co-encapsulation of the guests *via* multivalent stabilizing interactions shed light that chemical selection can be obtained from mixtures of 1,ω-amino-acids. Our study involving a comprehensive screening of 18 co-crystal structures help to understand the in-situ fixation of 1,ω-amino-acid guests and their accurate determination of unconventional structures under confinement.

Keywords: Molecular encapsulation · H-bonding · self-assembly · Pyrene box · biomimetics

Compartmentalization is a basic prerequisite for sustaining orderly biological processes.[1–3] A critical step to better understand the molecular encapsulation is to simulate the unique recognition features of host molecules under confinement. Molecular encapsulation in recent years has sparked great interest. Unexpected properties of guests or dynamic phenomena inside the cavity can be observed to generally differ from their counterparts in a bulk environment,[4–11] which to a large extent mimics the compartmentalization in cells, offering opportunities to explore behaviors of guests with biological interest very close to natural conditions.[5,12]

Until now, considerable attempts have been steadily devoted to develop suitable hosts for different types of guest molecules.[12] Compared with large organic molecules as host capsules,[13–17] self-assembled supramolecular hosts[4,11,18–20] which are comprised of two or more molecular components assembled *via* various non-covalent interactions could provide advantages of collective and adaptive encapsulation for specific guests.[5] The accurate determination of their structures is only possible on condition that suitable anchoring functional groups are present at the inner surface of capsuleto help fixate the guests.[12,21] Also it has some limitations toward practical applications related to selectivity between guests and to stability of the resulted self-assemblies.[12]

Amino acids are well-known for their indispensable roles in nature as building blocks of proteins and the source for chirality and molecular recognition.[22,23] Among them, much attention is paid to 1,ω-aminoacids with short carbon chains like β-alanine[24–26] and γ-amino-butyric acid,[27,28] which are significant importance in the signal neuro-transmission.[27–29] It seems more useful and meaningful to have a better understanding toward their collective behaviors such as conformational properties,[24] dynamic interactions[30,31] or specific recognition[32–34] under confined conditions, rather than in their solution solvated states.

Inspired by guanidinium-organo-sulfonates H-bonding networks developed by Ward et al.,[18,19] we have previously designed a crystalline superstructure, "Pyrene box" from available commercial 1,3,5,8-pyrenetetrasulfonate anions, $\mathbf{PTS^{4-}}$ and Guanidinium $\mathbf{G^{+}}$ counter cations.[3,35–39] This kind of self-organized capsule, not only is in accordance with the requirements of green chemistry (non-toxic, water soluble, environmentally benign), but also can readily integrate guests in a fixed orientation into the cavity formed by two $\mathbf{PTS^{4-}}$ platforms laterally capped by H-bonding guanidinium cations, resulting a stable host-guest system in aqueous solution.[12] Pyrene boxes have the ability to encapsulate guest molecules, offering interesting opportunities to explore their properties under confinement. With it, we've successfully achieved the

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complete structures of some non-crystalline biogenic amines,[38] and the exact behaviors of compressed alkanes at the molecular level.[3,36,39]

Based on our previous experience, herein, we tried to mimic a confined environment through "Pyrene box" as a host to encapsulate 1,ω-amino-acid guests: β-alanine: **C2**, γ-amino-butyric acid: **C3**, 5-aminovaleric acid: **C4**, by varying Guanidinium $\mathbf{G^+}$, Amino-guanidinium $\mathbf{AG^+}$ and alkali $\mathbf{M^+}$ = = Li^+, Na^+, K^+, Rb^+, Cs^+ counter cations (Figure 1). Adaptive encapsulation occur owing to different guests, specifically, their dynamic interactional behaviors within Pyrene box. The nature of the counter cations influence the encapsulation process and their stability, as well as the selective preference toward specific guests during the competitive screening of mixtures of guests.

