Clues from cocrystals: A ternary solid, polymorphism, and rare supramolecular isomerism involving resveratrol and 5-fluorouracil

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Clues from cocrystals: A ternary solid, polymorphism, and rare supramolecular isomerism involving resveratrol and 5-fluorouracil

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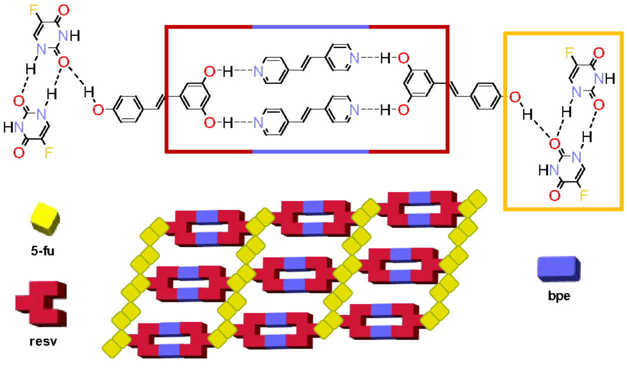
We describe a supramolecular synthesis of a ternary cocrystal involving resveratrol and 5-fluorouracil (5-fu) with *trans*-bis(4-pyridyl)ethylene (bpe). We also have discovered a polymorph of a binary cocrystal involving on 5-fu and bpe that originates from rare supramolecular isomerism.

Cocrystallization[1,2] is being widely employed to design and synthesize complex molecular solids to form functional materials. The formation of a cocrystal relies on the constituent molecules assembling *via* noncovalent interactions to form a lattice composed of two or more different molecules. Cocrystals with greater than two components (*i.e.* ternary cocrystals and beyond) represent a significant challenge to construct since there is an increasingly greater need to balance a landscape of intermolecular forces among the greater number of different molecules. The generation of higher-order cocrystals is, thus, emerging as an area with relevance to mechanochemistry,[3, 4] pharmaceutics,[5-9] and solid-state reactivity.[10, 11]

With the emergence of higher order cocrystals, it is important to understand how the different molecules interact in 'precursor' binary solids.[12, 13] A minimalist ternary cocrystal, for example, can involve supramolecular synthons of the three unique binary combinations (A)·(B), (A)·(C), and (B)·(C). Indeed, Desiraju[14, 15] has addressed how understanding interactions in a binary cocrystal aide the formation of a ternary solid. The idea is to identify a packing region in a binary solid that presents an opportunity for replacement with a third molecule using the concept of structural mimicry. Specifically, a third molecule is introduced intended to mimic the function of a second yet effectively exhibit enhanced recognition capabilities to satisfy packing requirements to form a ternary solid.



Scheme 1. Ternary cocrystal (**resv**)·(**bpe**)·(**5-fu**).

With this in mind, we describe here the construction of a ternary cocrystal of composition (**resv**)·(**bpe**)·(**5-fu**) (where: **resv** = resveratrol; **bpe** = *trans*-bis(4-pyridyl)ethylene; **5-fu** = 5-fluorouracil). Our interests in **resv** and **5-fu** originate not only from roles as nutraceuticals[16, 17] and active pharmaceutical ingredients (APIs),[18-20] respectively, but also capacities to serve as building blocks for solid-state [2+2] photodimerizations.[21] We now show how the hydroxyl groups of **resv** support the design of a ternary cocrystal. Specifically, we demonstrate a ternary cocrystal of **resv** to be achieved from knowledge of a related binary cocrystal without requirement of molecular mimicry of the third component. In the course of our studies, we have also discovered a polymorph of binary 4(**5-fu**)·(**bpe**).[22] The components self-assemble akin to the originally reported one-dimensional (1D) hydrogen-bonded polymorph. However, the assembly of the **5-fu** within the polymer affords rare supramolecular isomerism[23, 24] based on a subtle difference in hydrogen bonding. Collectively, our work guides efforts to construct higher order cocrystals and highlights interplay between binary and ternary solids.

Crystal landscapes of binary cocrystals of phloroglucinol (**pgl**) with **bpe** are diverse, with **pgl** and **bpe** acting as a trifunctional hydrogen-bond-donor and linear hydrogen-bond

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acceptor, respectively.[14] Non-planar and disordered **bpe** molecules were reported present in the solids. Moreover, it was hypothesized that the **bpe** molecules could be effectively replaced to generate a ternary cocrystal. Phenazine (**phe**) was selected as a third component. Owing to its rigid planar structure, **phe** would exhibit enhanced stacking versus a non-planar or disordered **bpe**. **Phe** would, thus, structurally mimic the bridging of **bpe** at the molecular level. Structural mimicry is attractive since the concept enables chemists to preselect building blocks with a goal to generate ternary solids. The strategy successfully afforded the ternary cocrystal (**pgl**)·2(**bpe**)·(**phe**).

