

Structures of benzoic acids with substituted pyridines and quinolines: salt *versus* co-crystal formation†

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A series of five substituted benzoic acids with 10 substituted pyridines and quinolines have been crystallized so that their ΔpK_a , defined as $pK_{a \text{ base}} - pK_{a \text{ acid}}$, varied from -1.14 to $+4.16$. This spans the 'uncertainty' region for the formation of salt *versus* co-crystals. Although most of our results confirmed that structure formation of co-crystal *versus* salt parts at $\Delta pK_a \approx 2$, we report here a structure that does not follow the general rule and serves as a cautionary tale.

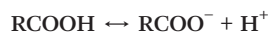
Introduction

The question of pH control in the formation of salts *versus* co-crystals is a topic of current research interest. This is particularly important in the pharmaceutical industry which is continually seeking Active Pharmaceutical Ingredients (APIs) with desirable properties such as stability and taste.

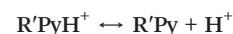
When an acid is reacted with a base, the ensuing product will be a salt or a co-crystal, and the general rule is that if ΔpK_a ($pK_{a \text{ base}} - pK_{a \text{ acid}}$) is greater than 2–3, the product will be a salt.¹ This is not an absolute rule, because the pK_a is an acid dissociation constant measured in water at a fixed temperature. However, the product of the reaction depends upon the solvent or mixture of solvents, the temperature and, if the product is a crystalline solid, on the packing forces impinging on the molecules or ions in the crystal structure.

However the ΔpK_a can be used as a guideline and may be justified by a simplified analysis of the equilibria between a carboxylic acid RCOOH and a substituted pyridine base R'Py.

If the equilibrium constants of the base and the acid are K_{a1} and K_{a2} respectively:

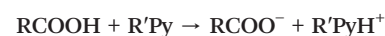


$$K_{a2} = \frac{[\text{RCOO}^-][\text{H}^+]}{[\text{RCOOH}]}$$



$$K_{a1} = \frac{[\text{R'Py}][\text{H}^+]}{[\text{R'PyH}^+]}$$

Here we have approximated concentration with activities. For the reaction:



$$K_{\text{eq}} = \frac{[\text{RCOO}^-][\text{R'PyH}^+]}{[\text{RCOOH}][\text{R'Py}]}$$

$$\approx \frac{K_{a2}}{K_{a1}}$$

and

$$\begin{aligned} \log K_{\text{eq}} &= \log K_{a2} - \log K_{a1} \\ &= pK_{a1} - pK_{a2} \\ &= \Delta pK_a (\text{base} - \text{acid}) \end{aligned}$$

If $\Delta pK_a = 0$ there are equal quantities of ions and neutral molecules in the solution.

If $\Delta pK_a > 0$, the ionic species will predominate and *vice versa*.

For example, if $pK_{a1} = 5$ and $pK_{a2} = 3$, $\Delta pK_a = +2$ so $K_{\text{eq}} \approx K_{a2}/K_{a1} = 10^{-3}/10^{-5} \approx 100$. Thus the concentration of the

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† The structures were deposited at the Cambridge Crystallographic Data Centre and allocated the numbers: CCDC 963007–963012, 963014–963021. CIF files have been submitted as ESI. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ce41963k



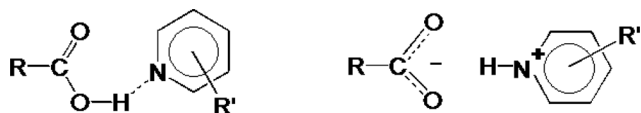


Fig. 1 Co-crystal versus salt formation.

ionized species is in excess, giving a greater likelihood of the salt being formed.

In the crystalline solid state, the difference between a salt and a co-crystal is subtle, being dependent in the unambiguous location of a hydrogen atom as shown in Fig. 1.

Thus if the O...N distance is typically ≈ 2.7 Å and O-H and N⁺-H distances are ≈ 1.0 Å, the movement of the H atom is small, approximately 0.7 Å.

Fig. 1, however displays schematically the extreme, either-or situation. It has been pointed out by Childs, Stahly and Park² that there are cases where the location of the proton is ambiguous and is not clearly covalently bonded to either the oxygen or the nitrogen atom. The proton transfer should thus be regarded as a continuum and can, in addition, be traced by the difference in bond lengths in the carboxyl group.

These are distinctly different in the acid (d C=O ≈ 1.2 Å, d C-OH ≈ 1.30 Å) but tend to equalize in the carboxylate anion (d C-O ≈ 1.26 Å).

Recently, Cruz-Cabeza³ carried out a survey of over 6000 structures comprising ionised and non-ionised acid-base pairs. She found a linear relationship between ΔpK_a and the

probability of proton transfer, in the pK_a range of -1 to $+4$. The cross-over point occurs at $\Delta pK_a = 1.3$, beyond which there is a greater than 50% probability of the product being a salt. Gilli & Gilli⁴ have devised a slide rule which predicts the strength of a Donor-Acceptor hydrogen bond based on the ΔpK_a of the system. It is noteworthy that their device predicts salts if $\Delta pK_a > 3$, co-crystals when $\Delta pK_a < -3$ and the uncertainty region which contains the strong hydrogen bonds is pictured as $D \cdots H \cdots A$, which may be regarded as the true three-centre-four-electron system.

The Gilli & Gilli review points out that the interval of ΔpK_a matching should be shifted by 1.5 units when interpreting crystal structures,⁵ which agrees with the findings in the survey by Cruz-Cabeza.

Based on the above, we have crystallized a series of five substituted benzoic acids with 10 substituted pyridines and quinolines as shown in Fig. 2.

