ChemComm



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Journal:	ChemComm
Manuscript ID	CC-COM-04-2020-002671.R1
Article Type:	Communication



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Superstructural diversity in salt-cocrystals: higher-order hydrogen-bonded assemblies formed using U-shaped dications and with assistance of $\pi^--\pi$ stacking

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Salt cocrystals with components that assemble by hydrogen bonds and aromatic anion-molecule stacks ($\pi^--\pi$ stacks) are reported. U-shaped bipyridines and an isocoumarin carboxylic acid self-assemble to form 5-, 6-, and 10-component aggregates with components in double and quadruple face-to-face stacks. DFT calculations support the $\pi^--\pi$ stacks to help stabilize the salt cocrystals.

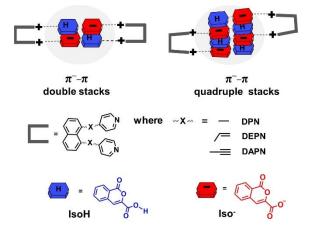
While it is now clear that cocrystals are experiencing a variety of applications (e.g. solid-state reactivity, organic electronics, pharmaceutics),^{1, 2} strategies for their design and formation remain under development. In this context, a salt cocrystal represents an intriguing class of cocrystals, being composed of a salt BA (salt co-former) and an included acid HA lattice molecule as general form B⁺A⁻·HA.³ Contributions to the lattice energy of a salt cocrystal will, arguably, be dominated by the charged ions, which can present a challenge to reliably predict the integration of the neutral acid molecule within the lattice. ^{4, 5} A neutral molecule is not expected to be integrated into a crystal lattice based on charge effects. Indeed, while important progress is being made, there still remains a general lack of systematic examples of salt cocrystals reported in the literature.⁶⁻¹⁰

In this context, U-shaped receptors are important ditopic building blocks in the fields of supramolecular chemistry and molecular recognition. The receptors exhibit convergent recognition sites to direct the assembly of approaching molecules. Here, we report on the formation of a robust series of salt cocrystals formed using U-shaped monomolecular dications. The dications orchestrate face-to-face anion-molecule stacks of aromatics, or $\pi^--\pi$ stacks, to form hydrogenbonded aggregates with 5, 6, and 10 molecules in the self-

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assembly. While nonbonding $\pi^* - \pi$ interactions have been investigated both computationally¹¹ and in crystal structures,^{12,13} contributions of $\pi^- - \pi$ interactions have, to our knowledge, not been documented. The presence of an anion and molecule in a crystal lattice is an intrinsic characteristic of a salt cocrystal. We are also unaware of a series of salt cocrystals involving monomolecular dications.

HA is isocoumarin-3-carboxylic acid (IsoH). Isocoumarins are abundant in microbes and higher plants.¹⁴ We combined IsoH with members of the series of U-shaped ditopic bipyridines DAPN, DEPN, and DPN (Scheme 1). We determined dicationic DAPN and DEPN to assemble with copies of Iso⁻ and IsoH to form salt cocrystals with aggregates that contain six components in the self-assembly. The components are sustained by N⁺-H···O⁻ and neutral O-H···O⁻ hydrogen bonds. Dicationic **DPN** forms a salt cocrystal composed of tweezer-like aggregates with five components in the self-assembly and generate interdigitated structure with 10 components. That salt cocrystals form in each case is predicated on the formation of double and guadruple face-to-face anion-molecule $\pi^- - \pi$ stacks of [Iso]⁻/IsoH, pairs. DFT calculations show the $\pi^--\pi$ stacks to be comparable and preferred over alternative moleculemolecule and anion-anion stacked pairs.



