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New pharmaceutical salts containing pyridoxine

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Two mixed crystals were obtained by crystallizing the active pharmaceutical ingredient pyridoxine [systematic name: 4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol, PN] with (*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid (ferulic acid) and 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid). PN and the coformers crystallize in the form of pharmaceutical salts in a 1:1 stoichiometric ratio, namely 3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium (*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate, $C_8H_{12}NO_3^+ \cdot C_9H_9O_5^-$, and 3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium 4-hydroxy-3,5-dimethoxybenzoate monohydrate, $C_8H_{12}NO_3^+ \cdot C_{10}H_{11}O_5^- \cdot H_2O$, the proton exchange between PN and the acidic partner being supported by the differences of the pK_a values of the two components and by the C—O bond lengths of the carboxylate groups. Besides complex hydrogen-bonding networks, π–π interactions between aromatic moieties have been found to be important for the packing architecture in both crystals. Hirshfeld surface analysis was used to explore the intermolecular interactions in detail and compare them with the interactions found in similar pyridoxine/carboxylic acid salts.

1. Introduction

Multicomponent solids, designed by applying crystal engineering tools, have been, and continue to be, an active field of research in many areas dealing with functional materials. In particular, in the last decade, pharmaceutical chemists have expended a great deal of effort in synthesizing new crystalline phases, called pharmaceutical cocrystals (PCCs), where at least one component is an active pharmaceutical ingredient (API). PCCs are generally classified as mixed crystals in which a drug and other substances (coformers) present in neutral form cocrystallize in a stoichiometric ratio and are held together by intermolecular interactions, in such a way as to maintain unaltered the chemical structure of the API and hence its pharmacological profile. The increasing interest in PCCs is due to the fact that they display intermolecular motifs and crystal structures different from the pure API components and consequently can exhibit diverse specific physical properties, *e.g.* API dissolution rate and solubility (Nehm *et al.*, 2006; Good & Rodríguez-Hornedo, 2009; Goud *et al.*, 2012), API pharmacokinetics (Cheney *et al.*, 2010; Shan *et al.*, 2014; Suresh *et al.*, 2014, 2016), bioavailability (Bak *et al.*, 2008; Jung *et al.*, 2010) and permeability (Ferretti *et al.*, 2015; Dalpiaz *et al.*, 2017), efficiency and safety of the API native solid form, available in pharmaceutical formulations, and processability and stability of the sole crystalline form of PCC with a unique structure (Newman & Wenslow, 2016; Battini *et al.*, 2014; Trask, 2007) in comparison with all the solid forms in which the API may exist (Morissette *et al.*, 2004; Almarsson *et al.*, 2003). For these reasons, both the United States Food and

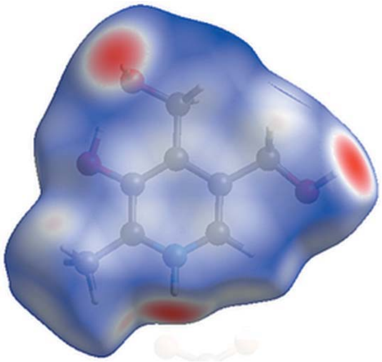
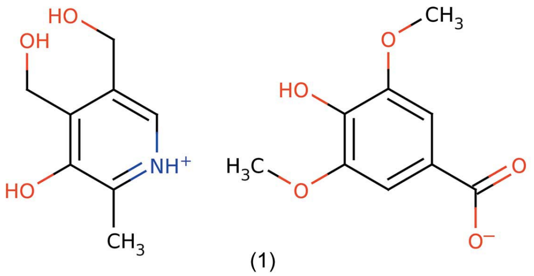


Table 1
Experimental details.

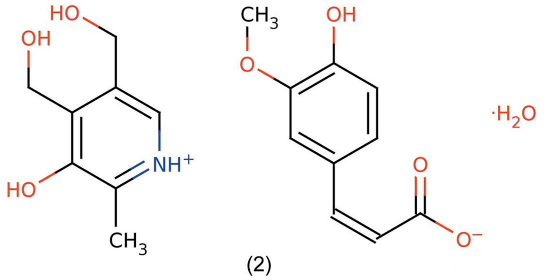
	(1)	(2)
Crystal data		
Chemical formula	$C_8H_{12}NO_3^+\cdot C_9H_9O_5^-$	$C_8H_{12}NO_3^+\cdot C_{10}H_{11}O_5^-\cdot H_2O$
M_r	367.35	381.37
Crystal system, space group	Triclinic, $P\overline{1}$	Monoclinic, $P2_1$
Temperature (K)	295	295
a, b, c (Å)	6.9085 (2), 8.4524 (2), 17.9702 (5)	7.2440 (3), 17.1615 (5), 7.2706 (2)
α, β, γ (°)	101.8010 (16), 92.7110 (16), 109.8290 (14)	90, 98.806 (2), 90
V (Å^3)	958.47 (5)	893.21 (5)
Z	2	2
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.10	0.11
Crystal size (mm)	0.52 × 0.20 × 0.09	0.35 × 0.22 × 0.13
Data collection		
Diffractometer	Nonius KappaCCD	Nonius KappaCCD
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	18203, 4387, 3191	11173, 4578, 3822
$R_{\rm int}$	0.035	0.034
$(\sin \theta/\lambda)_{\rm max}$ (Å^{-1})	0.650	0.703
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.053, 0.167, 1.06	0.040, 0.108, 1.07
No. of reflections	4387	4578
No. of parameters	256	272
No. of restraints	0	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\rm max}$, $\Delta\rho_{\rm min}$ (e Å^{-3})	0.38, −0.27	0.27, −0.18
Absolute structure	–	Flack x determined using 1452 quotients $[(I^+) - (I^-)]/[(I^+) + (I^-)]$ (Parsons *et al.*, 2013)
Absolute structure parameter	–	−0.4 (4)

Computer programs: *COLLECT* (Nonius, 1997), *DENZO-SMN* (Otwinowski & Minor, 1997), *SIR97* (Altomare *et al.*, 1999), *ORTEPIII* (Burnett & Johnson, 1996), *MarvinSketch* (ChemAxon, 2010), *SHELXL2014* (Sheldrick, 2015) and *WinGX* (Farrugia, 2012).

Drug Administration (US FDA) and the European Medicines Agency (EMA) have delivered position documents about PCCs attesting the growing interest of their use in drug products and providing guidance to industry (FDA, 2016; EMA, 2014).



(1)



(2)

In continuation of our interest in this field (Cvetkovski *et al.*, 2016; Cvetkovski & Ferretti, 2016), we have initiated a project on the synthesis of PCCs using the API pyridoxine and aromatic acids. Pyridoxine (henceforth referred to as PN), in the form of an alcohol derivative of pyridine, is one of three members of the vitamin B6 family. The other two members, the aldehyde form pyridoxal and an amine form pyridoxamine, are known as pseudopyridoxines (Urbanski, 1949). These three forms are derivatives of β-hydroxypyridine; the presence of the pyridine ring is a structural characteristic shared with other vitamins of group B, *i.e.* nicotinic acid and nicotinamide (niacin, vitamin B3), obtained by substituting the β-position with a carboxylic acid or amide group (Mooney *et al.*, 2009). Due to the presence of a basic N atom (PN pK_a = 5.1; Santos *et al.*, 2010), pyridoxine can easily form salts with acidic molecules and, in fact, is mainly commercialized as pyridoxine hydrochloride.