The acids were selected to have different Hammett substituent constants varying from *p*-amino ($\sigma = -0.66$) to *p*-nitro ($\sigma = +0.78$), yielding different pK_a values,⁶ while the pK_a values of the substituted bases varied from 3.63 to 7.62.

The ΔpK_a values of our chosen compounds varied from -1.14 to $+4.16$, thus spanning the 'uncertainty' region identified by both Cruz-Cabeza and Gilli & Gilli.

In this work we discuss the bonding of 22 structures made up of acid-base pairs which either form salts or co-crystals. They give rise to 26 ΔpK_a due to some bases having two pK_a values. In Table 3 we label these 1 to 26. Eight structures⁸⁻²³

ACID					
Name	4-nitrobenzoic acid	4-bromobenzoic acid	Benzoic acid	4-methoxybenzoic acid	4-aminobenzoic acid
Label	A1	A2	A3	A4	A5
σ	+0.78	+0.23	0	-0.28	-0.66
pK_a	3.46	4.04	4.08	4.37	4.77
BASE					
Name	Nicotinamide	2-acetamidopyridine	4,4'-bipyridine	Quinoline	2-acetamido-6-methylpyridine
Label	B1	B2	B3	B4	B5
pK_a	3.63	4.05	4.44 / 5.25	4.50	4.79
BASE					
Name	6-aminoquinoline	5-aminoquinoline	2-aminopyridine	2-amino-6-methylpyridine	2-amino-4-methylpyridine
Label	B6	B7	B8	B9	B10
pK_a	5.15	5.22	6.84	7.60	7.62

Fig. 2 List of acids and bases used in this project and their pK_a .



		CSD Refcode	Structure	ΔpK_a
1	CSD	ABULIU ⁸	A5-B1 (H ₂ O)	-1.14
2	I	-	A5-B2	-0.72
3	CSD	UDUZOI ⁹ UDUZOI01 ¹⁰	2A5-B3(1)	-0.33
4	II	-	A3-B2	-0.03
5	III	-	A5-B5	0.02
6	IV	-	2A4-B3(1)	0.07
7	CSD	COZXUL ¹¹	A3-B3(1)	0.36
8	V	-	A5-B6	0.38
9	CSD	UDUZOI ⁹ UDUZOI01 ¹⁰	2A5-B3(1)	0.48
10	IV	-	2A4-B3(2)	0.88
11	CSD	DAQZIF ¹² DAQZIF01 ¹³	2A1-B3(1)	0.98
12	VI	-	A1-B4	1.04
13	CSD	COZXUL ¹¹	A3-B3(2)	1.17
14	CSD	DAQZIF ¹² DAQZIF01 ¹³	2A1-B3(1)	1.79
15	CSD	LAPPIC ¹⁴	A5-B8	2.07
16	VII	LUPZOL ¹⁵ LUPZOL01 ¹⁶	A3-B8	2.76
17	VIII	-	A2-B8	2.8
18	IX	RIZBUY ¹⁷	A5-B10	2.85
19	X	-	A4-B9	3.23
20	XI	-	A4-B10	3.25
21	CSD	ODAZID ¹⁸ ODAZID01 ¹⁹ ODAZID02 ²⁰	A1-B8	3.38
22	XII	-	A3-B9	3.52
23	XIII	-	A2-B9 (2H ₂ O)	3.56
24	XIV	-	A2-B10	3.58
25	CSD	ULEHID ²¹	A1-B9	4.14
26	CSD	DUNCOF ²²	A1-B10	4.16

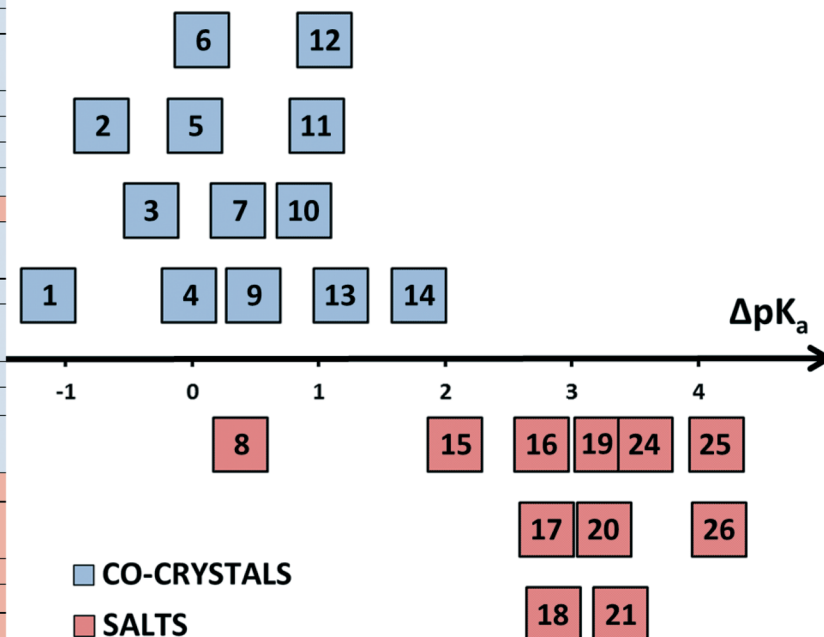


Fig. 3 22 structures (14 new) illustrate the formation of co-crystals *versus* salts as a function of the ΔpK_a (base-acid). In the case of bases with two pK_a , the ΔpK_a was calculated for both, hence the repeats in the table, for example: A4-B3 has two ΔpK_a at 0.07 and 0.88.

were taken from the CSD⁷ while the remainder were newly elucidated and are labelled I to XIV as shown in Fig. 3.

