Organic LETTERS

Letter

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Adaptive Encapsulation of ω-Amino Acids and Their Guanidinium−Amide Congeners

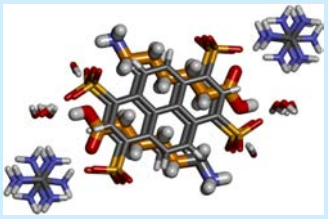
Wei-Xu Feng,[†,‡] Arie van der Lee,[‡] Yves-Marie Legrand,[‡] Eddy Petit,[‡] Dan Dumitrescu,[‡] Cheng-Yong Su,[†] and Mihail Barboiu*[,†,‡]

[†]Lehn Institute of Functional Materials, School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China

[‡]Adaptive Supramolecular Nanosystems Group, Institut Europeen des Membranes, ENSCM/UMII/UMR-CNRS 5635, Pl. Eugene Bataillon, CC 047, 34095 Montpellier, Cedex 5, France

Supporting Information

ABSTRACT: The binding and the encapsulation of the 6-aminohexanoic acid (**1**) and 11-aminoundecanoic acid (**2**) are achieved in aqueous solution and in crystalline Pyrene-box cages. Unexpectedly, the amino-guanidinium **AG**$^+$ and the amino acids **1** or **2** are reacting in aqueous solution in the absence and in the presence of Pyrene-box cages. The formation of an amide bond between a carboxylic acid and the amino-guanidine unit under mild acidic conditions in water without the use a coupling reagent is extremely interesting and unexpected. The resulted adducts **AG1** and **AG2** show adaptive binding behaviors and compressions.

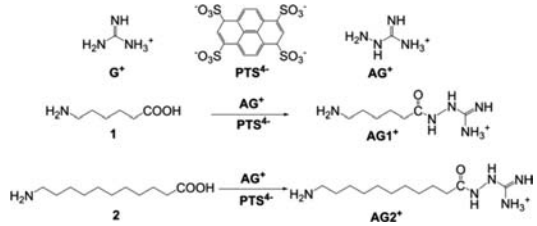


Guest molecules confined inside hollow cage architectures can show structurally unexpected high energy conformations or special enhanced reactivity compared to their behaviors in the bulk unprotected solution environment.[1,2] One of the important processes observed to date concerns the compression of *n*-alkanes inside dimensionally smaller cages in water. Attempts have generally furnished interesting details on their constitutional flexibility, inducing synergetic dynamic shape changes and adaptation.[3−5] Variable conformations of the chains under the pressure of the biomimetic compression have been proposed.[3] Dynamic selection of congruent hydrophobic hosts can be adaptively obtained on guest encapsulation.[4]

We know from previous works that the adaptive conformational behaviors of compressed alkanes constrained within crystalline Pyrene-box cages could be precisely controlled as confirmed by joint X-ray single-crystal and molecular modeling studies in solid state as well as the NMR spectroscopic studies in aqueous solution.[5] The Pyrene-box cages are self-assembled from the 1,3,5,8-pyrene-tetrasulfonate anions, **PTS**$^{4-}$, and the guanidinium cations, **G**$^+$ (Scheme 1). The encapsulation of alkanes in biological pockets is reinforced by strong ionic interactions and carboxylic groups are usually used to fix the host substrates.[2]

The dynamic shape changes are strongly dependent on anchoring behaviors of the host molecules within the Pyrene-box. The sulfonate anchoring groups of the **PTS**$^{4-}$ platforms are used as binding sites for the functional alkane guests decorated with cationic ammonium groups. The distances between them influence the binding/compression behaviors of the hydrophobic chains and may be controlled in the presence of different guanidinium cations used as Pyrene-box constituents.[5a,b] Herein we expand our studies toward ω-amino acids hosts of high biological interest, which present ammonium and carboxylate anchoring groups for an unsymmetrical encapsulation and

Scheme 1. "Pyrene Boxes" Are Self-Assembled from PTS^{4-}, Anions, the Guanidinium G$^+$, and the ω-Amino Acids 1, 2 or Cationic AG1$^+$, AG2$^+$ Guest Molecules Obtained in Situ



compression in the presence of **PTS**$^{4-}$ anions and **G**$^+$ or **AG**$^+$ cations. To our surprise, within the Pyrene boxes the carboxyl groups of the ω-amino acid hosts react with the amino group of the **AG**$^+$ results in the formation of amide bonds in water in the absence of a classical coupling catalyst. The resulted guanidinium-functionalized amino acids show adaptive encapsulation inside the "Pyrene box" compared with their the ω-amino acid congeners.