The coformers selected for the present study were ferulic and syringic acids, belonging to the class of nutraceutic acids, whose pK_{a1} values are 4.27 (Erdemgil *et al.*, 2007) and 3.86 (Chuysinuan *et al.*, 2009), respectively. According to the so-called 'rule of three', when synthesizing a mixed crystal, a salt is expected if ΔpK_a [p$K_{a(base)}$ − p$K_{a(acid)}$] is greater than 2 or 3 units, while the formation of a cocrystal is observed if ΔpK_a is less than 0 (Childs *et al.*, 2007; Bhogala *et al.*, 2005). ΔpK_a ranging between 0 and 2 or 3 is generally considered to indicate a salt–cocrystal continuum, so that it was not possible to predict *a priori* the formation of a salt or a cocrystal. The structures presented here for 3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium 4-hydroxy-3,5-dimethoxyben-

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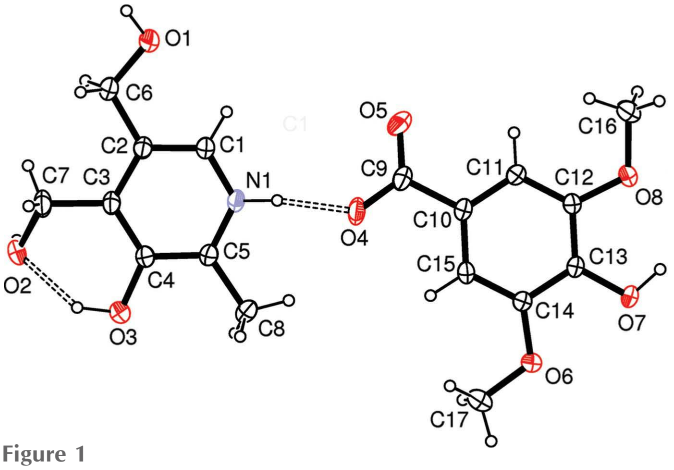


Figure 1
The molecular structure and atom-numbering scheme for (1), with displacement ellipsoids drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines.

zoate, (1), and 3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium (*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate monohydrate, (2), are both molecular salts.

2. Experimental

2.1. Synthesis and crystallization

Pyridoxine, the other cocrystal formers and the solvents were purchased from Sigma–Aldrich and were used without further purification. All chemicals were of analytical or chromatographic grade.

2.1.1. Synthesis of pharmaceutical salt (1). The sediment of single crystals of PN–syringic acid (SYR) were prepared by slow evaporation from the isopropanol solution obtained after filtration of the slurry containing PN hydrochloride (173 mg) neutralized with sodium hydroxide (33.6 mg) (1:1 molar ratio) and syringic acid (166.7 mg) (PN neutral form–syringic acid in a 1:1 molar ratio) in isopropanol (20 ml).

2.1.2. Synthesis of pharmaceutical salt (2). Colourless needle-shaped single crystals of the PN–ferulic acid (FER) salt were grown by slow evaporation from the clear solution obtained after filtration of the slurry prepared by mixing PN hydrochloride (68.63 mg) and sodium hydroxide (13.3 mg) (1:1 molar ratio) with feluric acid (64.8 mg) (PN neutral form/base–ferulic acid in a 1:1 molar ratio) in a mixture of isopropanol and acetonitrile (15 ml, 1:1 *v*/*v*).

2.2. Data collection and refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. In salt (1), the electron-density difference map showed some rather large broad peaks located in the centre of the unit cell. Attempts to identify the solvent molecules failed. Instead, a new set of F^2 (*hkl*) values with the contribution from solvent molecules withdrawn was obtained using the SQUEEZE procedure (Spek, 2015) implemented in *PLATON* (Spek, 2009). The potential solvent volume in the crystals is *ca* 124 Å^3 per unit-cell volume. In both structures, H atoms bound to N or O atoms were located in difference Fourier maps and refined isotropically, whereas H atoms bonded to C atoms were included at idealized positions and allowed to ride on their respective C atoms. The arene and methylene H atoms were constrained with C—H = 0.93 Å [$U_{\rm iso}$(H) = 1.2$U_{\rm eq}$(C)] and the methyl H atoms with C—H = 0.96 Å [$U_{\rm iso}$(H) = 1.5$U_{\rm eq}$(C)].

2.3. Hirshfeld surfaces and fingerprints evaluation

Molecular Hirshfeld surfaces (Hirshfeld, 1977) and their 2D (two-dimensional) fingerprint plots (Spackman & McKinnon, 2002; McKinnon *et al.*, 2007) have been evaluated in order to gain additional insight into the network of intermolecular interactions in the crystals. The Hirshfeld surface represents the molecule when interacting with the crystal environment and the decomposition of this surface gives a 'molecular fingerprint', *i.e.* a 2D map indicating which intermolecular interactions are present and the relative area of the surface corresponding to each kind of interaction. The Hirshfeld surfaces and 2D fingerprint plots were generated using *CrystalExplorer 3.0* (Wolff *et al.*, 2012).

3. Results and discussion

The crystal of (1) (Fig. 1) is composed of cationic PN moieties, *i.e.* pyridoxinium, and syringate anions in a 1:1 stoichiometric ratio, as well as cocrystallized solvent molecules (*vide supra*), while the asymmetric unit of (2) (Fig. 2) is composed by one pyridoxinium cation, one ferulate anion and one water molecule in a 1:1:1 stoichiometric ratio. According to the 'rule of three', the ΔpK_a values of the PN–ferulic acid (0.83) and PN–syringic acid (1.24) pairs are in the so-called 'salt–cocrystal continuum' region. In both structures, proton transfer from the carboxylic acid group to the basic pyridine N atom of the drug molecule is confirmed by (i) the delocalization of the –COO$^-$ group, in terms of bond length and angle equalization [C—O = 1.235 (2) and 1.275 (2) Å in (1), and 1.253 (3) and 1.267 (3) Å in (2); C—C—O = 116.84 (16) and 118.93 (16)° in (1) and 118.83 (17) and 118.69 (17)° in (2)], and (ii) the values of the C1—N1—C5 bond angles, which are wider than those

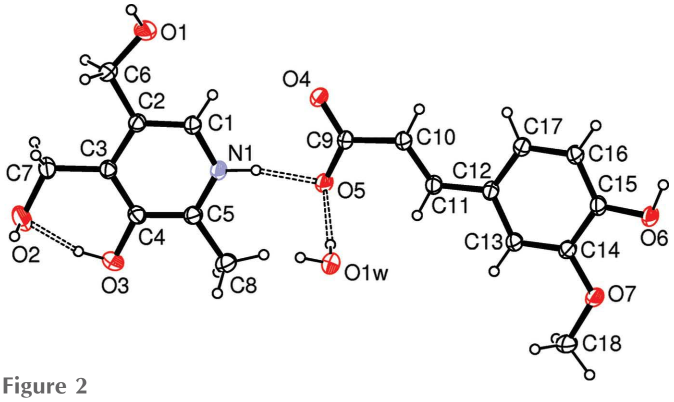


Figure 2
The molecular structure and atom-numbering scheme for (2), with displacement ellipsoids drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines.

Table 2
Structural parameters for hydrogen-bond and π–π interactions (Å, °) for (1) and (2).

Cg represents a ring centroid.

D—H···*A*	*D*—H	*D*···*A*	H···*A*	*D*—H···*A*
Cocrystal (1)				
N1—H1N···O4	0.91 (2)	2.671 (2)	1.77 (2)	171 (2)
O3—H3O···O2	0.95 (4)	2.663 (2)	1.83 (4)	144 (3)
C8—H8*A*···O4	0.96	3.308 (2)	2.52	139
C1—H1···O1^{i}	0.93	3.359 (2)	2.47	158
O1—H1O···O5^{i}	0.85 (3)	2.663 (2)	1.83 (3)	166 (3)
C6—H6*B*···O5^{ii}	0.97	3.576 (3)	2.64	161
O2—H2O···O4^{iii}	0.87 (4)	2.620 (2)	1.77 (4)	165 (3)
O7—H7O···O2^{iv}	0.89 (2)	2.728 (1)	1.93 (2)	146 (3)
Cg(C10–C15)···*Cg*(N1/C1–C5)^{v}	3.552			
Cg(C10–C15)···*Cg*(N1/C1–C5)^{vi}	3.577			
Cocrystal (2)				
N1—H1N···O5	0.93 (4)	2.641 (2)	1.73 (5)	166 (4)
O3—H3O···O2	0.90 (5)	2.564 (3)	1.68 (5)	165 (4)
O1*W*–H2*W*···O5	0.90 (5)	2.893 (3)	2.02 (5)	161 (5)
C8—H8*A*···O5	0.96	3.307 (3)	2.51	140
O2—H2O···O1^{vii}	0.91 (6)	2.747 (3)	1.84 (6)	171 (5)
C8—H8*C*···O4^{vii}	0.96	3.541 (3)	2.63	158
C17—H17···O1*W*^{viii}	0.93	3.472 (3)	2.55	167
O6—H6O···O4^{ix}	0.94 (4)	2.545 (2)	1.62 (4)	166 (4)
O1—H1O···O1*W*^{x}	0.86 (3)	2.683 (3)	1.82 (3)	175 (3)
O1*W*—H1*W*···O6^{x}	0.82 (5)	2.896 (2)	2.12 (5)	156 (4)
O1*W*—H1*W*···O7^{x}	0.82 (5)	2.994 (3)	2.37 (5)	132 (4)
Cg(C12–C17)···*Cg*(N1/C1–C5)^{xi}	3.608			
Cg(C12–C17)···*Cg*(N1/C1–C5)^{xii}	3.671			