Table 1 for the co-crystals and Table 2 & 3 for the salts report the crystal data, structure and refinement parameters for I to XIV.

Experimental section

Crystal growth

The acid and base to be combined were selected and equal molar amounts were weighed accurately. The compounds were dissolved in separate vials in ethanol with gentle stirring and heating. The solutions were filtered and combined. The acid-base mixtures were allowed to crystallise at room temperature upon slow evaporation of the solvent to afford crystals suitable for single crystal structure determination.

Crystal structure

For structures II, III, VII, X, XI, XII and XIV, the intensity data measured on a Bruker KAPPA CCD diffractometer using graphite-monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) were used to determine the cell dimensions. The strategy for the data collections was evaluated using COLLECT software.²³

For these structures, the intensity data were collected by the standard ϕ scan and omega scan techniques, scaled and reduced using the program DENZO-SMN.²⁴

Crystal structure determinations for I, IV, V, VI, VIII, IX and XIII were performed by single crystal X-ray diffraction using a Bruker KAPPA APEX II DUO diffractometer with graphite monochromated Mo-K α radiation. Unit cell refinement and data reduction were performed using the program SAINT.²⁵

All structures were determined at low temperature (173 K) and the refinement parameters are presented in Tables 1–3.

Structures VII and IX were previously reported in the literature^{15–17} but for data collections at room temperature (VII and IX) and 208 K (for VII).

The structures were solved using direct methods and refined by full-matrix least squares with SHELX-97,²⁶ refining on F^2 . The program X-Seed²⁷ was used as a graphical interface. For all the structures the non-hydrogen atoms were found in the difference electron density map. The aromatic and methyl hydrogen atoms were placed in calculated positions and refined isotropically using a riding model. The hydrogen atoms belonging to amine, protonated pyridyl or hydroxyl groups were placed using the electron density map and refined isotropically. At times, the N–H distance in



Table 1 Crystal structures of the co-crystals and their refinement parameters

	A5·B2	A3·B2	A5·B5	2A4·B3	A1·B4
	I(1)	II(4)	III(5)	IV(6)	VI(12)
Co-crystal	$\Delta\rho K_a = -0.72$	$\Delta\rho K_a = -0.03$	$\Delta\rho K_a = 0.02$	$\Delta\rho K_a = 0.07$	$\Delta\rho K_a = 2.46$
Molecular formula	C ₇ H ₇ NO ₂ · C ₇ H ₈ N ₂ O	C ₇ H ₆ O ₂ · C ₇ H ₈ N ₂ O	C ₇ H ₇ NO ₂ · C ₈ H ₁₀ N ₂ O	2(C ₈ H ₈ O ₃)· C ₁₀ H ₈ N ₂	C ₇ H ₅ NO ₄ · C ₈ H ₇ N
Molecular mass	273.29	258.27	287.32	460.47	296.28
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>Pna</i> 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁
<i>a</i> , Å	14.864(1)	12.776(3)	8.435(2)	9.0319(1)	3.759(1)
<i>b</i> , Å	18.554(2)	5.184(1)	23.547(5)	10.860(1)	27.082(9)
<i>c</i> , Å	4.709(1)	19.547(4)	7.127(1)	23.561(2)	6.551(2)
α , deg	90	90	90	90	90
β , deg	90	103.08(3)	90.22(3)	97.950(2)	90.735(8)
γ , deg	90	90	90	90	90
<i>V</i> , Å ³	1298.8(2)	1261.1(5)	1415.5(5)	2288.8(3)	666.9(4)
<i>Z</i>	4	4	4	4	2
<i>D_c</i> , Mg m ⁻³	1.398	1.360	1.348	1.336	1.475
μ , mm ⁻¹	0.101	0.097	0.096	0.096	0.108
<i>F</i> (000)	576	544	608	968	308
θ_{\min} – θ_{\max} , deg	1.8–25.2	4.1–27.8	3.5–27.9	1.8–28.3	1.5–26.5
Index ranges min./max. <i>h,k,l</i>	–17 : 17 –22 : 22 –5 : 5	–16 : 16 –6 : 6 –25 : 25	–11 : 11 –30 : 23 –9 : 6	–7 : 12 –14 : 14 –31 : 31	–4 : 4 –33 : 34 –8 : 8
Reflections collected	12 991	4851	7340	31 250	5055
Independent reflections	2330	2852	3315	5695	2702
<i>R</i> _{int}	0.047	0.027	0.075	0.040	0.039
Data/parameters refined	2330/198	2852/182	3315/208	5695/317	2702/204
No. of reflections with <i>I</i> > 2σ(<i>I</i>)	2032	1873	1563	4225	1894
Goodness of fit, <i>S</i>	1.04	0.97	0.99	1.03	0.99
<i>R</i> (<i>F</i>) [<i>I</i> > 2σ(<i>I</i>)]	0.0329	0.0401	0.0583	0.0398	0.0470
Final w <i>R</i> ₂ (all data)	0.0788	0.1076	0.1566	0.1133	0.1029
Largest diff. peak and hole, e Å ⁻³	–0.19, 0.12	–0.23, 0.25	–0.29, 0.25	–0.22, 0.25	–0.21, 0.16