Crystal landscapes of binary cocrystals of **resv** with **bpe** are also diverse.[25] The binary cocrystal (**resv**)·2(**bpe**) is polymorphic while **resv** and **bpe** also form the binary solvates (**resv**)·1.5(**bpe**)·S (where: S = acetone, methanol). For acetone, a bridging **bpe** exhibits disorder of the central C=C bond, with the components giving a 1D hydrogen-bonded polymer. The disordered C=C bond was promising to us for progression of (**resv**)·1.5(**bpe**) into a ternary cocrystal. A third component that acts as a bridge could form a more robust lattice with or without solvent. What we show here is the generation of a ternary cocrystal without structural mimicry at the molecular level. A third component acts as a bridge and does so supramolecularly.

When **resv** (0.17 mmol), **bpe** (0.17 mmol), and **5-fu** (0.17 mmol) were combined to give a solution in methanol (2.0 mL), plate-like single crystals grew upon slow evaporation after a period of 1 day. The composition of (**resv**)·(**bpe**)·(**5-fu**) was confirmed by single-crystal and powder X-ray diffraction, as well as ^{1}H NMR spectroscopy.

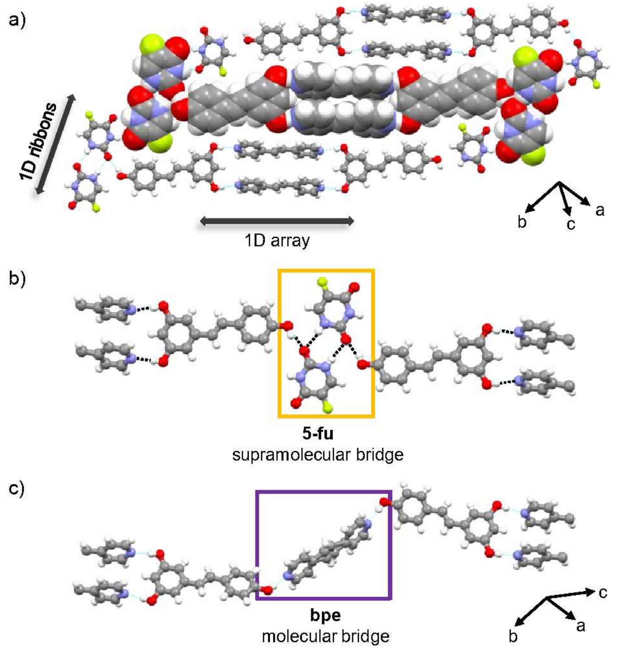

Figure 1. X-ray structures: (a) 2D arrangement and (b) supramolecular bridge of (**resv**)·(**bpe**)·(**5-fu**), and (c) molecular bridge **bpe** (disordered) in (**resv**)·1.5(**bpe**)·0.5(acetone) (acetone solvent removed for clarity).

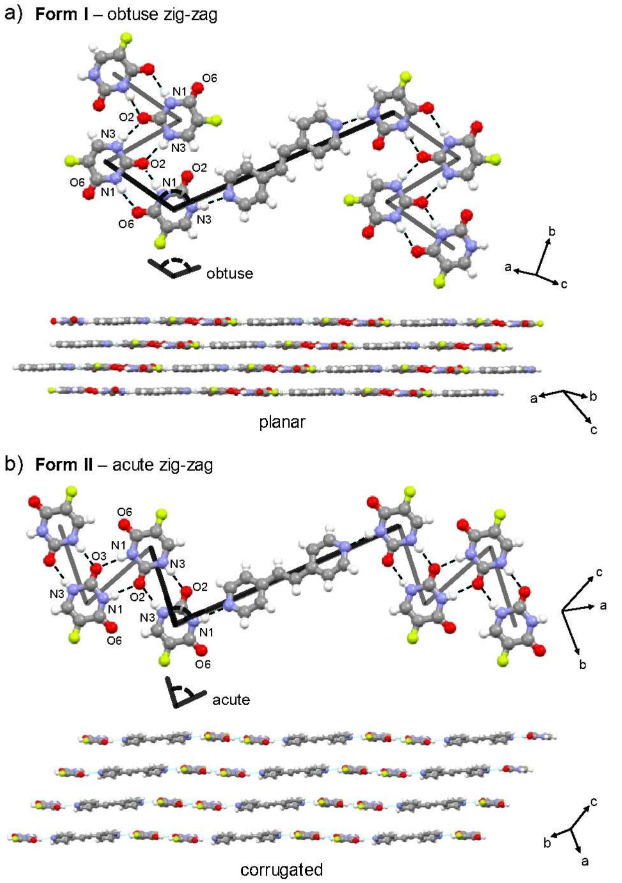

Figure 2. Polymorphs of (**5-fu**)·(**bpe**): (a) Form I with obtuse zig-zag topology and planar sheets and (b) Form II with acute zig-zag topology and corrugated sheets.

