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pH-Responsive Pillar[6]arene-based Water-Soluble Supramolecular Hexagonal Boxes

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Abstract: We describe the preparation of the first water-soluble pH-responsive supramolecular hexagonal boxes (SHBs) based on multiple charge-assisted hydrogen bonds between peraminopillar[6]arenes 2 with the molecular "lid" mellitic acid (1a). The interaction between 2 and 1a, as well as the other "lids" pyromellitic and trimesic acids (1b and 1c, respecively) were studied by a combination of experimental and computational methods. Interestingly, the addition of 1a to the complexes of the protonated form of pillar[6]arene 2, i.e. 3, with bis-sulfonate 4a or 4b, immediately led to guest escape along with the formation of closed 1a₂2 supramolecular boxes. Moreover, the process of the openning and closing of the supramolecular boxes along with threading and escaping of the guests, respectively, was found to be reversible and pH-responsive. This study paves the way for the easy and modular preparation of different supramolecular HBs that may have myriad applications.

Supramolecular chemistry in confined spaces has attracted much interest in recent decades because it provides new opportunities in basic and applied sciences that may have implications on daily life.^[1] In this context self-assembled molecular containers such as cages^[2,3] and capsules^[4-6] play a pivotal role since they can be regarded as nano-reactors or nano-flasks where new phenomena may occur and new chemistry may be realized.^[7-11] For example, Rebek dimeric capsules have been used to affect the course of reactions and to probe different mode of isomerism^[9] while the Raymond and Fujita cages^[2,3] were used for catalysis in water.^[7,8] The deep cavitands have been mostly used to affect the course of photochemical reactions,^[10] while the hydrogen bond-based hexameric capsules of Atwood, which structures, in solution, have been known for nearly twenty years now,^[5] have been utilized to catalyze reactions in organic solvents mainly in the last five years.^[11] However, the synthesis of hydrogen-bondbased supramolecular containers in competitive solvent like water remains challenging^[12] but the importance of the preparation of such systems cannot be overstated.

In the last decade, the cylindrical-shaped macrocycles, pillar[n]arenes,^[13] have emerged as an attractive building block in supramolecular chemistry.^[14] This occurred, inter alia, since

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molecular manipulations at both sides of these easy-to-prepare symmetric macrocycles is straightforward.^[14] However, contrary to the concave macrocycles such as calix[n]arenes, deep cavitands, resorcin[4]arenes and more, that can self-assemble into closed molecular containers, [4-6] their symmetric cylindricalshaped counterparts, pillar[n]arenes, tend to form nano-tubular structures in their rim-to-rim self-assembly.^[15] Therefore, not surprisingly, in spite of the wealthy and varied chemistry of these symmetric double entranced macrocycles, pillararene-based supramolecular cages, capsules or boxes have not been reported yet. Given our ongoing interest in the synthesis and applications of pillar[n]arenes derivatives as anti-biofilm agents and ¹²⁹Xe-NMR biosensors, ^[16,17] and our recent findings that per-amino- and per-caboxylato-pillararenes can serve as low molecular weight organic gelators,^[18] we became interested in the potential of forming supramolecular hexagonal boxes (SHBs) with these species (Figure 1). Based on their structural characteristics we hypothesized that one can cover the hexagonal-body of per-diethyl-amino-pillar[6]arenes (PAP[6]A, 2) with hexagonal "lids" such as mellitic (1a), pyromellitic (1b) and trimesic (1c) acids via multiple charge-assisted hydrogen bonds which in turn may provide SHBs. Herein we disclose the first pillar[6]arene-based water-soluble SHBs obtained by simple mixing, in water, of 2 or 3 with 1a-c according to equations 1 and 2 (Scheme 1). Spectroscopic (NMR, diffusion NMR, DOSY and ESI-HRMS) and computational methods as well as host-guest interactions with di-sulfonates (4a and 4b) reveal the existence and the structural features of these intriguing SHBs. Compounds 4a and 4b were also used to demonstrate that the 1a₂2 HBs are, in fact, pH-responsive supramolecular boxes. These findings pave the way for easy and modular access to a myriad of tunable pillararene-based supramolecular boxes and capsules that may have many different applications.



