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Progressive Folding and Adaptive Multivalent Recognition of Alkyl Amines and Amino Acids in *p*-Sulfonatocalix[4]arene Hosts: Solid-State and Solution Studies

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

Calix[4]arenes have the ability to encapsulate biomimetic guests, offering interesting opportunities to explore their molecular recognition, very close to biological scenarios. In this study, *p*-sulfonatocalix[4]arene (C4 A) anions and hydrated alkali cations have been used for the in situ recognition of cationic 1, ω -diammonium-alkanes and 1, ω -amino-acids of variable lengths. NMR spectroscopy illustrates that these systems are stable in aqueous solution and the interaction process involves several binding states or stabilized conformations within the C4 A anion, depending of the nature of the guest. DOSY

experiments showed that monomeric 1:1 host-guest species are present, while the cation does not influence their self-assembly in solution. The folded conformations observed in the solid-state X-ray single-crystal structures shed light on the constitutional adaptivity of flexible chains to environmental factors. Furthermore, a comprehensive screening of 30 single crystal structures helped to understand the in situ conformational fixation and accurate determination of the folded structures of the confined guest molecules, with a compression up to 40% compared with their linear conformations.

Introduction

The deciphering of the supramolecular binding events under confined conditions or pore environments is of paramount importance for understanding interactional mechanisms.^[1] Highly flexible molecules could in principle self-assemble with a variable probability under confined conditions, depending on its own and host structural behaviors. Precise structural characterization of such complex interactions is a necessary step towards the development of new methods of non-covalent modification for interaction and function modulation or for increasing the crystallization abilities of such non-crystalline molecules.^[2,3]

Synthetic water soluble calixarenes, cucurbiturils or foldamers enable the recognition of various molecules of bio-

logical interest.^[1–3] The water soluble *p*-sulfonatocalix[4]arene, first reported by Shinkai et al. in 1984,^[4] have been shown to have a variety of biomedical applications including antiviral or anti-thrombotic activities, conducted *via* enzyme or protein recognition processes.^[5] The binding of different hosts by *p*-sulfonatocalix[4]arene receptors is largely driven in water by an hydrophobic effect, assisted by secondary non-covalent electrostatic and hydrogen bonding interactions. The structural information available to date has been used for potential applications in generating single crystals of cytochrome c^[3a] or lysozyme,^[3b] for which specific interactional mechanisms can be described from X-ray crystallographic studies. From these studies, we know that lysine protein sites adopt folded conformation of their alkyl chains buried on hydrophobic *p*-sulfonatocalix[4]arene cavity, enabling further formation of salt bridges between the ammonium and sulfonate substituents, favoring the displacement of water molecules initially located in the cavity.^[3]

Encapsulation methods offer excellent reasons for a complete characterization of molecular compression and recognition of small molecules under confinement inside artificial H-bonded capsules in aqueous solution.^[6,7] As in biological systems, the constitutional hydrophobic recognition of the alkyl chains is supplementary reinforced *via* strong interactions between the host-guest components.^[8,9] Of practical interest in such processes is to precisely determine the molecular conformations of the guest molecules themselves or their synergistic supramolecular interactions with the host molecules.^[10] If a crystal may be obtained in a solution containing a compound of interest, the compound is integrated into the cavity and if this is then analyzed by X-ray crystallography, the structure of the encapsulated compound can be elucidated. The reduced degrees of freedom of encapsulated guests can be limited by


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anchoring them to the crystalline host molecules/systems, allowing a reduced amount of disorder.^[10,11]

The use of water-soluble *p*-sulfonatocalix[4]arene alkali metal cation salts leads to a remarkably diverse range of crystalline bilayers, capsules, spheres or nanotubes that can encapsulate small, biologically important molecules in water.^[12] Crystalline Calix[4]box architectures, self-assembled from *p*-sulfonatocalix[4]arene, **C4 A** anions and guanidinium cations have been used for encapsulation of flexible non-crystalline biogenic guests, very close to confined biological conditions.^[10,11,13] We know from these studies that folded conformations of the guest molecules under confinement, are dramatically different from that observed in bulk solution. The ability to encapsulate molecular guests within crystalline *p*-sulfonatocalix[4]arene, offers novel interesting options to explore their flexible conformations and a whole range of interactional algorithms under confined biomimetic conditions, close to those observed for active pockets of natural proteins or enzymes.

Herein, we take advantage of hydrophobic folding *via* recognition within *p*-sulfonatocalix[4]arene of two series of 1, ω -diammonium-alkanes and 1, ω -amino acids of variable lengths and possessing variable ammonium and carboxylic anchoring groups, as presented in the most cases of natural protein recognition studies (Scheme 1). The exact structures of the complexes and, more important for this study, the novel folded conformations adopted by the bound molecular guests are revealed by X-ray crystallography.

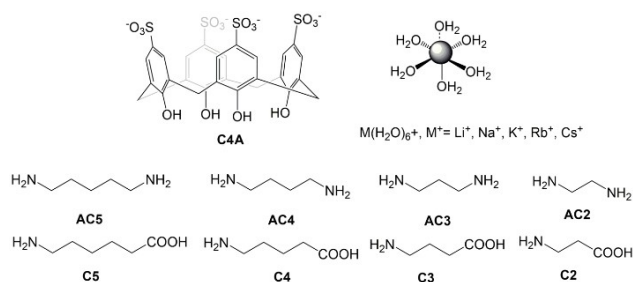
The crystallization of *p*-sulfonatocalix[4]arene is promoted in the presence of hydrated alkali cations. It relies on the formation of alternative layers of *p*-sulfonatocalix[4]arene anions and hydrated alkali cations / water molecules stabilized in a hydrogen-bonded network interacting on the upper-rim with the sulfonate moieties and presenting a variable relative spatial disposition within the crystal, depending on the nature of the alkali cation which strongly impacts on confined guest molecules recognition within crystals. The inclusion of alkali cations allows access to different binding geometries, changing the shape and size of the confined space for the particular recognition regimes. Stabilization of folded alkyl chains is not a common process and very few reports show evidence of constrained adaptive conformations, giving answers on how

alkane compression occurs and how this can impact further supplementary interactions under confined conditions.^[14]