The components of (**resv**)·(**bpe**)·(**5-fu**) crystallize in the triclinic space group $P\bar{1}$ with full molecules of **resv**, **5-fu**, and **bpe** in the asymmetric unit (Fig. 1). Similar to (**resv**)·1.5(**bpe**)·(acetone), the molecules form 1D hydrogen-bonded arrays (Fig. 1a). In the arrangement, **resv** acts as a hydrogen-bond donor hub, interacting with a stacked pair of **bpe** molecules, each of which is disordered over two sites (occupancies: C6, 0.77/0.23) via O-H···N hydrogen bonds [O···N distances (Å): O(2)···N(1) 2.773(4), O(1)···N(2) 2.751(4)]. The third hydroxyl group of **resv**, however, forms an O-H···O hydrogen bond with **5-fu** [O···O distances (Å): O(3)···O(4) 2.756(3)]. **5-fu** self-assembles *via* N-H···O hydrogen bonds [N···O distances (Å): N(4)···O(4) 2.944(3)] to give hydrogen-bonded amide-supported dimers that connect adjacent **resv** molecules and give rise to ribbons approximately perpendicular to the 1D arrays. The ribbons are present in **5-fu** Form II.[26] The ribbons, thus, bridge adjacent hydrogen-bonded assemblies of **resv** and **bpe**. Overall, the hydrogen-bonding of the ternary cocrystal extends in two dimensions. In forming the ternary cocrystal, **5-fu** acts as a supramolecular bridge akin to the molecular role of **bpe** in the binary cocrystal solvate (**resv**)·1.5(**bpe**)·0.5(acetone) (Fig. 1b). A ternary cocrystal has, thus, been achieved yet without a need of structural mimicry at the molecular level. We are unaware of a ternary cocrystal involving either **5-fu** or **resv**.

We have also discovered a polymorph of the binary cocrystal 4(**5-fu**)·(**bpe**). Form II of 4(**5-fu**)·(**bpe**) formed by slow evaporation from equimolar **5-fu** and **bpe** in acetone (2.0 mL). We note that Form I was obtained from methanol. Yellow prism-like crystals suitable for single-crystal X-ray diffraction formed over a period of 3 days.

Form II of 4(**5-fu**)·(**bpe**) crystallizes in the monoclinic space group $P2_1/n$. The asymmetric unit, as with Form I,[22] consists of two molecules of **5-fu** and half a molecule of **bpe**. In the arrangement, **5-fu** and **bpe** participate in N-H···N hydrogen bonds [N···N distances (Å): N(2)···N(5) 2.949(2)]. **5-fu** also self-assembles *via* amide dimers [N···O distances (Å): N(1)···O(3) 2.805(1), N(3)···O(1) 2.813(1)]. The components of Form II give 1D hydrogen-bonded polymers nearly identical in shape versus Form I. The difference originates from a subtle difference in the orientation of **5-fu** within the 1D polymer. In Forms I and II, the pyridyl rings participate in hydrogen bonds with N-atoms in the 3- and 1-ring positions of **5-fu**, respectively. Consequently, 1D polymers based on obtuse and acute zigzag topologies form (Fig. 2a). **5-fu**, thus, occupies highly similar environments within the 1D frameworks. Formerly, the two 1D polymers of the binary cocrystals are supramolecular isomers, with the two solids being polymorphs. The 1D polymers of Forms I and Form II are planar and corrugated (Fig. 2b), respectively, giving stacked and interlocked structures.

To conclude, we have described the generation of the ternary cocrystal (**resv**)·(**bpe**)·(**5-fu**)**.** The cocrystal highlights a molecular bridge being replaced supramolecularly. Differences in polymorphs of binary cocrystals are also a result of rare supramolecular isomerism, which originates from **5-fu** occupying similar hydrogen-bonded environments. We plan to utilize these principles to design high order cocrystals and further study origins of polymorphism.

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Conflicts of interest

The authors declare no competing financial interest.