NMR Studies in Aqueous Solution

The ion-pairing proxy interactions between protonated cationic 6-aminoundecanoic acid (**1**) or 11-aminohexanoic acid (**2**) and **PTS**$^{4-}$ anions can be detected in aqueous solution (Figures 1, 2, and S1−S9). The formation of **PTS**$\{\mathbf{1}\}_2$, **PTS**$\{\mathbf{2}\}_2$ adducts can be clearly observed from the upfield (**1**) and downfield (**2**) shifts of the methylene protons of the encapsulated hosts **1** or **2** when compared with their spectra recorded in the absence of the Pyrene-box (Figure 1). In both cases the prevalent interaction in **PTS**$\{\mathbf{1}\}_2$, **PTS**$\{\mathbf{2}\}_2$ adducts results in a shielding of both

Received: September 17, 2016
Published: October 19, 2016

DOI: 10.1021/acs.orglett.6b02802
Org. Lett. 2016, 18, 5556−5559

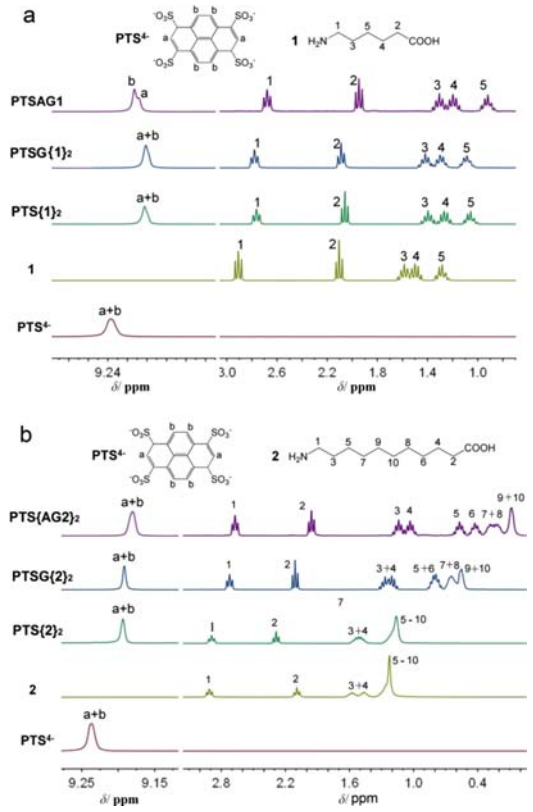


Figure 1. ^{1}H NMR of simply mixed components in aqueous solution for (a) the aromatic and aliphatic region for $\mathbf{PTS}^{4-}$, **1**, $\mathbf{PTS\{1\}_2}$, $\mathbf{PTSG\{1\}_2}$, and $\mathbf{PTS\{AG1\}_2}$ and (b) $\mathbf{PTS}^{4-}$, **2**, $\mathbf{PTS\{2\}_2}$, $\mathbf{PTSG\{2\}_2}$, and $\mathbf{PTS\{AG2\}_2}$ at room temperature.

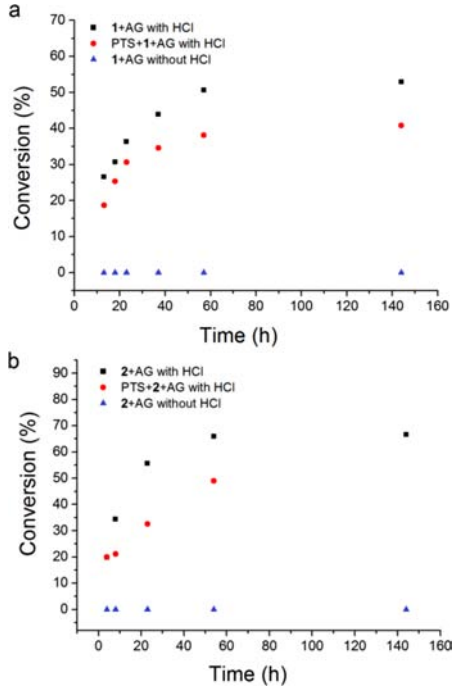


Figure 2. Conversion versus time profiles for the amide bond formation between $\mathbf{AG}^+$ and **1** or **2** under acidic conditions in the absence and the presence of the Pyrene-box cages. The reaction has been monitored by using NMR spectroscopy.

