Structural study of salt forms of amides; paracetamol, benzamide and piperine.

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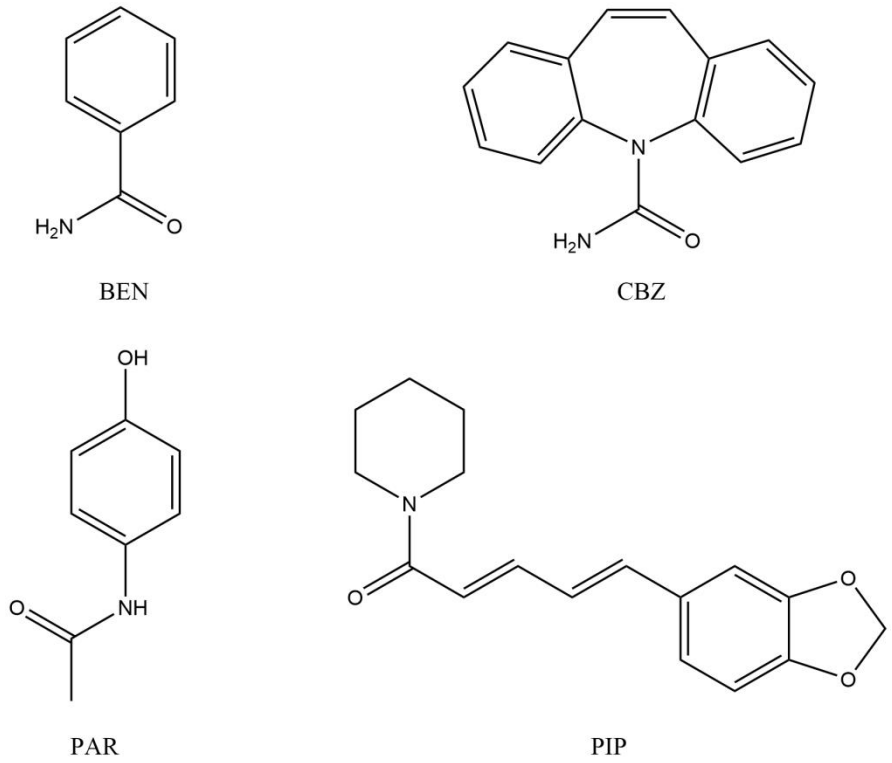
Abstract

Single crystal x-ray diffraction has been used to investigate the structures of six complexes containing O-atom protonated cations derived from the pharmaceutically relevant amides benzamide (BEN), paracetamol (PAR) and piperine (PIP). The structures of the salt forms [PAR(H)][$SO_3C_6H_4Cl$], [BEN(H)][$O_3SC_6H_4Cl$] and [BEN(H)][Br].H_2O are reported along with those of the hemi-halide salt forms [PAR(H)][I_3].PAR , [PIP(H)][I_3].PIP and [PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP. The structure of the cocrystal BEN.$HOOCCH_2Cl$ is also presented for comparison. The geometry of the amide group is found to systematically change upon protonation, with the C=O distance increasing and the C-N distance decreasing. The hemi-halide species all feature strongly hydrogen bonded amide(H)/amide pairs. The amide group C=O and C-N distances for both elements of each such pair are intermediate between those found for simple neutral amide and protonated amide forms. It was found that crystallising paracetamol from aqueous solutions containing Ba^{2+} ions gave orthorhombic paracetamol.

Introduction

It has been shown that although organic amide functionalities are normally thought of as being non-basic, it is possible to protonate them using strong acids and even to isolate and characterise their salt forms in the solid state. [1-3] Such salt formation reactions are a staple of pharmaceutical form screening, where they are used to modify the physicochemical properties of basic Active Pharmaceutical Ingredients (APIs).[4] Whilst the acidic materials formed by protonating amides are unlikely to make commercially viable APIs, it has been suggested that access to such forms may confer substantial benefits during the manufacturing process. For instance, salt forms of paracetamol have been shown to have improved compaction properties.[5] In 2012 Nanubolu et al. collated the then known crystal structures of a variety of protonated amides.[2] Since then several groups have crystallographically investigated series of multiple salt forms of particular amide APIs, notably the paracetamol work already mentioned above and structures of the model APIs carbamazepine (CBZ) and its congener dihydrocarbamazepine (DCBZ).[1, 6-8] The interest in looking at multiple related structures rather than single salt forms is of course the increased ability to compare and contrast both structures and the properties that arise from these structures. We are particularly interested in the CBZ and DCBZ studies that have shown systematic differences between the neutral and protonated forms in terms of both

molecular structure and of typical hydrogen bonding motifs. [1, 6-8] Here we report an extension of these comparative structural studies by examining new salt forms of three pharmaceutically relevant amides, the simple building block and primary amide benzamide (BEN), the well known analgesic and secondary amide paracetamol (PAR) and the naturally occurring alkaloid and tertiary amide piperine (PIP), see Scheme 1.



Scheme 1. Molecular structures of amides.

Materials and Methods.

