Volume 24 Number 12 28 March 2022 Pages 2181-2350

CrystEngComm

rsc.li/crystengcomm



ISSN 1466-8033



COMMUNICATION

CrystEngComm



COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: CrystEngComm, 2022, 24, 2213

Received 18th February 2022, Accepted 3rd March 2022

DOI: 10.1039/d2ce00232a

rsc.li/crystengcomm

Electrostatic co-assembly of pillar[n]pyridiniums and calix[4]arene in aqueous media†

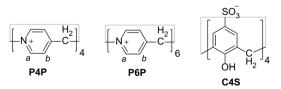
Kateryna Kravets, Mykola Kravets, Helena Butkiewicz, Sandra Kosiorek, Volodymyr Sashuk ** and Oksana Danylyuk **

Cationic pillar[n]pyridiniums and anionic p-sulfonatocalix[4]arene co-assemble into all-organic supersalts through encaging of the supercation units within/between the capsules that emerge from superanion pairs. The encapsulation occurs both in the solid state and in solution and allows the base-sensitive cationic pillar[n] pyridiniums to survive under otherwise destructive conditions. This property of supersalts makes them promising repositories for chemically vulnerable charged entities.

Electrostatic interactions play a key role in supramolecular chemistry, and they are also central to biology as the majority of biological macromolecules bear a charge which helps to regulate their functions. For example, DNA is negatively charged, proteins can be positively or negatively charged depending on the pH, etc.1 While Nature has mastered the rules of directed self-assembly in water and biological fluids, the assembly of synthetic molecular building blocks towards predictable complex architectures in an aqueous environment is still a challenge. Introduction of multiple charged functionalities into various macrocyclic platforms is an attractive strategy for fostering polyvalent interactions between assembling components and providing aqueous solubility.² Besides fundamental host-guest chemistry, macrocyclic hosts such as calix[n] arenes, cucurbit[n] urils and cyclodextrins have been richly exploited to design large, well organized assemblies and architectures, like supramolecular polymers,3 micelles,4 vesicles,5 giant polyhedra6 and supramolecular frameworks.7 We report here an aqueous selfassembly driven by the complementarity in charge and shape between two families of oligocharged macrocyclic hosts cationic pillar[n]pyridiniums and anionic p-sulfonatocalix[4] arene.

Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: odanylyuk@ichf.edu.pl

Pillar[n]pyridiniums (P[n]Ps) are permanently charged cationic macrocycles of electron-deficient cavities, now available in two sizes - the rigid square-shape tetramer (P4P)⁸ and the flexible roughly hexagonal hexamer (P6P) (Scheme 1). 9 P[n]Ps have been shown to act as versatile nanoreceptors for the visual detection and differentiation of linear diacids.10 aromatic and fatty p-sulfonatocalix[4] arene (C4S) is a key player in aqueous supramolecular chemistry and crystal engineering, with tremendous applications ranging from simple host-guest systems¹¹ to sophisticated drug delivery ensembles,¹² sensors,13 vesicles,14 crystals,15 and in interactions with proteins, 16 to name a few. Given the propensity of P[n]Ps to trap water wires or clusters8,9 and of C4S to include intracavity water molecules via non-conventional $OH \cdots \pi$ hydrogen bonding, 17 we anticipated a peculiar interplay between their combined supramolecular cavities and water molecules. Interestingly, our hybrid pillar[n]pyridinium/ calix[4]arene systems are devoid of any coordination or classical hydrogen bonding interactions between macrocyclic components, rendering the assembly guided, besides electrostatic attraction, by less conventional interactions, such as anion $\cdots \pi^+$, anion $\cdots \pi^+ \cdots$ anion, and $\pi \cdots \pi^+$. We show that such self-assembly is indeed feasible and provides a useful pathway to create hybrid co-assemblies built from oppositely charged macrocycles in aqueous media. We also discuss the ability of the co-assemblies to improve the chemical stability of P[n]Ps both in solution and in the solid state.



Scheme 1 Chemical structure of pillar[4]pyridinium (P4P), pillar[6] pyridinium (P6P), and *p*-sulfonatocalix[4]arene (C4S).