Symmetry codes: (i) $-x, -y+1, -z$; (ii) $x+1, y+1, z$; (iii) $x, y+1, z$; (iv) $x-1, y-2, z$; (v) $x-1, y-1, z$; (vi) $x, y-1, z$; (vii) $x, y, z+1$; (viii) $x, y, z-1$; (ix) $-x+1, y+\frac{1}{2}, -z+1$; (x) $-x+1, y-\frac{1}{2}, -z+2$; (xi) $-x+1, y+\frac{1}{2}, -z+2$; (xii) $-x+2, y+\frac{1}{2}, -z+2$.

found in unprotonated pyridines [123.59 (14)° in (1) and 123.26 (18)° in (2)].

The pyridoxinium cations are characterized by an intramolecular O3—H3O···O2 hydrogen bond, while the protonated N atom forms a strong N—H···O interaction with the coformer carboxylate group, whose short N···O distance is typical of charge-assisted hydrogen bonds (Table 2). Due to the plethora of good donor and acceptor groups, the hydrogen-bonding network appears to be rather complicated in both structures. In salt (1), the molecules are arranged in planar layers (in the *bc* plane), forming $R^4_4(20)$ and $R^4_4(30)$ adjacent rings, marked as **A** and **B**, respectively, in Fig. 3. These parallel layers are stacked along the *a* direction and linked through O2—H2O···O4^{iii} hydrogen bonds, with the possible involvement of the cocrystallized solvent molecules (*vide supra*). Indeed, the solvent is located in tunnels running along the *a* direction, as shown in Fig. 4(*a*). Layers are also formed in salt (2); in this case, the role played by the cocrystallized water molecule in joining adjacent layers is evident, acting both as hydrogen-bonding donor (towards O6 and O7) and acceptor (from O1). The unit-cell contents, viewed along the *b* axis, are shown in Fig. 5(*a*). It is worth noting that, besides hydrogen bonding, in both structures, π–π interactions contribute to the robustness of the crystal (Table 2 and Figs. 4*b* and 5*b*). In both structures, drug/coformer mixed columns with heterogeneous interstack separations (André *et al.*, 1997) are

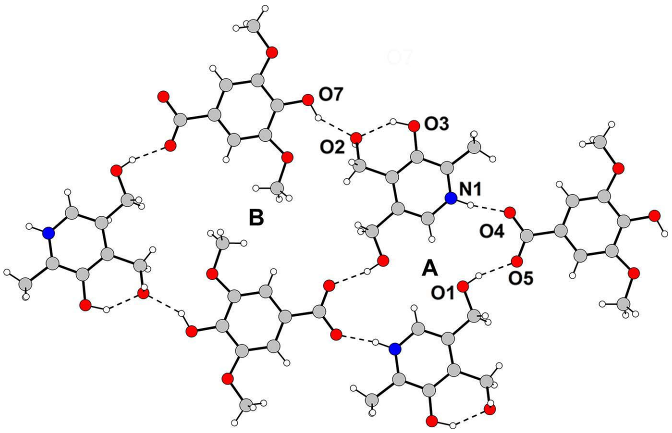


Figure 3
$R^4_4(20)$ (denoted **A**) and $R^4_4(30)$ (denoted **B**) rings formed in the *bc* plane of (1). Hydrogen bonds are drawn as dashed lines.

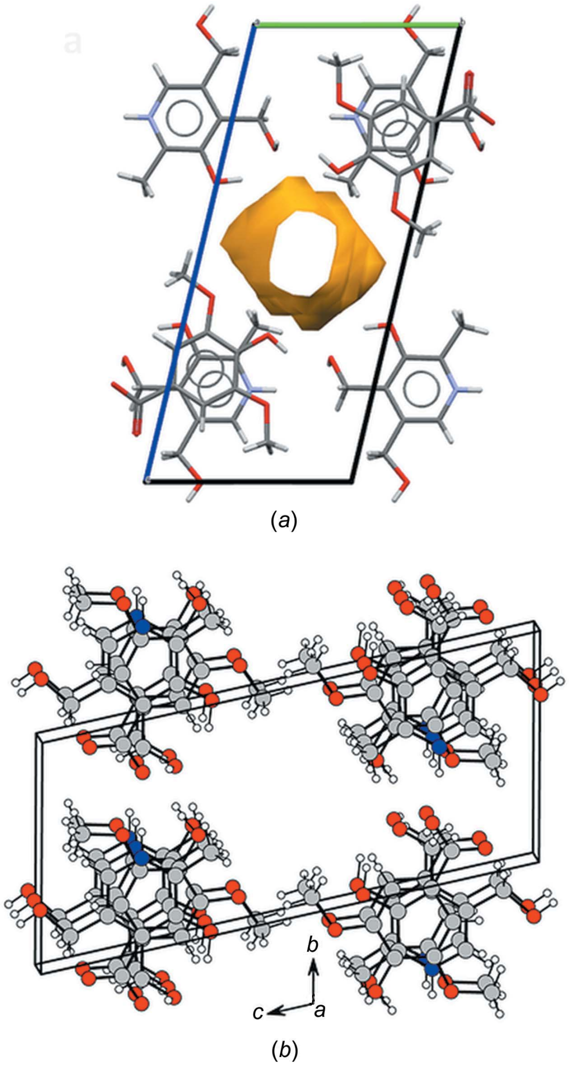
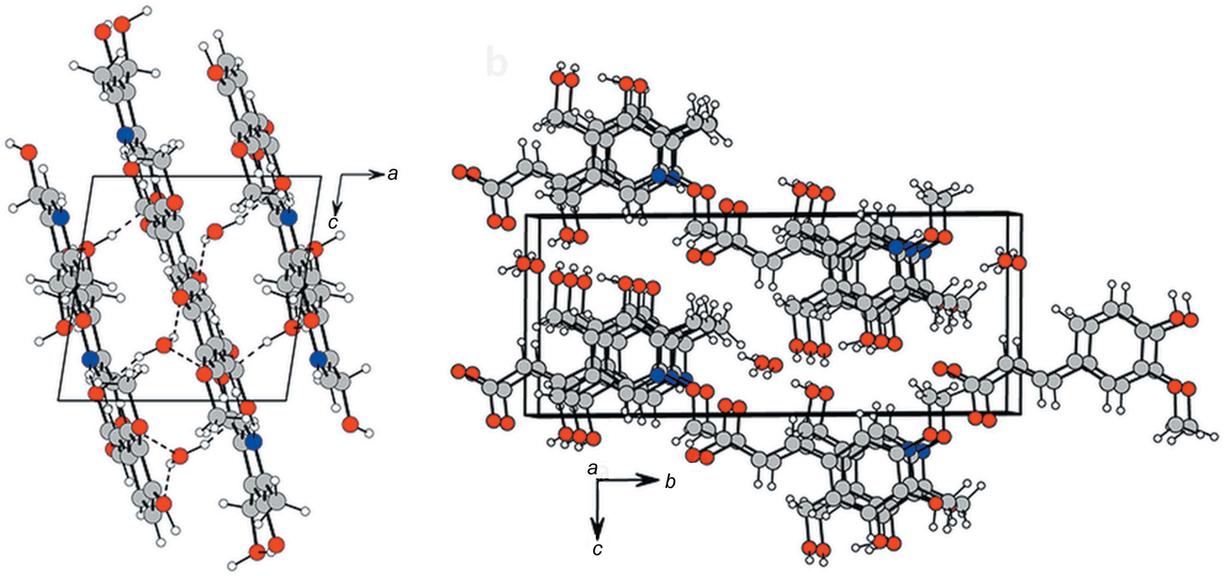


Figure 4
(*a*) The empty space in (1), viewed in projection along the *a* axis. (*b*) The crystal projection showing the molecular stacking.