Selected crystallographic and refinement details together with the structure numbers adopted throughout are given in Table 1 and Table 2. Displacement ellipsoid figures showing the asymmetric unit contents of all structures have been supplied as supplementary information. Crystallographic data were measured at low temperature with monochromated Mo Kα (λ= 0.71073 Å) or Cu Kα (λ= 1.5418 Å) radiation. Data for structures (**1b**) and (**1c**) were measured by the UK National Crystallography Service.[9] In all cases structure solution was by direct methods (SHELXS or SIR92) and refinement was to convergence on F^2 and against all

independent reflections by the full-matrix least squares method using the SHELX program.[10, 11] The SQUEEZE routine within PLATON was used to account for residual electron density equivalent to approximately 139 electrons within 398 $Å^3$ of unit cell space in compound (**1b**).[12] This is thought to be due to the presence of small amounts of disordered I_2 coformer. Assuming this to be true, the electron count corresponds to approximately 0.07 molecules of I_2 per I_3 anion.[13] H atoms on O and N atoms were found by difference synthesis but refinement of structure (**1b**) required a riding model to be adopted, with the H atoms in idealized positions. CCDC 1563871 through to 1563879 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

All samples were prepared using general methods described elsewhere. [1, 8] In each case approximately 0.2 g of API was dissolved with heating in the minimum amount (2 to 4 ml) of methanol. After cooling to room temperature, 2 equivalents of the selected acid were added with gentle stirring. Sample vials were sealed with parafilm, which was then pierced to allow slow evaporation of solvent. Crystals grew over a period of 2 to 7 days and were measured directly from solution. No attempt was made to maximize yield. As well as through the general method above, [BEN(H)][Br].H_2O (**2a**) was also isolated after slow addition of acetyl bromide to a methanolic solution of BEN. The [PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP variant (**3b**) of the protonated PIP structure was formed using ethanol rather than methanol.

Results and Discussion

Salt forms of paracetamol. Of the three chosen amides, PAR is that which has received most previous attention from the crystallographic community. As a model API its polymorphs have been extensively studied,[14] as have its solvate and cocrystal forms.[15-17] Recently salt forms have also been investigated. The structure of the hemichloride [PAR(H)][Cl].PAR has been reported, as have the structures of three hydrated species [PAR(H)][X].H_2O where X = Cl, Br, I. [3, 18, 19] Here we report two further structures including that of the first salt form of PAR with an organic anion. The structure of this compound, [PAR(H)][$SO_3C_6H_4Cl$] (**1a**), is shown in

Figure 1 and clearly shows protonation at the O atom of the amide group. Here, and elsewhere in this work, the positions of amide H atoms were found by difference synthesis. Although a simple hydrated iodide structure of PAR has previously been reported,[19] in our hands the same reactants (PAR and aqueous HI) gave a more complicated structure. In detail and ignoring minor disorder, the structure of [PAR(H)][I_3].(PAR) (**1b**) contains five crystallographically independent PAR(H)-PAR pairs where the formally neutral PAR and formally cationic PAR(H) moieties are linked by amide-to-amide O-H...O hydrogen bonds involving the acidic H atoms (Figure 2).

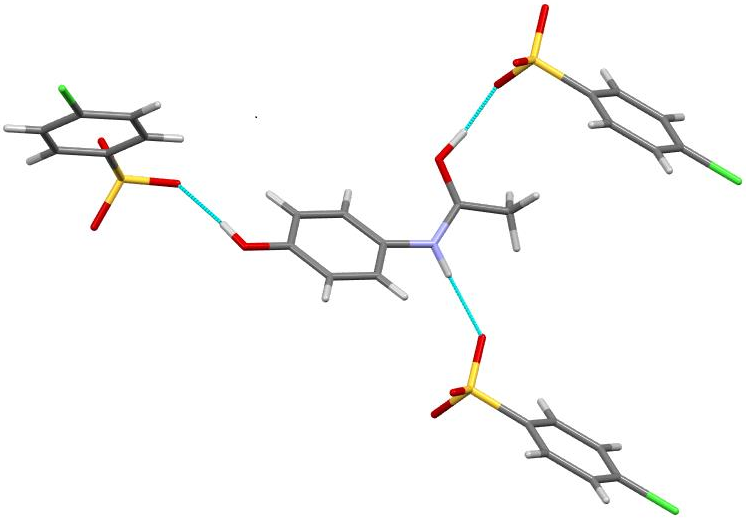


Figure 1. Part of the structure of [PAR(H)][$SO_3C_6H_4Cl$] (**1a**) showing that each cation forms three hydrogen bonds to three separate anions.