We have dedicated our studies to the confinement of two classes of guest molecules of biological interest with variable length and functional groups a) 1, ω -diammonium-alkanes: 1,5-diammonium-pentane, **AC5** 1,4-diammonium-butane, **AC4** 1,3-diammonium-propane, **AC3** and 1,2-diammonium-ethane, **AC2** or b) 1, ω -amino-acids: 6-aminohexanoic acid, **C5** 5-amino-pentanoic acid, **C4** 4-aminobutyric acid, **C3** and 2-amino-ethanoic acid, **C2**. The host-matrixes has been readily obtained and crystallized in aqueous solutions of *p*-sulfonatocalix[4]arene anions **C4 A** and hydrated alkali cations $M(H_2O)_n^+$ ($M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$). At this point, several important questions are shedding light on: a) how important is the length of molecules squeezing progressively inside a fixed smaller chemical space and how does their folding contribute to the stabilization of the overall host-guest superstructure? b) How important is the nature of anchoring groups interacting with the sulfonate groups of *p*-sulfonatocalix[4]arene anions for the recognition? Systematic attempts to encapsulate biogenic protein side arms in confined space may generally furnish very interesting interactional details on their constitutional flexibility and interactional behaviors, inducing simultaneous changes of both capsule and host molecules. The conformation and compression could be precisely understood and confirmed by X-ray single-crystal structures in the solid state, as well as by NMR spectroscopy showing strong guest binding in aqueous solution.

Results and Discussion

¹H-NMR Studies in Aqueous Solution. The host-guest interactions between the **C4 A** *p*-sulfonatocalix[4]arene host anions and protonated 1, ω -diammonium-alkanes, **AC5** to **AC2** or 1, ω -amino acids **C5** to **C2** cationic guests can be detected in aqueous solution. (Figure 1 and Figure 1S-7S in the Supporting Information). As a general trend, similar downfield shielding effects of 0.06–0.09 ppm are detected for the singlet aromatic H_A and methylene H_B protons of the **C4 A** platform adapting a cone conformation, when binding 1, ω -diammonium-alkanes or 1, ω -amino-acids, indicating the alkali metal cations and cavity included guests are placed as connecting bridges between sulfonate moieties to compensate their overall charges. The formation of inclusion complexes of **C4 A** host anions with **AC5** - **AC2** or **C5** - **C2** protonated cationic guests in saline aqueous solutions of NaCl, KCl, RbCl, CsCl can be clearly observed from the strong upfield shifts of the protons of the encapsulated guests (Figure 1) when compared with their spectral signals recorded in the absence of the **C4 A**. The signals corresponding to the protons are shielded: H_1 (1.12 and 1.27 ppm) for **AC4** or (0.8 and 1.22 ppm) for **C4**; H_2 (1.21 and 1.29 ppm) for **AC4** or (0.6 and 0.8 ppm) for **C4** and $H_{3,4}$ (1.0 and 1.3 ppm) for **C4** in the presence of Na^+ and K^+ cations. These broad proton signals are reminiscent of complex behaviors with the alkane chains fixed in two different conformations in fast dynamic exchange within the cavity. The prevalent interactions are C–H– π between



Scheme 1. *p*-sulfonatocalix[4]arene anion hosts **C4 A**, hydrated alkali cations $M(H_2O)_n^+$ ($M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$) and 1, ω -diammonium-alkanes **AC2-AC5** and 1, ω -amino acids **C2-C5** guests.

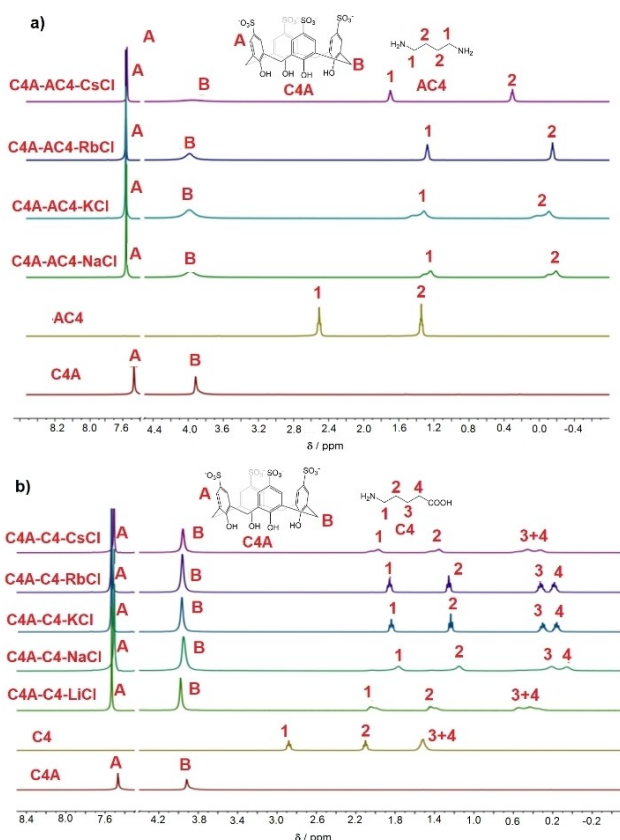


Figure 1. $^1\text{H-NMR}$ spectra at 25 °C (400 MHz, D_2O) of **C4A** host, **AC4**, **C4** guests and *p*-sulfonatocalix[4]arene hosts: a) **C4A-AC4-MCl** and b) **C4A-C4-MCl** prepared in saline solutions of MCl: LiCl NaCl, KCl, RbCl, CsCl. See Figures 15–75 in the Supporting Information for NMR data of all other systems.