aromatic protons of the $\mathbf{PTS}^{4-}$ anions by about 0.044 ppm and of the methylene groups of the alkyl chains by about 0.14−0.23 ppm for **1** and about 0.06 ppm for **2** (Figure 1). As previously observed for 1, ω-diammoniumalkanes,[5b] these results are reminiscent with the formation of a preorganized capsule in aqueous solution in the absence of the guanidinium cations, positioning the $\mathbf{PTS}^{4-}$ anions in close proximity of the ω-amino acids **1** or **2**. They are interacting via C−H (alkane chains)/π(PTS) and electrostatic interactions within the $\mathbf{PTS\{1\}_2}$, $\mathbf{PTS\{2\}_2}$ adducts. The addition of $\mathbf{G}^+$ cations to the aqueous solutions of $\mathbf{PTS\{1\}_2}$ results in the similar upfielded shifts of the protons of encapsulated **1**, probably due to similar binding and conformation of **1** in both $\mathbf{PTS\{1\}_2}$ and $\mathbf{PTSG\{1\}_2}$. The encapsulation of more hydrophobic guest molecules of **2** is enhanced by the presence of the $\mathbf{G}^+$ cations, resulting in an supplementary upfield shielding (0.37−0.61 ppm) of the central methylene groups in $\mathbf{PTSG\{2\}_2}$ compared with $\mathbf{PTS\{2\}_2}$. This means that the $\mathbf{G}^+$ counterions are contributing for the stabilization of the "Pyrene box", in which the dynamic behaviors of the more confined hydrophobic alkyl chains are largely restricted. It results in the downfield shifts of the H^a and H^b of the $\mathbf{PTS}^{4-}$ for $\mathbf{PTSG\{1\}_2}$ and $\mathbf{PTS\{AG1\}_2}$ (0.007−0.012 ppm), together with the upfield shifts (0.012 ppm) for $\mathbf{PTSG\{2\}}$ and $\mathbf{PTS\{AG2\}_2}$. The encapsulation of guest molecules of **1** or **2** is enhanced by the presence of the $\mathbf{AG}^+$ cations, resulting in a supplementary upfield shielding of 0.17 and 0.27 ppm of the central methylene groups in $\mathbf{PTS\{AG1\}_2}$ versus $\mathbf{PTSG\{1\}_2}$ and $\mathbf{PTS\{AG2\}_2}$ versus $\mathbf{PTSG\{2\}_2}$, respectively. The broad signals of the central proton $H^{9,10}$ of the alkyl chains of **2** inside the capsules are reminiscent of dynamic behaviors of alkane chains under confined conditions.

Unexpectedly, the addition of the amino-guanidinium $\mathbf{AG}^+$ cation to the aqueous solution of $\mathbf{PTS\{1\}_2}$ or $\mathbf{PTS\{2\}_2}$ led to the amide bond coupling of the amino group of the $\mathbf{AG}^+$ and the carboxyl group of the ω-amino acids **1** or **2**. Usually, the amide bond formation in the absence of the catalysts is a big challenge and the use of coupling catalysts is mandatory to promote this reaction. This reaction may be promoted by supramolecular encapsulation, moving the amide bond formation in water, even this reaction involves dehydration.[6]

Surprisingly, in the present case the acidic pH conditions favor the amide bond coupling between the activated amino-guanidinium $\mathbf{AG}^+$ and carboxylic groups of **1** or **2** in water. The amide bond formation is not occurring at neutral pH, and the presence of the Pyrene-box cages is not mandatory (Figure 2). The simply deconvolution/integration of the specific methylene protons peaks of the carboxylic and amide groups results in the quantification of **1**/**AG1** or **2**/**AG2** molar ratios (Figures S10−S13). As expected, the reaction is displaying a slow kinetics yielding after 60 h and in the absence of the Pyrene-box cages to 50% conversion for the shorter **AG1** and 70% conversion for the longer more hydrophobic **AG2**. The reaction occurring in water under acidic conditions is slower owing to the delay caused by the rate of participation of the amino-guanidinium reagent in the Pyrene-box formation (Figure 2).