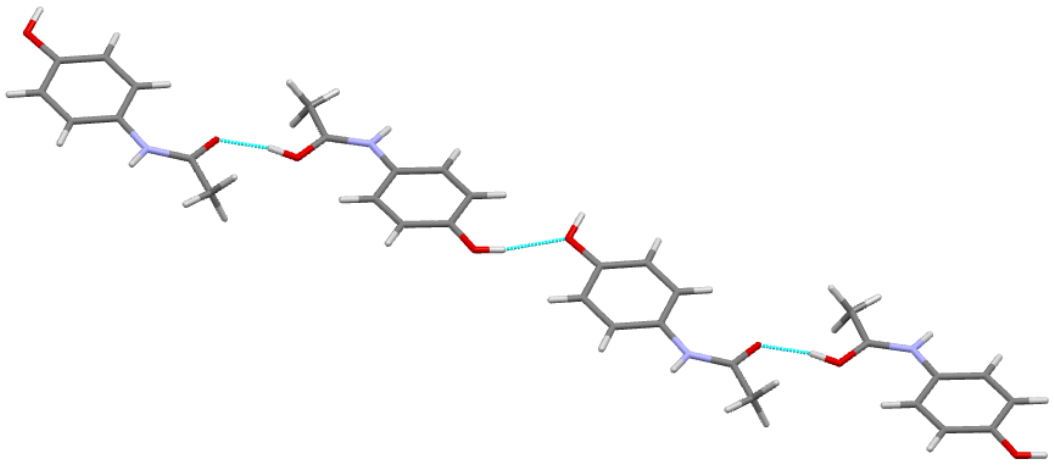
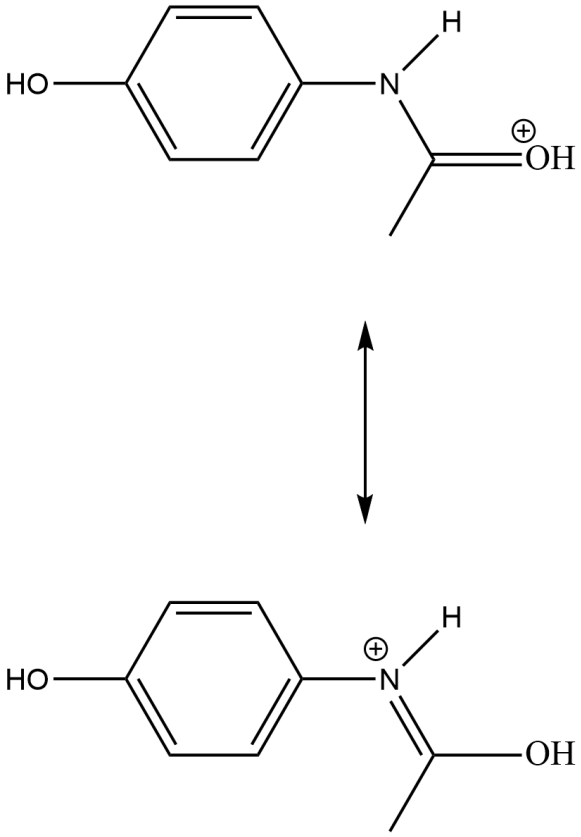


Figure 2. Part of the 1-dimensional hydrogen bonding motif in (**1b**) that propagates in the crystallographic *a* direction. Shown are two of the five crystallographically unique PAR(H).PAR dimers, linked by an unusual phenol to phenol hydrogen bond..

Previously, analysis of CBZ and DCBZ structures showed that protonation of the amide O atom led to characteristic lengthening of the C=O bond length and shortening of the C-NH_2 and C-N(ring) bond lengths.[1,7] This effect was so diagnostic of neutral and cationic species that it could even be used to assign "intermediate" status to structures where the acidic proton was in dynamic equilibrium between CBZ(H) and an O atom of a second crystal component.[6,8] A similar analysis of bond length variation for the known PAR(H) species (Scheme 2) is shown in Figure 3. As with CBZ and DCBZ, it is clear that protonated and neutral PAR species show different geometries with the C=O bond lengthening by approximately 0.05 to 0.06 Å and C-N shortening by 0.03 to 0.04 Å upon protonation. These differences are comparable to those found for CBZ (0.04 to 0.07 Å lengthening for C=O and 0.02 to 0.04 and 0.03 to 0.05 Å shortening for

the C-NH_2 and C-N(ring) bond lengths respectively). Note that the C-N bond length decrease for PAR(H) is not any greater than that found for CBZ(H) species, despite the CBZ(H) species having two N centres and thus two alternative resonance forms.[6-8] Figure 3 also shows that the hemi-triiodide (**1b**) and the hemi-chloride structures feature C=O and C-N distances that are intermediate between those of neutral and cationic PAR. As the bond lengths within the amide-to-amide O-H…O hydrogen bonded PAR(H).PAR pairs do not have clearly defined anionic and neutral character this suggests that the H atom may be in dynamic equilibrium between the two sites. Similar bond length arguments have been employed to identify dynamic equilibrium in CBZ(H) species.[8,14]



Scheme 2. Resonance forms of protonated paracetamol, PAR(H).