^b Department of Chemical and Biomolecular Engineering, Lehigh University, B336 lacocca Hall, 111 Research Drive, Bethlehem, Pennsylvania 18015, United States Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data, and Cartesian coordinates of the DFT minimized discrete assemblies. ESI and crystallographic information in (CIF) or (PDF) files are available. See DOI: 10.1039/X0xX00000x

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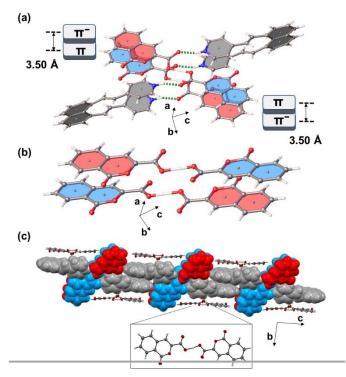
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Scheme 1. Double and quadruple face-to-face stacks of anion-molecule [Iso]⁻/IsoH pairs and self-assembly.

Figure 1. X-ray structure **1**: (a) 6-component aggregate, (b) $\pi^-\pi$ stacks, and (c) extended 1D packing highlighting hydrogen-bonded bis(carboxylates).

DEPN,¹⁵ DPN,¹⁶ and IsoH¹⁷ were prepared as reported while DAPN¹⁸ was prepared according to a modified procedure. When DEPN (11 mg, 0.03 mmol) and IsoH (25 mg, 0.13 mmol) were combined in nitromethane/methanol (v:v 4:1), pale yellow parallelepiped single crystals of [DEPN-2H][Iso]₂·2(IsoH) (1) formed by slow evaporation after a period of 3 d. Similar syntheses afforded pale orange plate-like crystals of [DAPN-2H][Iso]₂·2(IsoH) (2) and [DPN-2H][Iso]₂·2(IsoH)·3NO₂Me (3) after 1 d. For **3**, ethanol was used instead of methanol. The composition of each salt cocrystal was confirmed by singlecrystal and powder X-ray diffraction, as well as ¹H NMR spectroscopy.

The components of 1 crystallize in the monoclinic space group $P2_1/c$ (Fig. 1). The asymmetric unit is complex, consisting of a [DEPN-2H]²⁺ ion, two [Iso]⁻ ions, and two IsoH molecules. The pyridinium groups adopt a cofacial conformation (angle of planes: 15.2°; centroid-centroid 4.23 Å). Each dication participates in a N⁺-H···[−]O₂C- and N⁺-H···O₂HC- hydrogen bonds to a carboxylate (anion) and a carboxyl group (molecule), respectively. The geometries of the carboxyl groups are consistent with anionic [Iso]⁻ (see SI, Table S5) and neutral IsoH (1.231(3)/1.281(4) Å) moieties. This means that a face-to-face double-stacked anion-molecule [Iso]⁻/IsoH pair of $\pi^- - \pi$ type sits adjacent to each dication (plane-to-plane 3.50 Å). The remaining O-atoms of the carboxylate and carboxyl groups participate in intermolecular O-H···O⁻ hydrogen bonds. As a consequence, two bis(pyridinium) ions, two carboxylates [Iso]ions, and two molecules of IsoH form a discrete 6-component self-assembled aggregate sustained by six hydrogen bonds. Two sets of stacked [Iso] / IsoH pairs are present in the aggregate, while two additional and isolated hydrogen-bonded bis(carboxylates) reside exterior in the lattice. We are unaware



of a salt cocrystal composed of a U-shaped monomolecular dication. The components form a 1D structure based on face-to-face and edge-to-face stacking of naphthyl-naphthyl and pyridinium-carboxylate moieties, respectively.

The self-assembly process involving $\pi^--\pi$ stacks is persistent, with 6-component aggregates forming in salt cocrystal 2 with DAPN. The components of 2 crystallize in the triclinic space group P ī (Fig. 2). [DAPN-2H]²⁺ assembles with four [Iso]⁻ anions and four IsoH molecules as a 6-component aggregate sustained by N⁺-H···[−]O₂C-, N⁺-H···O₂HC-, and O-H···O[−] hydrogen bonds. The dications adopt a cofacial conformation (angle of planes: 15.7°; centroid-centroid 4.55 Å), with the pyridiniums separated greater than 1. The larger separation likely reflects strain introduced by the shorter distance of the C=C bond. The face-to-face anion-molecule [Iso] / IsoH pairs stack offset (plane-to-plane 3.52 Å). The components assemble by stacking of naphthyl-naphthyl and carboxylate-carboxylate moieties. That the 6-component aggregate is preserved despite differences in crystal packing attests to the robustness of the hydrogen bonding and $\pi^- - \pi$ stacking interactions.