 $[\]dagger$ Electronic supplementary information (ESI) available: Experimental details, additional figures, and X-ray crystallographic files in CIF format. CCDC 2127199 and 2127200. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2ce00232a

Communication

P4P and C4S are a perfect match in terms of charge, shape, and symmetry. Both macrocycles have good solubility in water. However, mixing of their aqueous solutions results in rapid clouding and precipitation of white microcrystals. This demonstrates a very strong interaction rapidly leading to a product of much lower solubility than the starting components of the assembly. In order to slow down the formation of a new low-soluble phase, we turned our attention to the replacement of the self-assembly and crystallization environment from aqueous solution to agarose hydrogel medium. Crystallization in gel has long been recognized as a simple, effective, and inexpensive method for improving the quality of single crystals, for tuning the crystal size and morphology, for the inhibition or promotion of nucleation, and even for the control of crystal forms. 18 As a crystallization set-up we used a U-tube filled with agarose gel with one arm filled with an aqueous solution of P4P and another arm with a solution of C4S. Such crystallization involving diffusion of each macrocyclic component through the gel medium succeeded in obtaining yellow single crystals of the product. The crystals were recovered manually from gel and characterized by single crystal X-ray diffraction. The isolated solid form is a highly symmetric complex of P4P with C4S $(P4_2/m)$ space group) of 1:1 stoichiometry as can be expected from perfect charge complementarity. However, two different ways of complexation between macrocyclic components are manifested in the crystalline assembly, as shown in Fig. 1A. First is the inclusion capsular arrangement of two C4S molecules holding one P4P (colored in cornflower blue) with entrapped water molecules (Fig. 1B). One of the water molecules O2W sits exactly in the center of the small P4P cavity at the intersection of the mirror plane and the two-fold rotation axis (Fig. 1C). This intracavity water molecule is in the same distance from all four pyridinium walls of P4P suitable for O-H \cdots π^+ hydrogen bonding. The O…centroid distances of 3.10 Å are surprisingly short, even shorter than the O-H $\cdots\pi$ hydrogen bonds between intracavity water molecules embedded into C4S, as determined from neutron diffraction data (3.12-3.15 Å).17b Two other water molecules reside over each rim of the P4P macrocyclic box interacting with the intracavity water molecule via O-H···O HB (2.73 Å) in the nearly linear arrangement (Fig. 1D). The electron-deficient skeleton of P4P interacts with the electronrich inner walls of C4S and its anionic upper rim via a set of non-conventional interactions (Fig. 1E). There are anion $\cdots \pi^+$ short contacts between two opposite sulfonate groups of C4S and two π^+ aromatic systems of **P4P**, with O(sulfonate) ···C(pyridinium) distances in the range of 2.93-3.22 Å. The interaction energies of such anion- π^+ complexes are known to be dominated by strong electrostatic effects exhibiting very large binding energies. 19 Additionally, the $\pi \cdots \pi^+$ interaction between the aromatic walls of C4S and P4P (the interplane separation being 3.57 Å) reinforce the capsular assembly. Also, $(C-H)^+ \cdots \pi$ and $(C-H)^+ \cdots O^-$ interactions between methylene and pyridinium (C-H)+ donors of P4P and

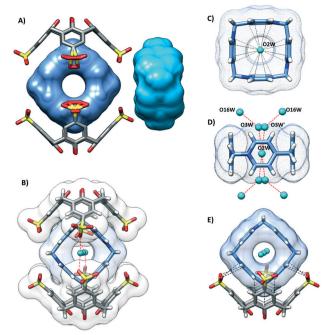


Fig. 1 A) Expanded asymmetric unit of the P4P–C4S co-assembly, wherein two crystallographically non-equivalent P4P are colored in cornflower blue and sky blue, and all water molecules have been omitted for clarity; B) capsular 1:2 P4P–C4S ensemble with trapped water molecules (in cyan) inside the P4P cavity; C) water molecule in the exact center of the P4P cavity interacting with electron-deficient pyridinium walls of P4P, wherein the O···centroid distances are of 3.10 Å; D) the expansion of a hydrogen bonded network around an intracavity water molecule; E) anion··· π ⁺ and (C–H)⁺··· π interactions between C4S and P4P (in black dashed lines); π ··· π ⁺ interactions between C4S electron-rich and P4P electron-deficient rings are not shown for clarity.

C4S contribute to the complexation. Another crystallographically independent P4P (colored in sky blue) resides in the cage formed by exo-walls of four C4S molecules (Fig. S1†). The complexation is again realized via a set of anion··· π^+ , π ··· π^+ , and (C-H)⁺···O⁻ interactions. The center of the P4P cavity is also occupied by a water molecule.