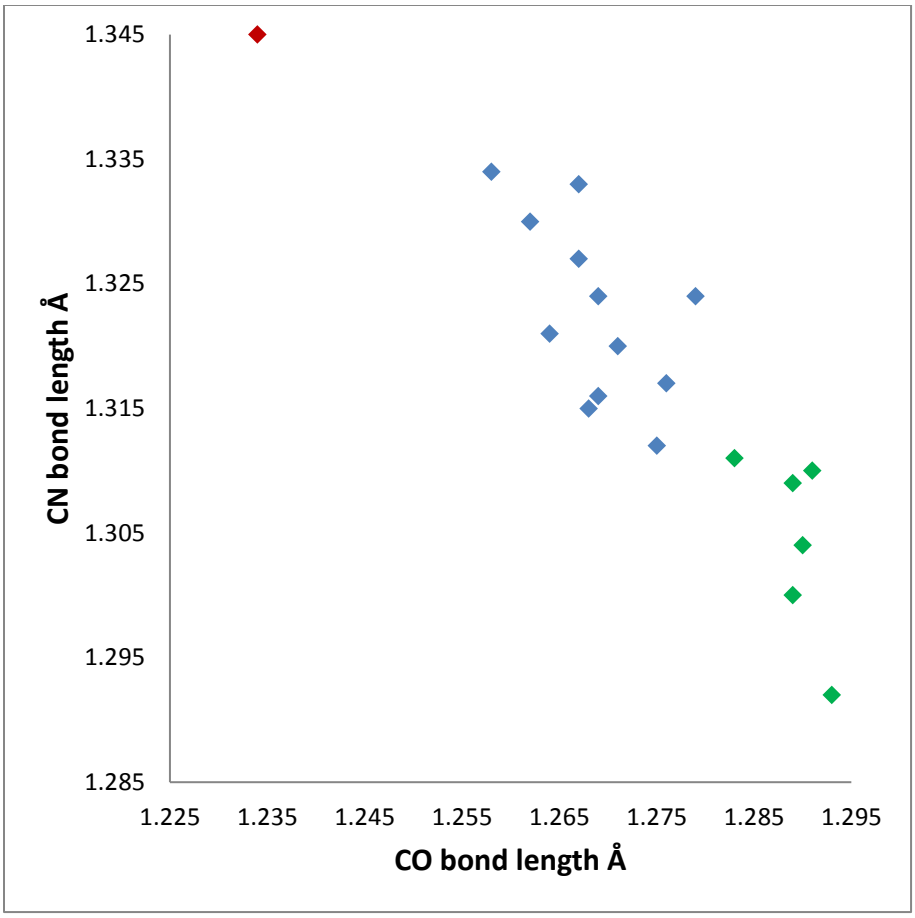


Figure 3. Comparison of C-N and C=O bond lengths (Å) for all known PAR and PAR(H) crystal structures. Red diamond = average values based on 66 well characterized neutral PAR species available in the CDS database. Green diamonds = cationic PAR(H) species. Blue diamonds = hemi-halides, the partially protonated species featuring H shared between hydrogen bonded PAR(H) and PAR moieties.

Prior work on paracetamol and its cocrystal forms has shown that hydrogen bonded PAR…PAR chains are robust motifs that commonly occur, either through phenol O-H…O=C interactions or, where coformer moieties accept hydrogen bonds from the phenolic H, through N-H…O=C interactions.[15] Cationic PAR(H) has three potential hydrogen bond donors, including the presumably strongly donating acidic H. For [PAR(H)][$SO_3C_6H_4Cl$] (**1a**) each donor atom forms a single hydrogen bond with an O atom of separate neighbouring sulfonate anions, Fig 1. Thus this salt form lacks the typical hydrogen bonded paracetamol chains seen elsewhere for neutral forms of PAR. The triiodide structure does have a variation of the common hydrogen bonded

paracetamol chain motif, with PAR(H).PAR dimers being linked by an unusual motif involving the paracetamol phenol group acting as both an acceptor and as a donor.
It can be seen from Table 3 that the O…O distances for the hydrogen bonds involving the amide O-H donors of PAR(H) are consistently much shorter than is typical for a O-H…O interaction.[20] The table and reference 18 shows that this is also true for the other protonated amide species. The hemi-species of both PAR and PIP all have hydrogen bonds between formally neutral and charged amide O atoms, and these have even shorter O…O separations than the simple salt forms. A final interesting intermolecular interaction occurs in the structure of (**1a**). An oxygen atom of the sulfonate group makes a short contact with the N and C atoms of the potonated amide group to form an unusual dipole-dipole interaction. The O..N and O…C distances are 3.035(3) and 2.962(3) Å respectively, not much longer than the hydrogen bonded N…O separations given in Table 3.

Other reactions involving paracetamol. During our investigations PAR was also reacted with various other strong acids, but analysis of the solids produced showed that these were decomposition products formed by hydrolysis of the N-C(amide) bond. Similar problems were reported with HCl addition to PAR by Perumalla et al.[5] A typical product was the simple salt$[H_3NC_6H_4OH][O_3SMe]$, (**1c**). Of more interest is the product isolated on reaction of PAR with benzenesulfonic acid. This is the hydronium containing species $[H_3NC_6H_4OH][H_3O][O_3SC_6H_5]_2.H_2O$ (**1d**) shown in Figure 4. A further series of experiments involved attempts to produce inorganic cocrystal forms of PAR. To do this, s-block metal salts were added to the acidic reaction mixtures. This is analagous to the technique used to prepare NaI complexes of CBZ. [21] With PAR no such complexes were obtained but it was observed that in the presence of $BaCl_2$ the orthorhombic polymorph of PAR was prepared rather than the typical and generally more stable monoclinic form.[14] Further investigation showed that the presence of acid was not required to achieve this effect and that simply crystallizing PAR from aqueous solutions of $BaCl_2$, BaO or $Ba(OH)_2$ also gave orthorhombic PAR, as judged by unit cell determinations and by IR spectroscopy. In contrast, crystallising PAR from aqueous solutions containing various salts of Ca, Sr, K, Na and NH_4 gave only the monoclinic form of PAR. Thomas et al. have previously reported a similar observation that orthorhombic PAR can

be prepared by recrystallisation in the presence of carboxylic acids,[22] but we are not aware of any prior description using inorganic materials.

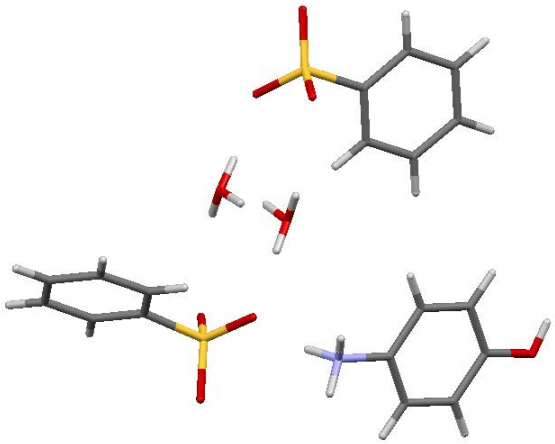


Figure 4**.** Asymmetric unit contents of $[H_3NC_6H_4OH][H_3O][O_3SC_6H_5]_2.H_2O$, (**1d**). The proton positions situated between the water molecules each have a sof of 50%.

