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ARTICLE TYPE

Solid-state assembly of carboxylic acid substituted pillar[5]arene and its host–guest complex with tetracaine

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The solid state structures of the carboxylic acid substituted pillar[5]arene PA5 host–guest complexes with ethanol and anesthetic drug tetracaine are reported. The PA5 forms inclusion complex with ethanol of 1:2 stoichiometry that assembles into hydrogen-bonded polymeric chains in the solid state. The macrocyclic cavity of PA5 can include large pharmaceutical molecules like tetracaine via a combination of different non-covalent interactions.

Pillar[n]arenes, first reported in 2008,[1] are synthetic macrocycles composed of hydroquinone units linked by methylene bridges at the *para*-positions. This new generation of macrocyclic hosts has received considerable attention for their unique symmetric electron-rich cavities and easy functionalization. The exceptional host–guest and self-assembly properties of pillar[n]arenes provide new opportunities for supramolecular chemistry and materials science.[2] The introduction of carboxylate anions at both rims of pillar[n]arenes leads to water-soluble macrocycles with confined pillar-shaped cavities.[3] Host–guest studies in aqueous media are always desirable because this is where the most biological processes takes place and it opens up new possibilities to explore the potential biopharmaceutical applications of these fascinating macrocyclic hosts.[4] The water-soluble pillar[5]arene (**PA5**) carrying ten carboxylate anions has been shown to form strong inclusion complexes with L-lysine, L-arginine and L-histidine.[5] Carboxylato-pillar[n]arenes show potential in the construction of supramolecular nanocarriers for drug delivery,[6] sensing of various biomolecules[7] and even virus inhibition.[8] However, no solid-state structural studies have been undertaken so far on these promising macrocycles. Here we report for the first time two X-ray structures of carboxylic acid substituted pillar[5]arene in the form of its host–guest complexes with ethanol and anesthetic drug tetracaine (Fig. 1). The structural aspects of carboxylic acid **PA5** inclusion capabilities, main non-covalent interactions between host and guest, as well as self-assembly of the resulting complexes in the solid state have been elucidated.

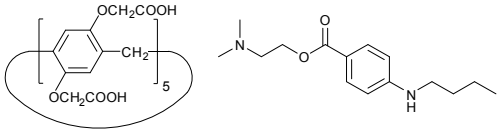

Fig. 1 Chemical structures of carboxylic acid substituted pillar[5]arene (**PA5**) and tetracaine.

Carboxylic acid substituted **PA5** is poorly soluble in water in the contrary to its carboxylate form, but we have found that its solubility in 1:1 water-ethanol mixture is much higher probably due to formation of inclusion complex with ethanol. We were successful in growing suitable crystals of **PA5** from water-ethanol mixture upon slow cooling of the solution. Single crystal X-ray analysis revealed that the inclusion complex **1** crystallizes in the triclinic P-1 space group with the asymmetric unit containing one carboxylic acid pillar[5]arene, two ethanol and numerous water molecules.

