

Salt and Ionic Cocrystalline Forms of Amides: Protonation of Carbamazepine in Aqueous  
Media.

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**Abstract;** The products of reactions of the pharmaceutical amide carbamazepine (CBZ) with strong acids under aqueous conditions were investigated by both powder and single crystal X-ray diffraction. Despite previous claims to the contrary, it was found that salt forms with CBZ protonated at the amide O atom could be isolated from reactions with both HCl and HBr. These forms include the newly identified hydrate phase [CBZ(H)][Cl].H<sub>2</sub>O. Reactions with other mineral acids (HI and HBF<sub>4</sub>) gave ionic cocrystalline (ICC) forms (CBZ.[acridinium][I<sub>3</sub>].2.5I<sub>2</sub> and CBZ.[H<sub>5</sub>O<sub>2</sub>]<sub>0.25</sub>[BF<sub>4</sub>]<sub>0.25</sub>.H<sub>2</sub>O) as well as the salt form CBZ.[CBZ(H)][BF<sub>4</sub>].0.5H<sub>2</sub>O. Reaction of CBZ with a series of sulfonic acids also gave salt forms, namely [CBZ(H)][O<sub>3</sub>SC<sub>6</sub>H<sub>5</sub>], [CBZ(H)][O<sub>3</sub>SC<sub>6</sub>H<sub>4</sub>(OH)].0.5H<sub>2</sub>O, [CBZ(H)]<sub>2</sub>[O<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>SO<sub>3</sub>] and [CBZ(H)][O<sub>3</sub>SC<sub>6</sub>H<sub>3</sub>(OH)(COOH)].H<sub>2</sub>O. CBZ and protonated CBZ(H) moieties can be differentiated in the solid state both by changes to molecular geometry and by differing packing preferences.

**Introduction;** Carbamazepine (CBZ) is an Active Pharmaceutical Ingredient (API) used in the treatment of epilepsy. As a relatively simple molecule with a non-polar backbone and a single amide functionality, it has been widely studied by those interested in solid-form generation and the selection of APIs. Although extensive, this work has concentrated largely on CBZ polymorphs and on cocrystal or solvate forms where CBZ is accompanied in the solid by neutral cofomers.<sup>[1-7]</sup> A much smaller body of work exists on other classes of solid-state forms. Ionic cocrystalline (ICC) forms of CBZ with NH<sub>4</sub>, OH<sub>3</sub> and Na cations have been structurally described,<sup>[12-14]</sup> as, recently, have salt forms which feature protonation of CBZ at the amide O atom.<sup>[14-16]</sup> These ICC and salt forms are interesting as they can and do exhibit different intermolecular bonding types and supramolecular synthons from those hydrogen bonding motifs that are well described in, and common to, CBZ polymorphs and cocrystals. The ICC compounds do however seem to retain the non-polar supramolecular constructs first described by Gelbrich and Hursthouse.<sup>[17]</sup> This change in intermolecular bonding may in turn result in useful differences in material properties.<sup>[13-15, 18,19]</sup>

Salt forms of CBZ are also of interest simply because of the amide group acting as a Brønsted base. Many chemists assume that amide groups will not protonate under normally accessible conditions, and indeed CBZ itself has been used as a model “non-ionisable” API.<sup>[20,21]</sup> However, although relatively rarely reported, salt forms of amides are accessible and isolatable in the solid as is shown by the elucidation of the crystal structures of salt forms of CBZ and of other amide species.<sup>[22]</sup> Perumalla and Sun’s original preparation of the salt [CBZ(H)][Cl] utilised *in-situ* generation of HCl in non-aqueous solvents.<sup>[15]</sup> Similarly our own extension of this work to multiple phases of both CBZ hydrochloride and hydrobromide was based upon water free conditions and *in-situ* generation of HX.<sup>[14]</sup> The original Perumalla and Sun work specified that this approach with non-aqueous conditions was necessary as H<sup>+</sup> generated in organic solution was more active than the solvated species (e.g. H<sub>3</sub>O<sup>+</sup>) that would be generated when using water as a solvent. Furthermore, with respect to aqueous acids, it was reported that “*Attempts for synthesizing hydrochloride salt of CBZ, following the common salt formation approach, using even concentrated hydrochloride acid invariably led to the isolation of CBZ dihydrate*”.<sup>[15]</sup> Later reports have led us to reinvestigate the use of aqueous acids. Notable prompts were Frampton and co-workers’ isolation of [CBZ(H)][MeSO<sub>3</sub>] from a reaction of CBZ with what was described as “neat” methanesulfonic acid (pKa approx. -2.6) and, perhaps even more interestingly, their

characterisation of the product formed by reaction of CBZ with trifluoroethanoic acid (pKa approx. -0.26) as an intermediate or equilibrium species with a partial ionised, salt nature and a partial neutral, cocrystal nature.<sup>[16]</sup> Thus protonation of CBZ seems to be possible with species that have pKa values that are higher than would be expected for say concentrated aqueous HCl. Finally, whilst our own work showed that adding drops of water to solid [CBZ(H)][Cl] did indeed lead to a reversion to CBZ dihydrate,<sup>[14]</sup> it also showed that slow addition of water to [CBZ(H)][X] (X = Br or Cl) through exposure to air gave [CBZ(H)][Br].H<sub>2</sub>O and [CBZ]<sub>2</sub>[H<sub>3</sub>O][Cl] thus showing that the presence of water was not incompatible with the existence of ionic phases of CBZ.<sup>[14]</sup> Reported herein is a structural investigation of salt and ICC forms of CBZ derived from reactions of CBZ with strong aqueous acids.

**Experimental;** Single crystal X-ray diffraction (SXD) measurements were performed at 123(2) K using Oxford Diffraction instruments and 0.71073 Å radiation. Structural refinements with all unique reflections and against  $F^2$  to convergence were performed using programs from the SHELX suite.<sup>[23]</sup> Hydrogen atoms bound to carbon were placed in idealized positions and refined in riding modes. Where possible, H atoms bound to nitrogen or oxygen were placed as found in difference Fourier syntheses and their positions were freely refined, but this was not possible for the N-H atom on acridinium in structure CBZ.[C<sub>13</sub>H<sub>10</sub>N][I<sub>3</sub>].2.5I<sub>2</sub> for which a geometrically idealized riding model was required. Selected crystallographic and refinement parameters are given in Table 1. Full details have been deposited in cif format. See CCDC 1419992 to 1419998.

Powder X-ray diffraction (PXRD) measurements were performed using a Bruker D8-Advance diffractometer equipped with a LynxEye detector and operating in transmission capillary mode using Cu K $\alpha$ <sub>1</sub> incident radiation, 1.54056 Å. Samples were filled into 0.7 mm borosilicate glass capillaries and data collected using a step size of 0.017° 2 $\theta$ . Data were analysed using TOPAS.<sup>[24]</sup> Diffraction patterns are given in the Electronic Supplementary Information.

FTIR measurements were made on crushed, solid samples and with an A<sub>2</sub> Technologies ATR instrument.