Salt and cocrystal forms of benzamide. Benzamide, BEN, is the simplest possible aromatic amide and has a special place in crystal science as the first material for which crystalline polymorphs were described.[23] Although it is not itself an API, many of its derivatives are. Its fundamental nature has resulted in previous interest in the crystal structures of BEN and of its cocrystals. [23, 24] Only two protonated crystal structures containing the BEN(H) cation have been previously described, those of the hemi-triiodide [BEN(H)][I_3].BEN and the hydrated perchlorate salt [BEN(H)][ClO_4].H_2O. [25, 26, 27] Reactions were attempted between BEN and: the mineral acids HCl and HBr; the sulfonic acid $HO_3SC_6H_4Cl$, and; the carboxylic acid chloroethanoic acid. No reaction was observed with HCl despite several attempts. The other strong acids both gave salt forms containing the BEN(H) cation, namely [BEN(H)][Br].H_2O (**2a**) and [BEN(H)][$O_3SC_6H_4Cl$], (**2b**). The weaker carboxylic acid gave a cocrystalline species, BEN.$HOOCCH_2Cl$ (**2c**) with no transfer of H to the amide (Figure 5). The geometric parameters for the BEN(H) cations in the two salt structures are essentially identical and are also similar to those of the known perchlorate salt (Table 4). Taking the equivalent parameters for the cocrystal (**2c**) as a comparison shows that for BEN, protonation of the amide at the O atom results in an approximate 0.04 Å increase in the C-O length and a small 0.02 Å decrease in the C-N length. These changes are smaller than those found for PAR(H), above, and at the low end of the range

found previously for CBZ(H) and DCBZ(H).[6-8] A further geometric change occurs on protonation of BEN as is apparent from Table 4. The O-C-C angle of the BEN(H) fragment has narrowed and the N-C-C angle has widened with respect to neutral BEN. An equivalent effect is apparent for the other primary amide CBZ but no similar angular changes are observed for the secondary amine PAR.

The hydrogen bonded $R_2^2(8)$ heterodimer found in the structure of BEN.$HOOCCH_2Cl$ (**2c**) is ubiquitous throughout the known structures of cocrystals of BEN with carboxylic acids.[24] This and similar dimeric constructs (e.g. the classic $R_2^2(8)$ carboxylic acid dimer) are known to be extremely robust structural motifs. For cocrystals of CBZ with organic acids, a similar heterodimer is a typical construct.[28,29] Indeed it was the only typical CBZ hydrogen bonding motif to be found for both CBZ and protonated CBZ(H), as illustrated by the structure of [CBZ(H)][SO_3Ph].[8] However, the structure of [BEN(H)][$O_3SC_6H_4Cl$] (**2b**) shows no such retention of the motif (Figure 5). Instead the three donors of BEN(H) form hydrogen bonds with three neighboring sulfonate anions. These hydrogen bonds combine to give a 1-dimensional hydrogen bonded construct propagating parallel to the crystallographic *a* direction. Somewhat similarly, the BEN(H) cation in the bromide species (**2a**) also forms hydrogen bonds with three neighbours, in this case with two anions and the water molecule. The large anion and extra water molecule of (**2a**) allow a 2-dimensional hydrogen bonded construct to form, propagating parallel to the *a* and *b* directions, as compared to the 1-dimensional construct of (**2b**), Figure 6.