(a) (b)

Figure 5
(*a*) The unit-cell contents of (2), viewed along the *b* axis. Hydrogen bonds are drawn as dashed lines. (*b*) The crystal projection showing the molecular stacking.

formed. In salt (1), neighbouring aromatic rings of PN and syringic acid molecules are stacked at centroid–centroid ($Cg\cdots Cg$) distances of 3.552 and 3.577 Å in an almost parallel way, the mean dihedral angle between two adjacent molecules being 2.6°. Along the columns, the centroids of the aromatic rings are only slightly shifted, as shown by the angles formed by the $Cg\rightarrow Cg$ vector and the normal to the plane of one ring (13.5 and 16.2°). In (2), the $Cg\cdots Cg$ distances become larger, due to the fact that the molecular layers are more puckered than in (1). Indeed, while the dihedral angle between two adjacent molecules is very similar (1.3°), the angles formed by the $Cg\rightarrow Cg$ vector and the normal to plane of one ring are larger, being 15.9 and 21.9°. Calculations concerning π–π interactions were performed using *PLATON* (Spek, 2009).

A comparison can be made with an analogous series of PN cocrystals/salts published recently (Ganduri *et al.*, 2015), where the coformers are 4-amino-, 4-hydroxy-, 4-cyano- and 4-nitrobenzoic acids. To better visualize and analyze all intermolecular interactions, Hirshfeld surfaces (HS) and their corresponding 2D fingergerprint plots (Hirshfeld, 1977; Spackman & McKinnon, 2002; McKinnon *et al.*, 2007) have been generated. The surfaces and plots of the PN molecule in (1) and (2) are shown in Figs. 6 and 7, respectively. The function mapped onto the Hirshfeld surface is $d_{\rm norm}$, *i.e.* the normalized contact distance, defined in terms of $d_{\rm e}$ (distance to the nearest atoms outside), $d_{\rm i}$ (distance to the nearest atoms inside) and the van der Waals (vdW) radii of the two atoms external and internal to the surface; the red regions represent distances shorter than the sum of the vdW radii, while the white-coloured regions correspond to weak contacts and the blue-coloured regions are considered to be free of significant contacts. When the values of $d_{\rm i}$ and $d_{\rm e}$ for any HS surface point are plotted against each other, a fingerprint plot is obtained. Here, the different colours are related to the density of points giving that particular $d_{\rm i}-d_{\rm e}$ combination; for high density, the

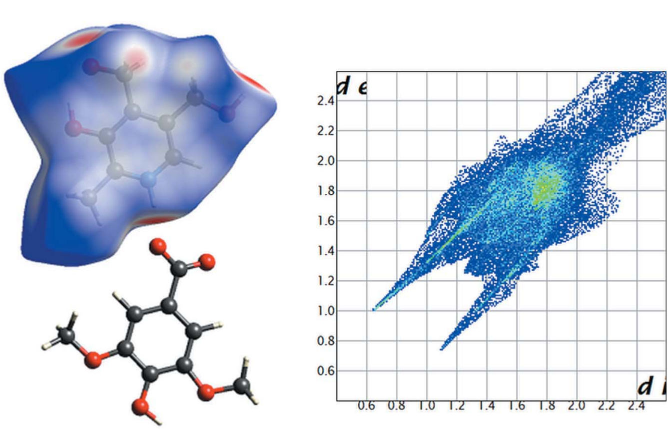


Figure 6
Hirshfeld surface and fingerprint plot for the PN molecule in (1).

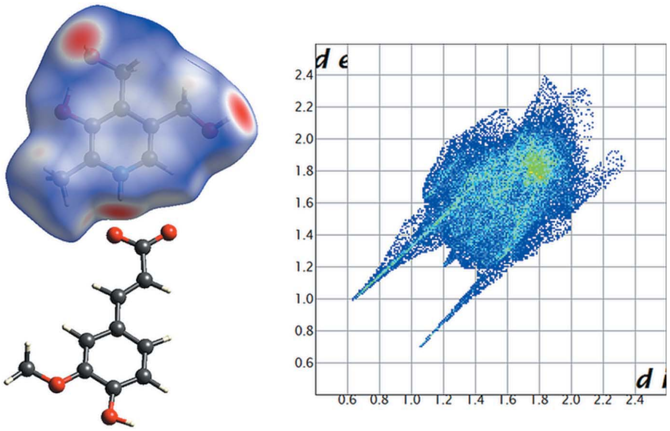
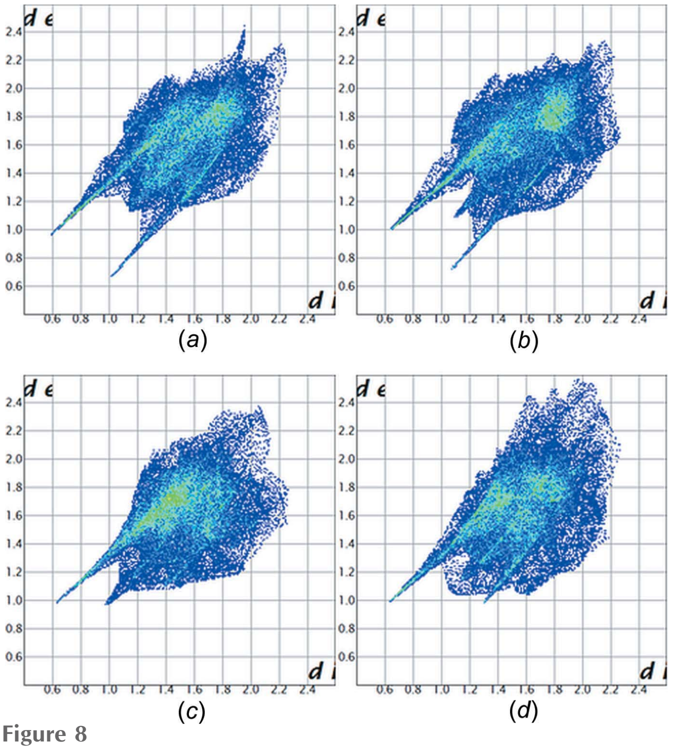


Figure 7
Hirshfeld surface and fingerprint plot for the PN molecule in (2).



(*a*) (*b*) (*c*) (*d*)

Figure 8
Fingerprint plots for the PN molecule in (*a*) 4-aminobenzoate, (*b*) 4-hydroxybenzoate, (*c*) 4-nitrobenzoate and (*d*) 4-cyanobenzoate salts (Ganduri *et al.*, 2015).

colour is red, for moderate density the colour is green and for relatively few points the colour is blue. It is also possible to highlight on the plot a single contact of the type atomtype1···atomtype2, to focus attention on the individual interaction types present (Spackman & Jayatilaka, 2009).