aliphatic protons of **AC4** or **C4** and aromatic phenyls of **C4A** and the ion-pairing between the sulfonate groups of **C4A** and protonated ammonium groups of **AC4** or **C4**. It is important to note that stronger upfield shielding is observed for the signals of the dicationic guest **AC4** (Figure 1a) when compared with the mono-cationic amino-acid **C4** (Figure 1a). It is supposing that **AC4** molecule is doubly anchored *via* bis-ammonium groups and it is positioned on the deep part of the cavity, while mono-anchored **C4** guest is situated more at the entry of the cavity. Moreover, differently to central H_2 protons of **AC4** which remain identical upon binding, the signals of central protons H_3 and H_4 of **C4** present two sets of distinct signals, consistent their presence in different environments of **C4A**, showing that host-guest interactions induce symmetric (**AC4**) or asymmetric (**C4**) confined placement of the respective guests upon guest recognition. The proton resonances are becoming sharp in the presence of Rb^+ and Cs^+ (**AC4**) or K^+ and Rb^+ (**C4**) alkali cations, reminiscent with a lower mobility of included guest molecules **AC4** or **C4** guests within the cavity of **C4A** host, better stabilized in the presence of bigger cations bridging the sulfonate anions in solution. In addition, comparing the proton signals H_1 (1.02 ppm) and H_2 (0.71 ppm) for Cs^+ with the proton signals H_1 (1.19 ppm) and H_2 1.29 ppm for Rb^+ , they are both shifted upfield $\blacksquare\blacksquare\text{OK?}\blacksquare\blacksquare$ by about 0.2 ppm in the presence

of Cs^+ . This is consistent with that the guest **AC4** changes the orientation toward the entry of host **C4A** cavity in the presence of Cs^+ , while its binding is highly increased in the presence of Rb^+ cations, dimensionally more adapted and better stabilizing the rim of the **C4A** molecules than Cs^+ . Very interestingly the addition of different alkali cations (Figure 2b) do not induce any further changes in the recognition of monocationic **C4** by **C4A** anions and not affect much the equilibria in solution, as observed for **AC4** guests in the presence of different alkali cations.

Furthermore, the DOSY spectroscopy (Figure 8S-14S) showed that monomeric 1:1, host : guest complexes are present in solution for the most of the studied systems. The calculated diffusion coefficients are presented in Table 1. The molecular volumes for **C4A**, **C4A-AC4-RbCl** and **C4A-C4-RbCl** calculated from available crystal structure data reported in this paper, are 515.5 \AA^3 , 730.4 \AA^3 and 910.8 \AA^3 respectively, Assuming that all molecules and self-assemblies are spherical, these volumes provide average hydrodynamic radii of 4.98 Å for **C4A**, 5.58 Å for **C4A-AC4-RbCl** and 6.02 Å for **C4A-C4-RbCl**, values, that predict the theoretical $D_{\text{C4A-AC4-RbCl}}/D_{\text{C4A}}$ ratio of 0.89 and $D_{\text{C4A-C4-RbCl}}/D_{\text{C4A}}$ ratio of 0.82. The experimental diffusion coefficients agree well with the theoretical ratios, indicating the presence of 1:1 complexes in solution and showing a small influence of the nature of alkali cations ($D_{\text{C4A-C4-KCl}}/D_{\text{C4A}}$ ratio of 0.72) on self-assembly behavior of monomeric 1:1 host : guest species in solution. The theoretical $D_{\text{C4A-AC4-RbCl}}/D_{\text{C4A}} = 0.56$ provide an average hydrodynamic radius of 8.89 Å and a total volume of 2941.5 \AA^3 for **C4A-AC4-RbCl** complex prepared at **C4A:AC4**, 2:1, mol : mol ratio, which is consistent with an increase of the aggregation toward the self-assembly of polymolecular capsules, as previously reported by Atwood et al.^[12]

On the basis of the NMR studies, one may conclude that alkyl strands of cationic $1,\omega$ -diammonium-alkanes, **AC5** to **AC2** or $1,\omega$ -amino-acids **C5** to **C2** are confined within *p*-sulfonatocalix[4]arene hosts, with a special emphasis for $1,\omega$ -diammonium-alkanes showing stronger stabilization when compared with the $1,\omega$ -amino-acids, probably due to the double anchoring ammonium-sulfonate bridge-interactions on the rim of **C4A** platform. This is also consistent with the multiple bent conformations of the alkyl chains under confinement observed

Table 1. DOSY diffusion coefficients for **C4A-AC4-RbCl**, (1:1 or 2:1 mol: mol), **C4A-C4-KCl**, **C4A-C4-RbCl**, **C4A-RbCl**, **AC4** and **C4**.

Complex	Diffusion coefficient, D [$\text{m}^2 \text{s}^{-1}$] ^[a]	D/D_{C4A}
C4A-AC4-RbCl 1:1	2.54×10^{-10}	0.89
C4A-AC4-RbCl 2:1	1.31×10^{-10}	0.56
C4A-C4-KCl	2.32×10^{-10}	0.72
C4A-C4-RbCl	2.44×10^{-10}	0.82
C4A-RbCl	2.95×10^{-10}	–
AC4	5.76×10^{-10}	–
C4	4.93×10^{-10}	–

[a] A diffusion constant value of $2.00 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ was assigned to the water signal. This value was used as reference for the calibration of the diffusion constant values assigned to the other species present in solution.

