Supramolecular synthon polymorphism in 2 : 1 co-crystal of 4-hydroxybenzoic acid and 2,3,5,6-tetramethylpyrazine†‡

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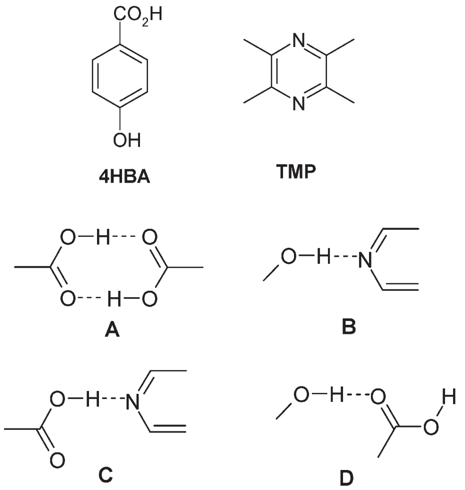
Co-crystals of 4-hydroxybenzoic acid and 2,3,5,6-tetramethylpyrazine (2 : 1) exhibit the first supramolecular synthon polymorphism in a co-crystal; metastable anti-hierarchic polymorph I converts to stable hierarchic form II.

Polymorphism,[1] the existence of more than one crystalline form of a compound has great importance in drugs, agrochemicals, pigments, dyes and explosives. Obtaining a specific polymorph is of utmost importance because different polymorphs exhibit different physical and chemical properties. Polymorphism perhaps tends to be prominent in molecules that contain multifunctional groups (thereby forming multiple supramolecular synthons) and/or conformationally flexible molecules. Polymorphism has been studied widely in single-component molecules but study in multi-component systems *e.g.* co-crystals is scanty. A co-crystal is a multi-component crystal in which two or more components that are solids under ambient conditions coexist through non-covalent interactions.[2] Co-crystals are long known[3] but relatively unexplored class of compounds. Study of co-crystals is of current interest[4] since they are exploited to improve the physical and/or chemical properties of active pharmaceutical ingredients (APIs).[2a,5] Herein we report supramolecular synthon[6] polymorphism in a 2 : 1 co-crystal of 4-hydroxybenzoic acid (4HBA) and 2,3,5,6-tetramethylpyrazine (TMP).§

4HBA and TMP were dissolved in 2 : 1 molar ratio in acetone and left for slow evaporation at ambient conditions. After a few days suitable single crystals were obtained and characterized through single-crystal X-ray diffraction. The crystal structure confirms the 2 : 1 stoichiometry. The co-crystal crystallized in the monoclinic system ($P2_1$ space group) with four independent molecules of 4HBA and two of TMP in the asymmetric unit.¶ The co-crystal does not follow the hierarchy of hydrogen bonding, *i. e.*, the best hydrogen bond donor and the best hydrogen acceptor will preferentially form hydrogen bonds to one another.[4f,g,7] The best hydrogen bond donor and the best acceptor in the co-crystal are carboxylic acid O–H of 4HBA and pyridine moiety of TMP respectively, however they do not hydrogen bond to one another. Instead, four independent 4HBA molecules form two sets of carboxylic acid dimers [Scheme 1, synthon A, graph set $R_2^2(8)$] and hydroxyl groups form O–H···N hydrogen bonds (synthon B) with TMP (Fig. 1(a), Table 1). Assembly of 4HBA and TMP results in linear chains along [3 1 1] as shown in Fig. 2(a).



Scheme 1 Supramolecular homo- and heterosynthons exhibited by $(4HBA)_2\cdot(TMP)$ co-crystal polymorphs.

A second crystalline form of $(4HBA)_2\cdot(TMP)$ co-crystal was obtained from acetonitrile–methanol (1 : 1) solvent mixture at room temperature (RT). The co-crystal was characterized by FT-IR, ^1H NMR, DSC and PXRD (see ESI‡). Single-crystal X-ray data was collected at RT. Form II was crystallized in the monoclinic system with one molecule of 4HBA and half a molecule of TMP in the asymmetric unit (space group $P2_1/c$).¶ The TMP molecule is sited at the inversion centre special position. The crystal structure reveals that form II follows the hierarchy of hydrogen bonding. The best donor in the co-crystal, carboxylic acid O–H forms carboxylic acid–pyridine supramolecular heterosynthon[5o,8] C with the pyridyl moiety of TMP (best acceptor) and the second best donor, hydroxyl moiety engaged in O–H···O hydrogen bond with the second best acceptor (carbonyl oxygen of CO_2H) (Fig. 1(b), Table 1). Association of 4HBA and TMP molecules generates a herringbone network parallel to the (1 0 −2) plane (Fig. 2(b)). Herringbone networks are generally observed in organometallic compounds but very few examples are known for organic molecules.[9]