Figure 1. Rational design of pillar[6]arene-based supramolecular HBs and structures of the compounds involved in the study.

PAP[6]A 2, which was prepared as previously described (see Figures S1-S4 in the supporting information (SI)),^[18] is poorly soluble in water in contrast to 1a-c. Therefore, 2 was reacted with acetic acid (12 equiv.), to form its water-soluble derivative PAP[6]A-HOAc (3), before mixing with 1a-c (Eq.1, Scheme 1). In the case of mellitic acid (1a) that has high solubility in water the solution of this "lid" was also simply added to neat PAP[6]A 2 until complete dissolution (Eq. 2, Scheme 1). We assumed that in line with the multivalency concept,^[19] on the one hand, and the relatively high acidity^[20] of **1a-c**, on the other, these "lids" would immediately replace the acetate ions along with acetic acid release. Indeed, when 3 was mixed with two equivalents of 1a, 1b or 1c significant changes in the ¹H and ¹³C-NMR spectra were observed (Figures S7-S12). As seen in Figures S7 and S10, the ¹H NMR peaks and some of the ¹³C-NMR peaks of 3 and 1a broadened upon addition with 1a. This broadening was accompanied by chemical shifts changes of all components. In addition, the chemical shift change ($\Delta\delta$ 0.14 ppm) of the narrow peak at 2.03 ppm, attributed to the acetate ion also suggests the release of acetic acid due to the addition of 1a. Similar behavior was also observed for the mixtures of 3 with 1b or 1c (see Figures S8-9 and S11-12) although there the line broadening was much less pronounced.



Scheme 1. Reaction schemes for the preparation of the supramolecular HBs.

Taking into account the geometry and symmetry of **2** and **1a-c**, the above results appear to indicate the formation of the first SHBs based on multiple charge-assisted hydrogen bond interactions between these components in water. However diffusion NMR and mass spectrometry provide the much needed further evidence for the formation of these HBs.

Diffusion NMR and diffusion-ordered spectroscopy (DOSY) which are powerful non-invasive techniques for characterizing supramolecular systems in solution^[21] have been used extensively to study supramolecular cages and capsules.^[5c,22] Indeed, diffusion NMR and DOSY measurements confirmed the formation of **1a**:**2**:**1a**, **1b**:**2**:**1b** and **1c**:**2**:**1c** systems as clearly demonstrated in Figures 2 and the data presented in Table 1.



Table 1. Diffusion coefficients of the species involved.

Sustam	D_{PAP[6]A} x 10^{5 [а]} .	D _{"lid"} x 10 ^{-5 [a]}		D_{асон} х 10^{-5 [а]}			
System		mix.	free	mix.	free		
3	0.16 ±0.01		-	0.75 ±0.01	1.02		
1a₂2 [♭]	0.16 ±0.01 0.14°	0.14 ^c	0.42 ^c	0.98 ±0.01			
1 b₂2^b	0.17 ±0.01	0.17 ±0.01	0.48 ±0.01	0.92 ±0.04	±0.01		
1c₂2 ^b	0.17 ±0.01	0.17 ±0.01	0.48 ±0.01	0.92 ±0.04			

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 $^{[a]}$ in cm²s⁻¹ units, obtained from ¹H diffusion NMR unless stated otherwise; $^{[b]}$ In the presence of 12 eq. of CH₃COOH; $^{[c]}$ obtained from ¹³C diffusion NMR, concentrations were double the ones used in ¹H diffusion NMR, only one experiment.

From the tabulated data in all three cases one can conclude that the "lids" (1a-c) and the hexagonal body 2 are strongly bound and diffuse together as a single entity.^[22a] The attachment of 1ac to 3 is accompanied by a near complete release of AcOH all in line with the expectations from the formation of SHBs. For further corroboration, ESI-TOF mass spectra for all three complexes were also measured. As shown in Figure 3 and Figures S13-S15, the compositions of all three types of supramolecular systems revealed the expected mass spectra, showing intense peaks at m/z of 2605.4, 2429.5 and 2341.5 which correspond with the mass of the $1a_22$, $1b_22$ and $1c_22$, respectively. Also the experimental isotopic patterns of these peaks were found to be in accordance with the calculated ones (Figures S13-S15). Note also that the obtained mass spectra revels low intensity m/z peaks that correspond to $1a_32$ (Figure 3), $1b_32$ and $1b_42$ (Figure S13) and $1c_32$ (Figure S15) along with peaks corresponding to 1a-c2.