The surface coloured according to $d_{\rm norm}$ (−0.72 to 1.25 Å) values shows where the short intermolecular interactions occur; in particular, the red spot corresponding to the interaction with the carboxylate group is represented in the fingerprints plot by the end of the sharper upper spike in both structures (Figs. 6 and 7); in this zone, the contribution of the O—H···O hydrogen bond involving the O1—H PN hydroxy group is also added. The lower spike corresponds instead to O7—H7O···O2$^{\rm iv}$ and O2—H2O···O1$^{\rm vii}$ in (1) and (2), respectively, *i.e.* hydrogen bonds where PN is acting as the acceptor molecule. The central marker present in both fingerprint plots, formed by C···C and C···N interactions, is a typical and characteristic hint towards significant π–π interactions (Spackman & Jayatilaka, 2009). Examination of decomposed 2D fingerprint plots shows that the percentage of intermolecular H···O interactions is very similar in the two salts, *viz.* 36.1 and 29.8%, respectively. The fingerprint plots of the PN molecule present in the literature salts mentioned above are shown in Fig. 8. The fingerprint plots of both the aminobenzoate and hydroxybenzoate salts (Figs. 8*a* and 8*b*) show some similarities with the present structures, in particular, as far as the two sharp spikes are concerned. Indeed, they refer to similar O/N—H···O interactions, with N···O and O···O distances in the ranges 2.66–2.76 and 2.65–2.90 Å, respectively. In nitro- and cyanobenzoate salts, the lower spike is much less evident (Figs. 8*c* and 8*d*). Due to the lack of good hydrogen-bonding donor groups in the coformer molecule, in fact, they mark the existence of weaker C—H···O interactions. The differences visible in the fingerprint plots shown in Fig. 8 may result also from different stacking types, *i.e.* heterogeneous in parts (*a*) and (*b*) and homogeneous in part (*c*). Moreover, in the case of cyanobenzoate (Fig. 8*d*), the aromatic rings are stacked at a distance greater than 4 Å and accordingly no marker appears in the fingerprint plot. These findings, besides indicating the robustness of the pyridine/carboxylic acid supramolecular synthon, point to its importance in driving the assembly process of different cocrystal units.

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supporting information

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New pharmaceutical salts containing pyridoxine

Aleksandar Cvetkovski, Valeria Ferretti and Valerio Bertolasi

Computing details

For both structures, data collection: *COLLECT* (Nonius, 1997); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and MarvinSketch (ChemAxon, 2010); software used to prepare material for publication: *SHELXL2014* (Sheldrick, 2015) and *WinGX* (Farrugia, 2012).

3-Hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium 4-hydroxy-3,5-dimethoxybenzoate monohydrate (shelx1)

Crystal data

$C_8H_{12}NO_3^+\cdot C_9H_9O_5^-$	$Z = 2$
$M_r = 367.35$	$F(000) = 388$
Triclinic, $P\overline{1}$	$D_x = 1.273$ Mg m^{-3}
$a = 6.9085$ (2) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 8.4524$ (2) Å	Cell parameters from 18203 reflections
$c = 17.9702$ (5) Å	$\theta = 3$–$27°$
$\alpha = 101.8010$ (16)°	$\mu = 0.10$ mm^{-1}
$\beta = 92.7110$ (16)°	$T = 295$ K
$\gamma = 109.8290$ (14)°	Plate, colourless
$V = 958.47$ (5) Å^3	0.52 × 0.20 × 0.09 mm

Data collection

Nonius KappaCCD diffractometer	$R_{\rm int} = 0.035$
φ scans and ω scans	$\theta_{\rm max} = 27.5°$, $\theta_{\rm min} = 3.1°$
18203 measured reflections	$h = -8\rightarrow8$
4387 independent reflections	$k = -10\rightarrow10$
3191 reflections with $I > 2\sigma(I)$	$l = -23\rightarrow23$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
Least-squares matrix: full	$w = 1/[\sigma^2(F_o^2) + (0.0972P)^2 + 0.1657P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.053$	$(\Delta/\sigma)_{\rm max} < 0.001$
$wR(F^2) = 0.167$	$\Delta\rho_{\rm max} = 0.38$ e Å^{-3}
$S = 1.06$	$\Delta\rho_{\rm min} = -0.27$ e Å^{-3}
4387 reflections	
256 parameters	
0 restraints	
Hydrogen site location: mixed	

Extinction correction: SHELXL2014 (Sheldrick, 2015), Fc*=kFc[1+0.001xFc$^2\lambda^3$/sin(2θ)]$^{-1/4}$
Extinction coefficient: 0.049 (12)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.0285 (2)	0.59703 (18)	0.20164 (8)	0.0356 (3)
O1	0.1171 (3)	0.72836 (18)	−0.00103 (9)	0.0750 (6)
O2	0.2464 (2)	1.24197 (14)	0.27041 (7)	0.0437 (3)
O3	0.2151 (2)	0.99184 (17)	0.34344 (7)	0.0500 (4)
O4	−0.0942 (2)	0.26847 (15)	0.21330 (8)	0.0491 (4)
O5	−0.2842 (3)	0.0993 (2)	0.10465 (8)	0.0679 (5)
O6	−0.3275 (2)	−0.10970 (16)	0.40501 (7)	0.0571 (4)
O7	−0.4868 (2)	−0.42453 (16)	0.32123 (7)	0.0503 (4)
O8	−0.5267 (2)	−0.49958 (15)	0.16857 (7)	0.0530 (4)
C1	0.0551 (2)	0.6461 (2)	0.13492 (10)	0.0355 (4)
H1	0.0187	0.5630	0.0888	0.043*
C2	0.1360 (3)	0.8185 (2)	0.13488 (9)	0.0352 (4)
C3	0.1906 (2)	0.9421 (2)	0.20504 (10)	0.0351 (4)
C4	0.1620 (3)	0.8850 (2)	0.27271 (10)	0.0358 (4)
C5	0.0775 (3)	0.7085 (2)	0.27035 (9)	0.0358 (4)
C6	0.1681 (3)	0.8730 (2)	0.06041 (10)	0.0484 (5)
H6A	0.0821	0.9399	0.0530	0.058*
H6B	0.3118	0.9460	0.0622	0.058*
C7	0.2845 (3)	1.1324 (2)	0.20618 (12)	0.0475 (5)
H7A	0.4332	1.1639	0.2061	0.057*
H7B	0.2289	1.1520	0.1597	0.057*
C8	0.0449 (3)	0.6418 (3)	0.34144 (11)	0.0504 (5)
H8A	−0.0269	0.5188	0.3277	0.076*
H8B	−0.0361	0.6959	0.3719	0.076*
H8C	0.1769	0.6680	0.3704	0.076*
C9	−0.2191 (3)	0.1241 (2)	0.17279 (11)	0.0406 (4)
C10	−0.2906 (2)	−0.0230 (2)	0.21191 (9)	0.0344 (4)
C11	−0.3779 (3)	−0.1917 (2)	0.16787 (9)	0.0359 (4)
H11	−0.3938	−0.2134	0.1147	0.043*
C12	−0.4411 (3)	−0.3270 (2)	0.20417 (9)	0.0352 (4)
C13	−0.4236 (3)	−0.2945 (2)	0.28378 (9)	0.0361 (4)
C14	−0.3377 (3)	−0.1254 (2)	0.32759 (9)	0.0374 (4)
C15	−0.2698 (3)	0.0107 (2)	0.29161 (10)	0.0368 (4)
H15	−0.2106	0.1239	0.3206	0.044*
C16	−0.5400 (4)	−0.5445 (3)	0.08700 (11)	0.0617 (6)

