



ChemComm

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

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

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Scheme 1. Double and quadruple face-to-face stacks of anion-molecule $[\text{Iso}]^-/\text{IsoH}$ pairs and self-assembly.

DEPN,¹⁵ **DPN**,¹⁶ and **IsoH**¹⁷ were prepared as reported while **DAPN**¹⁸ 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 single-crystal 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 $[\text{Iso}]^-$ 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 $\text{N}^+-\text{H}\cdots\text{O}_2\text{C}-$ and $\text{N}^+-\text{H}\cdots\text{O}_2\text{HC}-$ hydrogen bonds to a carboxylate (anion) and a carboxyl group (molecule), respectively. The geometries of the carboxyl groups are consistent with anionic $[\text{Iso}]^-$ (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 $[\text{Iso}]^-/\text{IsoH}$ 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 $\text{O}-\text{H}\cdots\text{O}^-$ hydrogen bonds. As a consequence, two bis(pyridinium) ions, two carboxylates $[\text{Iso}]^-$ ions, and two molecules of **IsoH** form a discrete 6-component self-assembled aggregate sustained by six hydrogen bonds. Two sets of stacked $[\text{Iso}]^-/\text{IsoH}$ pairs are present in the aggregate, while two additional and isolated hydrogen-bonded bis(carboxylates) reside exterior in the lattice. We are unaware

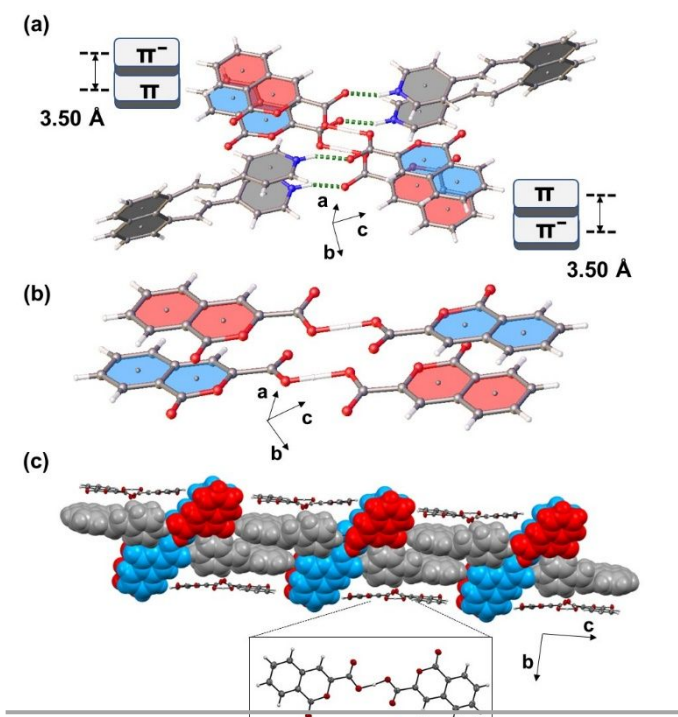


Figure 1. X-ray structure **1**: (a) 6-component aggregate, (b) $\pi-\pi$ stacks, and (c) extended 1D packing highlighting hydrogen-bonded bis(carboxylates).

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 $P\bar{1}$ (Fig. 2). **[DAPN-2H]²⁺** assembles with four $[\text{Iso}]^-$ anions and four **IsoH** molecules as a 6-component aggregate sustained by $\text{N}^+-\text{H}\cdots\text{O}_2\text{C}-$, $\text{N}^+-\text{H}\cdots\text{O}_2\text{HC}-$, and $\text{O}-\text{H}\cdots\text{O}^-$ 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 $\text{C}\equiv\text{C}$ bond. The face-to-face anion-molecule $[\text{Iso}]^-/\text{IsoH}$ 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.