^{1}H-NMR Studies in Aqueous Solution. The encapsulation of 1,ω-amino-acid guests confined within self-assembled Pyrene box capsules could be clearly observed through the upfield or downfield shifts of the methylene protons ^{1}H-NMR signals of the encapsulated guest molecules (Figure 2). In the

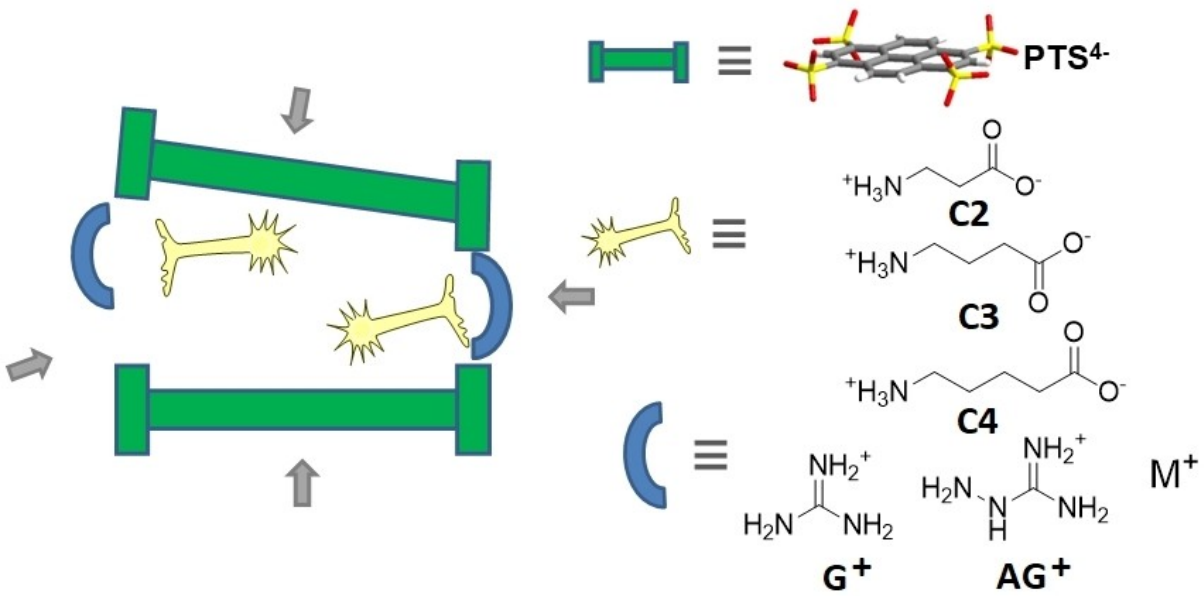

Figure 1. Schematic representation of the encapsulation of 1,ω-amino-acids **C2**- **C4** within self-assembled Pyrene-boxes self-assembled from $\mathbf{PTS^{4-}}$ anions and $\mathbf{G^+}$, $\mathbf{AG^+}$ and $\mathbf{M^+}$ cations.