Figure 3. MS spectrum of the supramolecular HB 1a₂2.

All these results are consistent with the formation of $(1a-c)_22$ -type complexes but does not probe necessarily that the formed

complexes are indeed SHBs. Although this is in fact a plausible option due to the geometry, the multivalency, and the relative acidities of the different species involved in the reactions, we still need to eliminate the possibility that these electron poor aromatic compounds reside inside the cavity of pillararene 2 or even are attached to 2 externally. Unfortunately the ultimate SHB 1a₂2 cannot be followed by ¹H-NMR so we focused our NOE studies on the solution of 1b₂2. Since conventional NOESY and ROESY (mixing times, t_M , of 400 and 800ms) were uninformative we turned to 1D NOE which showed, after screening a wide range of t_{M} s, that at shorter mixing times the NOEs between the aromatic protons of 1b and the aromatic and bridge protons of 2, which are at the center of the molecules, are not observable while that with other peaks are (Figure S17), implying that indeed 1b resides in the proximity of the portals of 2 (see Figures S16-S17 and the short discussion in the SI)

To corroborate our findings even further we turned to computational methods. Due to the large size of 2 ($C_{114}H_{192}N_{12}O_{12}$, M_w = 1923), we chose PM6 semi-empirical Hamiltonian to calculate these species.^[23] The accuracy of semiempirical methods is certainly lower than that of the density functional theory ones. PM6, however, was shown to reproduce the heats of formation and geometries of small organic molecules with a decent accuracy.^[23] This method was also recently used by Rescifina and coworkers to calculate large supramolecular capsules.[11e,f] In addition, we used conductorlike polarizable continuum model (CPCM) to calculate these capsules in water.^[24] This model of course ignores the solvation effects, which have significant influence on both structure and energy of the molecule. However, estimates and trends can still be made based on this level of calculations. Thus the structures of 2,1a-c and their 1:2 complexes, i.e. 1a₂2, 1b₂2 and 1c₂2, were optimized, and Gibbs free energies for the formation of 1a₂2, 1b₂2 and 1c₂2 were extracted from frequency calculations. The optimized structure of 2 reveal the hexagonal shape of this macrocyce (Figure 4). Interestingly, it was found that eight out of 12 diethylaminoethyl groups lie in the same plane of the aromatic rings, but the four remaining groups adopt an endo position toward the hexagonal plane of the macrocycle (Figure 4, see top view of 2). The reaction of 2 with two equivalents of 1a was found to be highly favoured having ΔG value of -583 kcal/mole, probably, due to the formation of multiple multivalent charge-assisted hydrogen bonds, i.e. carboxyl-amine interactions.²⁵ Moreover, the resulting structures show tightly closed complexes of the 1a₂2-type having a hexagonal shape where almost all the diethylamine groups are now in exo position to the plane of the macrocycle. Expectedly, the reaction between 2 and two equivalents of 1b or 1c (four or three carboxylic groups each) was found to be less exergonic than the abovementioned reaction, but yet high, with a ΔG values of -352 and -240kcal/mole, respectively (see Figure S18-S19, SI). Importantly, when we tried to calculate the optimized structure of 2 with 1b, the narrowest "lid", nested in the cavity of 2, calculations did not converge. These results clearly corroborate the notion that the planar compounds 1a-c indeed act as "covering moieties" for the hexagonal body of pillar[6]arene 2, thus forming in fact SHBs.

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Figure 4. The calculated structures of 2 and its $1a_22$ complex.