Table 2 Crystal structures of the salts (part 1) and their refinement parameters

	A5·B6	A3·B8	A2·B8	A5·B10	A4·B9
	V(8)	VII(16)	VIII(17)	IX(18)	X(19)
Salts	$\Delta\rho K_a = 0.38$	$\Delta\rho K_a = 2.76$	$\Delta\rho K_a = 2.80$	$\Delta\rho K_a = 2.85$	$\Delta\rho K_a = 3.23$
Molecular formula	C ₇ H ₆ NO ₂ · C ₉ H ₉ N ₂	C ₇ H ₅ O ₂ · C ₅ H ₇ N ₂	C ₇ H ₄ BrO ₂ · C ₅ H ₇ N ₂	C ₇ H ₆ NO ₂ · C ₆ H ₉ N ₂	C ₈ H ₇ O ₃ · C ₆ H ₉ N ₂
Molecular mass	281.31	216.24	295.13	245.28	260.29
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>Pbca</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> , Å	7.335(2)	11.500(2)	9.686(1)	5.554(1)	9.440(2)
<i>b</i> , Å	9.187(2)	15.191(3)	10.333(1)	8.553(2)	11.509(2)
<i>c</i> , Å	21.307(4)	12.228(2)	12.002(1)	25.380(5)	12.690(3)
α , deg	90	90	90	90	90
β , deg	93.30(3)	90	97.765(2)	90	110.77(3)
γ , deg	90	90	90	90	90
<i>V</i> , Å ³	1433.3(5)	2136.2(7)	1190.2(1)	1205.7(4)	1289.2(5)
<i>Z</i>	4	8	4	4	4
<i>D_c</i> , Mg m ⁻³	1.304	1.345	1.647	1.351	1.341
μ , mm ⁻¹	0.089	0.094	3.444	0.094	0.095
<i>F</i> (000)	592	912	592	520	552
θ_{\min} – θ_{\max} , deg	2.4–27.5	3.8–27.9	2.1–26.4	2.9–25.3	2.9–25.4
Index ranges min./max. <i>h,k,l</i>	–9 : 9 –11 : 11 –27 : 27	–14 : 14 –19 : 19 –14 : 15	–12 : 12 –12 : 12 –15 : 15	–6 : 6 –10 : 10 –30 : 30	–11 : 11 –13 : 13 –15 : 15
Reflections collected	6289	4451	18 549	2199	4578
Independent reflections	3266	2433	2439	2199	2355
<i>R</i> _{int}	0.014	0.050	0.032	0	0.036
Data/parameters refined	3266/210	2433/157	2439/198	2199/184	2355/186
No. of reflections with <i>I</i> > 2σ(<i>I</i>)	2867	1432	2182	1468	1445
Goodness of fit, <i>S</i>	1.06	0.95	1.04	0.94	0.96
<i>R</i> (<i>F</i>) [<i>I</i> > 2σ(<i>I</i>)]	0.0363	0.0443	0.0208	0.0389	0.0423
Final w <i>R</i> ₂ (all data)	0.1032	0.1106	0.0540	0.0796	0.0972
Largest diff. peak and hole, e Å ⁻³	–0.19, 0.28	–0.25, 0.22	–0.39, 0.26	–0.22, 0.16	–0.24, 0.19



Table 3 Crystal structures of the salts (part 2) and their refinement parameters

	A4·B10	A3·B9	A2·B9·2(H ₂ O)	A2·B10
	XI(20)	XII(22)	XIII(23)	XIV(24)
Salts	$\Delta pK_a = 3.25$	$\Delta pK_a = 3.52$	$\Delta pK_a = 3.56$	$\Delta pK_a = 3.58$
Molecular formula	C ₈ H ₇ O ₃ · C ₆ H ₉ N ₂	C ₇ H ₅ O ₂ · C ₆ H ₉ N ₂	C ₇ H ₄ BrO ₂ · C ₆ H ₉ N ₂ ·2(H ₂ O)	C ₇ H ₄ BrO ₂ · C ₆ H ₉ N ₂
Molecular mass	260.29	230.26	345.15	309.15
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>Pca</i> 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> , Å	10.337(2)	11.888(2)	17.124(2)	9.579(2)
<i>b</i> , Å	11.727(2)	12.313(3)	4.132(1)	11.539(2)
<i>c</i> , Å	11.031(2)	16.815(3)	22.882(2)	11.311(2)
α , deg	90	90	90	90
β , deg	105.53(3)	90	111.762(2)	100.45(3)
γ , deg	90	90	90	90
<i>V</i> , Å ³	1288.4(4)	2461.3(9)	1503.5(2)	1229.4(4)
<i>Z</i>	4	8	4	4
<i>D_c</i> , Mg m ⁻³	1.342	1.243	1.525	1.670
μ , mm ⁻¹	0.096	0.085	2.748	3.339
<i>F</i> (000)	552	976	704	624
θ_{\min} – θ_{\max} , deg	3.5–27.9	2.9–28.0	1.9–26.4	4.1–27.9
Index ranges min./max. <i>h</i> , <i>k</i> , <i>l</i>	–13 : 12 –11 : 14 –13 : 13	–13 : 13 –15 : 15 –21 : 21	–19 : 21 –5 : 5 –28 : 19	–10 : 12 –11 : 14 –14 : 12
Reflections collected	5041	4641	8753	6862
Independent reflections	2887	4641	3036	2789
<i>R</i> _{int}	0.036	0	0.028	0.027
Data/parameters refined	2887/186	4641/333	3036/204	2789/176
No. of reflections with <i>I</i> > 2σ(<i>I</i>)	1640	3081	2400	2326
Goodness of fit, <i>S</i>	0.94	1.02	1.00	1.05
<i>R</i> (<i>F</i>) [<i>I</i> > 2σ(<i>I</i>)]	0.0462	0.0525	0.0303	0.0242
Final w <i>R</i> ₂ (all data)	0.1205	0.1297	0.0821	0.0556
Largest diff. peak and hole, e Å ⁻³	–0.29, 0.26	–0.24, 0.21	–0.40, 0.59	–0.53, 0.49

amines was restricted to an acceptable value using DFIX. We were careful to establish whether the compound was a co-crystal or a salt. In the case of co-crystals, the hydroxyl hydrogen atom was located in a difference density map and refined freely. In the case of salts, we located the hydrogen atom as being bonded to the N⁺ of the base and in addition we noted the equalisation of the C–O bond length of the carboxyl moiety.