The crystallization of the larger hexacationic P6P with C4S posed a similar challenge of charge-neutralization induced precipitation. In this case the liquid-liquid diffusion of layered aqueous solutions of C4S and P6P in the NMR tube has been successfully applied to slow down nucleation and obtain single crystals of the P6P-C4S complex. Single crystal X-ray diffraction revealed the 2:3 P6P-C4S co-assembly to be in the $P\bar{1}$ space group, comprising 2 P6P hexacations and 3 C4S, Fig. 2A tetraanions. Again, there are two modes of complexation in the solid state: two C4S molecules hold one P6P molecule in the capsule-type arrangement, and one C4S molecule shroud one P6P molecule in the open geometry. Interestingly, the P6P conformation is different from the honeycomb columnar shape with all the aromatic walls aligned. Such a columnar conformation was previously confirmed in the up to now solely reported crystal structure of **P6P** in the form of its hexachloride salt hydrate. Here, the

electron-rich aromatic systems or sulfonate oxygen atoms of

CrystEngComm Communication

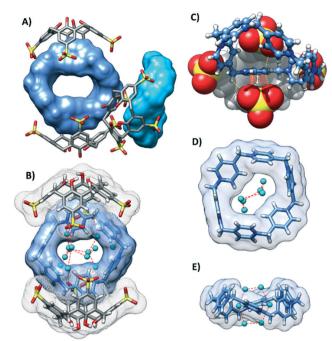


Fig. 2 A) Asymmetric unit of the P6P-C4S co-assembly, wherein two crystallographically non-equivalent P6P are colored in cornflower blue and sky blue, and all water molecules have been omitted for clarity; B) capsular 1:2 P6P-C4S ensemble with included and surrounded water molecules (in cyan); C) anion $\cdots \pi^+$ and $(C-H)^+ \cdots O^-$ interactions between C4S and P6P (in yellow dashed lines); $\pi \cdots \pi^+$ interactions between C4S electron-rich and P6P electron-deficient rings are not shown for clarity; D) hexameric ice-like water cluster included in the P6P cavity; E) side view of the P6P and trapped water cluster.

P6P nanoring in the capsular assembly is significantly distorted from the columnar geometry with two opposite aromatic rings oriented roughly perpendicular with respect to their neighboring walls (Fig. 2B). Such a distorted conformation of P6P is similar to the theoretically predicted saddle-like P6P geometry in aqueous solution.9 Two twisted aromatic walls of P6P are inserted into pinched cone C4S cavities suitable for anion- π^+ -sandwiching (Fig. 2C). The O(sulfonate)···C(pyridinium) distances are in the range of 3.01–3.33 Å (the O⁻···centroid distances in the anion– π ⁺sandwich are 3.08 and 3.15 Å). The $(C-H)^+ \cdots \pi$ interactions between methylene and pyridinium (C-H)+ donors of P4P and electron-rich aromatic systems of C4S contribute to the complexation. The central elongated hole of P6P is occupied by 6 water molecules in an ice-like chair arrangement, (Fig. 2D and E). Two of these water molecules reside in the central part of the cavity and are in close contact with four internal pyridinium walls evidencing $O-H\cdots\pi^+$ interactions, with O…centroid distances in the range of 3.00-3.34 Å. The hexameric water clusters are not isolated, but hydrogen bonded to more water molecules surrounding the capsular assembly and to sulfonate groups of the C4S molecules. Another type of complexation is the 1:1 open complex, with P6P in a different conformation, in which all pyridinium rings are twisted alternately in and out from the macrocycle plane (Fig. S2†). While the **P6P** position is almost vertical in

the capsular assembly, here the P6P is arranged slant-wise with respect to C4S molecular axes. This assembly is also spanned and surrounded by multiple water molecules; however, detailed analysis of the interaction mode is hampered by heavy disorder of P6P and water molecules.