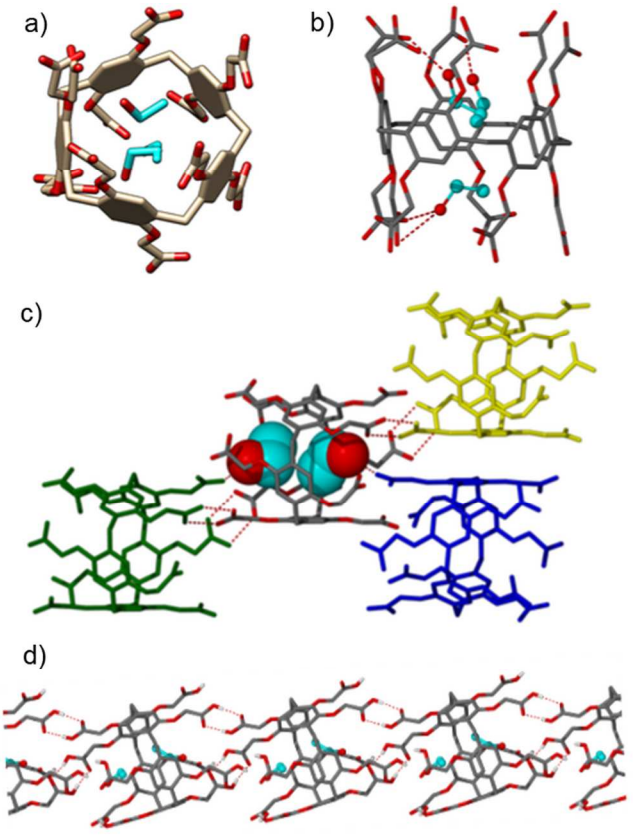

Fig. 2 Top (a) and side (b) views of the carboxylic acid substituted **PA5** inclusion complex **1** with ethanol highlighting hydrogen bonding between guest and host (note the disorder of ethanol and some of the **PA5** substituents); (c) the interactions between neighbouring **PA5**s: yellow and green **PA5**s form two pairs of strong hydrogen bonds to the central **PA5**, blue one is hydrogen bonded to ethanol included in the cavity of the

central **PA5**; (d) hydrogen-bonded chain of **PA5**. All hydrogen bonds are shown as dashed red lines

The cavity of **PA5** accommodates two ethanol guests, one of which was modelled as disordered over two positions, Fig. 2a. The hydroxyl groups of ethanol molecules are oriented toward carboxylic acid functions of macrocyclic host indicating hydrogen bonding with O···O distances in the range of 2.63-3.17 Å, Fig. 2b. It appears that inclusion of ethanol interferes with water wires that would probably otherwise exist inside **PA5** skeletons and as is seen in the **PA5** ethyl ester analogue.[9] The water wires in the nanotubes assembled from **PA5** ethyl ester derivatives are responsible for the selective proton transport along the channels.[10] Ethanol as a cosolvent seems to play a significant role both in solubilizing carboxylic acid **PA5** and stabilizing conformation of the macrocycle. It is not surprising in the light of recent studies on the template effect of solvents on high yield synthesis and interconversions of pillar[n]arenes.[11] It should be noted that there are no intra-molecular hydrogen bonds between neighbouring carboxylic acid moieties at **PA5** rims as reported for solution NMR study of this macrocycle in DMSO.[3] Instead of this there are numerous hydrogen bonds between carboxylic acid groups of adjacent symmetry-related **PA5**s, water molecules in the crystal lattice and ethanol molecules included into host cavity, Fig. 2c.

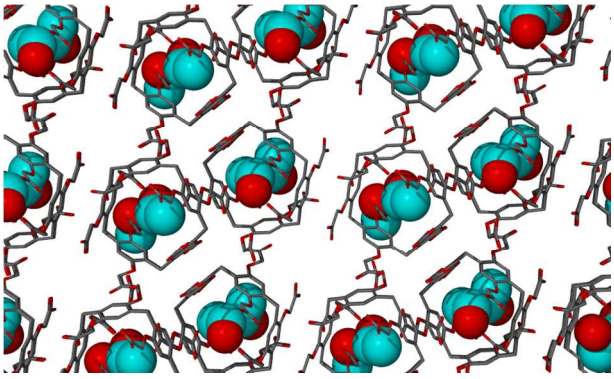

Fig. 3 Packing of **PA5**-ethanol host–guest complex **1** viewed along the *b* axis. Water molecules and hydrogen atoms removed for clarity. The guests are displayed in space-filling mode.

The packing behaviour of **PA5** is dominated by pairs of strong hydrogen bonds involving carboxylic acid functions of neighbouring **PA5** molecules (O-H···O distances in the range of 2.61-2.67 Å). Such intermolecular motifs occur at both rims of **PA5** resulting in the formation of hydrogen bonded chains of **PA5** molecules in the solid state, Fig. 1d. Ethanol molecules as guests also play a significant role in the self-assembly of neighbouring **PA5** by accepting hydrogen bonds from carboxylic acid groups of symmetry-related **PA5** macrocycles. Adjacent chains assemble in the crystal lattice via π···π and C-H···π interactions between external surfaces of **PA5** molecules, Fig. 3. It should be emphasized that carboxylic acid functions are crucial in the crystallization and self-assembly of **PA5** molecules and the behaviour of the corresponding carboxylate-**PA5** might be quite different both in solution and solid state. Indeed, it is known that anionic carboxylate **PA5** possess good solubility in water compared to the previously described neutral carboxylic acid **PA5** meaning that aqueous solubility of the macrocycle can be controlled by tuning the pH.