Carboxylic acid is one of the most commonly used functional groups in crystal engineering. Carboxylic acids generally form carboxylic acid–pyridine supramolecular synthons reliably in the presence of a pyridine moiety, hence this robust heterosynthon has been extensively used in crystal engineering.[4m,9b] However, our understanding of the factors that direct hydrogen bonding motifs when other functional groups are also present in a molecule is still

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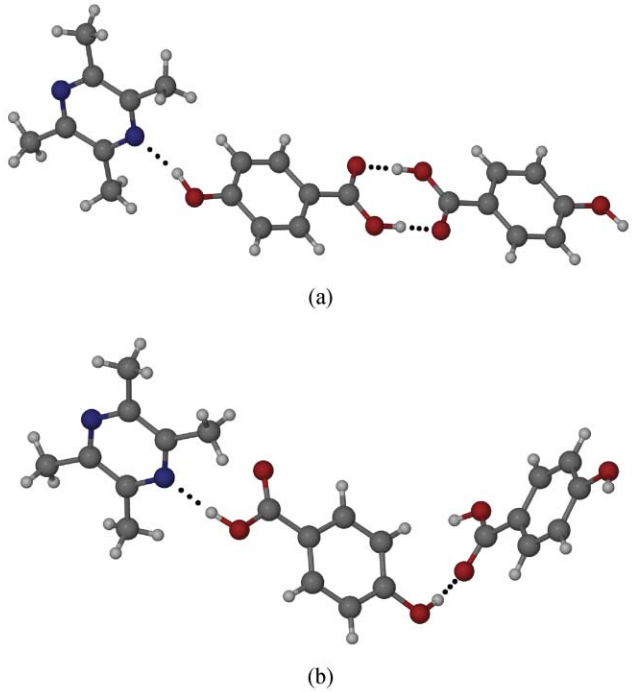

Fig. 1 Supramolecular synthons in $(4HBA)_2{\cdot}(TMP)$ polymorphs. (a) Homosynthon A and heterosynthon B in form I. (b) Heterosynthons C and D in form II.

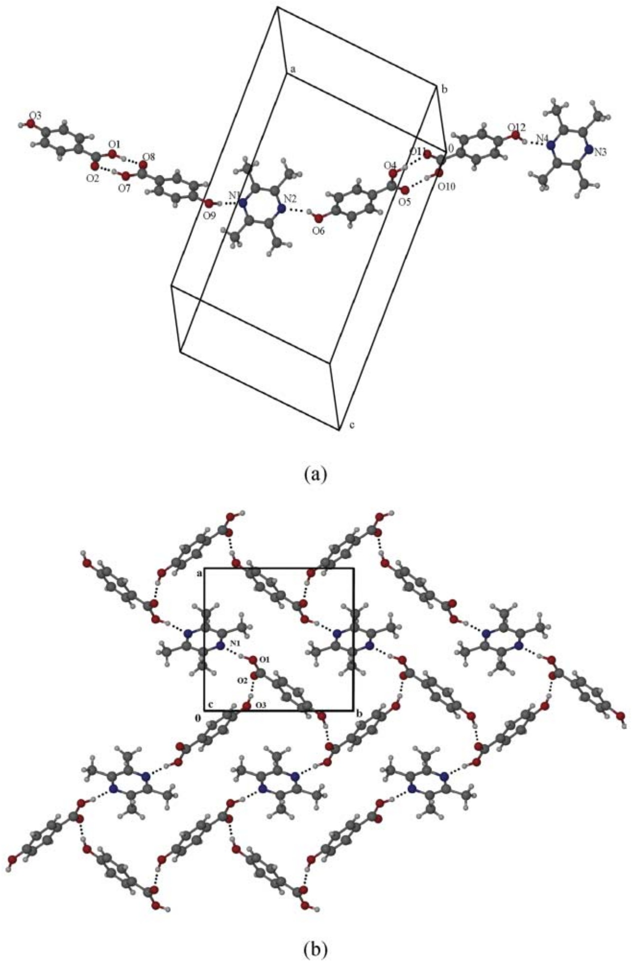

Fig. 2 (a) Form I: Linear chain formed through carboxylic acid dimer and hydroxyl O–H···N hydrogen bonds. (b) Herringbone network in form II.

evolving. The $(4HBA)_2{\cdot}(TMP)$ co-crystal contains three functional groups *viz*, carboxylic acid, hydroxyl and pyridine moiety. Various combinations of these groups can result in at least six different supramolecular synthons: A, B, C, D, hydroxyl···hydroxyl and carboxylic acid···hydroxyl. Form I exhibits synthons A and B and form II shows synthons C and D. Hydroxyl···hydroxyl and carboxylic acid···hydroxyl synthons were not observed in these forms. The two polymorphs have quite different stabilities. The hierarchic polymorph (form II) is the stable form while form I crystals become opaque after some time. PXRD indicates that it is converting to stable form II upon standing at RT.