H16A	−0.4507	−0.4482	0.0697	0.093*
H16B	−0.6805	−0.5734	0.0650	0.093*
H16C	−0.4978	−0.6422	0.0715	0.093*
C17	−0.2404 (5)	0.0579 (3)	0.45295 (13)	0.0834 (9)
H17A	−0.1217	0.1245	0.4326	0.125*
H17B	−0.1986	0.0504	0.5034	0.125*
H17C	−0.3415	0.1130	0.4554	0.125*
H1O	0.155 (4)	0.770 (4)	−0.0395 (17)	0.080 (8)*
H2O	0.123 (5)	1.243 (4)	0.2578 (18)	0.097 (10)*
H3O	0.252 (5)	1.108 (4)	0.3378 (18)	0.102 (10)*
H1N	−0.019 (3)	0.482 (3)	0.2007 (11)	0.046 (5)*
H7O	−0.554 (4)	−0.525 (4)	0.2870 (16)	0.074 (8)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0409 (7)	0.0255 (7)	0.0409 (8)	0.0094 (6)	0.0070 (6)	0.0128 (6)
O1	0.1270 (15)	0.0346 (7)	0.0400 (8)	−0.0016 (8)	0.0173 (9)	0.0095 (6)
O2	0.0503 (8)	0.0241 (6)	0.0490 (7)	0.0076 (5)	0.0025 (6)	0.0024 (5)
O3	0.0740 (9)	0.0329 (7)	0.0379 (7)	0.0146 (6)	0.0051 (6)	0.0049 (5)
O4	0.0563 (8)	0.0271 (6)	0.0626 (8)	0.0084 (5)	0.0065 (6)	0.0191 (6)
O5	0.0870 (11)	0.0577 (9)	0.0480 (8)	0.0022 (8)	0.0044 (7)	0.0303 (7)
O6	0.0896 (11)	0.0348 (7)	0.0301 (6)	0.0022 (7)	0.0041 (6)	0.0066 (5)
O7	0.0725 (9)	0.0283 (6)	0.0394 (7)	0.0005 (6)	0.0056 (6)	0.0150 (5)
O8	0.0810 (10)	0.0268 (6)	0.0364 (7)	0.0030 (6)	0.0077 (6)	0.0035 (5)
C1	0.0388 (8)	0.0284 (8)	0.0376 (8)	0.0086 (6)	0.0059 (7)	0.0095 (6)
C2	0.0376 (8)	0.0292 (8)	0.0393 (9)	0.0105 (6)	0.0070 (7)	0.0113 (7)
C3	0.0383 (8)	0.0251 (7)	0.0432 (9)	0.0111 (6)	0.0095 (7)	0.0104 (6)
C4	0.0428 (8)	0.0277 (8)	0.0369 (8)	0.0132 (7)	0.0048 (7)	0.0070 (6)
C5	0.0427 (9)	0.0293 (8)	0.0374 (8)	0.0133 (7)	0.0056 (7)	0.0116 (6)
C6	0.0672 (12)	0.0320 (9)	0.0423 (10)	0.0094 (8)	0.0113 (9)	0.0136 (7)
C7	0.0585 (11)	0.0251 (8)	0.0588 (11)	0.0121 (8)	0.0202 (9)	0.0117 (8)
C8	0.0719 (13)	0.0418 (10)	0.0416 (10)	0.0195 (9)	0.0106 (9)	0.0194 (8)
C9	0.0429 (9)	0.0353 (9)	0.0478 (10)	0.0123 (7)	0.0134 (7)	0.0199 (7)
C10	0.0348 (8)	0.0288 (8)	0.0399 (9)	0.0082 (6)	0.0070 (6)	0.0134 (6)
C11	0.0401 (8)	0.0332 (8)	0.0328 (8)	0.0086 (7)	0.0073 (6)	0.0112 (6)
C12	0.0390 (8)	0.0272 (8)	0.0339 (8)	0.0050 (6)	0.0041 (6)	0.0070 (6)
C13	0.0416 (8)	0.0266 (8)	0.0365 (8)	0.0052 (6)	0.0057 (7)	0.0115 (7)
C14	0.0451 (9)	0.0303 (8)	0.0312 (8)	0.0058 (7)	0.0048 (7)	0.0083 (6)
C15	0.0411 (8)	0.0242 (7)	0.0400 (9)	0.0049 (6)	0.0055 (7)	0.0082 (6)
C16	0.0843 (15)	0.0441 (11)	0.0381 (10)	0.0057 (10)	0.0084 (10)	−0.0012 (8)
C17	0.136 (2)	0.0461 (12)	0.0380 (11)	0.0031 (14)	0.0042 (13)	−0.0030 (9)

Geometric parameters (Å, º)

N1—C5	1.340 (2)	C5—C8	1.495 (2)
N1—C1	1.347 (2)	C6—H6A	0.9700
N1—H1N	0.91 (2)	C6—H6B	0.9700

O1—C6	1.399 (2)	C7—H7A	0.9700
O1—H1O	0.85 (3)	C7—H7B	0.9700
O2—C7	1.420 (2)	C8—H8A	0.9600
O2—H2O	0.87 (3)	C8—H8B	0.9600
O3—C4	1.352 (2)	C8—H8C	0.9600
O3—H3O	0.95 (3)	C9—C10	1.503 (2)
O4—C9	1.275 (2)	C10—C11	1.390 (2)
O5—C9	1.235 (2)	C10—C15	1.393 (2)
O6—C14	1.366 (2)	C11—C12	1.385 (2)
O6—C17	1.409 (2)	C11—H11	0.9300
O7—C13	1.3626 (19)	C12—C13	1.392 (2)
O7—H7O	0.90 (3)	C13—C14	1.391 (2)
O8—C12	1.3727 (19)	C14—C15	1.389 (2)
O8—C16	1.427 (2)	C15—H15	0.9300
C1—C2	1.372 (2)	C16—H16A	0.9600
C1—H1	0.9300	C16—H16B	0.9600
C2—C3	1.405 (2)	C16—H16C	0.9600
C2—C6	1.505 (2)	C17—H17A	0.9600
C3—C4	1.396 (2)	C17—H17B	0.9600
C3—C7	1.512 (2)	C17—H17C	0.9600
C4—C5	1.396 (2)		

C5—N1—C1	123.59 (14)	H8A—C8—H8B	109.5
C5—N1—H1N	117.5 (13)	C5—C8—H8C	109.5
C1—N1—H1N	118.8 (13)	H8A—C8—H8C	109.5
C6—O1—H1O	104.7 (19)	H8B—C8—H8C	109.5
C7—O2—H2O	105 (2)	O5—C9—O4	124.23 (16)
C4—O3—H3O	108.1 (19)	O5—C9—C10	118.93 (16)
C14—O6—C17	117.84 (15)	O4—C9—C10	116.84 (16)
C13—O7—H7O	109.3 (17)	C11—C10—C15	120.72 (14)
C12—O8—C16	117.14 (14)	C11—C10—C9	119.43 (15)
N1—C1—C2	120.10 (15)	C15—C10—C9	119.85 (15)
N1—C1—H1	120.0	C12—C11—C10	119.23 (15)
C2—C1—H1	120.0	C12—C11—H11	120.4
C1—C2—C3	119.16 (15)	C10—C11—H11	120.4
C1—C2—C6	120.06 (15)	O8—C12—C11	125.88 (15)
C3—C2—C6	120.77 (14)	O8—C12—C13	113.64 (14)
C4—C3—C2	118.66 (14)	C11—C12—C13	120.47 (15)
C4—C3—C7	121.44 (15)	O7—C13—C14	118.00 (15)
C2—C3—C7	119.87 (15)	O7—C13—C12	121.94 (15)
O3—C4—C5	115.73 (15)	C14—C13—C12	120.06 (14)
O3—C4—C3	123.78 (15)	O6—C14—C15	125.48 (15)
C5—C4—C3	120.48 (15)	O6—C14—C13	114.76 (14)
N1—C5—C4	118.00 (15)	C15—C14—C13	119.77 (15)
N1—C5—C8	119.78 (14)	C14—C15—C10	119.72 (15)
C4—C5—C8	122.21 (15)	C14—C15—H15	120.1
O1—C6—C2	110.61 (14)	C10—C15—H15	120.1
O1—C6—H6A	109.5	O8—C16—H16A	109.5

C2—C6—H6A	109.5	O8—C16—H16B	109.5
O1—C6—H6B	109.5	H16A—C16—H16B	109.5
C2—C6—H6B	109.5	O8—C16—H16C	109.5
H6A—C6—H6B	108.1	H16A—C16—H16C	109.5
O2—C7—C3	113.71 (14)	H16B—C16—H16C	109.5
O2—C7—H7A	108.8	O6—C17—H17A	109.5
C3—C7—H7A	108.8	O6—C17—H17B	109.5
O2—C7—H7B	108.8	H17A—C17—H17B	109.5
C3—C7—H7B	108.8	O6—C17—H17C	109.5
H7A—C7—H7B	107.7	H17A—C17—H17C	109.5
C5—C8—H8A	109.5	H17B—C17—H17C	109.5
C5—C8—H8B	109.5		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O4	0.91 (2)	1.77 (2)	2.671 (2)	171 (2)
O3—H3*O*···O2	0.95 (4)	1.83 (4)	2.663 (2)	144 (3)
C8—H8*A*···O4	0.96	2.52	3.308 (2)	139
C1—H1···O1$^{\text{i}}$	0.93	2.47	3.359 (2)	158
O1—H1*O*···O5$^{\text{i}}$	0.85 (3)	1.83 (3)	2.663 (2)	166 (3)
C6—H6*B*···O5$^{\text{ii}}$	0.97	2.64	3.576 (3)	161
O2—H2*O*···O4$^{\text{iii}}$	0.87 (4)	1.77 (4)	2.620 (2)	165 (3)
O7—H7*O*···O2$^{\text{iv}}$	0.89 (2)	1.93 (2)	2.728 (1)	146 (3)

Symmetry codes: (i) $-x, -y+1, -z$; (ii) $x+1, y+1, z$; (iii) $x, y+1, z$; (iv) $x-1, y-2, z$.