**Table 1.** Selected crystallographic and refinement parameters.

| <b>Compound</b>   | <b>CBZ.<br/>[C<sub>13</sub>H<sub>10</sub>N][I<sub>3</sub>]<br/>.2.5I<sub>2</sub></b> | <b>CBZ.<br/>[CBZ(H)][BF<sub>4</sub>]<br/>.0.5H<sub>2</sub>O</b>                 | <b>CBZ.<br/>[H<sub>5</sub>O<sub>2</sub>]<sub>0.25</sub>[BF<sub>4</sub>]<sub>0.25</sub><br/>.H<sub>2</sub>O</b> |
|---|--|---|--|
| <b>Formula</b>  | C <sub>28</sub> H <sub>22</sub> I <sub>8</sub> N <sub>3</sub> O                      | C <sub>30</sub> H <sub>26</sub> BF <sub>4</sub> N <sub>4</sub> O <sub>2.5</sub> | C <sub>15</sub> H <sub>15.25</sub> B <sub>0.25</sub> FN <sub>2</sub> O <sub>2.5</sub>                          |
| <b>Formula Weight</b>                                   | 1431.69  | 569.36  | 285.24   |
| <b>Crystal system</b>                                   | Monoclinic   | Monoclinic  | Monoclinic   |
| <b>Space Group</b>                                      | P 2 <sub>1</sub> /n  | C 2   | C 2/c  |
| <b>λ Å</b>  | 0.71073  | 0.71073   | 0.71073  |
| <b>a Å</b>  | 17.7346(16)  | 26.8750(3)  | 29.788(2)  |
| <b>b Å</b>  | 9.2416(7)  | 8.9636(7)   | 5.1199(2)  |
| <b>c Å</b>  | 22.5168(15)  | 11.7505(13)   | 21.1130(16)  |
| <b>α°</b>   | 90   | 90  | 90   |
| <b>β°</b>   | 99.498(7)  | 104.459(12)   | 120.804(10)  |
| <b>γ°</b>   | 90   | 90  | 90   |
| <b>Volume Å<sup>3</sup></b>                             | 3639.8(5)  | 2741.0(4)   | 2765.7(3)  |
| <b>Temp. K</b>  | 123(2)   | 123(2)  | 123(2)   |
| <b>Z</b>  | 4  | 4   | 8  |
| <b>Refls. Collected</b>                                 | 14505  | 4949  | 6940   |
| <b>2θ max °</b>   | 50.0   | 57.6  | 58.8   |
| <b>Refls. Unique</b>                                    | 6390   | 4121  | 3340   |
| <b>Refls. Obs.</b>                                      | 3321   | 3053  | 2515   |
| <b>R<sub>int</sub></b>                                  | 0.0982   | 0.0312  | 0.0234   |
| <b>Goodness of Fit</b>                                  | 0.950  | 1.011   | 1.092  |
| <b>R[ I&gt;2s(I) ], F</b>                               | 0.0595   | 0.0454  | 0.0479   |
| <b>R<sub>w</sub>, F<sup>2</sup></b>                     | 0.1298   | 0.1032  | 0.1115   |
| <b>Max/min<br/>electron density<br/>eÅ<sup>-3</sup></b> | 1.461/-1.216   | 0.197/-0.212  | 0.219/-0.255   |

**Table 1 continued.** Selected crystallographic and refinement parameters.

| <b>Compound</b>   | <b>[CBZ(H)]<br/>[O<sub>3</sub>SC<sub>6</sub>H<sub>5</sub>]</b>  | <b>[CBZ(H)]<sub>2</sub>[O<sub>3</sub>S<br/>CH<sub>2</sub>CH<sub>2</sub>SO<sub>3</sub>]</b> | <b>[CBZ(H)]<br/>[O<sub>3</sub>SC<sub>6</sub>H<sub>3</sub>(OH)(<br/>COOH)]<br/>.H<sub>2</sub>O</b> | <b>[CBZ(H)]<br/>[O<sub>3</sub>SC<sub>6</sub>H<sub>4</sub>(OH)]<br/>.0.5H<sub>2</sub>O</b> |
|---|---|--|---|---|
| <b>Formula</b>  | C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S | C <sub>32</sub> H <sub>30</sub> N <sub>4</sub> O <sub>8</sub> S <sub>2</sub>               | C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>8</sub> S                                   | C <sub>21</sub> H <sub>19</sub> N <sub>2</sub> O <sub>5.5</sub> S                         |
| <b>Formula Weight</b>                                   | 394.43  | 662.72   | 472.46  | 419.44  |
| <b>Crystal system</b>                                   | Monoclinic  | Triclinic  | Triclinic   | Monoclinic  |
| <b>Space Group</b>                                      | P 2 <sub>1</sub> /c   | P -1   | P -1  | P n   |
| <b>λ Å</b>  | 0.71073   | 0.71073  | 0.71073   | 0.71073   |
| <b>a Å</b>  | 10.5380(3)  | 7.3746(7)  | 7.1788(4)   | 12.5378(9)  |
| <b>b Å</b>  | 15.4546(4)  | 8.6949(10)   | 12.3752(6)  | 12.2352(7)  |
| <b>c Å</b>  | 12.0765(3)  | 12.9832(11)  | 13.2726(7)  | 13.5144(11)   |
| <b>α°</b>   | 90  | 92.746(8)  | 114.329(5)  | 90  |
| <b>β°</b>   | 109.358(3)  | 98.386(7)  | 93.133(4)   | 109.876(9)  |
| <b>γ°</b>   | 90  | 104.180(9)   | 97.161(4)   | 90  |
| <b>Volume Å<sup>3</sup></b>                             | 1855.59(9)  | 795.46(14)   | 1058.68(10)   | 1949.6(3)   |
| <b>Temp. K</b>  | 123(2)  | 123(2)   | 123(2)  | 123(2)  |
| <b>Z</b>  | 4   | 1  | 2   | 4   |
| <b>Refls. Collected</b>                                 | 8881  | 7642   | 9988  | 8477  |
| <b>2θ max °</b>   | 59.1  | 55.9   | 58.0  | 54.0  |
| <b>Refls. Unique</b>                                    | 4509  | 3436   | 5069  | 5421  |
| <b>Refls. Obs.</b>                                      | 3461  | 2699   | 3801  | 4306  |
| <b>Rint</b>   | 0.0234  | 0.0411   | 0.0323  | 0.0341  |
| <b>Goodness of Fit</b>                                  | 1.025   | 1.073  | 1.045   | 1.059   |
| <b>R[I&gt;2s(I)],F</b>                                  | 0.0433  | 0.0616   | 0.0537  | 0.0494  |
| <b>Rw, F<sup>2</sup></b>                                | 0.1001  | 0.1578   | 0.1403  | 0.1089  |
| <b>Max/min<br/>electron density<br/>eÅ<sup>-3</sup></b> | 0.298/-0.388  | 0.770/-0.360   | 0.744/-0.361  | 0.533/-0.439  |

**Reactions of CBZ with Aqueous HCl;** 10 ml of concentrated hydrochloric acid (approximately 36 %) was added to a test tube containing 0.492 g (1.96 mmol) of CBZ. Despite stirring and heating for 30 minutes the CBZ did not appear to dissolve and there was no obvious, visible change. The solid was collected by filtration. PXRD analysis showed this to be a 89:11 mixture of  $[\text{CBZ(H)}][\text{Cl}]\cdot\text{H}_2\text{O}:[\text{CBZ(H)}][\text{Cl}]$  (form II). The filtrate was poured into a test tube and sealed with parafilm. Holes were pierced in the parafilm to aid evaporation. Slow evaporation over a period of ten days gave a small number of colorless crystals. SXD and IR analyses showed that the previously known hydronium species  $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$  had formed.<sup>[14]</sup>

0.242 g (1.02 mmol) of CBZ was dissolved in 4 ml of ethanol. The solution was heated in a water bath until the CBZ had dissolved. Once the solution had cooled to room temperature, 2 ml of concentrated hydrochloric acid was slowly added. The test tube was then sealed with parafilm. Small holes were made in the parafilm to aid evaporation. Crystals formed over a period of a few days. SXD analysis showed that these were  $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$ .