The compression of the alkane chains is confirmed by COSY/ROESY experiments (Figures S14−S21). In the case of $\mathbf{PTSG\{1\}_2}$, the alkane chains appears to have an elongated zigzag conformation, with no correlation detected on a distance larger than two vicinal carbons (Figure 3a). On the contrary, in the case of $\mathbf{PTSG\{2\}}$, spatial correlations even up to four carbons are visible (H_1 to H_9) for compressed alkyl chains of longer amino acid **2** molecules (Figure 3b). As expected the

DOI: 10.1021/acs.orglett.6b02802
Org. Lett. 2016, 18, 5556−5559

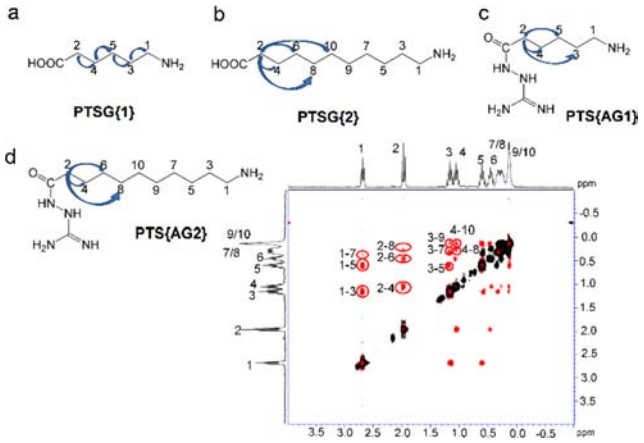


Figure 3. Long range spatial interactions in (a) **PTSG{1}**$_2$, (b) **PTSG{2}**, (c) **PTS{AG1}**$_2$, and (d) **PTS{AG2}**$_2$ capsules; ROESY spectra of **PTS{AG2}**$_2$.

confinement of guanidinium-functionalized amino acids, is spatially dictated by the **AG** cation binding and alkyl chain coiling. Spatial correlations are visible up to three carbons away (H_1 to H_4 for **1**; H_1 to H_7 for **2**) for the compressed forms of both **PTS{AG1}**$_2$ and **PTS{AG2}**$_2$ Pyrene-box cages (Figure 3c,d).

X-ray Single Crystal Structures

The encapsulation and compression behaviors of ω-amino acids are supported by the X-ray single-crystal structures of the "Pyrene boxes" **PTSNa{1}**$_2$, **PTS{2}**$_2$, **PTSG{1}**$_2$, **PTSG{2}**, **PTS{AG1}**$_2$, and **PTS{AG2}**$_2$. We have previously observed that "Pyrene-box" cages result from the self-assembly of two PTS^{4-} anions and two G^+ cations via H-bonding. This network is reinforced by two bridging water molecules, which are H-bonded to G^+ and to PTS^{4-}, playing an important role in organizing the partners via three sulfonate moieties on the faces of the "Pyrene box".[5]

PTSNa{1}$_2$ and **PTS{2}**$_2$ superstructures are obtained by crystallizing the 1:2 or 1:4 mol/mol mixtures of **1**:PTS^{4-} and **2**:PTS^{4-}, respectively (Figures 3 and 4). In **PTSNa{1}**$_2$, two confined guest molecules of **1** are filling the space between two PTS^{4-} platforms (Figure 4). The PTS^{4-} aromatic platforms are spatially oriented in a "face to face disposition" arrangement with two hydrated Na^+ cations compensating the negative charge of the sulfonate groups of the PTS^{4-} and coordinating five water molecules, which are H-bonded to PTS^{4-} platforms in a very similar manner than the G^+ cations, so that the structures of encapsulated guests of **1** in **PTSNa{1}**$_2$ and **PTSG{1}**$_2$ are almost nearly the same.

Then using a longer 11-aminoundecanoic-acid molecule instead of the initial 6-aminohexanoic acid guest, the increased length of the alkyl chain is not anymore adapted to completely fit the new constraints and encapsulation. Within this context there are two different linear or bent conformations of **2**, filling the space between successive PTS^{4-} platforms (Figure 5).

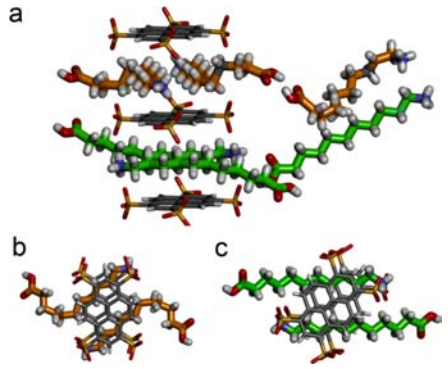


Figure 5. (a) Side and top views of X-ray single-crystal structure of **PTS{2}**$_2$ showing two sets of the (b) bent and (c) linear conformations of two confined guests and nonconfined molecules of **2** within the Pyrene box.