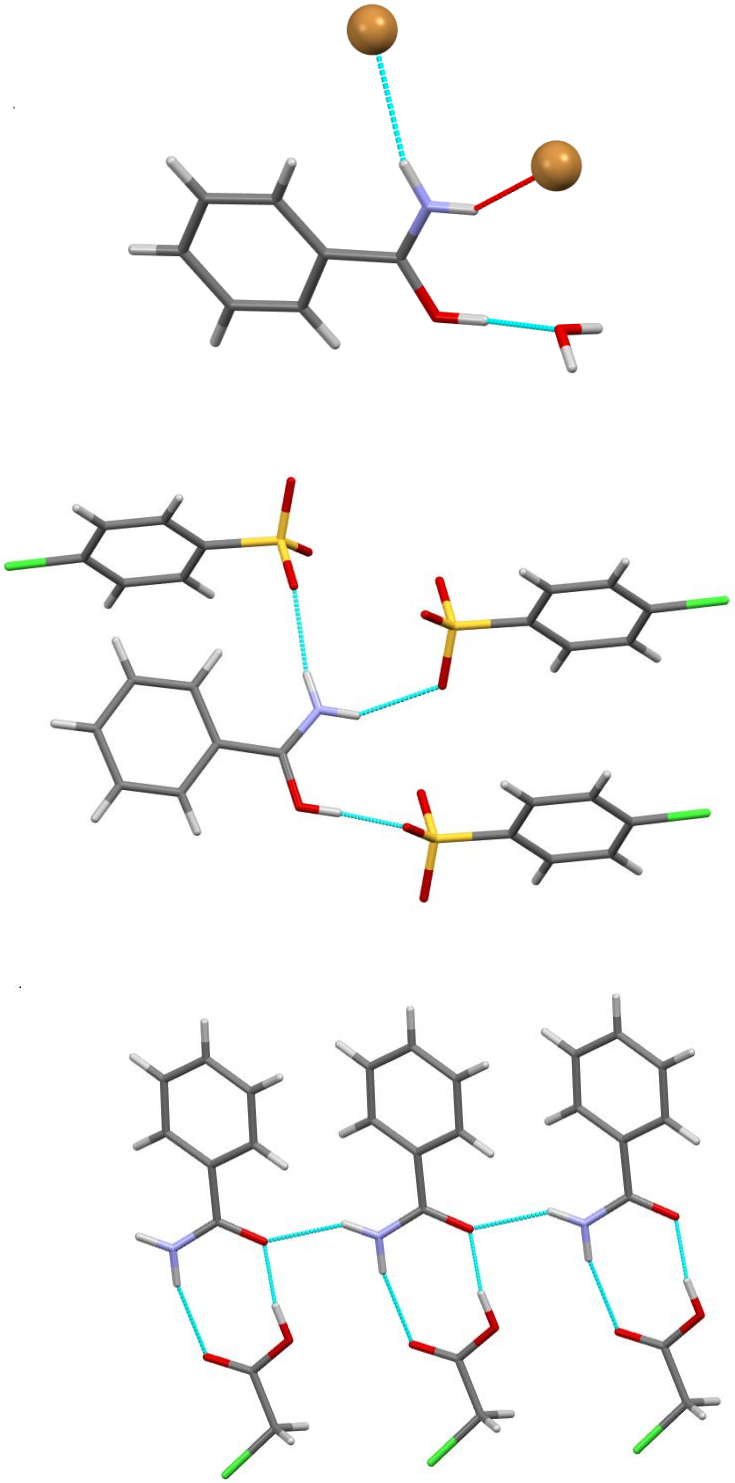


Figure 5. Each BEN(H) cation in salt forms [BEN(H)][Br].H_2O (**2a**, top) and [BEN(H)][$O_3SC_6H_4Cl$] (**2b**, middle) donates three hydrogen bonds to three neighbouring anions/molecules. However, the hydrogen bonding in the cocrystal BEN.$HOOCCH_2Cl$ (**2c**, bottom) is based on the classic amide/carboxylic acid $R_2^2(8)$ heterodimer.

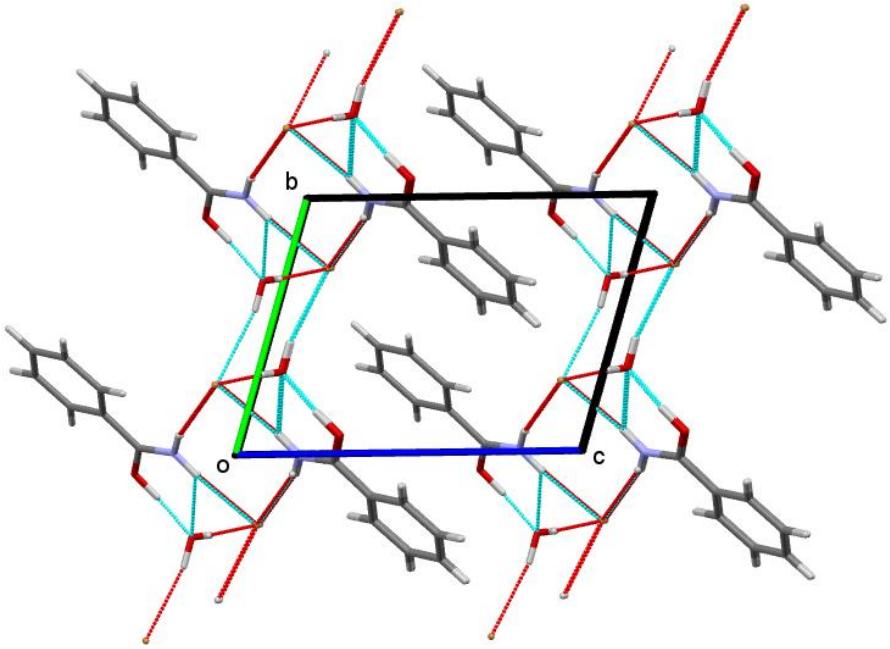


Figure 6. Packing diagram for structure (**2a**) viewed along the crystallographic a direction. Note the formation of hydrophobic and hydrophilic layers.

Salt forms of Piperine. Piperine (PIP) is a tertiary amide and the alkaloid responsible for the hot sensation in some varieties of pepper. It is of interest as an API and as an insecticide and as such its polymorphism has been studied.[30-32] We are not aware of any prior determinations of structures of salt or of cocrystalline forms of PIP. The amide was reacted with the strong acids HX (X = Cl, Br or I) but only with HI were novel crystalline products isolated. Growing directly from the reaction solutions, two separate hemi-halide species were identified, [PIP(H)][I_3].PIP (**3a**) and [PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP (**3b**). The organic parts of the two structures are similar, both are discrete hydrogen bonded dimers featuring an acidic H atom sited between the O atoms of the two amide groups formally designated as PIP(H) and PIP (Figure 7). This is a similar structure to the hemi-halide species described above for the [PAR(H)][X].PAR (X = Cl, I_3) species. The I_3 anion of (**3a**) is disordered. Unsurprisingly, disorder in such an electron rich fragment adversely