Water-soluble macrocycles, such as cyclodextrins, calixarenes crown ethers and cucurbiturils, have been widely studied as supramolecular hosts for the complexation (inclusion) of biorelevant and pharmaceutical molecules. The easy-to-make pillar[n]arenes with their rigid pillar-shaped molecular structures and electrodonating cavities have potential to enrich and expand the area of supramolecular drug improvement, delivery and sensing. We have chosen a tetracaine as a model drug to explore ability of carboxylic **PA5** to include large pharmaceutical molecules inside the macrocyclic cavity. Tetracaine is a potent anesthetic drug widely used in topical and spinal anesthesia, as well as in ophthalmology. However, as a local anesthetic, tetracaine shows a short duration of action and adverse side effects, such as cardiac and neurological toxicity, accompanied sometimes by skin or tissue irritation. In order to improve the applications of tetracaine, its inclusion into macrocyclic cavities of cyclodextrins,[12] *p*-sulfonatocalixarenes[13] and cucurbiturils[14] have been studied both in solution and solid state.

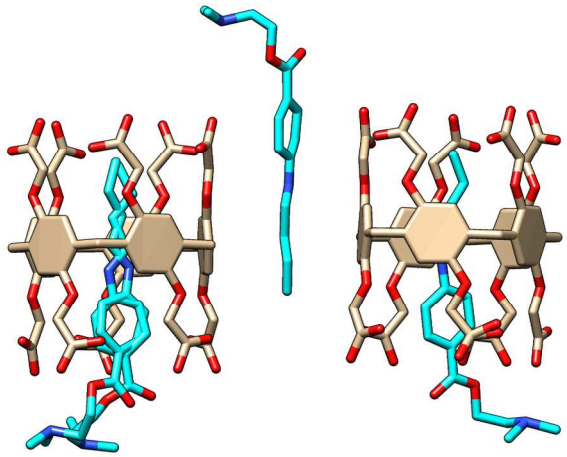

Fig. 4 The asymmetric unit of **PA5**-tetracaine host–guest complex **2**. One of the included tetracaine was modelled as disordered over two positions inside **PA5** cavity. Water molecules and hydrogen atoms removed for clarity.

We were able to grow single crystals of carboxylic acid **PA5** complex **2** with tetracaine from water-ethanol solution. The asymmetric unit comprises two symmetry distinct **PA5**s, three tetracaine and disordered water molecules. Both cavities of two crystallographically independent **PA5**s are filled with tetracaine guests. The remaining tetracaine is complexed externally to the **PA5** molecules with its aromatic core and butylamino chain inserted between external walls of two adjacent **PA5** macrocycles, Fig 4.

A closer look at the inclusion complex reveals that the tetracaine penetrates host cavity with the butylamino chain, while dimethylammonium end protrudes from one rim of **PA5** with the ammonium group hydrogen bonded to one of the carboxylic acid functions of the host (N-H···O distance 2.96 Å), Fig. 5a and 5b. The aromatic ring of tetracaine is enclosed within the wreath of ethoxy carboxylic acid moieties with some short C-H···π and C-H···O contacts between guest and host. The secondary amino group of butylamino chain is directed towards one of the phenyl ring of **PA5** (N-H···π centroid distance is 3.76 Å). Second crystallographically independent tetracaine-**PA5** inclusion

complex is quite similar to that previously described with the exception of tetracaine being badly disordered inside the cavity. This tetracaine was modeled as disordered over two positions with the occupancies 52 and 48 % using SAME, SIMU and DELU soft restraints. As mentioned earlier, the third independent tetracaine is complexed externally to the macrocyclic cavities. The host–guest complex **2** packs in columns that run along *a* axis with some tetracaine inserted between, Fig. 6. There is no pairwise hydrogen bonding between adjacent **PA5** in the column because of the strong engagement of **PA5** functionalities in the host–guest interactions with tetracaine molecules both *endo* and *exo* with respect to the macrocyclic cavities.