Notes and references

‡ Crystal data for (**resv**)·(**bpe**)·(**5-fu**) (M_W = 540.54 g mol^{-1}): triclinic, space group $P\bar{1}$ a = 9.4819(9), b = 10.652(1), c = 13.506(1), α = 76.407(5), β = 85.696(5), γ = 88.382(5), V = 1322.1(2) Å^3, Z = 2, T = 298.15 K, λ(Mo-Kα) = 0.71073 , D_c = 1.358 g cm^{-3}, 8647 reflections measured (3.934° ≤ 2Θ ≤ 53.498°), 5440 unique (R_{int} = 0.0518, R_{sigma} = 0.1108) which were used in all calculations. The final R_1 was (0.0583 ($I > 2\sigma(I)$) and wR_2 was 0.1656 (all data). CCDC 2050224. Crystal data for 4(**5-fu**)·(**bpe**) (M_W = 702.55 g mol^{-1}): monoclinic, space group $P2_1/n$ a = 9.1087(9), b = 10.997(1), c = 14.935(1), α = 90, β = 93.732(5), γ = 90, V = 1492.7(3) Å^3, Z = 2, T = 298.15 K, λ(Mo-Kα) = 0.71073 , D_c = 1.563 g cm^{-3}, 8833 reflections measured (5.814° ≤ 2Θ ≤ 54.27°), 3110 unique (R_{int} = 0.0237, R_{sigma} = 0.0263) which were used in all calculations. The final R_1 was (0.0388 ($I > 2\sigma(I)$) and wR_2 was 0.1128 (all data). CCDC 2050223.

1. Etter, M. C., *Acc. Chem. Res.* **1990,** *23* (4), 120-126.
2. Shan, N.; Zaworotko, M. J., *Drug Discov. Today* **2008,** *13* (9), 440-446.
3. Bolla, G.; Nangia, A., *IUCrJ* **2016,** *3* (2), 152-160.
4. Lusi, M.; Vitorica-Yrezabal, I. J.; Zaworotko, M. J., *Cryst. Growth Des.* **2015,** *15* (8), 4098-4103.
5. Bolla, G.; Nangia, A., *Chem. Commun.* **2016,** *52* (54), 8342-8360.
6. Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A., *Angew. Chem. Int. Ed.* **2001,** *40* (17), 3240-3242.
7. Aakeröy, C. B.; Desper, J.; Smith, M. M., *Chem. Commun.* **2007,** (38), 3936-3938.
8. Bhogala, B. R.; Basavoju, S.; Nangia, A., *CrystEngComm* **2005,** *7* (90), 551-562.
9. Bhogala, B. R.; Nangia, A., *New J. Chem.* **2008,** *32* (5), 800-807.
10. Yelgaonkar, S. P.; Swenson, D. C.; MacGillivray, L. R., *Chem. Sci.* **2020,** *11* (13), 3569-3573.
11. Yelgaonkar, S. P.; Campillo-Alvarado, G.; MacGillivray, L. R., *J. Am. Chem. Soc.* **2020,** *142* (49), 20772-20777.
12. Kulla, H.; Michalchuk, A. A. L.; Emmerling, F., *Chem. Commun.* **2019,** *55* (66), 9793-9796.
13. Mir, N. A.; Dubey, R.; Desiraju, G. R., *Acc. Chem. Res.* **2019,** *52* (8), 2210-2220.
14. Dubey, R.; Desiraju, G. R., *Angew. Chem. Int. Ed.* **2014,** *53* (48), 13178-13182.
15. Dubey, R.; Desiraju, G. R., *IUCrJ* **2015,** *2* (4), 402-408.
16. King, R. E.; Bomser, J. A.; Min, D. B., *Comprehensive Reviews in Food Science and Food Safety* **2006,** *5* (3), 65-70.
17. Alarcón de la Lastra, C.; Villegas, I., *Mol. Nutr. Food Res.* **2005,** *49* (5), 405-430.
18. Bishayee, A., *Cancer Prevention Research* **2009,** *2* (5), 409.
19. Longley, D. B.; Harkin, D. P.; Johnston, P. G., *Nature Reviews Cancer* **2003,** *3* (5), 330-338.
20. Yu, Y.-M.; Wang, L.-Y.; Bu, F.-Z.*, et al.*, *CrystEngComm* **2020,** *22* (45), 7992-8006.
21. Duncan, A. J. E.; Dudovitz, R. L.; Dudovitz, S. J.*, et al.*, *Chem. Commun.* **2016,** *52* (89), 13109-13111.
22. Delori, A.; Eddleston, M. D.; Jones, W., *CrystEngComm* **2013,** *15* (1), 73-77.
23. MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A., *Chem. Commun.* **2001,** (11), 1034-1035.
24. Moulton, B.; Zaworotko, M. J., *Chem. Rev.* **2001,** *101* (6), 1629-1658.
25. Peng, B.; He, H.; Li, M.*, et al.*, *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials* **2019,** *75* (6).
26. Hulme, A. T.; Price, S. L.; Tocher, D. A., *J. Am. Chem. Soc.* **2005,** *127* (4), 1116-1117.