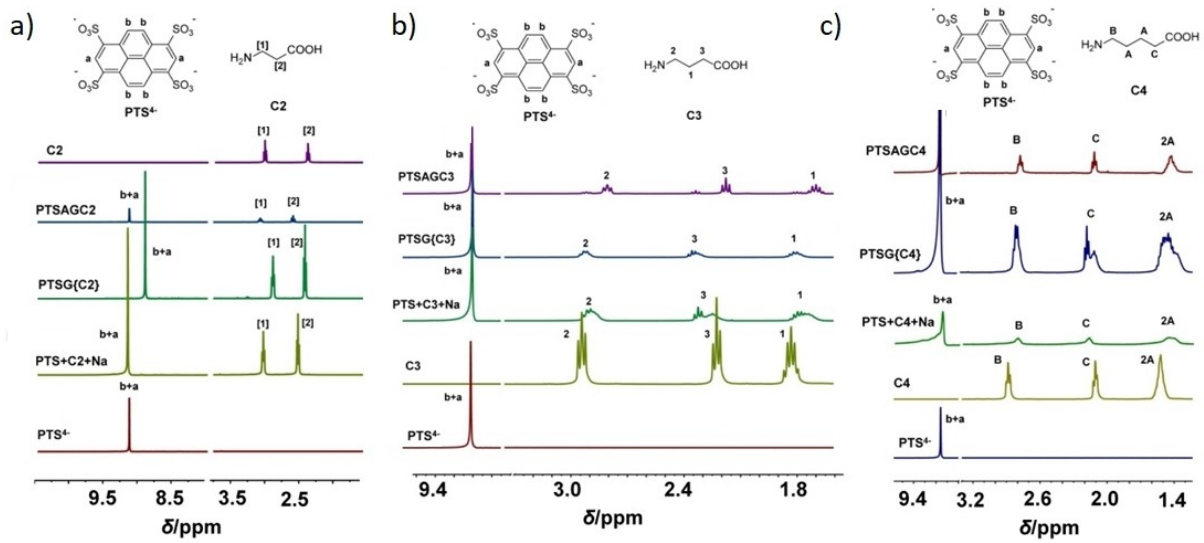

Figure 2. ^{1}H NMR for the aromatic and aliphatic regions for $\mathbf{PTS^{4-}}$ and amino acids (**C2**, **C3**, **C4**) with $\mathbf{Na^+}$, $\mathbf{G^+}$, $\mathbf{AG^+}$ at room temperature in D_2O.

case of **C2**, when Na^+ is used as counter cation, the methylene protons **[2]**, close to carboxyl group of **C2** has an apparent downfield shift of about 0.10 ppm while the methylene protons **[1]**, close to amino group remains nearly the same, suggestive for a strong fixation of the guests *via* carboxylic heads. Interestingly, opposite to Na^+, the addition of $\mathbf{G^+}$ into the "Pyrene-box" solution causes an upfield shift of the methylene protons near amino group **[1]** by about 0.15 ppm but the other side **[2]** keeps unchanged. Not just that, the aromatic protons from $\mathbf{PTS^{4-}}$ surprisingly are upfield shifted by 0.23 ppm, due to the strong host-guest interactions within Pyrene box. These result that the presence of the counter cations may have similar influences on the behavior of **C2** inside the cavity, even host itself. Unlike Na^+ and $\mathbf{G^+}$, both the methylene protons near amino group **[1]** and carboxyl group **[2]** show a downfield of about 0.03 ppm and 0.17 ppm in the presence of $\mathbf{AG^+}$ simultaneously.

Things become much different when it comes to **C3** and **C4**. The interaction between counter cation (Na^+ and $\mathbf{G^+}$) and host leads to a same downfield shift of the methylene protons close to carboxyl group of **3** by about 0.10 ppm. However, the broad signals of all protons of the alkyl chains are indicative to dynamic behaviors of guest molecules under confined conditions, probably with the alkane chains fixed in different conformations in fast dynamic exchange within the cavity. Differently to Na^+ and $\mathbf{G^+}$, the use of $\mathbf{AG^+}$ is contributing for the stabilization of the whole host-guest system, which could be seen from the new sharp methylene proton peaks and their largely alteration of positions, except that there are some old proton signals left (Figure S12 in SI). We previously discovered that an amide bond coupling reaction could take place between the amino group of the $\mathbf{AG^+}$ and the carboxyl group of amino acid,[37] which it seems may also happen in our case. 1,ω-amideguanidinium-ammonium-alkanes **AGC2** – **AGC4** guests are probably doubly anchored *via* ammonium and amide-guanidinium groups to sulfonate groups of $\mathbf{PTS^{4-}}$, positioning them on the deep part of the cavity, while mono-anchored **C2-C4** amino-acid guests are more dynamic within the cavity.

We have also checked if any specific external influence would be generated in the process of encapsulation when different hydrated alkali metal cations (Na^+, K^+, Rb^+, Cs^+) are employed as counter cations. As indicated in Figure 3, shifts of methylene protons of the **C2**, **C3** and **C4** guests are very similar and display nearly the same positions, indicative with similar conformations with the host molecules within Pyrene boxes in the presence of even different counter cations that do not induce any specific changes in the recognition patterns.

On the basis of the NMR results, we conclude that zwitterionic 1,ω-aminoacids **C2-C4** are confined within Pyrene-box. The broad proton signals observed in other cases are indicative of important dynamic behaviors of alkane **C3** chains during the ion-pairing process in the presence of $\mathbf{G^+}$ and alkali metal cations. A special emphasis is related to 1,ω-amideguanidinium-ammonium-alkanes obtained *via* amide coupling, showing stronger stabilization and very sharp signals when compared with the 1,ω-aminoacids, probably due to the double ammonium/guanidinium-sulfonate anchoring interactions on the rim of $\mathbf{PTS^{4-}}$ platform.