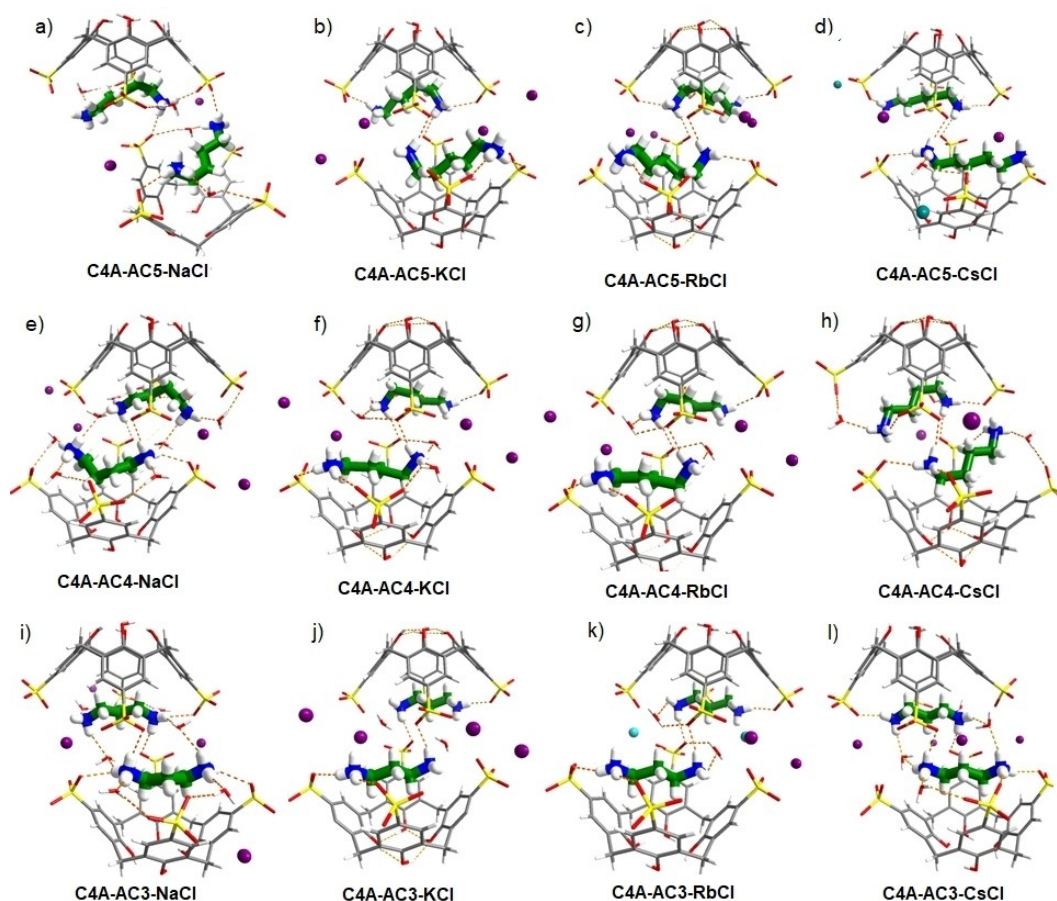


Figure 2. X-ray structures of a) C4 A-AC5-NaCl, b) C4 A-AC5-KCl, c) C4 A-AC5-RbCl, d) C4 A-AC5-CsCl, e) C4 A-AC4-NaCl, f) C4 A-AC4-KCl, g) C4 A-AC4-RbCl, h) C4 A-AC4-CsCl, i) C4 A-AC3-NaCl, j) C4 A-AC3-KCl, k) C4 A-AC3-RbCl, l) C4 A-AC3-CsCl: Side view of the inclusion complexes and of the H-bonded matrices formed by *p*-sulfonatocalix[4]arene anion C4 A, hydrated alkali cations $M(H_2O)_n^+$ ($M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$) cations and the 1, ω -diammonium-alkanes AC2-AC5 guests.

in the X-ray single-crystal structures presented below. The broad proton signals are reminiscent of important dynamic behaviors of alkane chains during the ion-pairing process in the presence of smaller Na^+ or K^+ alkali cations. Oppositely they became sharper in the presence of bigger Rb^+ or Cs^+ cations, bringing important conformational stabilization of the interior chemical space, due to their ability to bridge the upper rim sulfonate moieties of C4 A platform. DOSY NMR experiments indicate the presence of 1:1 complexes in solution, with practically no influence of the nature of various alkali cations. Higher, more complex aggregates are formed in solution when an excess of C4 A (2:1 mol: mol) is used in solution.

X-ray single crystal structures. The recognition of guests observed in solution is supported by the X-ray single-crystal structures of C4 A host anions and of AC5 - AC2 or C5 - C2 protonated guests (Table S1-S5),^[15] obtained by slow evaporation of aqueous saline solutions (MCl: LiCl NaCl, KCl, RbCl, CsCl). They are resulting from the self-assembly of C4 A anions, AC5 - AC2 or C5 - C2 guests and hydrated Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ alkali cations and additional water molecules (Figure 2, 3). The guests penetrate and interact with C4 A cavity positioning their ammonium or carboxyl/water terminal moieties on the close proximity of the sulfonate groups, to form anchoring H-bonds

on the rim of the C4 A host molecules. The hydrogen bonding is reinforced by bridging water molecules, playing an important role in filling the interstices of the network.

In the C4 A-AC5-LiCl (Figure 15S), C4 A-AC5-NaCl (Figure 2a), C4 A-AC5-KCl, (Figure 2b) C4 A-AC5-RbCl (Figure 2c) and C4 A-AC5-CsCl (Figure 2d) two protonated 1,5-Diammoniumpentane, AC5 guests are confined in the inner space between two C4 A anions, spatially disposed in a slightly slipped arrangement in parallel organic layers. They are stabilized with alternating inorganic lamellar phases of four hydrated Li^+ , Na^+ , K^+ , Rb^+ or Cs^+ / Na^+ cations and water molecules, bridging the sulfonate groups of C4 A, respectively. In all cases, the molecules of AC5 are doubly anchored *via* hydrogen bonding of one ammonium group between two sulfonate moieties ($d_{N...O} = 2.03-2.05 \text{ \AA}$) and of the second ammonium group H-bonded to bridging water molecules ($d_{N...O} = 1.99 \text{ \AA}$) positioned between the opposite sulfonate moieties of the C4 A.

Additional hydrogen bonding/bridging interactions take place between the ammonium groups of the AC5 guests and sulfonate groups of vicinal C4 A anions. In these structures the AC5 guest molecules are longer to fit the constraints of the recognition environment. The confined molecules of AC5

guests present folded conformations adapting and asymmetrically filling the space of the **C4 A** platform. The conformers of **AC5** present slightly different geometries depending on the nature of alkali cation. They have two gauche conformations between the C1-C2 and C2-C3 for **C4 A-AC5-LiCl**, **C4 A-AC5-NaCl**, **C4 A-AC5-KCl** or **C4 A-AC5-RbCl** and one gauche conformation between C1-C2 for **C4 A-AC5-CsCl**, respectively. They are unsymmetrically positioned at one end of the alkane chains, presenting close hydrophobic C-H (alkyl)/ π aromatic centroids (calix[4]arene) contacts of 2.50-2.90 Å and floating in the aromatic cavity of **C4 A**. The N_1-N_5 distances between the ammonium groups of the confined **AC5** guests in **C4 A-AC5-LiCl**, **C4 A-AC5-NaCl**, **C4 A-AC5-KCl** or **C4 A-AC5-RbCl**, are around 5.62-5.83 Å, corresponding to a 23.98-20.40% compression of the extended linear length of **AC5**, while conformer **AC5** immobilized in **C4 A-AC5-CsCl**, is more elongated at 6.71 Å, with a compression of 9.26%.