With these fascinating structures in hands we next asked the question of whether these compounds can host appropriate guests and act as molecular capsules. Since others and we, found that 3 is a good host mainly for sulfonates compared to other guests, we focused our attention on the hexane- and the decane-disulfonates (4a and 4b, respectively).^[26] Figure S20 shows the ¹H-NMR spectra of 4a and 4b in the presence of 3. The significant up-field shifts of more than 2 ppm observed for 4a and 4b clearly imply that these aliphatic di-sulfonates are threaded in the cavity of 3, thus forming pseudo rotaxanes.^[27] Therefore 4a and 4b should, in principle, be suitable guests for examining if the most effective "lid" i.e. 1a indeed forms with 3 pH-responsive SHBs. Figure S20 also shows that the formation of the complexes of 4a and 4b with 3 increase the complexity of their ¹H NMR spectra, probably by preventing aromatic ring flip and thus fast interconversion of the different isomers of the pillararenes.^[28] Interestingly, despite the fact that ITC showed that the association constants (Kas) of 3 with 4a and 4b, are $2.16\pm0.1\times10^4$ M⁻¹ and $3.16\pm0.04\times10^4$ M⁻¹, respectively (Figure S21), we found, in both cases, that addition of 1a to these complexes resulted in the release of the guest trapped in 3 as shown in Figure 5 and in Figures S22 and S23. This guest escape actually provides an additional indirect proof for the formation of SHBs in the case of 1a and 2. In addition, when 4 equivalent of 4a or 4b were added to the aqueous solution of the pre-prepared (1a)₂2 SHBs no guest penetration was observed even for days. This was true even when an excess of 10 equivalents of 4a or 4b were added to the closed box 1a₂2. Giving the pKa values of all components involved in the abovementioned supramolecular process, we hypothesized that opening and closing of the box along with threading and escaping of the guest, respectively, will be sensitive to pH changes of the system. The pKa values of all six carboxylate groups in 1a are in the range of 1.40 to 6.96, because of the fact that all carboxylic groups are attached to the same aromatic

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ring.^[20] The pH value of the $1a_22$ solution in the presence or absence of the disulfonate guests was found to be ~6. Therefore, we assumed that acidifying the solutions will cause an opening of the box along with threading of the guest into the cavity of **2**.



Figure 5. The pH-responsiveness of box **1a**₂**2** in the presence of guest **4a**; Partial ¹H-NMR spectra (400 MHz, 298K, D₂O) of a) Box **1a**₂**2**, pH = 6; b) The sample in (a) after addition of 4 equivalents of **4a**, pH = 6; c) Sample (b) after addition of DCI in D₂O, pH = 1; d) Sample (c) after addition of NaOH, pH = 7. The concentration of **2** was 3.8 mM in all the samples.

Indeed, as depicted in Figure 5 (see also Figures S22 and S23), lowering the pH value of a solution containing the closed box $1a_22$ and excess 4b, from 6 to 1, led immediately to box opening and threading the guest (Figure 5c). Moreover, raising the pH value back, from 1 to 7, causes immediate box closure along with de-threading of the guest (Figure 5d). We could repeat this process by addition of acid and base. These results provide further evidence for the existence of the SHBs, and show that these structures are, indeed, pH-responsive supramolecular boxes as illustrated in Figure 6.

A. guest escape while closing the box



Figure 6. Schematic representations of a) guest release from 3 by 1a (x = OAc⁻), and b) the pH-response of the water-soluble $1a_22$ box along with guest release and encapsulation upon addition of NaOH or HCl, respectively. Compound 6 is PAP[6]A•HCl.

In conclusion, by closing the per-alkylamino portals of the hexagonal-shaped pillar[6]arene 2 with 1a, we have created the first. pH-responsive, water-soluble pillar[6]arene-based supramolecular hexagonal boxes based on multiple chargeassisted hydrogen bonds. The formation and elucidation of the structure of these SHBs was performed by a combination of spectroscopic and computational methods. Interestingly, the addition of the "lid" 1a, to per-amino-pillar[6]arene that host 4a or 4b, immediately led to guest escape along with formation of closed boxes. This process was found to be reversible and pHdependent thus paving the way for easy and modular preparation of many such pH-responsive supramolecular HBs that may have different applications. Inverted and larger SHBs are currently under investigation in our group and will be reported in due course.

Keywords: molecular box • pillar[6]arene • supramolecular chemistry • mellitic acid • multivalency

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The first water soluble, pHresponsive, supramolecular hexagonal boxes (HBs) based on multiple charge-assisted hydrogen bonds were prepared by simple addition of "lids" to the per-diethylamino-pillar[6]arene **2**. These supramolecular HBs can be obtained from simple components and in a modular way thus paving the way for the preparation of different pH-responsive HBs that may have myriad applications.