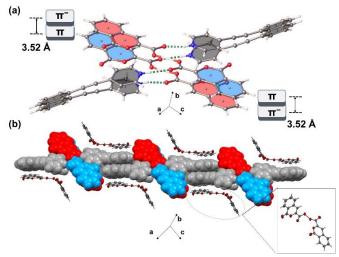


Figure 2. X-ray crystal structure **2**: (a) 6-component aggegate, (b) extended packing highlighting bis(carboxylates).

DFT calculations¹⁹ (RB97D3/def2-TZVP//RB97D3/6-31G* level zero-point corrected using methanol for implicit solvation) support the anion-molecule [**Iso**]⁻/**IsoH** face-to-face $\pi^--\pi$ stacks as stabilizing forces for self-assembly and salt cocrystal formation. Specifically, the stacks were calculated energetically favored by 3.1 kcal/mol versus a hypothetical anion-anion (i.e. salt with carboxylate-carboxylate) stack. Moreover, the $\pi^--\pi$ stacking was virtually isoenergetic (difference 0.4 kcal/mol) versus the stacking of two neutral **IsoH** molecules. Electrostatic potential maps (**Fig. 3**) reveal appreciable build-up of negative charge (**Fig. 3a**, red) for the anion compared to the molecule (**Fig. 3b**, blue). Evidence for nonbonding $\pi^--\pi$ stacks in the solid state also comes from a salt cocrystal based on 1,3-bis(4pyridyl)propane and 2,5-thiophenedicarboxylic acid.²⁰ In the **Journal Name**

solid, similar to **DPN**, **DEPN**, and **DAPN**, the dication adopted a bent conformation with an anion and molecule in a $\pi^--\pi$ stacked arrangement.

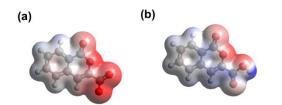


Figure 3. DFT-computed electrostatic potential maps: (a) ${\rm Iso^-}$ anion and (b) ${\rm IsoH}$ molecule (red: electron-rich, blue: electron-poor).

A 5-component aggregate with $\pi^--\pi$ stacking formed for **3** (**Fig. 4**). The aggregates of **3** are sustained by N⁺-H···⁻O₂C- and O-H···O⁻ hydrogen bonds, crystallizing in the space group P ī (**Fig. 3**). A larger splay of the cofacial pyridiniums of **DPN** (angle of planes: 29.8°) and shorter pyridinium separation (centroidcentroid 4.00 Å) generates an aggregate with a tweezer-like geometry (**Fig. 3**, both left and right). Remarkably, the tweezers form a dimeric 10-component stacked structure sustained by quadruple [**Iso**]⁻/**IsoH** $\pi^--\pi$ stacks. The interdigitated aggregates generate cavities occupied by solvent nitromethane molecules. The stacked and interdigitated structure of **3** further attests to the robustness of the $\pi^--\pi$ forces.

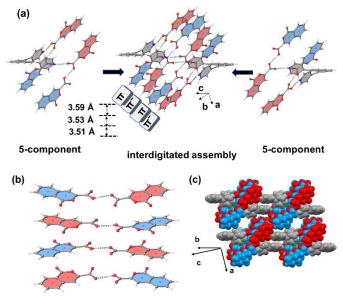


Figure 3. X-ray crystal structure **3**: (a) interdigitation of 5-component aggregates to give 10-component aggregate, (b) quadruple stacks, and (c) space-filling of packing to form cavities.

In conclusion, we have described a robust series of salt cocrystals sustained by hydrogen bonding and $\pi^--\pi$ anion-molecule stacking. The face-to-face $\pi^--\pi$ stacks stabilize the supramolecular structures versus $\pi^--\pi^-$ and $\pi-\pi$ stacking. We will now turn to exploit self-assembly process involving ditopic component for further salt cocrystal formation (e.g. pharmaceutical cocrystals). We also expect our study to be useful for future work that lead to a fundamental understanding of $\pi^--\pi$ stacking interactions.