**Reactions of CBZ with Aqueous HBr;** 10 ml of concentrated hydrobromic acid (approximately 48 %) was added to a test tube containing 0.506 g (2.14 mmol) of CBZ. Despite stirring and heating for 30 minutes there was no obvious change and the CBZ did not appear to dissolve, instead the solid agglomerated at the top of the solution. The solid was collected by filtration. PXRD analysis showed this to be a 90:10 mixture of  $[\text{CBZ(H)}][\text{Br}]\cdot\text{H}_2\text{O}:[\text{CBZ(H)}][\text{Br}]$  (form II).

0.204 g (0.86 mmol) of CBZ was dissolved in 4 ml of ethanol. The solution was heated in a water bath until the CBZ had dissolved. Once the solution had cooled to room temperature, 1 ml of concentrated hydrobromic acid was slowly added. The test tube was then sealed with parafilm. Small holes were made in the parafilm to aid evaporation. Crystals formed over a period of a few days. SXD analysis showed that these were  $[\text{CBZ(H)}][\text{Br}]\cdot\text{H}_2\text{O}$ .

**Reaction of CBZ with Aqueous HI;** 1 ml of concentrated hydroiodic acid (approximately 55 %) was slowly added to a test tube containing 0.223 g (0.94 mmol) of CBZ. Despite gently heating and stirring for 30 mins the bulk of the solid did not dissolve. The colorless solid was removed by filtration. On the basis of its IR spectrum this is not believed to be unreacted CBZ, but a positive identification was not possible. The remaining solution was allowed to slowly

evaporate over several days depositing dark crystals. These were shown by SXD to be the acridinium containing ICC species  $\text{CBZ} \cdot [\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3] \cdot 2.5\text{I}_2$ .

**Reactions of CBZ with Aqueous  $\text{HBF}_4$** ; 4 ml of concentrated hydrofluoroboric acid (approximately 40 %) was added to a test tube containing 0.228 g (0.97 mmol) of CBZ. Despite stirring and heating there was no obvious change and the carbamazepine did not appear to dissolve. The colorless solid was collected by filtration but remains unidentified – see text below. No CBZ containing material was isolated from the filtrate.

0.239 g (1.01 mmol) of CBZ was dissolved in 4 ml of methanol. The solution was heated in a water bath until the CBZ had dissolved. Once the solution had cooled to room temperature, 1 ml of concentrated hydrofluoroboric acid was slowly added. The test tube was then sealed with parafilm. Small holes were made in the parafilm to aid evaporation. Examining the sample approximately 10 days later showed that two crystalline forms were present. Colorless crystals were shown by SXD analysis to be the CBZ hydronium species  $\text{CBZ} \cdot [\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25} \cdot \text{H}_2\text{O}$ , whilst orange crystals were  $\text{CBZ} \cdot [\text{CBZ}(\text{H})][\text{BF}_4] \cdot 0.5\text{H}_2\text{O}$ .

**Synthesis of  $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})] \cdot 0.5\text{H}_2\text{O}$** ; CBZ (0.202 g, 0.85 mmol) was added to a beaker containing 2.5 ml of aqueous 4-hydroxybenzenesulfonic acid (65 %). The slurry was stirred and heated until the CBZ was fully dissolved. The clear solution was then poured into a small test tube wrapped in foil and covered with parafilm. Small holes were pierced in the film to allow evaporation to occur. After several days, crystals precipitated and were analyzed by SXD.

**Synthesis of  $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_5]$** ; 0.20 g (0.85 mmol) of CBZ was dissolved with heating in 3 ml of methanol. The solution was allowed to cool to room temperature and then 1 ml of the aqueous solution formed by deliquescence of benzenesulfonic acid was slowly added. Slow evaporation produced crystals within 1 week. These were analyzed by SXD.

**Synthesis of  $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})] \cdot \text{H}_2\text{O}$** ; 0.20 g (0.85 mmol) of CBZ was dissolved with heating in 4 ml of methanol. The solution was allowed to cool to room temperature and then 1 ml of the aqueous solution formed by deliquescence of 5-sulfosalicylic acid was added. Evaporation to dryness over 5 days gave a solid that was a mix of 5-sulfosalicylic acid and crystals of  $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})] \cdot \text{H}_2\text{O}$ , these were analyzed by SXD.



**Synthesis of  $[\text{CBZ}(\text{H})]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$ ;** 0.202 g ( 0.86 mmol) of CBZ and 0.269 g (1.42 mmol) of 1,2-ethanedisulfonic acid hydrate were dissolved in 4 ml of ethanol. The solution was heated in a water bath until both the CBZ and ethanedisulfonic acid had dissolved. The test tube was sealed with parafilm. Small holes were made in the parafilm to aid evaporation. Colorless crystals appeared within 5 days and were analyzed by SXD.

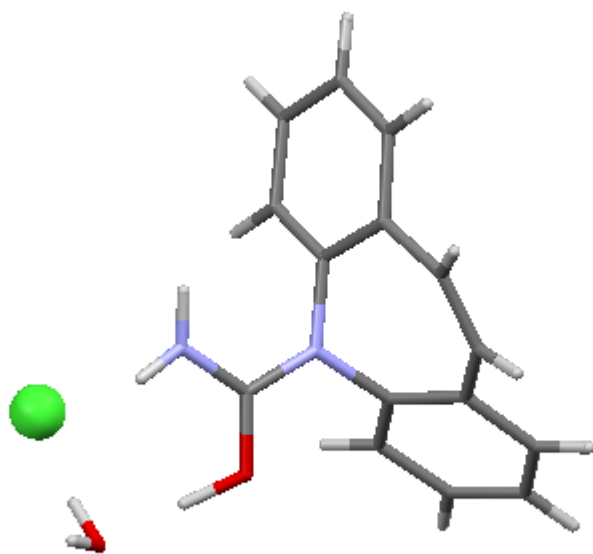
## **Results and Discussion.**

**Reactions of CBZ with concentrated strong mineral acids;** It has previously been shown that *in-situ* generation of HX (X = Cl or Br) by adding acetyl halide to alcohol solutions of CBZ gives salt forms  $[\text{CBZ}(\text{H})][\text{X}]$  with the  $\text{CBZ}(\text{H})$  cation formed by protonation at the amide O atom of CBZ.<sup>[14,15]</sup> Both the chloride containing and the bromide containing species were isolated as three solid phases. In each case the initially produced anhydrous salts designated as form I, transform with time into new polymorphs. These form II polymorphs of the hydrochloride and hydrobromide species are mutually isostructural. Prolonged exposure to air results in hydration of both form II species. In the case of bromide this gives simply a hydrated phase,  $[\text{CBZ}(\text{H})][\text{Br}]\cdot\text{H}_2\text{O}$ , but for the chloride there is a partial loss of HCl and a proton transfer from  $\text{CBZ}(\text{H})$  to water to give the solid-state hydronium species  $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$ .<sup>[14]</sup> As it contains only neutral CBZ, this last phase can best be described as an ICC phase rather than as a true salt form of CBZ.<sup>[13]</sup>

Our initial attempts to form salt forms of CBZ using aqueous acids simply involved adding concentrated strong acids (HCl, HBr, HI and  $\text{HBF}_4$ ) to solid CBZ. Despite heating there was no apparent dissolution of the CBZ nor was there any other visually apparent change. It is possible that the lack of apparent dissolution and of any other visual change contributed to the previous assertion that no reaction takes place under such conditions.<sup>[15]</sup> However, on recovering the solid powders from the acidic slurries, investigation by IR spectroscopy showed that the recovered materials were neither CBZ nor its dihydrate. For detail of the differences between CBZ and  $[\text{CBZ}(\text{H})][\text{X}]$ , X = Cl or Br, spectra see reference 14.