3-Hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridin-1-ium (*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate monohydrate (comp2)

Crystal data

$C_8H_{12}NO_3^+\cdot C_{10}H_{11}O_5^-\cdot H_2O$
$M_r = 381.37$
Monoclinic, $P2_1$
$a = 7.2440$ (3) Å
$b = 17.1615$ (5) Å
$c = 7.2706$ (2) Å
$\beta = 98.806$ (2)°
$V = 893.21$ (5) Å^3
$Z = 2$
$F(000) = 404$
$D_x = 1.418$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 11173 reflections
$\theta = 4$–30°
$\mu = 0.11$ mm^{-1}
$T = 295$ K
Prismatic, colourless
0.35 × 0.22 × 0.13 mm

Data collection

Nonius Kappa CCD
diffractometer
φ scans and ω scans
11173 measured reflections
4578 independent reflections
3822 reflections with $I > 2\sigma(I)$
$R_{\text{int}} = 0.034$
$\theta_{\max} = 30.0°$, $\theta_{\min} = 4.5°$
$h = -10\rightarrow 9$
$k = -24\rightarrow 22$
$l = -10\rightarrow 10$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.108$
$S = 1.07$
4578 reflections
272 parameters
1 restraint
Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.063P)^2 + 0.0278P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.18$ e Å^{-3}
Absolute structure: Flack *x* determined using 1452 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons *et al.*, 2013)
Absolute structure parameter: −0.4 (4)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.8860 (3)	−0.19960 (10)	1.1832 (2)	0.0354 (4)
O1	0.7016 (3)	−0.39465 (12)	0.8941 (2)	0.0551 (5)
O2	0.9773 (4)	−0.40722 (13)	1.6750 (3)	0.0622 (6)
O3	1.0560 (3)	−0.26271 (12)	1.6424 (2)	0.0526 (4)
O4	0.7236 (2)	−0.12996 (9)	0.7844 (2)	0.0457 (4)
O5	0.8366 (3)	−0.05993 (9)	1.0310 (2)	0.0473 (4)
O6	0.4671 (3)	0.36773 (9)	0.5400 (2)	0.0492 (4)
O7	0.6240 (3)	0.35956 (10)	0.8823 (2)	0.0565 (5)
O1W	0.5731 (3)	0.00760 (11)	1.2468 (2)	0.0502 (4)
C1	0.8257 (3)	−0.26552 (12)	1.0932 (3)	0.0352 (4)
H1	0.7760	−0.2635	0.9675	0.042*
C2	0.8367 (3)	−0.33573 (12)	1.1852 (3)	0.0325 (4)
C3	0.9116 (3)	−0.33702 (12)	1.3759 (3)	0.0331 (4)
C4	0.9767 (3)	−0.26757 (13)	1.4613 (3)	0.0356 (4)
C5	0.9623 (3)	−0.19785 (12)	1.3625 (3)	0.0352 (4)
C6	0.7702 (3)	−0.40987 (12)	1.0846 (3)	0.0384 (4)
H6A	0.8727	−0.4467	1.0934	0.046*
H6B	0.6719	−0.4330	1.1434	0.046*
C7	0.9194 (4)	−0.41369 (14)	1.4799 (3)	0.0466 (5)
H7A	0.7965	−0.4374	1.4580	0.056*
H7B	1.0047	−0.4483	1.4291	0.056*
C8	1.0285 (4)	−0.12139 (15)	1.4478 (3)	0.0464 (5)
H8A	1.0056	−0.0810	1.3557	0.070*
H8B	1.1599	−0.1243	1.4931	0.070*
H8C	0.9622	−0.1098	1.5492	0.070*
C9	0.7545 (3)	−0.06564 (11)	0.8646 (3)	0.0332 (4)
C10	0.6902 (3)	0.00681 (12)	0.7617 (3)	0.0368 (4)
H10	0.6318	0.0027	0.6390	0.044*

C11	0.7130 (3)	0.07718 (12)	0.8386 (3)	0.0332 (4)
H11	0.7754	0.0793	0.9602	0.040*
C12	0.6508 (3)	0.15162 (11)	0.7528 (3)	0.0320 (4)
C13	0.6705 (3)	0.21921 (12)	0.8628 (3)	0.0349 (4)
H13	0.7248	0.2159	0.9871	0.042*
C14	0.6101 (3)	0.29043 (12)	0.7888 (3)	0.0365 (4)
C15	0.5249 (3)	0.29579 (12)	0.6022 (3)	0.0363 (4)
C16	0.5067 (3)	0.22952 (12)	0.4926 (3)	0.0370 (4)
H16	0.4518	0.2330	0.3686	0.044*
C17	0.5697 (3)	0.15779 (12)	0.5661 (3)	0.0365 (4)
H17	0.5578	0.1137	0.4907	0.044*
C18	0.7096 (4)	0.35938 (16)	1.0716 (3)	0.0537 (6)
H18A	0.6440	0.3241	1.1411	0.081*
H18B	0.7053	0.4109	1.1221	0.081*
H18C	0.8373	0.3430	1.0797	0.081*
H1N	0.879 (5)	−0.153 (3)	1.116 (5)	0.080 (11)*
H1O	0.614 (4)	−0.428 (2)	0.855 (4)	0.046 (7)*
H2O	0.877 (8)	−0.403 (3)	1.737 (7)	0.115 (18)*
H3O	1.038 (6)	−0.313 (3)	1.674 (6)	0.081 (12)*
H6O	0.396 (5)	0.360 (3)	0.422 (6)	0.080 (11)*
H1W	0.537 (6)	−0.035 (3)	1.282 (6)	0.078 (11)*
H2W	0.674 (7)	−0.007 (3)	1.196 (6)	0.100 (14)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0409 (9)	0.0269 (8)	0.0361 (8)	0.0026 (7)	−0.0010 (7)	0.0031 (7)
O1	0.0745 (13)	0.0494 (10)	0.0396 (9)	−0.0207 (10)	0.0032 (8)	−0.0049 (8)
O2	0.0801 (14)	0.0624 (13)	0.0422 (9)	−0.0019 (11)	0.0025 (9)	0.0191 (9)
O3	0.0712 (12)	0.0515 (10)	0.0313 (7)	0.0014 (9)	−0.0048 (7)	−0.0008 (7)
O4	0.0667 (10)	0.0267 (7)	0.0392 (8)	0.0019 (7)	−0.0061 (7)	−0.0014 (6)
O5	0.0688 (11)	0.0296 (7)	0.0376 (8)	0.0047 (7)	−0.0103 (7)	0.0000 (6)
O6	0.0712 (11)	0.0276 (8)	0.0419 (8)	0.0069 (8)	−0.0129 (7)	0.0032 (6)
O7	0.0924 (13)	0.0285 (8)	0.0404 (8)	0.0096 (9)	−0.0163 (8)	−0.0027 (7)
O1W	0.0700 (12)	0.0332 (8)	0.0473 (9)	0.0067 (8)	0.0082 (8)	0.0033 (7)
C1	0.0406 (10)	0.0300 (9)	0.0333 (9)	0.0005 (9)	−0.0001 (8)	0.0016 (8)
C2	0.0336 (10)	0.0292 (9)	0.0345 (9)	0.0019 (8)	0.0047 (7)	0.0000 (8)
C3	0.0360 (10)	0.0309 (9)	0.0330 (9)	0.0039 (8)	0.0079 (7)	0.0029 (8)
C4	0.0398 (10)	0.0366 (10)	0.0296 (9)	0.0051 (9)	0.0030 (7)	0.0021 (8)
C5	0.0368 (10)	0.0331 (10)	0.0348 (9)	0.0010 (9)	0.0021 (8)	−0.0023 (8)
C6	0.0443 (11)	0.0310 (10)	0.0399 (10)	−0.0038 (9)	0.0066 (8)	−0.0031 (8)
C7	0.0655 (15)	0.0356 (11)	0.0404 (11)	0.0078 (11)	0.0135 (10)	0.0098 (9)
C8	0.0552 (13)	0.0369 (11)	0.0440 (11)	−0.0023 (10)	−0.0017 (9)	−0.0060 (9)
C9	0.0392 (10)	0.0262 (9)	0.0333 (9)	0.0041 (8)	0.0025 (7)	0.0028 (7)
C10	0.0450 (11)	0.0296 (9)	0.0333 (9)	0.0015 (9)	−0.0017 (8)	0.0030 (8)
C11	0.0349 (10)	0.0289 (9)	0.0347 (9)	0.0010 (8)	0.0020 (7)	0.0036 (8)
C12	0.0331 (10)	0.0255 (9)	0.0365 (9)	0.0000 (8)	0.0022 (7)	0.0032 (8)
C13	0.0405 (10)	0.0296 (10)	0.0323 (9)	0.0009 (8)	−0.0017 (7)	0.0020 (8)