The structures were deposited at the Cambridge Crystallographic Data Centre and allocated the numbers: CCDC 963007–963012, 963014–963021.

Results and discussion

Crystal structures of the co-crystals

Structure I, derived from 4-aminobenzoic acid and 2-acetaminopyridine, A5·B2, crystallises in the space group *Pna*2₁ with *Z* = 4. Each 4-aminobenzoic acid is stabilised by three hydrogen bonds as shown in Fig. 4, comprising a closed ring and an infinite chain running along [100]. In all figures, the same nomenclature has been employed whereby the acid molecules are always represented in orange while the base molecules display the conventional colours. Employing the graph nomenclature of Etter and Bernstein²⁸ these may be designated as R₂²(8) and C₂²(12) respectively. In this packing the chains are anti-parallel running along [100] and are hydrogen

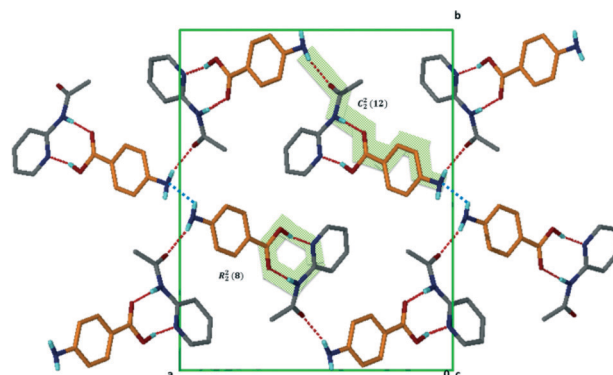


Fig. 4 Packing of structure I displaying anti-parallel ribbons running along [100]. The ribbons are weakly connected *via* (Acid)–N–H···N–(Acid) displayed in blue.

bonded *via* a weak (Acid)–N–H···N–(Acid) displayed in blue in Fig. 4. The metrics of the hydrogen bonding for this and the remaining structures are reported in Table 4.

Structure II consists of benzoic acid and 2-acetaminopyridine, A3·B2, in the space group *P*2₁/*n* with *Z* = 4. The structure is made of acid-base pairs which are hydrogen bonded with R₂²(8) motif similar to that of the previous structure.

Structure III of 4-aminobenzoic acid and 2-acetamido-6-methylpyridine, A5·B5, crystallises in space group *P*2₁/*c* with *Z* = 4. The structure is similar to that of