X-ray co-crystal structures. The recognition patterns observed in solution are supported by the X-ray co-crystal structures of host-guest of Pyrene-box structures. The co-crystals were obtained by slow evaporation of aqueous saline solutions (GCl, AGCl or MCl: LiCl NaCl, KCl, RbCl, CsCl) of $\mathbf{PTS^{4-}}$ anions and of 1,ω-amino-acid **C2-C4** guests (Table S2). They are resulting from the self-assembly of two $\mathbf{PTS^{4-}}$ anions as top and bottom platforms spatially oriented in a "face to face disposition" arrangement with balanced cations as H-bonded side platforms. The significant difference

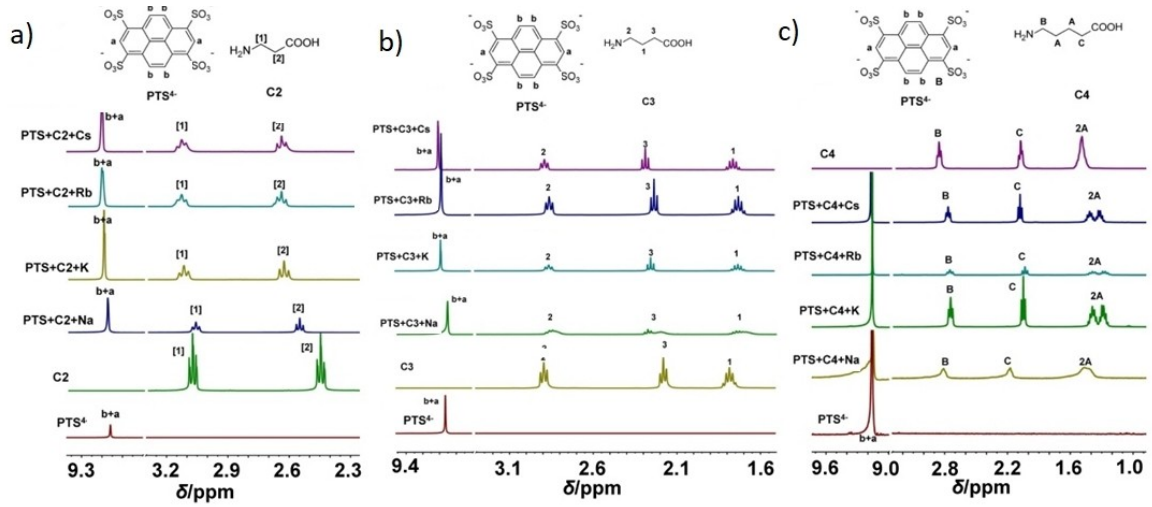

Figure 3. ^{1}H NMR for the aromatic and aliphatic regions for $\mathbf{PTS^{4-}}$ and amino acids (**C2**, **C3**, **C4**) with $\mathbf{Na^+}$, $\mathbf{K^+}$, $\mathbf{Rb^+}$, $\mathbf{Cs^+}$ at room temperature in D_2O.

between them is the different encapsulation behavior caused by different **C2-C4** guests and counter cations. Synergetic effects of coordination and/or H-bonds between amino and/or carboxyl groups from 1,ω-amino-acids and the sulfonate moieties of $\mathbf{PTS^{4-}}$ platforms together with the surrounding counter cations and water molecules.

In **PTSG{C3}**, one guest **C3** molecule fills the space between two $\mathbf{PTS^{4-}}$ planes. The guest **C3** molecules are connected in an orientation of "head to tail" *via* a bridging water molecule simultaneously H-bonded to the ammonium moiety of **C3** ($d_{N-O}=3.05$ Å) and to the carboxyl group ($d_{O-O}=2.70$ Å) of another neighboring guest molecule. Moreover, this central water molecule is stabilized by tethering to two different sulfonate groups at the top and bottom of the box ($d_{O-O}=2.82$ Å), while the ammonium moiety also forms another two H-bonds with $\mathbf{PTS^{4-}}$ sulfonates ($d_{O-O}=3.01$ Å). All $\mathbf{G^{+}}$ counter cations are anchored outside the Pyrene box through H-bonding to the sulfonate groups. **PTSG{C4}** has similar conformation behavior, except that the ammonium "head" and the carboxyl "tail" are directly connected through a H-bonding at a distance of 2.60 Å. The stability of the network is reinforced *via* other H-bonding interactions with $\mathbf{PTS^{4-}}$ platforms ($d_{N-O}=2.81$ Å) and with waters ($d_{O-O}=$ 2.67 Å or 2.82 Å).