C14	0.0426 (11)	0.0280 (10)	0.0366 (10)	−0.0003 (9)	−0.0014 (8)	−0.0014 (8)
C15	0.0414 (11)	0.0293 (9)	0.0360 (10)	0.0020 (9)	−0.0005 (8)	0.0059 (8)
C16	0.0438 (11)	0.0312 (9)	0.0333 (9)	−0.0003 (9)	−0.0030 (8)	0.0031 (8)
C17	0.0431 (11)	0.0293 (9)	0.0354 (9)	0.0000 (9)	0.0009 (8)	0.0006 (8)
C18	0.0772 (17)	0.0407 (12)	0.0377 (11)	0.0052 (12)	−0.0088 (11)	−0.0075 (10)

Geometric parameters (Å, º)

N1—C5	1.336 (3)	C6—H6A	0.9700
N1—C1	1.346 (3)	C6—H6B	0.9700
N1—H1N	0.93 (5)	C7—H7A	0.9700
O1—C6	1.423 (3)	C7—H7B	0.9700
O1—H1O	0.87 (3)	C8—H8A	0.9600
O2—C7	1.421 (3)	C8—H8B	0.9600
O2—H2O	0.92 (5)	C8—H8C	0.9600
O3—C4	1.356 (2)	C9—C10	1.488 (3)
O3—H3O	0.91 (5)	C10—C11	1.330 (3)
O4—C9	1.253 (3)	C10—H10	0.9300
O5—C9	1.267 (3)	C11—C12	1.462 (3)
O6—C15	1.359 (3)	C11—H11	0.9300
O6—H6O	0.94 (4)	C12—C17	1.398 (3)
O7—C14	1.363 (3)	C12—C13	1.404 (3)
O7—C18	1.421 (3)	C13—C14	1.379 (3)
O1W—H1W	0.82 (5)	C13—H13	0.9300
O1W—H2W	0.90 (5)	C14—C15	1.405 (3)
C1—C2	1.374 (3)	C15—C16	1.383 (3)
C1—H1	0.9300	C16—C17	1.391 (3)
C2—C3	1.409 (3)	C16—H16	0.9300
C2—C6	1.509 (3)	C17—H17	0.9300
C3—C4	1.393 (3)	C18—H18A	0.9600
C3—C7	1.514 (3)	C18—H18B	0.9600
C4—C5	1.391 (3)	C18—H18C	0.9600
C5—C8	1.498 (3)		

C5—N1—C1	123.26 (18)	H8A—C8—H8B	109.5
C5—N1—H1N	118 (2)	C5—C8—H8C	109.5
C1—N1—H1N	118 (2)	H8A—C8—H8C	109.5
C6—O1—H1O	109.4 (19)	H8B—C8—H8C	109.5
C7—O2—H2O	111 (3)	O4—C9—O5	122.47 (18)
C4—O3—H3O	98 (3)	O4—C9—C10	118.83 (17)
C15—O6—H6O	106 (3)	O5—C9—C10	118.69 (17)
C14—O7—C18	117.98 (18)	C11—C10—C9	122.54 (17)
H1W—O1W—H2W	102 (4)	C11—C10—H10	118.7
N1—C1—C2	120.66 (18)	C9—C10—H10	118.7
N1—C1—H1	119.7	C10—C11—C12	127.11 (18)
C2—C1—H1	119.7	C10—C11—H11	116.4
C1—C2—C3	118.51 (19)	C12—C11—H11	116.4
C1—C2—C6	120.87 (18)	C17—C12—C13	118.80 (18)

C3—C2—C6	120.62 (18)	C17—C12—C11	122.46 (18)
C4—C3—C2	118.58 (18)	C13—C12—C11	118.73 (17)
C4—C3—C7	122.45 (18)	C14—C13—C12	120.74 (18)
C2—C3—C7	118.97 (19)	C14—C13—H13	119.6
O3—C4—C5	115.8 (2)	C12—C13—H13	119.6
O3—C4—C3	123.4 (2)	O7—C14—C13	125.58 (18)
C5—C4—C3	120.81 (17)	O7—C14—C15	114.36 (18)
N1—C5—C4	118.13 (18)	C13—C14—C15	120.06 (18)
N1—C5—C8	118.81 (19)	O6—C15—C16	123.92 (18)
C4—C5—C8	123.06 (18)	O6—C15—C14	116.62 (19)
O1—C6—C2	110.78 (17)	C16—C15—C14	119.45 (18)
O1—C6—H6A	109.5	C15—C16—C17	120.63 (19)
C2—C6—H6A	109.5	C15—C16—H16	119.7
O1—C6—H6B	109.5	C17—C16—H16	119.7
C2—C6—H6B	109.5	C16—C17—C12	120.29 (19)
H6A—C6—H6B	108.1	C16—C17—H17	119.9
O2—C7—C3	114.4 (2)	C12—C17—H17	119.9
O2—C7—H7A	108.7	O7—C18—H18A	109.5
C3—C7—H7A	108.7	O7—C18—H18B	109.5
O2—C7—H7B	108.7	H18A—C18—H18B	109.5
C3—C7—H7B	108.7	O7—C18—H18C	109.5
H7A—C7—H7B	107.6	H18A—C18—H18C	109.5
C5—C8—H8A	109.5	H18B—C18—H18C	109.5
C5—C8—H8B	109.5		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O5	0.93 (4)	1.73 (5)	2.641 (2)	166 (4)
O3—H3*O*···O2	0.90 (5)	1.68 (5)	2.564 (3)	165 (4)
O1*W*—H2*W*···O5	0.90 (5)	2.02 (5)	2.893 (3)	161 (5)
C8—H8*A*···O5	0.96	2.51	3.307 (3)	140
O2—H2*O*···O1$^{\rm i}$	0.91 (6)	1.84 (6)	2.747 (3)	171 (5)
C8—H8*C*···O4$^{\rm i}$	0.96	2.63	3.541 (3)	158
C17—H17···O1*W*$^{\rm ii}$	0.93	2.55	3.472 (3)	167
O6—H6*O*···O4$^{\rm iii}$	0.94 (4)	1.62 (4)	2.545 (2)	166 (4)
O1—H1*O*···O1*W*$^{\rm iv}$	0.86 (3)	1.82 (3)	2.683 (3)	175 (3)
O1*W*—H1*W*···O6iv$^{\rm iv}$	0.82 (5)	2.12 (5)	2.896 (2)	156 (4)
O1*W*—H1*W*···O7iv$^{\rm iv}$	0.82 (5)	2.37 (5)	2.994 (3)	132 (4)

Symmetry codes: (i) *x*, *y*, *z*+1; (ii) *x*, *y*, *z*−1; (iii) −*x*+1, *y*+1/2, −*z*+1; (iv) −*x*+1, *y*−1/2, −*z*+2.