Table 4 Metrics of the hydrogen bonds in structure I to XIV

Structure	Donor-H in position x, y, z	Acceptor	Symmetry operator leading to acceptor position	d D–H (Å)	d H...A (Å)	d D...A (Å)	Angle (°) (D–H...A)
I	(Acid)–O1–H	N1–(Base)	x, y, z	0.97(3)	1.74(3)	2.703(2)	170(3)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.90(3)	1.95(3)	2.854(2)	179(3)
	(Acid)–N1–H	O1–(Base)	$1/2 + x, 1/2 - y, -2 + z$	1.00(3)	2.13(3)	3.101(2)	166(2)
	(Acid)–N1–H	N1–(Acid)	$-x, 1 - y, 1/2 + z$	0.93(2)	2.62(2)	3.285(3)	129(2)
II	(Acid)–O1–H	N1–(Base)	x, y, z	1.07(2)	1.55(2)	2.610(2)	169(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.91 (2)	2.06(2)	2.963(2)	174(2)
III	(Acid)–O1–H	N1–(Base)	x, y, z	1.02(4)	1.67(4)	2.678(3)	168(4)
	(Base)–N2–H	O2–(Acid)	x, y, z	1.03(3)	1.82(3)	2.839(3)	171(2)
	(Acid)–N1–H	N1–(Acid)	$2 - x, 1 - y, 2 - z$	1.01(2)	2.37(3)	3.035(4)	123(2)
	(Acid)–N1–H	O1–(Base)	$1 - x, -1/2 + y, 3/2 - z$	1.06(2)	1.96(2)	2.949(3)	155(2)
IV	(Acid1)–O1–H	N1–(Base)	x, y, z	0.97(3)	1.68(3)	2.640(2)	174(2)
	(Acid2)–O1–H	N2–(Base)	x, y, z	1.01(3)	1.61(3)	2.607(2)	168(2)
V	(Acid)–N1–H	O1–(Acid)	$-x, -1/2 + y, 1/2 - z$	0.90(2)	2.09(2)	2.971(1)	165(1)
	(Base)–N2–H	O2–(Acid)	$1 - x, 2 - y, -z$	0.97(1)	2.08(1)	3.036(1)	172(1)
	(Base)–N2–H	O2–(Acid)	$x, 1 + y, z$	0.91(2)	2.12(2)	2.985(1)	159(1)
	(Acid)–N1–H	O2–(Acid)	$1 - x, -1/2 + y, 1/2 - z$	0.91(2)	2.00(1)	2.901(1)	171(1)
	(Base)–N1–H	O1–(Acid)	x, y, z	1.06(2)	1.51(2)	2.583(1)	174(2)
	(Base)–N1–H	O2–(Acid)	x, y, z	1.06(2)	2.54(2)	3.152(1)	116(1)
VI	(Acid)–O1–H	N1–(Base)	x, y, z	1.02(4)	1.61(4)	2.621(3)	172(4)
VII	(Base)–N1–H	O1–(Acid)	x, y, z	0.99(2)	1.66(2)	2.651(2)	174(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.97(2)	1.84(2)	2.808(2)	172(2)
	(Base)–N2–H	O1–(Acid)	$-1/2 + x, y, 1/2 - z$	0.93(2)	1.93(2)	2.859(2)	173(2)
VIII	(Base)–N1–H	O1–(Acid)	x, y, z	0.91(2)	1.80(2)	2.699(2)	172(2)
	(Base)–N2–H	O1–(Acid)	$x, -1/2 - y, 1/2 + z$	0.94(2)	1.92(2)	2.843(2)	167(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.98(3)	1.79(2)	2.758(2)	171(2)
IX	(Base)–N1–H	O1–(Acid)	x, y, z	1.02(2)	1.59(2)	2.600(3)	173(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.96(2)	1.93(2)	2.880(3)	174(2)
	(Base)–N2–H	O2–(Acid)	$1/2 + x, 3/2 - y, -z$	1.00(2)	1.90(2)	2.836(3)	156(2)
	(Acid)–N1–H	O1–(Acid)	$1 - x, 1/2 + y, 1/2 - z$	0.95(3)	2.09(3)	2.969(3)	154(3)
X	(Base)–N1–H	O1–(Acid)	x, y, z	1.00(3)	1.76(3)	2.757(3)	180(3)
	(Base)–N2–H	O2–(Acid)	x, y, z	1.03(3)	1.69(2)	2.708(2)	172(2)
	(Base)–N2–H	O1–(Acid)	$1/2 + x, 1/2 - y, 1/2 + z$	0.92(2)	2.06(2)	2.976(2)	170(3)
XI	(Base)–N1–H	O1–(Acid)	x, y, z	0.93(2)	1.75(2)	2.669(2)	174(2)
	(Base)–N2–H	O1–(Acid)	$x, 1/2 - y, 1/2 + z$	0.87(2)	2.01(2)	2.851(2)	162(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.97(2)	1.78(2)	2.751(2)	174(2)
XII	(Base2)–N1–H	O1–(Acid2)	x, y, z	0.99(3)	1.78(3)	2.766(4)	170(2)
	(Base1)–N1–H	O1–(Acid1)	x, y, z	1.08(4)	1.67(4)	2.742(3)	168(3)
	(Base1)–N2–H	O2–(Acid1)	x, y, z	1.04(4)	1.70(4)	2.735(3)	176(2)
	(Base2)–N2–H	O2–(Acid2)	x, y, z	0.93(4)	1.84(4)	2.768(3)	176(4)
	(Base1)–N2–H	O1–(Acid1)	$-1/2 + x, 1 - y, z$	0.94(4)	1.92(4)	2.864(3)	176(3)
	(Base2)–N2–H	O1–(Acid2)	$1/2 + x, -y, z$	0.86(4)	2.07(4)	2.911(3)	168(4)
XIII	(Base)–N1–H	O1–(Acid)	x, y, z	0.89(3)	1.74(3)	2.629(3)	172(3)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.99(3)	1.97(3)	2.949(3)	171(2)
	(Base)–N2–H	O–(Water1)	$1/2 - x, 1/2 + y, 1/2 - z$	1.00(3)	1.94(4)	2.909(4)	163(3)
	(Water1)–O–H	O2–(Acid)	x, y, z	0.83(4)	1.88(4)	2.705(3)	175(4)
(Water1)–O–H	O2–(Acid)	$x, -1 + y, z$	0.83(3)	1.96(3)	2.777(3)	168(3)	
XIV	(Base)–N1–H	O1–(Acid)	x, y, z	0.93(2)	1.76(2)	2.681(2)	173(2)
	(Base)–N2–H	O1–(Acid)	$x, 5/2 - y, -1/2 + z$	0.97(2)	1.92(2)	2.868(2)	165(2)
	(Base)–N2–H	O2–(Acid)	x, y, z	0.96(2)	1.83(2)	2.780(2)	174(2)

I with the only difference arising from the 6-methyl group substitution on the base. The packing is still characterised by a chain of hydrogen bonds, $C_2^2(12)$, running along [010], as well as the ring formed by the interaction of the carboxylic moiety with the amino-pyridine nitrogens of the base.

Structure IV arose from a mixture of 4-methoxybenzoic acid and 4,4'-bipyridine, 2A4-B3 and crystallises in $P2_1/c$ with $Z = 4$. The bipyridine is di-basic and therefore has two distinct pK_a values, giving rise to two points on the co-crystal/salt *versus* ΔpK_a diagram reported in Fig. 3. The asymmetric unit consists of the bipyridine moiety hydrogen bonded to



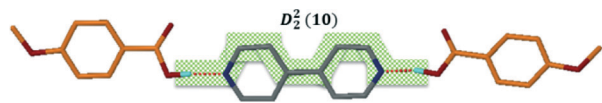


Fig. 5 Hydrogen bonding motif in structure IV.

two 4-methoxybenzoic acids which may be represented by $D_2^2(10)$ bonds (Fig. 5).

The packing is characterised by columns of 4-methoxybenzoic acids and bipyridine running in the [108] direction.