Consequently, other two molecules corresponding their linear and bent confined congeners are situated outside the Pyrene box. The bending of inside and outside conformers and have five (C50−C51, C52−C53, C55−C56, C56−C57, C57−C58, and C58−C59) and four (C48−C47, C47−C46, C46−C45, and C45−C44) gauche conformations unsymmetrically positioned along the alkane chain of **2**. We may note that the guest and the nonconfined molecules of **2** are connected via H-bonding between two carboxyl or ammonium/carboxyl groups.

For the **PTSG** capsules, the 6-aminohexanoic acid (**1**) and 11-aminoundecanoic acid (**2**) guests are confined within the confined inner space defined between the planes of two G^+ and two PTS^{4-} molecules (Figure 6). Two confined molecules of **1** are filling the space diagonally disposed between two sulfonate groups from PTS^{4-} platforms of Pyrene-box **PTSG{1}**$_2$.

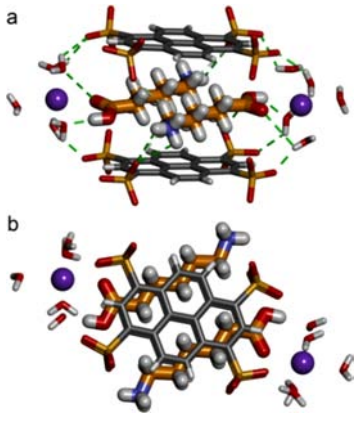


Figure 4. (a) Side and (b) top views of X-ray single-crystal structure of **PTSNa{1}**$_2$ showing two confined guest molecules of **1** within the Pyrene box.

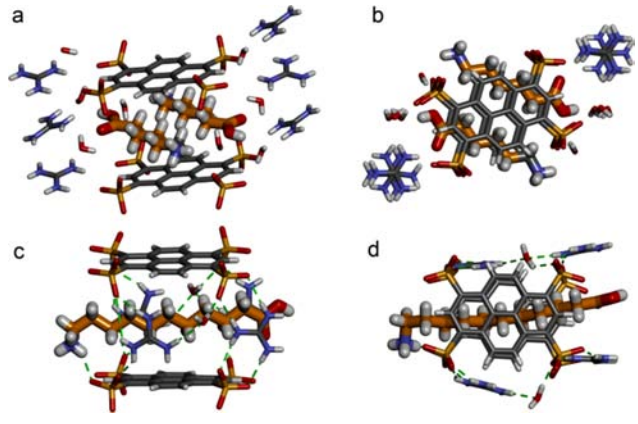


Figure 6. Side and top views of X-ray single-crystal structure of (a,b) **PTSG{1}**$_2$ and (c,d) **PTSG{2}**$_2$, showing two and one confined guest molecules of **1** and **2**, respectively, within the Pyrene box.

DOI: 10.1021/acs.orglett.6b02802
Org. Lett. 2016, 18, 5556−5559

Moreover, two ammonium moieties of **1** form two supplementary anchoring H-bonds ($d_{N\cdots O}$ = 2.87 Å) with two other sulfonate moieties of the $\mathbf{PTS}^{4-}$, and the carboxyl group form one anchoring H-bond ($d_{O\cdots O}$ = 2.69 Å) with one bridging water molecule (Figure 5a,b) and another H-bond with $\mathbf{G}^+$ ($d_{N\cdots O}$ = 3.00 Å) cation. The X-ray single-crystal structure of $\mathbf{PTSG\{2\}_2}$ shows that there is only one guest molecule of **2** inside the **PTSG** cage (Figure 5c,d). Two bridging $\mathbf{G}^+$ cations, simultaneously H-bonded to the sulfonate groups from two different $\mathbf{PTS}^{4-}$ platforms, play a significant role in stabilization of the Pyrene box. The ammonium moiety of **2** forms two anchoring H-bonds ($d_{N\cdots O}$ of 2.83 Å) with two sulfonate moieties, while the carboxyl group of **2** forms one anchoring H-bond ($d_{O\cdots O}$ of 2.70 Å) with one water molecule and another H-bond with an ammonium group ($d_{N\cdots O}$ of 2.89 Å) of a neighboring molecule of **2**.