effects the quality of the structural model and so caution is required in any analysis of small bond length changes. For (**3a**) the C=O distances found are 1.279(10) and 1.277(10) Å for the PIP(H) and PIP fragments respectively, whilst the C-N distances are 1.330(10) and 1.331(10) Å. The equivalent distances for (**3b**) are 1.269(9), 1.269(9), 1.318(9) and 1.322(9) Å. As for (**1b**) above, the similarities between the PIP(H) and PIP pairs argues against the proton being fixed to one position of the discrete hydrogen bonded dimer. Comparing the bond lengths with those of the [PAR(H)][X].PAR species (Figure 3) shows a reasonable agreement, whilst comparison with the equivalent bonds in neutral PIP shows the expected small increase (0.03 to 0.04 Å) in C=O length and decrease (0.02 to 0.03 Å) in C-N distance.[32] Despite the small magnitude of these changes compared to the large su values found in these structures, the sizes of these changes are broadly in line with those for the primary and secondary amides described above. With no such supporting evidence available for any similar analysis of potential resonance effects along the butadiene chain, the small changes observed there between (**3a**), (**3b**) and PIP are inconclusive.

Conclusions

This work presents the single crystal structures of 6 new O-protonated amide species relevant to the pharmaceutical community. Three of these are fully protonated salt forms, [PAR(H)][$SO_3C_6H_4Cl$], [BEN(H)][$O_3SC_6H_4Cl$] and [BEN(H)][Br].H_2O, a series that includes the first structures of salt forms of paracetamol and of benzamide with organic anions. Three structures of hemi-salts are also presented, those of [PAR(H)][I_3].PAR , [PIP(H)][I_3].PIP and [PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP. Comparison of C=O and C-N bond lengths shows that protonation of all the amides utilised here, whether primary, secondary or tertiary, gives similar C=O lengthening and C-N shortening effects to those previously described for carbamazepine. The hemi-salts have bonds lengths intermediate to those of pure neutral and protonated species. All the amide O-H acidic protons form short, strong hydrogen bonds and those formed between protonated and neutral amide moieties in the hemi-salts are found to have particularly short O…O distances. Finally, whilst unsuccessfully investigating a potential route to inorganic cocrystal forms of paracetamol via protonated paracetamol, it was observed that crystallizing paracetamol from aqueous solutions containing Ba^{2+} ions gave a repeatable route to the unusual orthorhombic form of paracetamol.

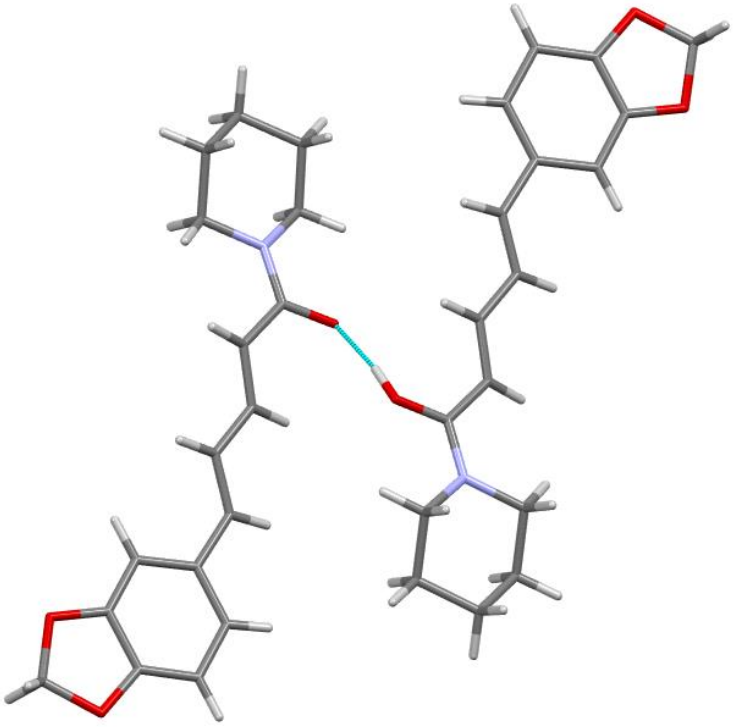


Figure 7. The acidic H atom of [PIP(H)][I_3].PIP (**3a**) lies between the two amide groups so as to form a short hydrogen bond. As this is the only hydrogen bond in this structure, the hydrogen bonding is based on this discrete dimer. This structural fragment is common to both (**3a**) and to [PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP (**3b**).

Acknowledgements. We wish to thank the National Crystallography Service based at the University of Southampton for data measurement on (**1b**) and (**1c**).

Table 1. Selected crystallographic and refinement parameters for structures derived from PAR .

	[PAR(H)] [$SO_3C_6H_4Cl$]	[PAR(H)][I_3].PAR	[$H_3NC_6H_4OH$] [O_3SMe]	[$H_3NC_6H_4OH$] [H_3O][$O_3SC_6H_5$]$_2$.H_2O
Compound number	**1a**	**1b**	**1c**	**1d**
Empirical formula	$C_{14}H_{14}ClNO_5S$	$C_{16}H_{19}I_3N_2O_4$[a]	$C_7H_{11}NO_4S$	$C_{18}H_{23}NO_9S_2$
Molecular Weight	343.77	684.03	205.23	461.49
Temperature (K)	123(2)	100(2)	100(2)	123(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1$
a (Å)	17.469(2)	17.4503(12)	8.9880(2)	5.6570(14)
b (Å)	9.9372(12)	18.5617(13)	13.6977(4)	21.769(5)
c (Å)	8.7440(15)	33.926(2)	7.3968(2)	8.438(2)
α (°)	90	90	90	90
β (°)	101.529(13)	100.077(1)	90.290(2)	90.580(3)
γ (°)	90	90	90	90
Cell volume (Å^3)	1487.3(4)	10819.5(13)	910.64(4)	1039.1(4)
Z	4	20	4	2
2θ max(°)	59.28	54.00	53.98	52.94
Reflections collected	7246	141009	9988	10729
Reflections unique	3657	23566	1990	3524
Reflections obs.	2878	19295	1821	3473
R_{int}	0.021	0.0467	0.0218	0.0188
No. Parameters	212	1175	135	311
GoF	1.043	1.052	1.038	1.045
R [I>2σ(I)]	0.0419	0.0363	0.0287	0.0243
Rw (all data)	0.1075	0.0964	0.0745	0.0616
Largest diff. peak and hole (e Å^{-3})	0.394, -0.477	2.089,-2.536	0.389, -0.354	0.328, -0.239
Flack parameter				0.03(5)