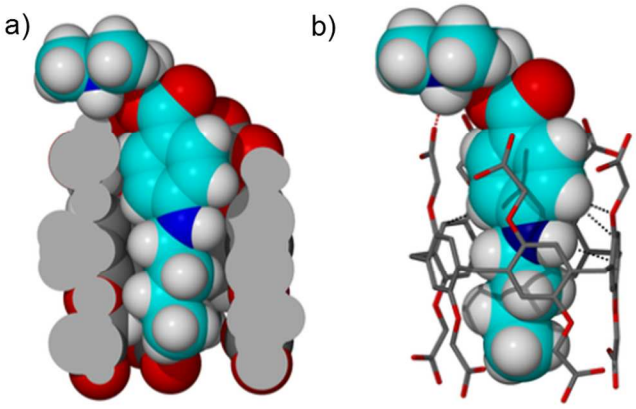

Fig. 5 **PA5**-tetracaine inclusion complex (a) **PA5** and tetracaine in space-filled representation with surface of the host molecule sliced perpendicular to viewing direction; (b) **PA5** in stick and tetracaine in space-filled representation highlighting host–guest non-covalent interactions.

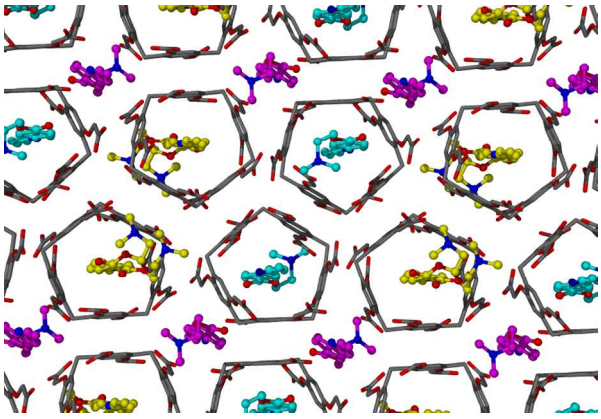

Fig. 6 Packing of **PA5**-tetracaine host–guest complex viewed along the *a* axis. The crystallographically independent tetracaine guests are displayed in different colours (blue, yellow included into **PA5** cavities and violet inserted between **PA5** external walls) in ball-and-stick mode. Water molecules and hydrogen atoms removed for clarity.

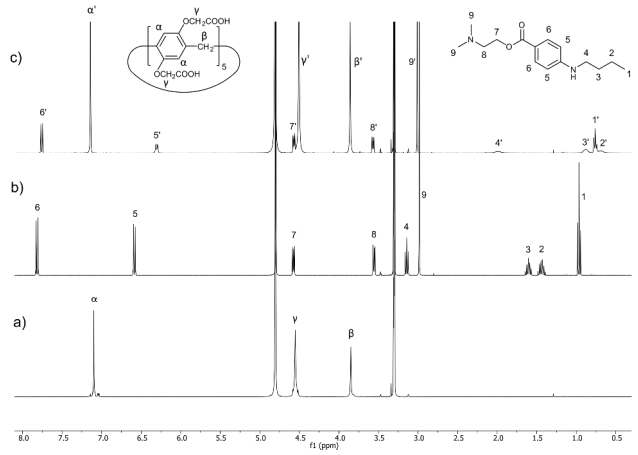

Fig. 7 The ^{1}H NMR spectra (CD_3OD) of (a) carboxylic acid substituted **PA5**, (b) tetracaine hydrochloride, (c) carboxylic acid substituted **PA5** and tetracaine hydrochloride at a ratio of 1:1.