The solid recovered from the reaction of CBZ with concentrated aqueous HCl was found by PXRD to be a mixed phase. Once a contribution from form II of  $[\text{CBZ}(\text{H})][\text{Cl}]$  was identified,

the remaining peaks were indexed to a unit cell ( $a = 5.0341(3) \text{ \AA}$ ,  $b = 11.1488(8) \text{ \AA}$ ,  $c = 25.7824(15) \text{ \AA}$ ,  $\beta = 91.251(3)^\circ$ ,  $V = 1446.68(15) \text{ \AA}^3$ ,  $P2_1/n$ ,  $T = 293 \text{ K}$ ) that closely matched that of the known species  $[\text{CBZ}(\text{H})][\text{Br}]\cdot\text{H}_2\text{O}$ ,<sup>[14]</sup> suggesting that a new hydrated CBZ hydrochloride phase isostructural to that of the hydrobromide has been identified, see Figure 1. A two-phase Pawley refinement, based on this cell and that of form II of  $[\text{CBZ}(\text{H})][\text{Cl}]$  gave an excellent fit ( $R_{\text{wp}} = 3.26$ ,  $6\text{-}70^\circ 2\theta$ ) to the PXRD data. A two-phase rigid-body Rietveld refinement ( $R_{\text{wp}} = 5.25$ ,  $6\text{-}70^\circ 2\theta$ ) showed the mixture composition to be 11% form II of  $[\text{CBZ}(\text{H})][\text{Cl}]$  and 89% of the novel hydrated CBZ hydrochloride. See Supporting Information for refinement details.



**Figure 1.** Structure of  $[\text{CBZ}(\text{H})][\text{Cl}]\cdot\text{H}_2\text{O}$  as determined by PXRD. Protonation of CBZ is at the O atom of the amide group and this group donates a short  $\text{O}\cdots\text{H}\cdots\text{O}$  hydrogen bond to the water molecule ( $\text{O}\cdots\text{O} \text{ 2.520 \AA}$ ).

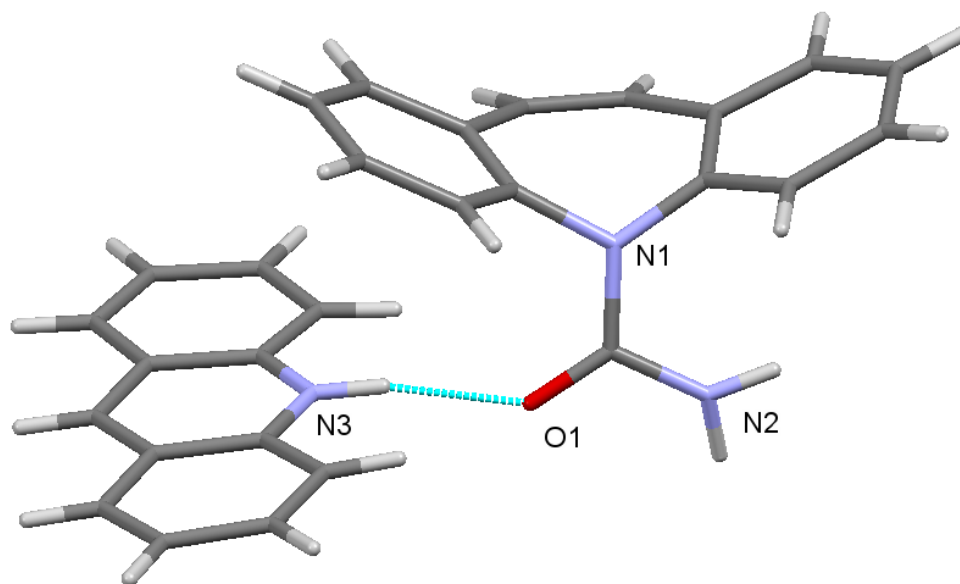
A third ionic form containing CBZ was also isolated from the same reaction. Evaporation of the remaining aqueous acid to dryness gave a small number of crystals suitable for SXD. These were shown to be the known hydronium species,  $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$ .<sup>[14]</sup> Low aqueous solubility of CBZ

and its ionic forms is an experimental hindrance here. In an attempt to form larger crystals of the new hydrochloride hydrate phase for SXD study, an ethanol solution of CBZ was prepared and concentrated aqueous HCl added to this. This approach did give large crystals, but these were not the desired hydrate phase. Instead they were also identified as the hydronium species,  $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$ .<sup>[14]</sup>