In the **C4 A-AC4-NaCl** (Figure 2e), **C4 A-AC4-KCl** (Figure 2f), **C4 A-AC4-RbCl** (Figure 2g) and **C4 A-AC4-CsCl** (Figure 2h) two protonated 1,4-Diammonium-butane, **AC4** guests are confined within the inner space between two **C4 A** anions spatially disposed in a slipping paralleled near face to face arrangement. Four Na^+ , K^+ , Rb^+ or Cs^+ cations with eight bridging water molecules constitute the inorganic layer, stabilizing parallel **C4 A** anion layers. The guest molecules are anchored *via* hydrogen bonding of bridging ammonium groups between two sulfonates groups ($d_{N-O} = 1.96-1.98$ Å) and *via* two water molecules bridging the other two opposite sulfonate groups ($d_{N-O} = 2.05-2.37$ Å). The stability of the network is reinforced *via* six or eight anchoring H-bonds ($d_{N-O} = 1.95-2.33$ Å) between the ammonium moieties of **AC4** guests and the sulfonate moieties of the vicinal **C4 A** host anions. The guests **AC4** get compressed and present folded asymmetrical conformations inside the **C4 A** cavity, with one gauche C1-C2 conformation positioned at one end of the alkane chains. This buried part of the chains is in hydrophobic C-H (alkyl) / π aromatic centroids (calix[4]arene) contacts of 2.90-3.00 Å and floating in the aromatic cavity of **C4 A**. The N_1-N_4 distances between the ammonium groups of confined **AC4** guests in **C4 A-AC4-NaCl**, **C4 A-AC4-KCl**, **C4 A-AC4-RbCl** or **C4 A-AC4-CsCl** are 5.09-5.44 Å, corresponding to a 10.20-17.05% compression of the extended linear length of **AC4**.

In the **C4 A-AC3-NaCl** (Figure 2i), **C4 A-AC3-KCl** (Figure 2j), **C4 A-AC3-RbCl** (Figure 2k) and **C4 A-AC3-CsCl** (Figure 2l) two 1,3-Diammonium-propane, **AC3** protonated guests are perfectly fitting to the distance between the sulfonate groups in the inner space of the **C4 A** anions, spatially disposed in a slipping paralleled near face to face arrangement. Four Na^+ , K^+ , Rb^+ or Cs^+ cations with bridging water molecules are stabilizing the inorganic layer, parallel to the layer of **C4 A** anions. The molecular chains of **AC3** adopting a classical 'zig-zag' linear conformation, are symmetrically anchored *via* multiple hydrogen bonding ($d_{N-O} = 1.91-2.10$ Å) of ammonium groups bridging the two sulfonates groups, on the opposite sides of **C4 A**. Remarkably any water molecule is present to reinforce this recognition motif. The N_1-N_3 distances of confined **AC3** guest in **C4 A-AC3-NaCl**, **C4 A-AC3-KCl**, **C4 A-AC3-RbCl** or **C4 A-AC3-**

CsCl are 4.82-4.90 Å, corresponding to practically no-compression, 1.44-3.27% of the extended linear length of the **AC3** guest. More remarkable, two confined molecules of **AC3** guest with linear non-folded conformations are filling the space within **C4 A** platforms, showing practically no hydrophobic C-H (alkyl) / π aromatic (calix[4]arene) contacts which are greater than 3.00 Å with the **C4 A** cavity.

When shorter deprotonated **AC2** 1,2-Diammoniumethane guests are used, interestingly they are not included in the aromatic cavity of **C4 A**. The single crystal structures of **C4 A-AC2-LiCl** (Figure 16Sa) and **C4 A-AC2-NaCl** (Figure 16Sb), consists of layered structures with **C4 A** anions, confining three water molecules within their cavity as previously observed^[16] and having lower hydroxyl rims connected by four Li^+ cations or upper rim of sulfonate moieties connected by four hydrated Na^+ cations, respectively. The protonated 1,2-Diammoniumethane, **AC2** guest are probably too hydrophilic to fill the inner space of the **C4 A** anions and they are disposed together with hydrated Li^+ and Na^+ cations and bridging water molecules outside the cavity of the **C4 A** anion. The **AC2** guests have gauche conformations of the C1-C2 alkane chain and they are H-bonded *via* ammonium groups to sulfonate groups of the **C4 A** anion.

In the **C4 A-C5-LiCl** (Figure 3a) and **C4 A-C5-KCl** (Figure 3b) two confined guests protonated 6-aminohexanoate, **C5** guest molecules are filling in the inner space between two **C4 A** anion hosts, spatially disposed in a slipping parallel arrangement. The guest molecules **C5** are anchored *via* hydrogen bonding of bridging ammonium groups between two sulfonates groups of **C4 A** ($d_{N-O} = 2.16-2.3$ Å). The hydrogen bonding network is reinforced by four hydrated Li^+ or K^+ cations and four bridging water molecules which are H-bonded to carboxyl groups of **C5** ($d_{O-O} = 2.02-2.17$ Å), playing a crucial role in the stabilization of the guests inside the cavity of the **C4 A** anions network. In addition, each carboxyl groups of one guest is H-bonded ($d_{N-O} = 1.89$ Å) to the ammonium moiety of a vicinal **C5** pair guest generating dimers of **C5**₂ within the capsule. The molecules of **C5** are presenting one gauche conformation (C1-C2) at the 'carboxylate' end of the alkane chain showing close hydrophobic C-H (alkyl) / π (calix[4]arene) contacts of 2.70-2.90 Å with the aromatic cavity of **C4 A**. The N_1-O_6 distances between the ammonium and carboxylate groups of confined **C5** guest in **C4 A-C5-LiCl** and **C4 A-C5-KCl**, are strongly dependent on the nature of the cation 6.61 Å (Li^+) and 5.66 Å (K^+) and directly influenced by the anchoring position of the carboxylate group within the network. They correspond to 11.53% and 24.03% compression of the extended linear length of **C5**. In the **C4 A-C4-NaCl** (Figure 3c), **C4 A-C4-KCl** (Figure 3d) **C4 A-C4-RbCl** (Figure 3e) **C4 A-C4-CsCl** (Figure 3f) two protonated 5-aminopentanoic acid, **C4** guests are confined within the confined inner cavity defined between two **C4 A** anions, variably disposed in a slipping parallel to face to face arrangements depending on the nature of hydrated cations. The hydrated Na^+ , K^+ , Rb^+ or Cs^+ / Na^+ cations forming inorganic layers are compensating the negative charge of **C4 A** and are subsequently coordinating the carboxylates of **C4** guests and