In both structures, **C3** and **C4** are constrained within Pyrene-box owing to the H-bonds with sulfonate groups and the C–H(alkane chains)/π(aromatic regions) interactions The X-ray co-crystal structures of **PTSAGC3** (Figure 4c) and **PTSAGC4** (Figure 4d) confirm the amide-bond coupling reaction,[37] resulting in the formation of longer molecular guests **AGC3** and **AGC4**, that adaptively bind to optimally fit the new constraints and encapsulation within Pyrene-box. With **PTSAGC3** (Figure 4c) the asymmetric resulting guest **AGC3** presenting a linear-geometry of the alkane chain is closing a lateral position within the box formed by "face to face" distorted packing of $\mathbf{PTS^{4-}}$ and it is double H-bonded *via* guanidinium ($d_{N\cdots O}=2.76$ Å) and ammonium ($d_{N\cdots O}=$ 2.87 Å) groups to the sulfonates of $\mathbf{PTS^{4-}}$.

The length of **AGC3** molecule is not optimally fitting the length of $\mathbf{PTS^{4-}}$ molecules, extending outwardly toward a neighboring $\mathbf{PTS^{4-}}$ platform. **AGC3** is co-encapsulated with the another $\mathbf{AG^{+}}$ molecule ($d_{N-O}=2.87$ Å and $d_{N-O}=2.81$ Å) which is immobilized in the middle of the Pyrene box. The longer **AGC4** guest increase the host/guest complementarity, thus changing the balance between the encapsulation forces so two guests are antiparallel disposed on the lateral sides of the Pyrene box **PTSAGC4**. The H-bonding encapsulation is mediated *via* a bridging water molecule linked to guanidinium groups ($d_{N-O}=2.70$–2.80 Å), reinforced with strong H-bond interactions between ammonium and $\mathbf{PTS^{4-}}$ platforms ($d_{N-O}=$ 3.00 Å).

The use of hydrated alkali metal counter cations brings some novel coordination patterns within Pyrene box architectures. In [**PTSNaC2**] (Figure 5a), two confined guests **C2** are diagonally disposed inside the Pyrene box, resulting in the formation of a dimers connected *via* the carboxyl groups ($d_{O-O}=2.68$ Å), which are simultaneously coordinated to hydrated Na^{+} cations simultaneously connected to the sulfonates of the $\mathbf{PTS^{4-}}$ platforms.

For [**PTSNaC3**] (Figure 5b), two molecules of **C3** are parallelly and directionally constrained inside the Pyrene box capsule through coordination to hydrated Na^{+} cations which are further H-bonded to sulfonate groups *via* water bridges. The same H-bonding patterns are maintained in the case of [**PTSNaC4**] (Figure 5c), where two linearly stretch guest molecules **C4** are oriented in an antiparallel orientation within the Pyrene box and are directly coordinated to the Na^{+} cations further connected to sulfonate groups via H-bonding water bridges.

The replacement of Na^{+} as the side platform of Pyrene "box" **PTSNaC2** with Rb^{+} and Cs^{+} did not lead to structural differences, but using hydrated K^{+} cations only one guest molecule **C2** is present inside the Pyrene box which is stabilized by coordination with two K^{+} cations and H-bonded with one hydrated K^{+} via water bridges (Figure 5d). Structures of [**PTSRb/KC3**] and [**PTSCsC4**] are quite similar to that of [**PTSNaC4**]. As shown in Figure 5e, two alkyl guest chains are antiparallelly positioned within the Pyrene box with two hydrated metal cations compensating the negative charge of the whole framework.

Competitive encapsulation experiments. In order to better understand the influences that different counter ions exert on the specific selective encapsulation behaviors of Pyrene box systems, we performed competitive crystallization experiments.