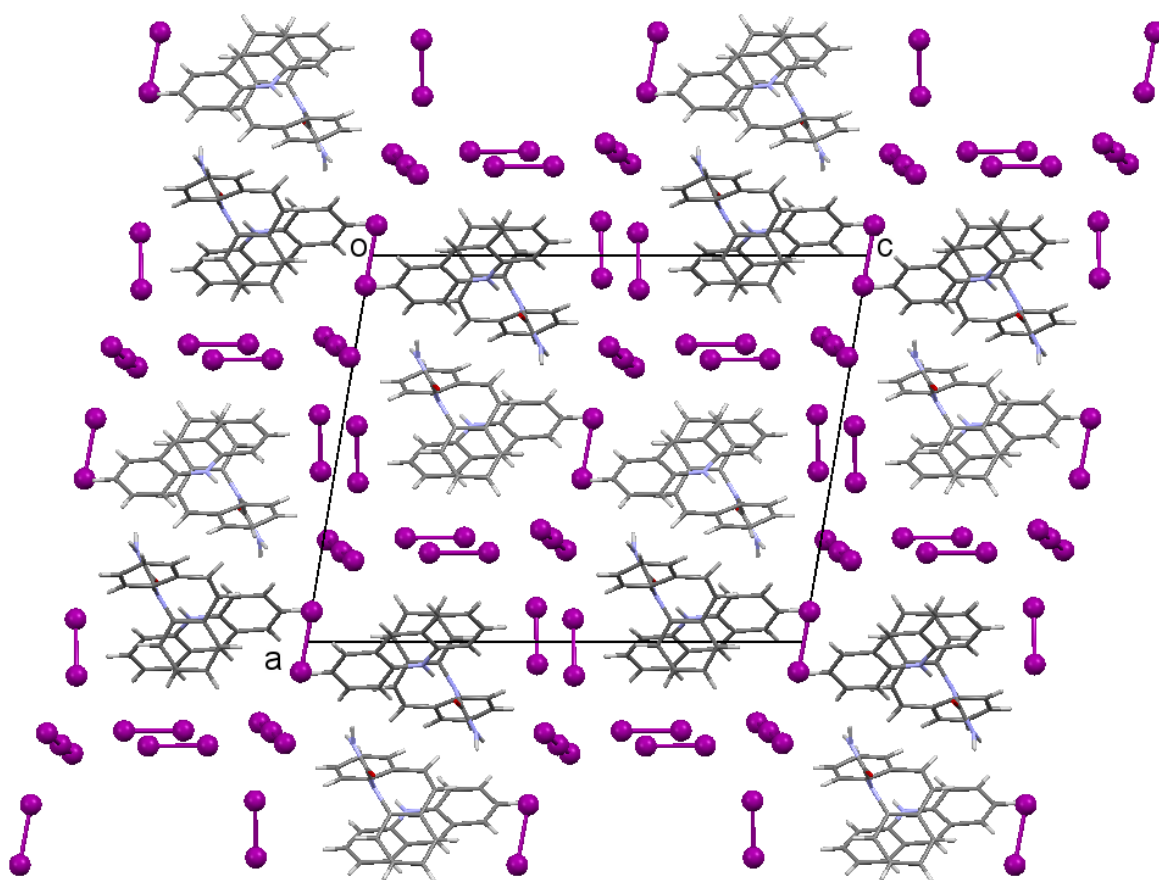
Reaction of CBZ with concentrated aqueous HBr followed a similar pattern to the equivalent reaction with HCl. The bulk of the CBZ appeared not to dissolve but analysis of the recovered powder by PXRD (following a similar Pawley and Rietveld-based approach to that already detailed for the HCl product; data range  $5\text{-}65^\circ 2\theta$ ) showed it to be composed of 90%  $[\text{CBZ}(\text{H})][\text{Br}]\cdot\text{H}_2\text{O}$  and 10%  $[\text{CBZ}(\text{H})][\text{Br}]$ , see Supporting Information. Reaction of an ethanol solution of CBZ with concentrated aqueous HBr yielded crystals only of the hydrated salt. To summarise, despite previous descriptions, reaction with concentrated HCl does not simply return CBZ dihydrate. Instead a number of ionic species were produced. From purely aqueous media the main product was found to be a new phase, namely the hydrate of CBZ hydrochloride, but both form II of anhydrous CBZ hydrochloride and the hydronium chloride form of CBZ were also present. Reaction of CBZ with concentrated aqueous HBr gave mostly the hydrated salt form, with a small amount of anhydrous salt material also present.

Reactions of CBZ with HI proceeded differently. The coloured product formed on treating solid CBZ with concentrated aqueous HI was found to contain  $\text{CBZ}\cdot[\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3]\cdot 2.5\text{I}_2$ , see Figure 2. Here an ICC species has been formed with the final product containing neutral CBZ molecules, cationic acridinium and a polyiodide array that can be best rationalized as one  $\text{I}_3$  anion and 2.5 neutral  $\text{I}_2$  molecules per CBZ. The structures of the somewhat related ICC species  $\text{CBZ}\cdot[\text{NH}_4][\text{X}]$ ,  $\text{X} = \text{Cl}$  and  $\text{Br}$  have previously been described.<sup>[12, 13]</sup> Acridine may seem like a surprising inclusion, but it is a well known metabolite of CBZ and is produced by decomposition of CBZ under a variety of chemical and biological conditions.<sup>[25-27]</sup> It has also previously been trapped during the crystallization of CBZ in the presence of NaI and HBr as the ICC complex  $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]$ .<sup>[13]</sup> The fibrous crystals of  $\text{CBZ}\cdot[\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3]\cdot 2.5\text{I}_2$  diffracted weakly and so the resulting crystal structure has a relatively low resolution especially with respect to the light atom organic components. It can though be seen that the acridinium cation forms a single  $\text{N-H}\cdots\text{O}$  hydrogen bond with the O atom of the CBZ amide group. Notably there

are no hydrogen bonds involving either the cation or CBZ and any of the I centres, indeed the I centres form only I...I short contacts. An ICC structure with no apparent short/strong cation to anion attractive interaction is unusual. The packing structure of  $\text{CBZ} \cdot [\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3] \cdot 2.5\text{I}_2$  is shown in Figure 3. It is obvious from this figure that this ICC form is very different from other phases of CBZ. The normal organic to organic interactions that dominate the packing and hence the physical properties of most known forms of CBZ cannot adequately define the packing of this species. Note the layering motif with most of the  $\text{I}_3$  and  $\text{I}_2$  species occupying layers parallel to the *ab* plane but with a single crystallographically independent  $\text{I}_2$  molecule lying within the otherwise wholly organic *ab* layer.



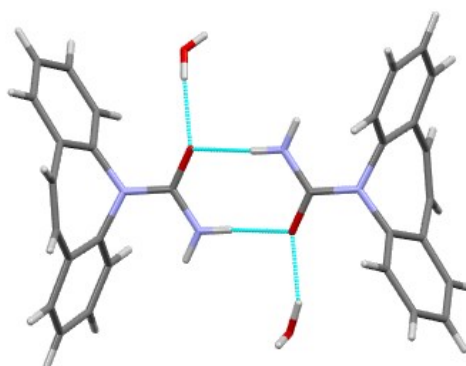
**Figure 2.** Hydrogen bonded CBZ/acridinium pair from the crystal structure of  $\text{CBZ} \cdot [\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3] \cdot 2.5\text{I}_2$ .



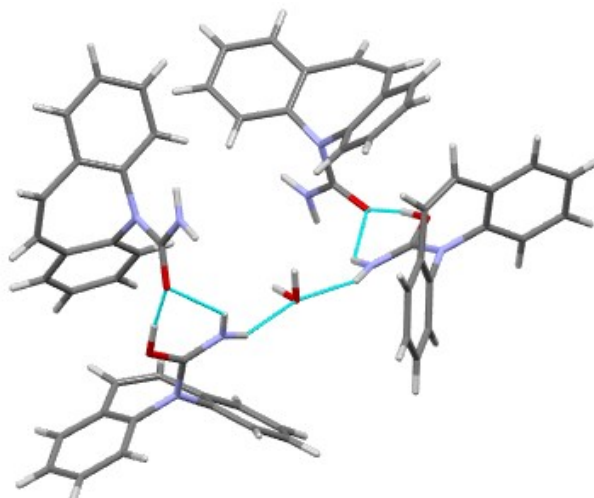
**Figure 3.** Packed structure of the ICC species  $\text{CBZ} \cdot [\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3] \cdot 2.5\text{I}_2$  with view down the  $b$  axis.