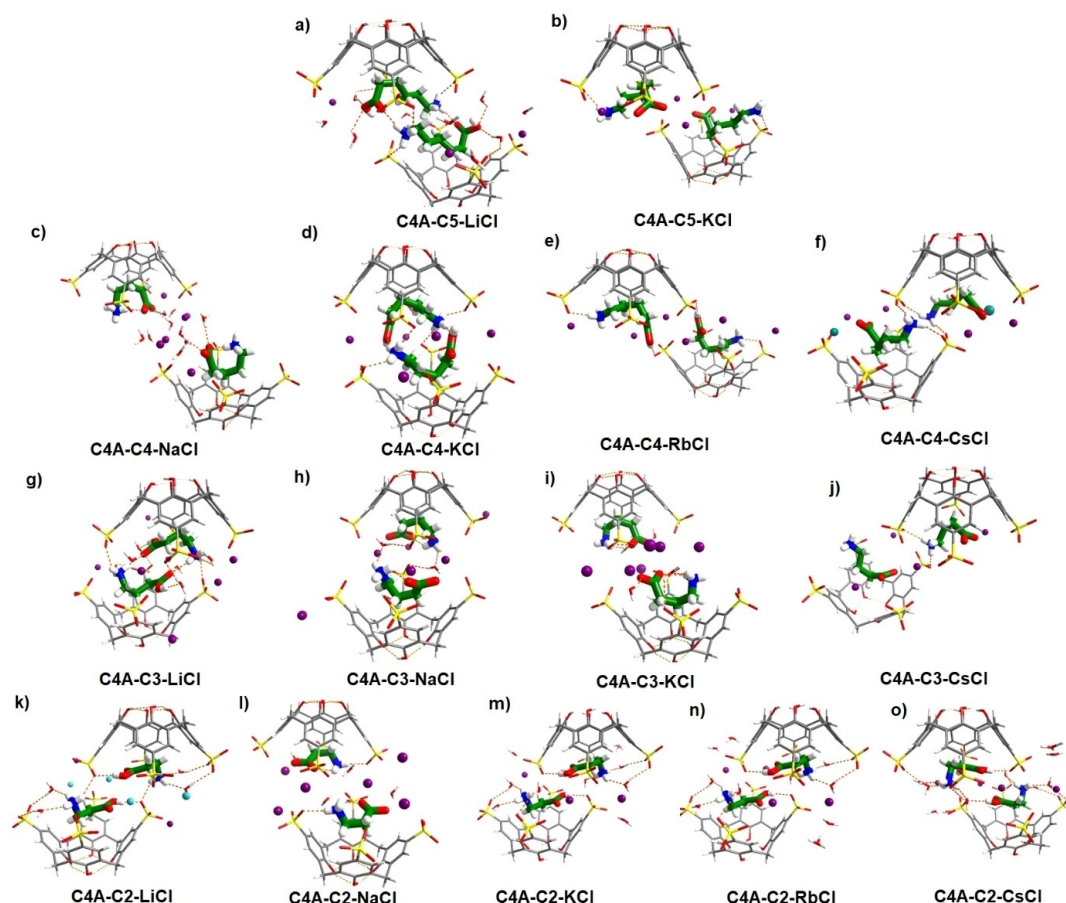


Figure 3. X-ray structures of a) C4 A-C5-LiCl, b) C4 A-C5-KCl, c) C4 A-C4-RbCl, d) C4 A-C4-KCl, e) C4 A-C4-RbCl, f) C4 A-C4-CsCl, g) C4 A-C3-LiCl, h) C4 A-C3-NaCl, i) C4 A-C3-KCl, j) C4 A-C3-CsCl, k) C4 A-C2-LiCl, l) C4 A-C2-NaCl, m) C4 A-C2-KCl, n) C4 A-C2-RbCl, o) C4 A-C2-CsCl: Side view of the inclusion complexes side view and of the H-bonded matrices formed by *p*-sulfonatocalix[4]arene anion C4 A, hydrated alkali cations $M(H_2O)_n^+$ ($M^+ = Li^+, Na^+, K^+, Rb^+, Cs^+$) cations and the 1, ω -diammonium-alkanes C5-C2 guests.

hydrogen bonding *via* bridging water molecules to the sulfonate groups of C4 A.

The hydrogen bonding network is reinforced by anchoring H-bonds between the ammonium moieties of C4 and sulfonate groups ($d_{N-O} = 2.18$ and 2.07 Å) or *via* bridging water molecules to the sulfonate groups of different C4 A platforms. Depending on the nature of the cation and of the positioning of the anchoring points in the network, the C4 guest is differently packed within the capsule. In the C4 A-C4-NaCl (Figure 3c) the C4 guest adopts an asymmetrical highly compressed conformation, with three gauche conformations among C1-C2, C2-C3, C3-C4 positioned all the length of the alkyl chain so that a strong hydrogen bonding ($d_{N-O} = 2.07$ Å) is intramolecularly established between the ammonium and carboxyl groups of the folding C4 guest. The C4 guests in C4 A-C4-KCl (Figure 3d) have two gauche conformations between C2-C3 and C3-C4 unsymmetrically and contiguously positioned at the end of ammonium group of the alkane chains, while in C4 A-C4-RbCl (Figure 3e) C4 A-C4-CsCl (Figure 3f) the C4 guests became more relaxed having one gauche conformations of C3-C4 unsymmetrically positioned at the neighboring end of carboxyl group of the alkyl chain. All the structures show close hydrophobic

C-H (alkyl)/ π (calix[4]arene) contacts of contacts of 2.50 – 2.70 Å of folded C4 guests with the aromatic cavity of C4 A. The N_1-O_5 distances between the ammonium and carboxylate groups of confined C4 guest in C4 A-C4-NaCl, C4 A-C4-KCl, C4 A-C4-RbCl, C4 A-C4-CsCl are strongly dependent on the nature of the cation and the relative intramolecular compression of the folded molecule of C4 directly influenced by the anchoring position of the carboxylate and ammonium group within the network and corresponding to strong 43.06% (Na^+) to 17.87% (Cs^+) compression of the extended linear length of C4.