With the equimolar amounts of guests **C2**, **C3** and **C4** in the aqueous solution, specific guests encapsulation is preferred as function of the used counter cation. The selective encapsulation is most of the cases expressed in the amplification of a selected guest encapsulation, which converts into its final unique crystalline architecture during the kinetically irreversible crystallization process (Table 1). The guest binding amplification in solution and crystallization process was followed by collecting 10 crystals/sample from three distinct experiments. Exceptionally the guest **C2** is uniquely encapsulated in the Pyrene box host system among three coexisting

Table 1. Selectivity experiments in aqueous solution and resulting crystallization architectures (composition: $\mathbf{PTS^{4-}}$: counter cation = 0.5 : 10, mol : mol).

Counter cations	Resulted crystallized structure	Molar composition **C2**:**C3**:**C4** analysis of encapsulated guests determined by ^{1}H NMR
G^{+}	**PTSGC4**	8.8%:32.4%:*58.8*%
AG^{+}	**PTSAGC3** or **PTSAGC4**	14.2%:*64.5*%:21.3% or 22.9%:25%:*52.1*%
Na^{+}	**PTSC3Na**	16.7%:*79.4*%:3.9%
K^{+}	NA	/
Rb^{+}	**PTSC3Rb**	18.9%:*81.1*%:0
Cs^{+}	**PTSC2Cs**	*1*:0:0

*NA: not available.