The final concentrated mineral acid reacted with CBZ was  $\text{HBF}_4$ . There were similarities to the  $\text{HCl}$  and  $\text{HBr}$  reactions in that treating solid CBZ with the concentrated acid did not give any apparent dissolution of the CBZ. Analysing the powder recovered from the acid by IR spectroscopy indicated that it contained both CBZ and  $\text{BF}_4^-$  anions, however PXRD of this material was inconclusive as we were unable to index the pattern. It is likely to consist of a mixture of phases. In an attempt to grow crystals suitable for SXD analysis, concentrated  $\text{HBF}_4$  was added to a methanol solution of CBZ. Crystals did indeed grow, but there were obviously two products, one colorless and one light orange. The colorless crystals were not a true salt form of CBZ as they contained a hydronium cation rather than  $\text{CBZ}(\text{H})$  and analysed as the ICC species  $\text{CBZ} \cdot [\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25} \cdot \text{H}_2\text{O}$ . In this structure there are four neutral CBZ molecules per  $[\text{H}_5\text{O}_2][\text{BF}_4]$  ion pair and the ions are disordered about the crystallographic 2 fold axis. The water

molecules are also disordered. Despite the requirement to model partially occupied H atoms to identify the cationic groups, the characterization of the chemical identity of this species is certain. Supporting this is the previous identification of hydronium ion ICC species found on reaction of aqueous HCl with CBZ (above) and after reaction of *in situ* generated HCl with the CBZ congener cytenamide.<sup>[14]</sup> Furthermore the presence of (partial) BF<sub>4</sub> is certain from both IR and SXD evidence and charge balance thus requires a cation to be present in the structure. Both molecular and intramolecular structural features also support a firm identification as a hydronium species. In more detail, protonation of CBZ has been shown to cause characteristic lengthening of the amide C=O bond accompanied by shortening of the C-N bonds.<sup>[14,16]</sup> Such bond length effects are absent here, see Table 2 for details. Finally, the supramolecular structures of neutral CBZ containing forms have received much attention and they are known to commonly contain either homodimeric hydrogen bonded pairs, or polymeric hydrogen bonded chains of CBZ molecules, or heterodimer hydrogen bonded pairs formed between CBZ and a suitable coformer such as a carboxylic acid.<sup>[4,7,17]</sup> In the structure of CBZ.[H<sub>5</sub>O<sub>2</sub>]<sub>0.25</sub>[BF<sub>4</sub>]<sub>0.25</sub>.H<sub>2</sub>O the solvated R2,2(8) homodimer motif is present (Figure 4). This motif is common in other neutral CBZ containing species (including hydronium ICC species) but absent from structures that contain the CBZ(H) cation.<sup>[14]</sup>



**Figure 4.** Hydrogen bonded solvated CBZ homodimer from the structure of the hydronium ion species CBZ.[H<sub>5</sub>O<sub>2</sub>]<sub>0.25</sub>[BF<sub>4</sub>]<sub>0.25</sub>.H<sub>2</sub>O. This supramolecular motif is common in other structures that also contain neutral CBZ.



**Figure 5.** Two hydrogen bonded CBZ/CBZ(H) dimers connected through further hydrogen bonding to a shared water molecule to give a discrete tetrameric (CBZ<sub>2</sub>.CBZ(H)<sub>2</sub>.H<sub>2</sub>O) unit.

**Table 2.** Amide group bond lengths for protonated and neutral CBZ.

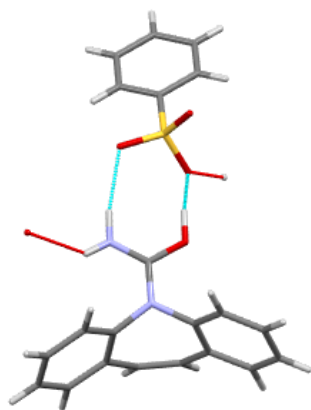
|   | C=O (Å)     | C-NH <sub>2</sub> (Å) | C-N <sub>ring</sub> (Å) |
|---|-------------|-----------------------|-------------------------|
| Neutral <b>CBZ</b> <sup>a</sup>   | 1.242       | 1.342                 | 1.373                   |
| Cationic <b>CBZ(H)</b> <sup>b</sup>   | 1.299-1.312 | 1.304-1.326           | 1.323-1.338             |
| <b>CBZ</b> .[H <sub>5</sub> O <sub>2</sub> ] <sub>0.25</sub> [BF <sub>4</sub> ] <sub>0.25</sub> .H <sub>2</sub> O | 1.2471(18)  | 1.340(2)              | 1.369(2)                |
| <b>CBZ</b> .[CBZ(H)][BF <sub>4</sub> ].0.5H <sub>2</sub> O  | 1.249(4)    | 1.364(4)              | 1.360(4)                |
| CBZ.[ <b>CBZ(H)</b> ][BF <sub>4</sub> ].0.5H <sub>2</sub> O   | 1.295(4)    | 1.313(4)              | 1.348(4)                |
| [ <b>CBZ(H)</b> ][O <sub>3</sub> SC <sub>6</sub> H <sub>5</sub> ]   | 1.2918(19)  | 1.318(2)              | 1.340(2)                |
| [ <b>CBZ(H)</b> ][O <sub>3</sub> SC <sub>6</sub> H <sub>4</sub> (OH)]   | 1.290(6)    | 1.306(6)              | 1.342(5)                |
| [ <b>CBZ(H)</b> ][O <sub>3</sub> SC <sub>6</sub> H <sub>4</sub> (OH)] <sup>+</sup>                                | 1.285(5)    | 1.322(5)              | 1.334(5)                |
| [ <b>CBZ(H)</b> ][O <sub>3</sub> SC <sub>6</sub> H <sub>3</sub> (OH)(COOH)]                                       | 1.287(3)    | 1.326(3)              | 1.336(3)                |
| [ <b>CBZ(H)</b> ] <sub>2</sub> [O <sub>3</sub> SCH <sub>2</sub> CH <sub>2</sub> SO <sub>3</sub> ]                 | 1.309(3)    | 1.308(3)              | 1.342(3)                |

<sup>a</sup> Average values from 47 non-disordered, well modeled, SXD determined molecules present in the CSD.<sup>[28]</sup>

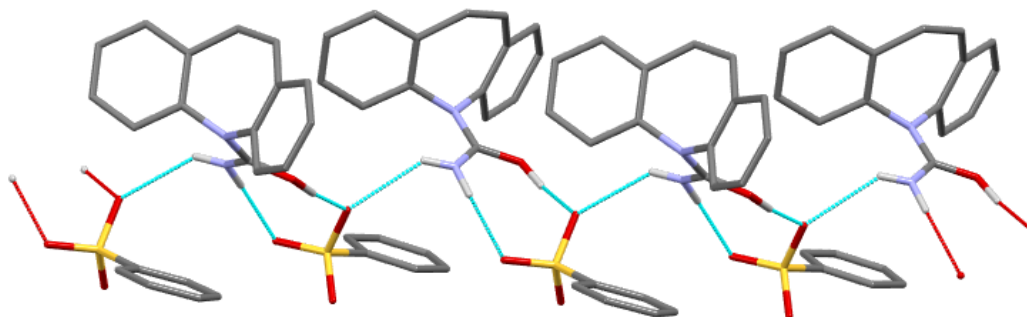
<sup>b</sup> Range of values found for the 5 forms described as being solely of salt character in references 14 and 16.