In the C4 A-C3-LiCl (Figure 3g), C4 A-C3-NaCl (Figure 3h), C4 A-C3-KCl (Figure 3i), C4 A-C3-CsCl (Figure 3j), two confined protonated γ -aminobutyric acid C3 guests are encapsulated in the inner space between two $C4^{4-}$ anions, variably disposed in a slipping parallel to face to face arrangements. This network is reinforced by hydrogen bonding of six hydrated Li^+ , Na^+ , K^+ or four Cs^+ cations and six bridging water molecules, playing a crucial role in stabilizing the network. Both guest molecules of C3 are anchored via hydrogen bonding of ammonium groups forming two anchoring H-bonds with sulfonates ($d_{N-O} = 2.28$ Å) and two H-bonds with bridging water molecule connecting to sulfonate ($d_{N-O} = 2.18$ Å) and carboxyl groups ($d_{N-O} = 2.07$ Å)

forming encapsulated dimers. In addition, the carboxy groups is anchored via hydrogen bonding to bridging water molecule in the inorganic cationic layer of the network ($d_{N-O} = 1.78 \text{ \AA}$). The molecules of **C3** are highly compressed inside the cavity, presenting two all-gauche conformations C1–C2 and C2–C3 and in the case of **C4 A-C3-NaCl** and **C4 A-C3-KCl** an intramolecular hydrogen bond ($d_{N-O} = 2.28\text{--}2.36 \text{ \AA}$) between ammonium and carboxyl groups is stabilizing the highly folded conformation of the guests. In the case of **C4 A-C3-CsCl** one gauche conformation of C1–C2 is positioned at the neighboring end of carboxyl group coordinated to hydrated Cs^+ cations, which are subsequently connected to sulfonate groups via hydrogen bonding to the **C4 A** platforms. The encapsulated **C3** guests are stabilized *via* hydrophobic C–H (alkane chains) / π (calix[4]arene) short contact of contacts of 2.50–2.70 \AA , which play important role in confining guests inside the **C4 A** cavity. The $N_1\text{--}O_3$ distances between the ammonium and carboxylate groups of confined **C3** guest in **C4 A-C3-LiCl** and **C4 A-C3-KCl**, are strongly dependent on the nature of the cation, directly determining the anchoring positions within the network or internal hydrogen bonding and presenting S-type gauche-gauche 3.83 \AA (Li^+) or gauche-4.28 \AA (Cs^+) conformers or highly compressed gauche-gauche 3.30 \AA (Na^+) or 3.23 \AA (K^+) conformers, corresponding to 13.51% to 34.81% compression of the extended linear length of **C3**.

In the **C4 A-C2-LiCl** (Figure 3k), **C4 A-C2-NaCl** (Figure 3l), **C4 A-C2-KCl** (Figure 3m), **C4 A-C2-RbCl** (Figure 3n), **C4 A-C2-CsCl** (Figure 3o), on contrary to their more hydrophilic diprotonated 1,2-Diammoniumethane **AC2**, two protonated 2-aminoethanoic acid, **C2** guests are confined within the inner cavity consisting of two **C4 A** platforms disposed in a slipping parallel to face to face arrangements. Several hydrated Li^+ , Na^+ , K^+ , Rb^+ or Cs^+ cations and bridging water molecules play a crucial role in stabilization of the network. The molecules of **C2** are anchored *via* hydrogen bonding of ammonium groups to sulfonates ($d_{N-O} = 2.09 \text{ \AA}$) or *via* two bridging water molecules further connecting to sulfonates ($d_{N-O} = 1.97\text{--}2.05 \text{ \AA}$). In addition, the carboxyl groups are H-bonded ($d_{O-O} = 1.93 \text{ \AA}$) to sulfonate moieties of **C4 A** platform. The intramolecular hydrogen bonding ($d_{N-O} = 2.28 \text{ \AA}$) between ammonium group and carboxyl group contributes to the stabilization of the folded conformation of the guests **C2** under confinement. The guests of **C2** present one gauche conformations of C1–C2 of the alkane chains and they are not interacting *via* hydrophobic C–H(alkane chains)/ π (calix[4]arene) inside the **C4 A** cavity. The $N_1 - O_3$ distances between the ammonium and carboxylate groups of confined guests **C2** are 3.02–3.15 \AA and are related to the gauche conformation of the confined **C2** guest within the cavity of **C4 A** and corresponding to 15.00% compression of the extended linear length of **C2**.

Conclusion

Molecular recognition of the flexible biogenic molecules has long intrigued chemists on account of their important role in regulating protein structures, functions, and aggregation be-


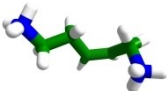





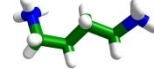
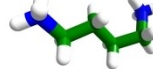
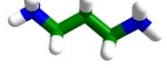
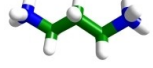
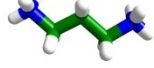
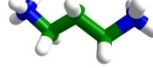

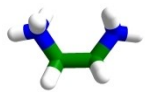
haviours.^{1–3} Simple molecular receptors can be used to recognize these systems with strained geometries and variable adaptive behaviours.

In this paper we highlighted that the 1, ω -diammonium-alkanes or the 1, ω -amino acids chains may be successfully constrained/anchored inside the p-sulfonatocalix[4]arene. Detailed comprehensive crystallographic characterization with more than 30 single crystal structures are supporting a complete survey on different structural behaviours that can affect the recognition events.

Variable relative spatial disposition of the p-sulfonatocalix[4]arene **C4 A** anionic platforms within the crystal strongly depend on the nature of alkali hydrated counter cations and induce a different dimensional disposition of the sulfonate and of the alkali cation anchoring points used for the guest binding. The guest molecules are double H-bonded *via* ammonium and carboxylate groups to the sulfonates and present a bent-geometry with one/two gauche conformations, unsymmetrically positioned in the terminal part of the alkane chain, buried within the hydrophobic part of p-sulfonatocalix[4]arene. The 1, ω -diammonium-alkanes are anchored *via* double ammonium-sulfonate bridges while 1, ω -amino acids are connected *via* combined ammonium-sulfonate / carboxylate water/alkali cation interactions on the rim of **C4 A** platform. The nature of the hydrated metal cations it is highly important in the positioning of the guest and determines its conformation upon recognition. In the case of 1, ω -diammonium-alkanes, the compression of longer molecules **AC5** and **AC4** follows the sequence: $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$ (Table 3), with a higher compression of the guests observed for Na^+ cations, which is almost twice stronger than for Cs^+ cations. This is related to their position closer to the sulfonate moieties on the upper-rim of p-sulfonatocalix[4]arene, that better stabilize the rigid cone conformation for the recognition space of the host. The Na^+ cations are probably fulfilling the best compromise to compensate the charge/H-bond interactions within the network. The same effect has been observed for 1, ω -amino acid guests for which the Na^+ cations are inducing a maximum folding with three or two gauche conformations, so that a strong hydrogen bonding is intramolecularly established between the ammonium and carboxyl groups of the folding **C4** and **C3** guests (Table 2).