Structure VI comprising 4-nitrobenzoic acid and quinoline, A1-B4, crystallises in space group $P2_1$ with $Z = 2$, the asymmetric unit displays the acid hydrogen bonded to the quinoline base *via* (Acid)O–H...N(Base). The packing is characterised by layers approximately parallel to the *bc* face, and stacked perpendicular to the [104] direction.

Crystal structures of the salts

Structure V from 4-aminobenzoic acid and 6-aminoquinoline, A5-B6, crystallises in space group $P2_1/c$ with $Z = 4$. The asymmetric unit comprises one aminoquinolinium hydrogen bonded to an aminobenzoate. An inspection of Fig. 3 makes structure V appear as an outlier. However, the ΔpK_a value of +0.38 yields a probability of salt formation of 34% as proposed by the Cruz-Cabeza assessment. In addition, this system is further stabilised by a complex hydrogen bonding network. In Fig. 6a, we show a central aminobenzoate anion which is hydrogen bonded to four neighbouring aminobenzoates and three aminoquinolinium cations. We note that there are five unique additional hydrogen bonds stabilising the structure as listed in Table 4. The packing shown in Fig. 6b displays alternate chains of anti-parallel aminobenzoates interleaved with aminoquinolates.

Structure VII is derived from benzoic acid and 2-aminopyridine, A3-B8. It crystallises in $Pbca$ with $Z = 8$ and its packing is characterised by infinite chains which may be described as $C_2^2(6) R_2^2(8)$ which run parallel to [100] (Fig. 7).

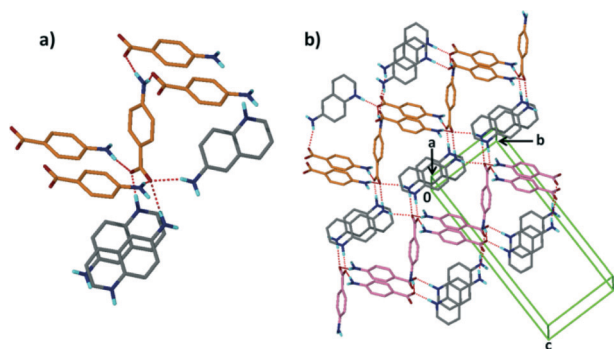


Fig. 6 Motif in structure V: a) a central aminobenzoate ion (in orange) is hydrogen bonded to seven ions-four aminobenzoates and three aminoquinoliniums, b) anti-parallel chains of aminobenzoate ions (in orange and pink) in the packing of V.

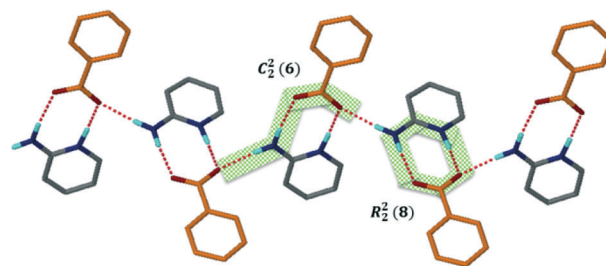


Fig. 7 Hydrogen bond motifs in structure VII displaying chains which run along [100].

Structure VIII arose from 4-bromobenzoic acid and 2-aminopyridine, A2-B8 and crystallises in the space group $P2_1/c$ with $Z = 4$. The hydrogen bonding is comparable to that of structure VII with the infinite chains running parallel to [001].

Structure IX derives from 4-aminobenzoic acid and 2-amino-4-methylpyridine, A5-B10. The packing is characterised by a chain of hydrogen bonds, $C_3^3(14) R_2^2(8)$ running along [001] which cross a spiral of hydrogen bonds $C_4^4(8)$ which extend along [110] (Fig. 8).

Structure X is derived from 4-methoxybenzoic acid and 2-amino-6-methylpyridine, A4-B9. It crystallises in $P2_1/n$ and the packing displays $C_2^2(6) R_2^2(8)$ similar to that of structure VII.

Structure XI crystallises from 4-methoxybenzoic acid and 2-amino-4-methylpyridine, A4-B10, in space group $P2_1/c$ with $Z = 4$ and displays the same hydrogen bond motif as structure VII.

Structure XII was derived from benzoic acid and 2-amino-6-methylpyridine, A3-B9. It crystallises in the space group $Pca2_1$ with $Z = 8$. The packing is characterised by two crystallographically independent chains of hydrogen bonded ions. These $C_2^2(6) R_2^2(8)$ chains run parallel to [100].

Structure XIII arose from 4-bromobenzoic acid and 2-amino-6-methylpyridine, A2-B9·2(H₂O). This compound crystallises as a di-hydrate in the space group $P2_1/n$ with $Z = 4$. One of the waters of crystallisation acts as a hydrogen bonding bridge creating a spiral of O–H...O bonds about the 2-fold screw axis at Wyckoff position *e*. In addition, the amino groups are hydrogen bonded to the oxygen of this water molecule. We again have the synthon of hydrogen bonds between the carboxylate moiety and the aminopyridinium cation. We may therefore describe this as two parallel chains running along [010] linked by ring systems. The motif resembles a ladder: $C_2^1(4) R_6^6(12)$. The second water molecule links ladders together, giving rise to hydrogen bonded sheets which run along [010] (Fig. 9).

Structure XIV arose from 4-bromobenzoic acid and 2-amino-4-methylpyridine, A2-B10, crystallising in space group $P2_1/c$ with $Z = 4$. The packing motif is again $C_2^2(6) R_2^2(8)$ similar to that of structure VII.