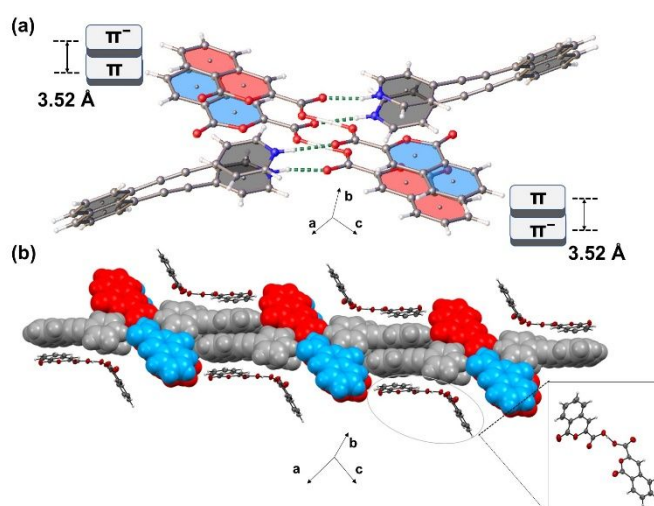


Figure 2. X-ray crystal structure **2**: (a) 6-component aggregate, (b) extended packing highlighting bis(carboxylates).

DFT calculations¹⁹ (RB97D3/def2-TZVP//RB97D3/6-31G* level zero-point corrected using methanol for implicit solvation) support the anion-molecule $[\text{Iso}]^-/\text{IsoH}$ 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(4-pyridyl)propane and 2,5-thiophenedicarboxylic acid.²⁰ In the

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

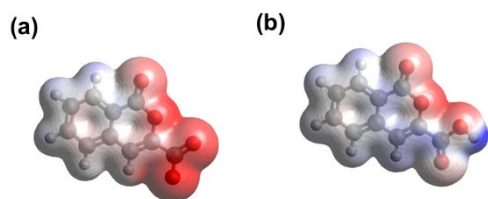


Figure 3. DFT-computed electrostatic potential maps: (a) Iso^- anion and (b) IsoH molecule (red: electron-rich, blue: electron-poor).

A 5-component aggregate with $\pi^--\pi$ stacking formed for **3** (Fig. 4). The aggregates of **3** are sustained by $\text{N}^+-\text{H}\cdots\text{O}_2\text{C}^-$ and $\text{O}-\text{H}\cdots\text{O}^-$ hydrogen bonds, crystallizing in the space group $P\bar{1}$ (Fig. 3). A larger splay of the cofacial pyridiniums of **DPN** (angle of planes: 29.8°) and shorter pyridinium separation (centroid-centroid 4.00 \AA) 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 $[\text{Iso}]^-/\text{IsoH}$ $\pi^--\pi$ 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.

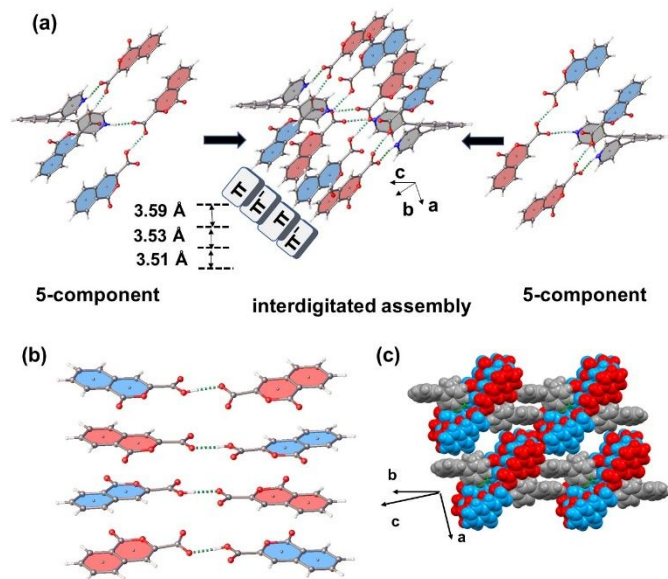


Figure 3. X-ray crystal structure **3**: (a) interdigitation of 5-component aggregates to give 10-component aggregate, (b) quadruple stacks, and (c) space-filling of packing to form cavities.

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.

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Table of Contents Figure

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