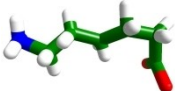
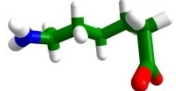



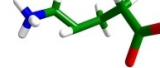
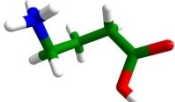
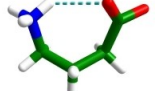
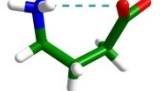
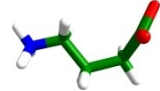
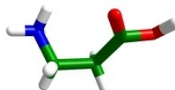
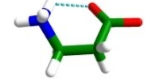
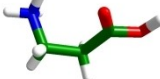
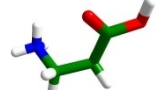
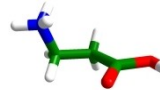
Another key function of p-sulfonatocalix[4]arene as receptor in water, is the burial of a part of the molecule of the guest within a confining space offered by its concave cavity and it is directly relating to progressive bent conformations of the alkyl chains under confinement. Regardless, it appears that the main driving forces for recognition are the steric compatibility of the alkyl chains fitting the cavity, optimal for the uncompressed 1,3-Diammonium-propane **AC3** guests, as well as intramolecular electrostatic/ hydrogen bonding stabilization of U-shape guests of γ -aminobutyric acid **C3** guests. The longer ones adopt folded conformations at different levels of compression depending on their molecular dimensional behaviours that can be detected in solution and are sufficiently kinetic stable under the confined conditions in the solid state, to allow a conventional structure determination by X-ray diffraction.

Table 2. Molecular conformations of 1, ω -diammonium-alkane, AC5 to AC2 guests encapsulated inside the p-sulfonatocalix[4]arene host.

Guest	LiCl	NaCl	KCl	RbCl	CsCl
AC5					
d_{N-N} [Å] ^[a]	5.6272	5.8231	5.8920	5.8348	6.7164
Compression ^[b]	23.98%	21.33%	20.40%	21.17%	9.26%
AC4	–				
d_{N-N} [Å]	–	5.0971	5.5127	5.5166	5.4447
Compression	–	17.05%	10.28%	10.22%	11.39%
AC3	–				
d_{N-N} [Å]	–	4.8239	4.9163	4.9061	4.8420
Compression	–	3.27%	1.44%	1.62%	2.91%
AC2			–	–	–
d_{N-N} [Å]	3.1339	3.1177	–	–	–
Compression	13.62%	14.07%	–	–	–

[a] d_{N-N} distance between the N atoms of the ammonium groups of encapsulated conformers, [b] Compression rate relative to the extended linear conformer. Compression% = $(L_{\text{linear}} - L_{\text{conformer}}) / L_{\text{linear}}$.

Table 3. Molecular conformations of 1, ω -amino acid C5 to C2 guests encapsulated inside the p-sulfonatocalix[4]arene host.

Guest	LiCl	NaCl	KCl	RbCl	CsCl
C5		–		–	–
d_{N-O} [Å] ^[a]	6.6118	–	5.6616	–	–
Compression ^[b]	11.53%	–	24.3%	–	–
C4	–				
d_{N-O} [Å] ^[a]	–	3.5394	4.4581	4.6328	5.0156
Compression ^[b]	–	43.06%	28.28%	25.47%	17.87%
C3				–	
d_{N-O} [Å] ^[a]	3.8315	3.3038	3.2313	–	4.2870
Compression ^[b]	22.70%	33.35%	34.81%	–	13.51%
C2					
d_{N-O} [Å] ^[a]	3.1179	3.0279	3.1459	3.1670	3.1579
Compression ^[b]	15.76%	18.19%	15%	14.13%	14.68%

[a] d_{N-O} distance between the terminal N atom of the ammonium and O atom of the carboxylate groups of encapsulated conformers; [b] Compression rate relative to the extended linear conformer. Compression% = $(L_{\text{linear}} - L_{\text{conformer}}) / L_{\text{linear}}$.

We mostly noticed the presence of broad signals in ¹H-NMR spectra of the guest molecules enclosed within p-sulfonatocalix[4]arene host. However in several cases, sharp signals have

been observed, but any clear correlation can be established between coupling constants obtained in solution and torsion angles measured in the solid state structures (Table 6S). This is

reminiscent with dynamic conformational equilibria of the confined guest with p-sulfonatocalix[4]arene host or with fast exchanges of the guest molecules in solution.

This contribution adds several new behaviours to the systematic rationalization and prediction of hydrophobic clustering in the p-sulfonatocalix[4]arene. Overall, these studies may provide new knowledge for understanding the dynamics and adaptivity of complex molecules under confined conditions, reminiscent of the specific binding of substrates in biological pockets.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amino acids · calixarenes · hydrogen bonding · molecular recognition · self-assembly

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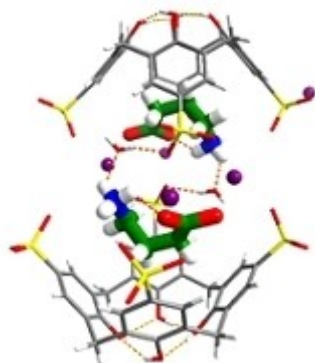
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Flexible guests: Molecular recognition of cationic 1, ω -diammonium-alkanes and 1, ω -amino-acids of variable lengths within *p*-sulfonatocalix[4]arene hosts sheds light on the constitutional adaptivity of flexible folded chains by maximizing multivalent contacts with the host receptor under confinement. A comprehensive screening of 30 single-crystal structures allowed the accurate determination of the folded guest molecules structures under confinement.



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Progressive Folding and Adaptive Multivalent Recognition of Alkyl Amines and Amino Acids in *p*-Sulfonatocalix[4]arene Hosts: Solid-State and Solution Studies



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