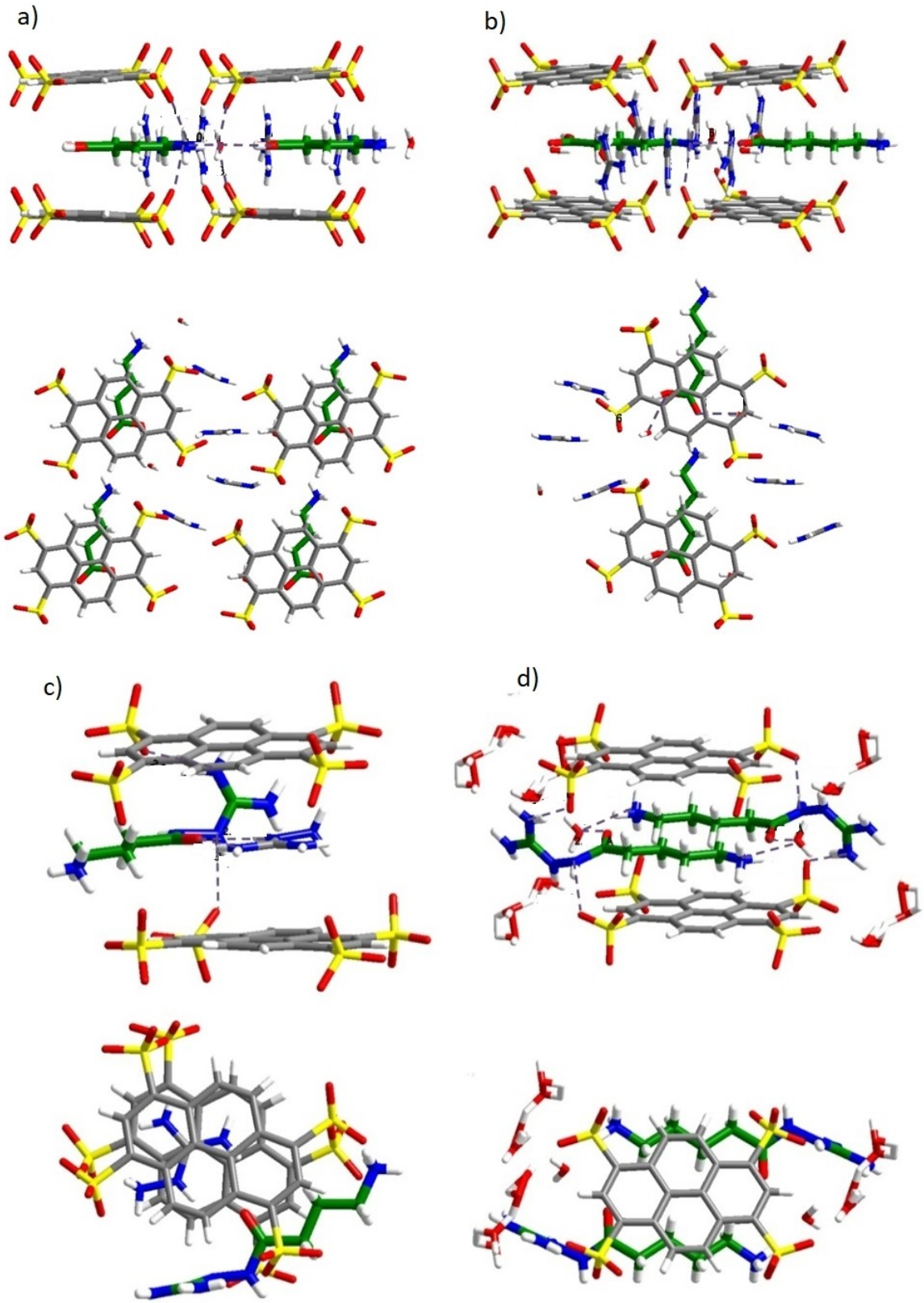

Figure 4. Side and top views of X-ray co-crystal structures for (a) **PTSG{C3}**, (b) **PTSG{C4}**, (c) **PTSAGC3**, (d) **PTSAGC4**. [Colors for elements: red, oxygen; yellow, sulfur; blue, nitrogen; grey, carbon; white, hydrogen; green, carbons of guests]