The complexation of tetracaine with carboxylic acid substituted **PA5** was also studied in solution by ^{1}H NMR. The tetracaine inclusion within the host cavity was observed through upfield shifts of selected drug proton resonances, Fig. 7. All methylene and methyl resonances of aminobutyl aliphatic chain and aromatic resonances shown upfield shifts indicating that the drug is included into **PA5** via its butylamino group and phenyl ring. The small downfield shifts for methyl proton resonances of dimethylammonium group indicate their position beyond host cavity, which coincides with the crystal structure.

To summarize, ethanol plays a significant role in the solubilization of carboxylic acid substituted **PA5**, stabilization of its conformation and in the solid-state assembly due to formation of 1:2 host–guest inclusion complex. Our findings show the possibility to tune solubility and host–guest properties of carboxylic acid **PA5** in aqueous media by addition of the cosolvent. We have also shown that carboxylic acid **PA5** forms host–guest complex with anesthetic drug tetracaine. The complex is of 2:3 host–guest stoichiometry with tetracaine bound in two different ways, namely two independent tetracaine penetrate **PA5** cavities to form pseudorotaxane type inclusion complexes, while another is complexed externally to host cavities. These first examples of carboxylic acid **PA5** crystal structures allow better understanding of pillar[n]arene host–guest chemistry in aqueous media and expand the potential of these water-soluble macrocycles as 'nanoscale containers' for future biopharmaceutical applications.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental details, comments on the refinement procedure and X-ray crystallographic files in CIF format. See DOI: 10.1039/b000000x/

‡ **Crystal data for 1:** : $C_{59}H_{55}O_{37}$, *Mr* = 1356.0, triclinic, space group *P*-1, *a* = 12.7515(7), *b* = 13.5858(7), *c* = 21.4957(14) Å, *α* = 107.207(5), *β* = 99.278(5), *γ* = 103.727(5) º, *V* = 3346.4(4) Å^3, *Z* = 2, ρ_{calc} = 1.346 g·cm^{-3}, $\mu(Cu_{K\alpha})$ = 0.991 mm^{-1}, θ_{max} = 67.7 º, 21968 reflections measured, 12216

unique, 998 parameters, R = 0.084, wR = 0.247 (R = 0.096, wR = 0.261 for all data), *GooF* = 1.04. CCDC 1028289.

Crystal data for 2: $C_{155}H_{152}O_{84}N_6$, Mr = 3442.8, triclinic, space group P-1, a = 17.0487(9), b = 21.1862(8), c = 24.7335(10) Å, α = 76.225(3), β = 80.707(4), γ = 85.563(4)º, V = 8555.8(7) Å^3, Z = 2, ρ_{calc} = 1.336 g·cm^{-3}, $\mu(Cu_{K\alpha})$ = 0.949 mm^{-1}, θ_{max} = 58.9º, 49869 reflections measured, 24528 unique, 2467 parameters, R = 0.145, wR = 0.351 (R = 0.231, wR = 0.427 for all data), *GooF* = 1.06. CCDC 1028290.

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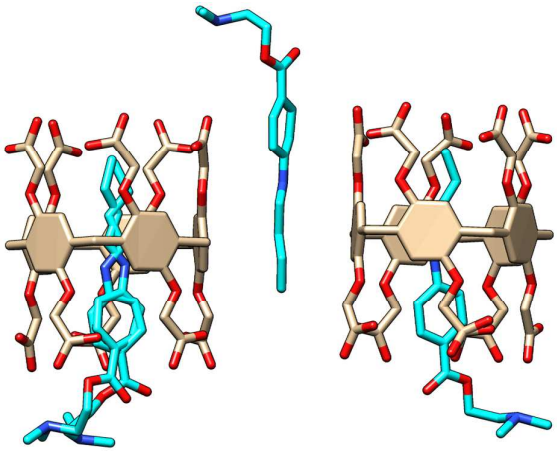

The first examples of carboxylic acid substituted pillar[5]arene structures in the form of its inclusion complexes with ethanol and anesthetic drug tetracaine are reported.

Solid-state assembly of carboxylic acid substituted pillar[5]arene and its host-guest complex with tetracaine

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