The orange crystals isolated from the same reaction of CBZ and  $\text{HBF}_4$  do contain protonated CBZ ions, but they also contain neutral CBZ molecules and have formula  $\text{CBZ} \cdot [\text{CBZ}(\text{H})][\text{BF}_4] \cdot 0.5\text{H}_2\text{O}$ . This is the first structurally characterized species known to contain crystallographically discrete CBZ and CBZ(H) fragments. Note though that the  $\text{CF}_3\text{COO}$  and hydrobromide hydrate salts of CBZ have been described as species that feature dynamic equilibria that imply the existence of CBZ and CBZ(H) on the same (disordered) sites.<sup>[14,16]</sup> The C=O and C-N bond lengths of the CBZ and CBZ(H) fragments are clearly different from each other (Table 2) and are in good agreement with other values for neutral and cationic CBZ species. This differentiation comes despite the O-H proton being situated between the O atoms of CBZ and CBZ(H), see Figure 5. Despite this arrangement and the short O...O distance of 2.499(3) Å, the distinct C=O and C-N distances indicate that there is no sharing of the central H atom here. The CBZ/CBZ(H) pair forms a R1,2(6) hydrogen bonded motif that is of a type not seen before for CBZ containing species. Two of these dimers are linked through N-H to water hydrogen bonds to form discrete tetramers as shown in Figure 5. The geometry about the water molecule is completed by O-H to  $\text{BF}_4$  hydrogen bonds. The water molecule thus has a rather typical 2 donor, 2 acceptor nature.<sup>[29]</sup> However, the very “normality” of its positioning is interesting as the other structures of water containing ionic CBZ species determined by SXD either contain protonated  $\text{H}_3\text{O}$  cations or, in the case of  $[\text{CBZ}(\text{H})][\text{Br}] \cdot \text{H}_2\text{O}$ , a neutral water molecule that has a partial  $\text{H}_3\text{O}$  character due to proton dynamics.<sup>[14]</sup>  $\text{CBZ} \cdot [\text{CBZ}(\text{H})][\text{BF}_4] \cdot 0.5\text{H}_2\text{O}$  is the first hydrated CBZ(H) species to feature no amide O-H...water interaction.





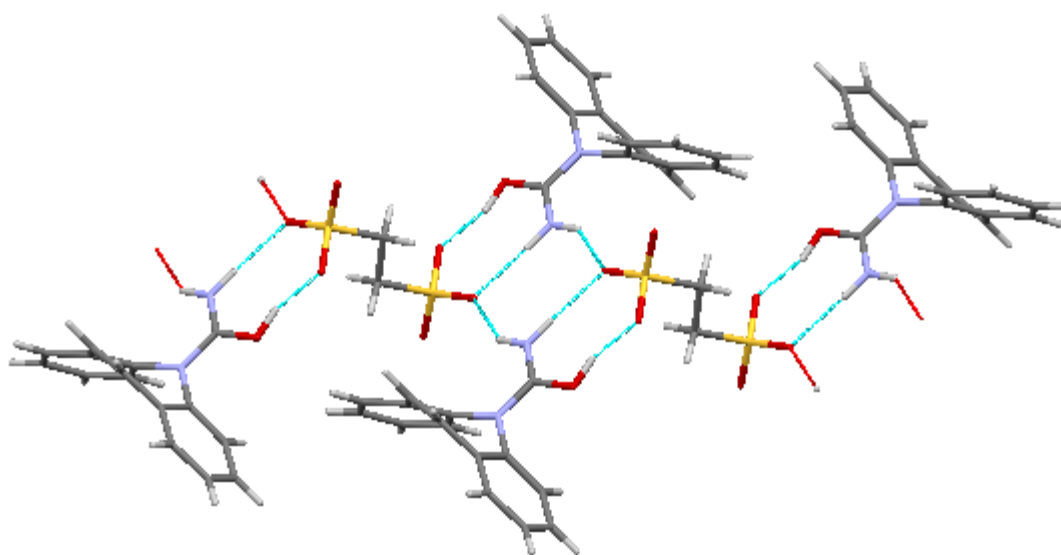
**Figure 6.** Heterodimer formed by hydrogen bonding between CBZ(H) cation and O<sub>3</sub>SPh anion. See figure 7 for the expanded polymeric motif.



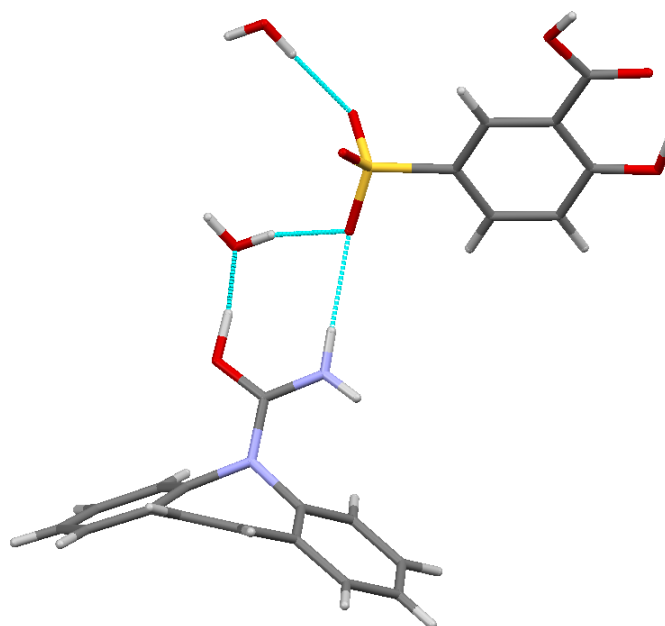
**Figure 7.** The cation/anion heterodimers shown in Fig 6 connect through further N-H...O hydrogen bonds to give a one dimensional polymer. Note that one O atom per sulfonate group is not involved in hydrogen bonding and this results in asymmetric chains with CBZ at one side and sulfonate anions on the other.

**Reactions of CBZ with sulfonic acids;** Four single crystal diffraction structures were obtained for [CBZ(H)][X] species where X is a sulfonate ion. All were obtained from reactions that involved the presence of some water, but the amount of water present varied widely. At the two

extremes,  $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})].0.5\text{H}_2\text{O}$  was isolated from an entirely aqueous reaction mixture whilst the only water present during the formation of  $[\text{CBZ(H)}]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$  was that introduced by using the hydrated phase of ethanedisulfonic acid. The other two species,  $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_5]$  and  $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})].\text{H}_2\text{O}$ , were obtained by treating methanol solutions of CBZ with aqueous solutions of the respective sulfonic acids. In all four structures the O atom of the CBZ amide group is protonated and this gives rise to the expected changes in C=O and C-N bond lengths, Table 2. The two anhydrous species both form R2,2(8) hydrogen bonded heterodimers as shown in Figure 6. This is the same motif seen in the anhydrous  $\text{MeSO}_3$  salt,<sup>[16]</sup> and is equivalent to the R2,2(8) hydrogen bonded heterodimers commonly described for CBZ cocrystals with carboxylic acids,<sup>[7]</sup> but with the obvious difference that here the acidic proton is placed on CBZ rather than on the acid coformer. In the benzenesulfonate, the N-H moiety not used in dimer formation donates a hydrogen bond to the same sulfonate O atom that takes part in the O-H...O interaction. These interactions combine to give a one dimensional hydrogen bonded chain that propagates parallel to the crystallographic *c* direction, see Figure 7. The chains pack so as to give alternate layers of cations and anions each parallel to the *bc* plane. In the ethane disulfonate the second NH atom also donates a hydrogen bond to a sulfonate O atom but here this forms a pair of heterodimers rather than a polymer with two R2,2(8) motifs joined by a central R2,4(8) motif, see Figure 8. In this structure the hydrogen bonded polymer relies upon the two headed nature of the anion to propagate, in this case parallel to the crystallographic *b* direction.