Zaworotko and co-workers have retrieved polymorphic co-crystals[10] from the Cambridge Structural Database (CSD)[11] and studied the similarities and differences between polymorphic forms.[5b] The CSD consists of 21 polymorphic co-crystals, of these only 11 co-crystals contain 3D co-ordinates for two or more forms.[12] Recently two hydrogen-bonded polymorphic co-crystals were also reported.[13] Analysis of crystal packing in these 13 polymorphic co-crystals suggest that polymorphism is not linked to the supramolecular synthons that sustain the co-crystal. Supramolecular synthons exhibited in all these polymorphic co-crystals are persistent. However, existence of polymorphism in these co-crystals is related to conformational and/or packing variations.

Table 1 Geometry of hydrogen bonds in forms I and II

Form	D–H···A[a]	H···A/Å	D···A/Å	D–H···A/°	Symmetry code
I	O_1–H···O_8	1.64	2.583(6)	172	
	O_7–H···O_2	1.65	2.592(6)	171	
	O_4–H···O_{11}	1.75	2.678(6)	163	
	O_{10}–H···O_5	1.70	2.624(6)	162	
	O_9–H···N_1	1.73	2.768(6)	153	
	O_6–H···N_2	2.03	2.825(7)	155	
	O_{12}–H···N_4	1.95	2.811(6)	151	
	O_3–H···N_3	1.95	2.786(6)	173	$3+x,\ 1+y,\ 1+z$
II	O_3–H···O_2	1.81	2.702(3)	170	$-x,\ ½+y,\ ½-z$
	O_1–H···N_1	1.68	2.706(3)	171	

[a] D = Donor, A = Acceptor.

In contrast, the reported polymorphic co-crystal $(4HBA)_2{\cdot}(TMP)$ exhibits different supramolecular synthons in form I and II. Form I consists of carboxylic acid dimer A and hydroxyl O–H···N synthon B whereas form II is sustained through carboxylic acid-pyridine heterosynthon C and hydroxyl O–H···O=C synthon D. Form I possesses both homo- and heterosynthons whereas form II consists of only heterosynthons. Existence of polymorphism in the reported co-crystal is related to different supramolecular synthons exhibited by the functional groups. Since the functional groups are engaged in different supramolecular synthons in these two polymorphs, this results in different crystal packing arrangements. To the best of our knowledge the reported co-crystal exhibits the first supramolecular synthon polymorphism in a co-crystal. Study of polymorphism in co-crystals is rare, despite being of current interest since co-crystals are used to improve the properties of APIs.

To conclude, in this contribution we have shown polymorphism in $(4HBA)_2\cdot(TMP)$ co-crystals exhibiting different supramolecular synthons in two polymorphs. Stable form II follows the hierarchy of hydrogen bonding whereas metastable form I does not.

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Notes and references

§ The compounds were obtained from Aldrich and used as such for co-crystallization experiments.

¶ The crystal structures were solved by direct methods (SIR 92) and refined by least-square procedures using *CrystalStructure* (version 3.6.0) from Rigaku/Molecular Structure Corporation, 9009 New Trials Dr. The Woodlands TX 77381-5209, USA. *Crystal data* of form I: $(C_7H_6O_3)_2\cdot C_8H_{12}N_2$, M = 412.44, monoclinic, space group $P2_1$, a = 13.039(7), b = 7.401(4), c = 22.560(12) Å, β = 102.440(5)°, V = 2125.8(19) $Å^3$, T = 298 K, Z = 4, D_c = 1.289 g cm^{-3}, μ(Mo-Kα) = 0.094 mm^{-1}, 24455 reflections measured, 5150 unique reflections, 1964 observed reflections [$I > 2.0\sigma(I)$], R_1_obs = 0.054, wR_2_all = 0.121, CCDC 632453. *Crystal data* of form II: $(C_7H_6O_3)_2\cdot C_8H_{12}N_2$, M = 412.44, monoclinic, space group $P2_1/c$, a = 10.5495(11), b = 10.3154(9), c = 10.2205(11) Å, β = 109.904(4)°, V = 1045.8(2) $Å^3$, T = 298 K, Z = 2, D_c = 1.310 g cm^{-3}, μ(Mo-Kα) = 0.096 mm^{-1}, 12161 reflections measured, 2371 unique reflections, 1382 observed reflections [$I > 2.0\sigma(I)$], R_1_obs = 0.050, wR_2_all = 0.074, CCDC 632454. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700082k

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