Conflicts of interest

There are no conflicts to declare.

Notes and references

We thank the National Science Foundation (L.R.M. DMR-1708673) for financial support.

- 1. A. K. Nangia and G. R. Desiraju, *Angew. Chem. Int. Ed.*, 2019, **58**, 4100-4107.
- O. N. Kavanagh, D. M. Croker, G. M. Walker and M. J. Zaworotko, *Drug Discov. Today*, 2019, 24, 796-804.
- 3. S. Mohamed, A. A. Alwan, T. Friščić, A. J. Morris and M. Arhangelskis, *Faraday Discuss.*, 2018, **211**, 401-424.
- S. Allu, G. Bolla, S. Tothadi and A. K. Nangia, *Cryst. Growth* Des., 2020, 20, 793-803.
- A. Gunnam, K. Suresh and A. Nangia, *Cryst. Growth Des.*, 2018, 18, 2824-2835.
- B. Lou, S. R. Perumalla and C. C. Sun, *Cryst. Growth Des.*, 2015, 15, 24-28.
- S. R. Perumalla and C. C. Sun, *CrystEngComm*, 2012, 14, 3851-3853.
- 8. H. G. Brittain, J. Pharm. Sci., 2013, 102, 311-317.
- 9. M. R. Chierotti, K. Gaglioti, R. Gobetto, D. Braga, F. Grepioni and L. Maini, *CrystEngComm*, 2013, **15**, 7598-7605.
- F. Grifasi, M. R. Chierotti, K. Gaglioti, R. Gobetto, L. Maini, D. Braga, E. Dichiarante and M. Curzi, *Cryst. Growth Des.*, 2015, 15, 1939-1948.
- 11. N. J. Singh, S. K. Min, D. Y. Kim and K. S. Kim, *J. Chem. Theory Comput.*, 2009, **5**, 515-529.
- A. Das, A. D. Jana, S. K. Seth, B. Dey, S. R. Choudhury, T. Kar, S. Mukhopadhyay, N. J. Singh, I.-C. Hwang and K. S. Kim, *J. Phys. Chem. B*, 2010, **114**, 4166-4170.
- S. K. Seth, P. Manna, N. J. Singh, M. Mitra, A. D. Jana, A. Das, S. R. Choudhury, T. Kar, S. Mukhopadhyay and K. S. Kim, *CrystEngComm*, 2013, **15**, 1285-1288.
- 14. H. Hussain and I. R. Green, *Expert Opin. Ther. Pat.*, 2017, **27**, 1267-1275.
- R. C. Laird, M. A. Sinnwell, N. P. Nguyen, D. C. Swenson, S. S. Mariappan and L. R. MacGillivray, *Org. Lett.*, 2015, **17**, 3233-3235.
- 16. C. Wolf and B. T. Ghebremariam, *Synthesis*, 2002, **2002**, 0749-0752.
- 17. M. S. Weerasinghe, S. T. Karlson, Y. Lu and K. A. Wheeler, *Cryst. Growth Des.*, 2015, **16**, 1781-1785.
- P. Bonakdarzadeh, F. Topić, E. Kalenius, S. Bhowmik, S. Sato, M. Groessl, R. Knochenmuss and K. Rissanen, *Inorg. Chem.*, 2015, 54, 6055-6061.
- M. Frisch, G. Trucks, H. Schlegel, G. Scuseria, M. Robb, J. Cheeseman, G. Scalmani, V. Barone, B. Mennucci and G. Petersson, See the Supporting Information for full reference, 2013.
- 20. S. J. Jennifer and P. T. Muthiah, Chem. Cent. J., 2014, 8, 20.

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Table of Contents Figure

A series of salt cocrystals with components that form complex aggregates based on hydrogen-bonding and $\pi^--\pi$ stacks is reported.