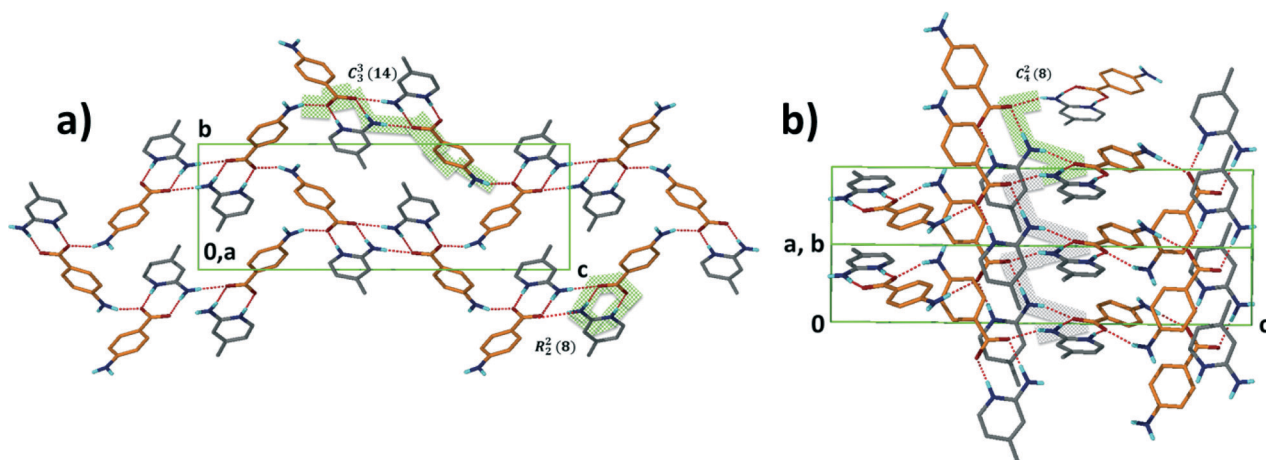


Fig. 8 Structure IX displaying the different hydrogen bond motifs with two types of chains running a) along [001] and b) along [110].

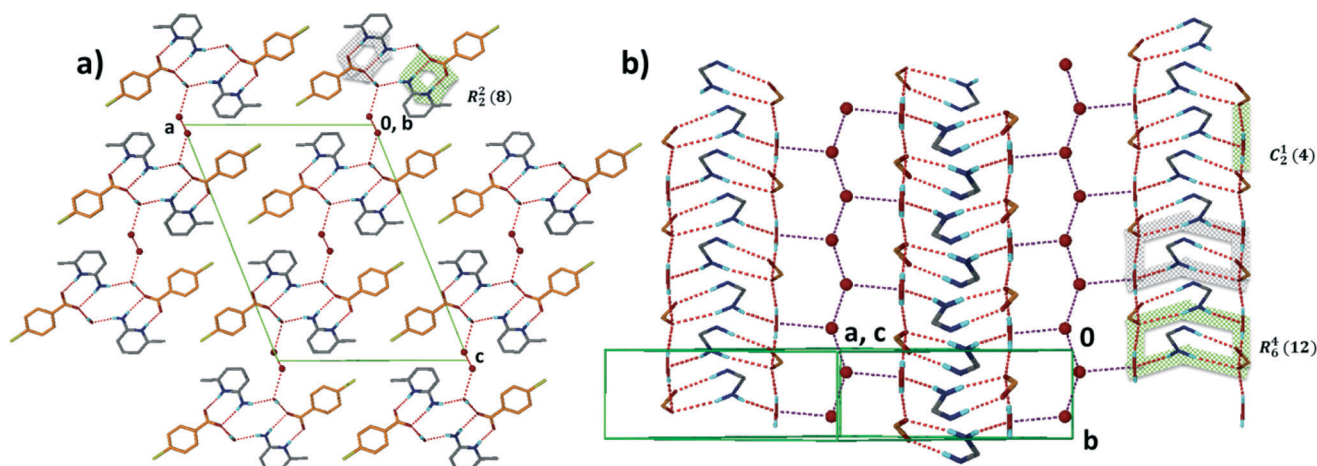


Fig. 9 Packing of the only solvated structure (XIII) obtained during this study: a) Packing of XIII viewed down [010] displaying sheets of hydrogen bonded molecules and solvents which run along [101]. b) Schematic representation of the ladders where only the moieties involved in hydrogen bonding are displayed. The ladders are connected through ribbons of hydrogen bonded water molecules running along [010].

Conclusions

Fig. 3 shows that the break from co-crystal to salt occurs at $\Delta pK_a \approx 2$. Structure 8(V), obtained from combining 4-aminobenzoic acid and 6-aminoquinoline, forms a salt. Its value of ΔpK_a is +0.38, and is clearly an outlier (Fig. 3). However, according to the Cruz-Cabeza survey, there is a 34% chance of the compound being a salt at this value of ΔpK_a , and the survey points out that secondary hydrogen bonds can influence the stabilisation of the ionic structure.²⁹ This is the case with structure 8(V) in which, in addition to the (quinolinium)- $N^+-H \cdots O^-$ -CO-(benzoate) hydrogen bond, the amino-benzoate anion is further stabilised by six other $N-H \cdots O-CO$ hydrogen bonds, the metrics of which are given in Table 4.

The hydrogen-bonding table is arranged so that each of the structures I to XIV displays the main H-bond (Acid)- $O1-H \cdots N1$ -(Base) in blue for the co-crystals or as (Protonated

Base)- $N1-H \cdots O1$ -(Anion) in red for a salt. One notes that most of the structures listed in Table 4 display additional hydrogen bonds, a feature which is obviously common on the systems under study.

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