Having established the structure of the supersalts, we proceeded to the study of the chemical properties of the coassembled components. Whereas C4S can generally be considered chemically resistant, P[n]Ps, like other pyridinium containing macrocycles, 20 are prone to deprotonation, which ultimately leads to irreversible structural changes and limits their application scope. We wondered if the co-assembly of P[n]Ps with C4S can improve their chemical stability. We prepared crystalline powders of P4P, P6P, and their complexes with C4S,

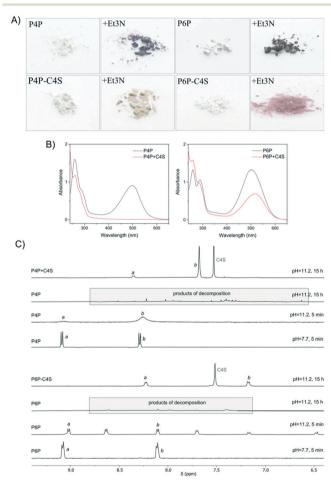


Fig. 3 A) Photographs of the powders of P[n]Ps and their complexes with C4S before (left) and after dropping triethylamine (right); B) UVvis spectra of P[n]Ps and their mixtures with C4S (1.5 eq.) in 0.8 M Tris buffer (pH \approx 11.2). A signal with a maximum close to 500 nm corresponds to the deprotonation and is responsible for the red color seen by the naked eye; C) partial ¹H NMR spectra of the solutions of P[n]Ps and their mixtures with C4S (1.5 eq.) in 0.8 M Tris buffer (pH \approx 11.2). For comparison, the spectra of P[n]Ps at near neutral pH are also shown. While free macrocycles practically completely decompose after 15 h, the complexed P[n]Ps remain intact. The acquired chemical resistance can be accounted for by the encapsulation of the cationic macrocycles within C4S cavities manifested by large upfield shifts of proton resonances belonging to P[n]Ps.

in solution.

and treated them with triethylamine, a common organic base $(pK_a = 10.7)$. The effect was immediate (Fig. 3A). The initially white neat P[n]P powders instantaneously turned dark, while the same colored C4S samples remained almost unchanged (P4P) or changed slightly (P6P). The visual differences between **P4P** (pale yellow) and **P6P** (pink, indicating deprotonation) correlate well with the base's access to each macrocycle in the crystal lattice. Smaller and better protected P4P is evidently less reactive than larger and more exposed P6P. The same behavior can be seen in the solution. While the alkaline aqueous solution of P4P mixed with C4S (pH ≈ 11.2) shows no sign of deprotonation, P6P under the same conditions deprotonates to some degree (Fig. 3B). Importantly, co-assembly with C4S not only attenuates or even ceases the deprotonation but also helps to avoid the decomposition, which is observed over time for the unprotected P[n]Ps (Fig. 3C). Such a marked change in reactivity can be rationalized by the encapsulation of P[n]P macrocycles within the C4S cavity that takes place both in the solid state and

Communication

In conclusion, pillar[n]pyridiniums and p-sulfonatocalix[4] arene co-assemble in aqueous media through encaging of the cationic pillar[n]pyridinium units within/between the capsules that emerge from superanion calix[4] arene pairs. The decisive supramolecular forces responsible for the co-assembly and supramolecular architecture are electrostatic attractions between oppositely charged macrocycles combined with specific anion $\cdots \pi^+$, anion $\cdots \pi^+ \cdots$ anion, and $\pi \cdots \pi^+$ interactions. The conshaped calix[4] arene cavity serves as host for the cationic pillar[n]pyridiniums in both co-assemblies, while pillar[n] pyridinium cavities are further filled with either a single water molecule in P4P or a hexameric water cluster in P6P. The encaging and protection of pillar[n]pyridiniums by calix[4]arene take place both in the solid state and in solution, and this allows the base-sensitive cationic macrocycles to survive under otherwise destructive conditions. This ability of supramolecular supersalts to improve the chemical stability of pillar[n]pyridiniums makes them promising repositories for chemically pregnable charged entities.

This project was funded by the National Science Centre of Poland (grant PRELUDIUM BIS-1 no. 2019/35/O/ST4/01865).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) B. Honig and A. Nicholls, Science, 1995, 268, 1144; (b)
 A. G. Cherstvy, Phys. Chem. Chem. Phys., 2011, 13, 9942.
- (a) N. K. Beyeh, Nonappa, V. Liljestrom, J. Mikkila, A. Korpi,
 D. Bochicchio, G. M. Pavan, O. Ikkala, R. H. A. Ras and
 M. A. Kostiainen, ACS Nano, 2018, 12, 8029; (b) N. M.
 Mockler, K. O. Ramberg, F. Guagnini, C. L. Raston and P. B.