[a] Formula does not include traces of disordered and partially present cocrystallised material. The PLATON SQUEEZE program was used for this – see experimental text.

Table 2. Selected crystallographic and refinement parameters for structures derived from BEN and PIP.

	[BEN(H)] [Br].H_2O	[BEN(H)] [$SO_3C_6H_4Cl$]	BEN. $ClCH_2COOH$	[PIP(H)] [I_3].PIP	[PIP(H)] [I_3]$_{0.5}$[I]$_{0.5}$.PIP
Compound number	**2a**	**2b**	**2c**	**3a**	**3b**
Empirical formula	$C_7H_{10}BrNO_2$	$C_{13}H_{12}ClNO_4S$	$C_9H_{12}ClNO_3$	$C_{34}H_{39}I_3N_2O_6$	$C_{34}H_{39}I_2N_2O_6$
Molecular Weight	220.07	313.75	217.65	952.37	825.47
Temperature (K)	123(2)	123(2)	123(2)	123(2)	123(2)
Wavelength (Å)	0.71073	0.71073	0.71073	1.5418	1.5418
Crystal system	triclinic	triclinic	triclinic	monoclinic	monoclinic
Space group	P-1	P-1	P-1	$P2_1/c$	P2/c
a (Å)	5.8036(8)	5.4326(3)	5.0989(5)	10.1661(10)	16.0719(13)
b (Å)	7.7447(10)	9.0904(4)	7.9040(7)	20.3025(9)	13.0773(12)
c (Å)	10.2138(13)	13.5037(7)	12.6364(13)	17.3784(8)	16.0097(13)
α (°)	73.205(12)	88.304(4)	99.174(8)	90	90
β (°)	78.482(11)	85.942(4)	94.552(9)	99.158(7)	90.797(8)
γ (°)	85.241(11)	86.128(6)	104.102(8)	90	90
Cell volume (Å^3)	430.49(10)	663.48(6)	483.87(8)	3541.1(4)	3364.5(5)
Z	2	2	2	4	4
2θ max(°)	58.54	58.56	58.55	138.26	139.04
Reflections collected	3962	12667	5829	12307	11591
Reflections unique	2080	3396	2375	6409	6128
Reflections obs.	1800	3005	1930	3692	4027
R_{int}	0.0285	0.0277	0.0309	0.0589	0.0561
No. Parameters	120	193	139	419	403
GoF	1.065	1.109	0.973	1.023	1.016
R [I>2σ(I)]	0.0357	0.0411	0.0401	0.0710	0.0620
Rw (all data)	0.0870	0.1144	0.1056	0.1978	0.1586
Largest diff. peak and hole (e Å^{-3})	0.746, -0.828	0.656, -0.465	0.402, -0.259	2.428, -0.917	1.018, -0.820

Table 3. Selected hydrogen bonding distances for protonated amides.

Compound	O(amide)-H…O O…O distance (Å)	O(amide)-H…O O-H…O angle (°)	Other O-H…O O…O distances (Å)	N-H…O N…O distance (Å)
[PAR(H)][$SO_3C_6H_4Cl$] (1a)	2.557(2)	173(4)	2.751(3)	2.826(2)
[PAR(H)][I_3].PAR (1b)	2.418(3) to 2.435(3)	162 to 175	2.727(3) to 2.800(3)	
[BEN(H)][Br].H_2O (2a)	2.494(3)	176(4)		
[BEN(H)] $SO_3C_6H_4Cl$] (2b)	2.5033(18)	177(4)		2.874(2), 2.914(2)
[PIP(H)][I_3].PIP (3a)	2.429(8)	173(10)		
[PIP(H)][I_3]$_{0.5}$[I]$_{0.5}$.PIP (3b)	2.430(7)	171(10)		

Table 4. Selected geometric parameters for BEN and BEN(H) species.

Compound	C=O (Å)	C-NH_2 (Å)	O-C-N (°)	O-C-C (°)	N-C-C (°)
Salt forms					
[BEN(H)][Br].H_2O (2a)	1.292(3)	1.302(4)	121.4(3)	116.3(3)	122.3(3)
[BEN(H)][$O_3SC_6H_4Cl$] (2b)	1.290(2)	1.303(2)	121.99(16)	115.89(15)	122.07(16)
[BEN(H)][ClO_4].H_2O	1.287	1.307	120.6	117.3	121.8
Cocrystal form					
BEN.$HOOCCH_2Cl$ (2c)	1.249(2)	1.326()	121.72(15)	119.44(14)	118.84(14)

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