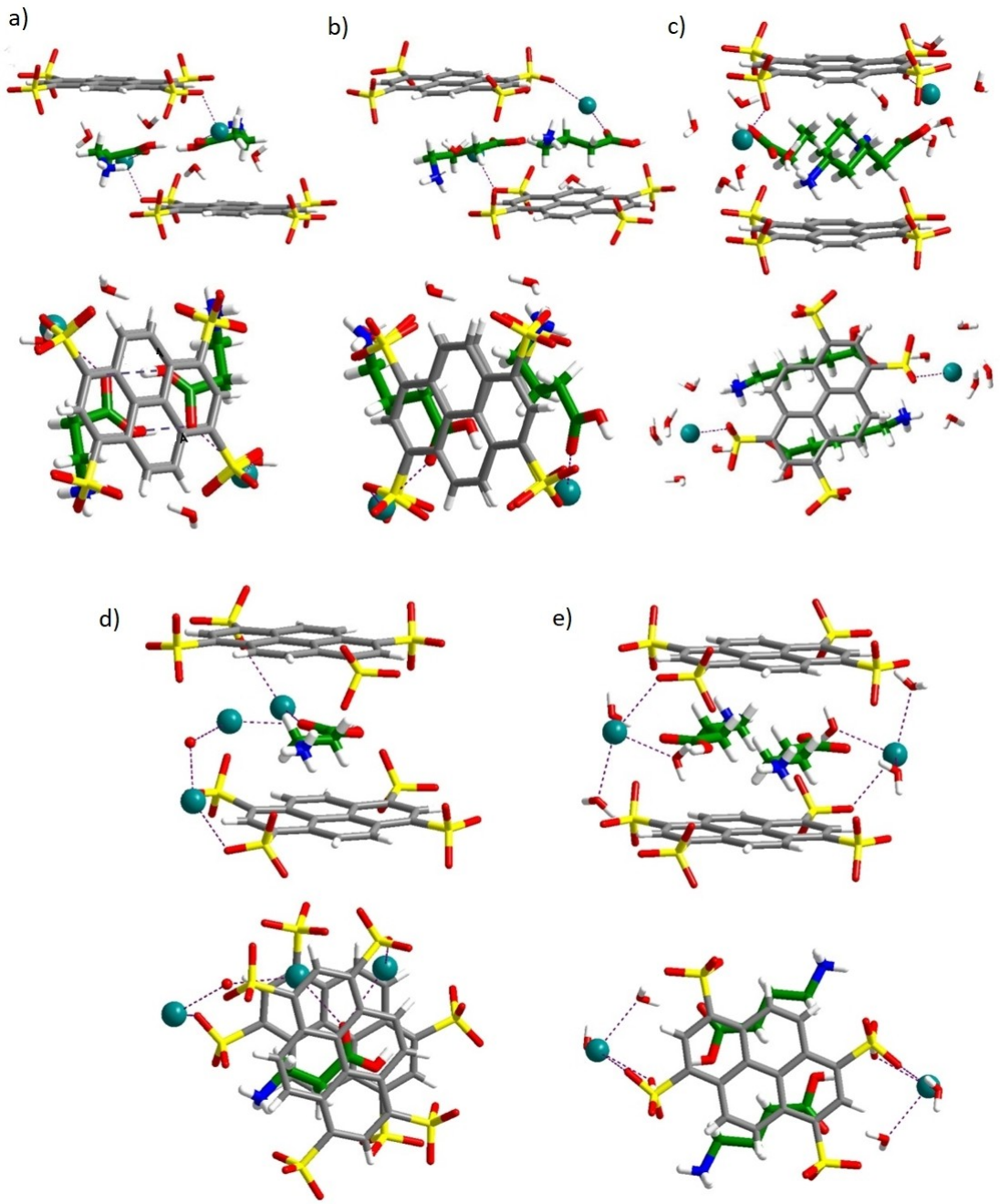

Figure 5. Side and top views of X-ray co-crystal structures for (a) [**PTSNaC2**], (b) [**PTSNaC3**] (c) [**PTNa4**] (d) [**PTSC2**], (e) [**PTSKC3**] [Colors for elements: red, oxygen; yellow, sulfur; blue, nitrogen; grey, carbon; white, hydrogen; teal, metal cation; green, carbons of guests]

amino acids when Cs^+ is used as counter cation. **C3** guest is preferentially selected when smaller alkali cations Na^+ and Rb^+ are used. The use of $\mathbf{G^+}$ and $\mathbf{AG^+}$ counter cations both **C3** and **C4** are preferred with a superior preference for the longer **C4** guest. This is related to the fact that both **C3** and **C4** are fitting the length of the $\mathbf{PTS^{4-}}$ platform, so that **PTSAGC3** and **PTSAGC4** structures are equally stable.

Conclusions

In summary, a biomimetic host-guest model has been proposed here, in which Pyrene boxes are used utilized as host for 1,ω-amino acids (β-alanine, γ-aminobutyric acid, 5-aminovaleric acid) as guests. It's been proven that 1,ω-amino acids would adopt specific conformations under confined conditions depending on their structural interaction with capsules. These

combined structural behavior changes subsequently bring about influences on the stability of the whole host-guest system, related to its dynamic preference toward specific amino acids, paralleling to molecular recognition in biology. Regardless, it appears that the main driving forces for encapsulation are the steric compatibility of the linear unfolded alkyl chains fitting the cavity, as well as electrostatic/H bonding stabilization via water bridges. Of practical interest, the X-ray co-crystal structures elucidate the interactional pathways observed in solution allowing to accurate determinate the guest(s) conformations under confined conditions. Overall, these studies may improve our understanding for the specific binding of molecules of biological interest under confined conditions. Since self-assembly process can readily be adapted for simultaneous integration of various functional guests, our work may provide new ideas for developing materials with promising properties for biomedical applications.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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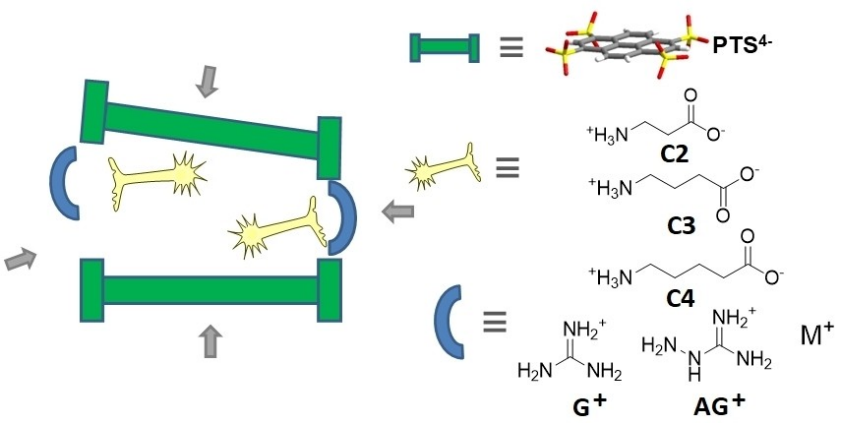

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