- Crowley, *Cryst. Growth Des.*, 2021, 21(3), 1424; (*c*) M. L. Rennie, A. M. Doolan, C. L. Raston and P. B. Crowley, *Angew. Chem., Int. Ed.*, 2017, **56**, 5517.
- 3 X. Ji, M. Ahmed, L. Long, N. M. Khashab, F. Huang and J. L. Sessler, *Chem. Soc. Rev.*, 2019, 48, 2682.
- 4 (a) S. Fujii, Y. Sanada, T. Nishimura, I. Akiba, K. Sakurai, N. Yagi and E. Mylonas, *Langmuir*, 2012, 28(6), 3092; (b) K. Suwinska, B. Leśniewska, M. Wszelaka-Rylik, L. Straver, S. Jebors and A. W. Coleman, *Chem. Commun.*, 2011, 47, 8766.
- 5 T. Xiao, W. Zhong, L. Xu, X.-Q. Sun, X.-Y. Hu and L. Wang, Org. Biomol. Chem., 2019, 17, 1336.
- 6 S. Pasquale, S. Sattin, E. C. Escudero-Adán, M. Martínez-Belmonte and J. de Mendoza, *Nat. Commun.*, 2012, 3, 785.
- 7 (a) Y. Zhou, K. Jie, R. Zhao and F. Huang, Adv. Mater., 2020, 32, 1904824; (b) S. Lim, H. Kim, N. Selvapalam, K. J. Kim, S. J. Cho, G. Seo and K. Kim, Angew. Chem., Int. Ed., 2008, 47(18), 3352.
- 8 S. Kosiorek, B. Rosa, T. Boinski, H. Butkiewicz, M. P. Szymański, O. Danylyuk, A. Szumna and V. Sashuk, *Chem. Commun.*, 2017, 53, 13320.
- 9 S. Kosiorek, H. Butkiewicz, O. Danylyuk and V. Sashuk, *Chem. Commun.*, 2018, 54, 6316.
- 10 (a) M. Kravets, G. Sobczak, N. Rad, I. Misztalewska-Turkowicz, O. Danylyuk and V. Sashuk, *Chem. Commun.*, 2020, 56, 8595; (b) M. Kravets, I. Misztalewska-Turkowicz and V. Sashuk, *Sens. Actuators, B*, 2021, 343, 130083.
- 11 D.-S. Guo and Y. Liu, Acc. Chem. Res., 2014, 47(7), 1925.
- 12 W.-C. Geng, J. L. Sessler and D.-S. Guo, *Chem. Soc. Rev.*, 2020, 49, 2303.
- 13 D.-S. Guo, V. D. Uzunova, X. Su, Y. Liu and W. M. Nau, Chem. Sci., 2011, 2, 1722.
- 14 S. Peng, K. Wang, D.-S. Guo and Y. Liu, Soft Matter, 2015, 11, 290.
- (a) M. J. Hardie and C. L. Raston, J. Chem. Soc., Dalton Trans., 2000, 2483; (b) J. L. Atwood, L. J. Barbour, M. J. Hardie and C. L. Raston, Coord. Chem. Rev., 2001, 222, 3; (c) S. J. Dalgarno, J. L. Atwood and C. L. Raston, Chem. Commun., 2006, 4567; (d) O. Danylyuk and K. Suwinska, Chem. Commun., 2009, 5799.
- 16 (a) F. Perret and A. W. Coleman, Chem. Commun., 2011, 47, 7303; (b) R. E. McGovern, A. A. McCarthy and P. B. Crowley, Chem. Commun., 2014, 50, 10412.
- 17 (a) J. L. Atwood, F. Hamada, K. D. Robinson, G. W. Orr and R. L. Vincent, *Nature*, 1991, 349, 683; (b) K. Fucke, K. M. Anderson, M. H. Filby, M. Henry, J. Wright, S. A. Mason, M. J. Gutmann, L. J. Barbour, C. Oliver, A. W. Coleman, J. L. Atwood, J. A. K. Howard and J. W. Steed, *Chem. – Eur. J.*, 2011, 17, 10259.
- 18 D. K. Kumar and J. W. Steed, Chem. Soc. Rev., 2014, 43, 2080.
- 19 J. J. Fiol, M. Barceló-Oliver, A. Tasada, A. Frontera, À. Terrón and Á. García-Raso, *Coord. Chem. Rev.*, 2013, **257**, 2705.
- 20 W. R. Dichtel, O. S. Miljanić, J. M. Spruell, J. R. Heath and J. F. Stoddart, J. Am. Chem. Soc., 2006, 128(32), 10388.