Interestingly, the addition of the $\mathbf{AG}^+$ cation to the $\mathbf{PTS\{1\}_2}$ or $\mathbf{PTS\{2\}_4}$ systems lead to the amide-bond coupling reaction between the carboxyl group of the amino acids with the amino group of the $\mathbf{AG}^+$ cation, resulting in the formation of $\mathbf{PTS\{AG1\}_2}$ and $\mathbf{PTS\{AG2\}_2}$ Pyrene boxes (Figure 7). The

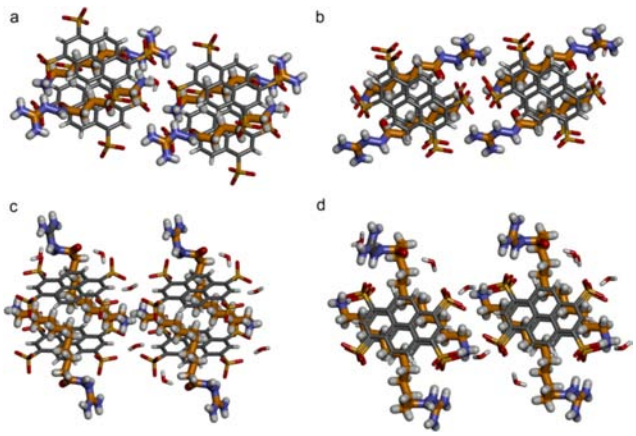


Figure 7. Side and top views of X-ray single-crystal structure of (a,b) $\mathbf{PTS\{AG1\}_2}$ and (c,d) $\mathbf{PTS\{AG2\}_2}$, showing confined guest molecules of **AG1** and **AG2**, within the Pyrene box.

newly formed $\mathbf{AG1_2}$ and **AG2** host molecules are confined within Pyrene-box network via a double anchoring motifs consisting of the guanidinium ($d_{N\cdots O}$ = 2.95 Å) and the ammonium moieties of **1** ($d_{N\cdots O}$ = 2.88 Å) or **2** ($d_{N\cdots O}$ = 2.85 Å).

These groups form strong H-bonding with the sulfonate moieties of two parallel $\mathbf{PTS}^{4-}$ anions, while three water molecules play an important role in stabilization of the whole network. In each case two confined molecules are filling the space between the two $\mathbf{PTS}^{4-}$. Interestingly the **AG2** host molecule adopts two gauche conformations, unsymmetrically positioned along the alkane chain, between C18−C17 and C15−C14. The conformation of the alkyl chain of **AG2** in $\mathbf{PTS\{AG2\}_2}$ is less compressed with the respect of the amino acid congener **2** in $\mathbf{PTSG\{2\}}$. This is probably related to the fact that the $\mathbf{AG}^+$ groups of the **AG2** molecules are externally H-bonded between two sulfonate groups of two neighboring $\mathbf{PTS}^{4-}$ platforms.

In this letter, we highlighted that the ω-amino acids can be successfully and adaptively confined inside Pyrene-box cages. This is reminiscent of the specific binding of amino acids in biological pockets of interest for different biological scenarios. Specific interactions and compressed conformations in aqueous solution and the crystalline structures are determined by NMR spectroscopy and X-ray diffraction.

Interestingly, the acidic pH conditions favor the amide bond coupling between the activated amino-guanidinium $\mathbf{AG}^+$ and carboxylic groups of **1** or **2** in water in the absence of a classical coupling catalyst. The reaction is slowed down in the presence of the Pyrene-box cages, reminiscent of hindered coupling under confined conditions. The resulted guanidinium-functionalized amino acids show adaptive encapsulation inside the "Pyrene box" compared with the ω-amino acid congeners. Overall, these studies may provide new knowledge for understanding the dynamics of complex biomolecules under confined conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02802.

Supplementary NMR and X-ray diffraction details (PDF)
X-ray crystal file for $\mathbf{PTS\{1\}_2}$ (CIF)
X-ray crystal file for $\mathbf{PTS\{2\}_2}$ (CIF)
X-ray crystal file for $\mathbf{PTSG\{1\}_2}$ (CIF)
X-ray crystal file for $\mathbf{PTSG\{2\}_2}$ (CIF)
X-ray crystal file for $\mathbf{PTS\{AG1\}_2}$ (CIF)
X-ray crystal file for $\mathbf{PTS\{AG2\}_2}$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mihail-dumitru.barboiu@univ-montp2.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was conducted within ANR-15-CE29-0009 DYNAFUN and 1000 Talent Program in China.

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DOI: 10.1021/acs.orglett.6b02802
Org. Lett. 2016, 18, 5556−5559