**Figure 8.** Hydrogen bonding in  $[\text{CBZ}(\text{H})]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$  illustrating the three fused hydrogen bonded rings and their connection through the two headed  $\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3$  anions.



**Figure 9.** Cyclic hydrogen bonded motif in  $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]\cdot\text{H}_2\text{O}$  with a water molecule substituted into the R2,2(8) heterodimer pair seen in Figure 6.

Neither of the hydrated sulfonated species feature the R2,2(8) heterodimer. In  $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]\cdot\text{H}_2\text{O}$  a water molecule replaces one of the sulfonate O atoms as the acceptor of the amide O-H hydrogen bond. This forms the three fragment R2,3(8) motif illustrated in Fig 9. The similar motif involving both water and anion is formed by one of the two crystallographically independent CBZ(H) ions of  $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]\cdot 0.5\text{H}_2\text{O}$  although here two O atoms of the sulfate group are involved rather than one, giving a R3,3(10) motif. The second independent CBZ(H) ion does form a heterodimer with the sulfonate anion but bonds to only one of the sulfonate group's O atoms to give a R1,2(6) motif.

**Conclusions;** Despite earlier reports that protonation of CBZ requires non-aqueous media, we find that this is not true. Indeed, far from giving only CBZ dihydrate, reaction of CBZ with strong acids in strictly aqueous media is found to give a variety of product types, namely anhydrous salt forms ( $[\text{CBZ(H)}][\text{X}]$ , X = Cl or Br), hydrated salts ( $[\text{CBZ(H)}][\text{X}]\cdot n\text{H}_2\text{O}$ , X = Cl, Br,  $\text{O}_3\text{SC}_6\text{H}_4(\text{OH})$ ), mixed CBZ/CBZ(H) salts ( $\text{CBZ}\cdot[\text{CBZ(H)}][\text{BF}_4]$ ), and ICC forms containing hydronium ( $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$ ,  $\text{CBZ}\cdot[\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25}$ ) or acridinium cations ( $\text{CBZ}\cdot[\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3]\cdot 2.5\text{I}_2$ ). Mixed alcohol/water solvent systems were adopted to improve solubility and hence crystal growth properties and these conditions were also found to allow access to salt forms of CBZ with both mineral acids and sulfonic acids. In total this approach has increased the number of structurally characterized CBZ(H) salt forms from seven to thirteen and allows access to two new ICC forms of CBZ. Neutral CBZ and cationic CBZ(H) species have been shown to have distinctly different C=O and C-N amide bond lengths from each other, to such an extent that intermediate bond lengths can be taken to indicate the presence of a dynamic equilibrium between CBZ and CBZ(H) moieties.<sup>[14,16]</sup> CBZ(H) cations also differ from CBZ molecules in the nature of their hydrogen bonding. Neither of the common homo-CBZ supramolecular structures (dimer or chain) are observed for CBZ(H) species but a close relative of the heterodimer observed for CBZ/carboxylic acid cocrystals is seen in the R2,2(8) dimers formed here between CBZ(H) cations and sulfonate anions. This structural motif is absent from hydrated crystals of sulfonate salts of CBZ(H).

**Supporting Information.** This consists of cif files for all new structures discussed and details of the Pawley and Rietveld fits of the PXRD data measured for the powders isolated from reactions of CBZ with concentrated aqueous HCl and HBr.

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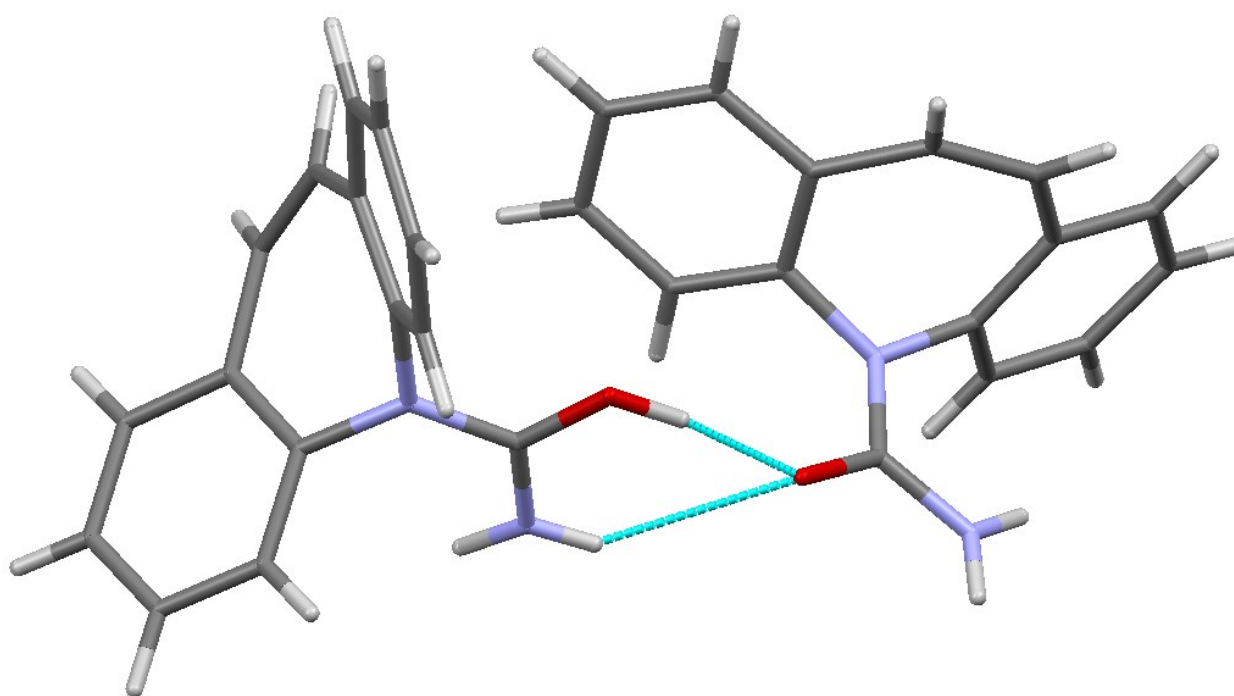
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FOR TABLE OF CONTENTS USE ONLY

Salt and Ionic Cocrystalline Forms of Amides: Protonation of Carbamazepine in Aqueous Media

by Amanda R. Buist,<sup>†</sup> David S. Edgeley,<sup>‡</sup> Elena A. Kabova,<sup>‡</sup> Alan R. Kennedy,<sup>\* †</sup> Debbie

Hooper,<sup>†</sup> David G. Rollo,<sup>†</sup> Kenneth Shankland,<sup>‡</sup> and Mark J. Spillman<sup>‡</sup>



Despite previous reports to the contrary, reaction of the organic amide carbamazepine with aqueous mineral acids and sulfonic acids gives both O protonated salt forms of the amide and ionic cocrystalline forms.

## ESI

### **Salt and Ionic Cocrystalline Forms of Amides: Protonation of Carbamazepine in Aqueous Media.**

Amanda R. Buist,<sup>†</sup> David S. Edgeley,<sup>‡</sup> Elena A. Kabova,<sup>‡</sup> Alan R. Kennedy,<sup>\*†</sup> Debbie Hooper,<sup>†</sup>  
David G. Rollo,<sup>†</sup> Kenneth Shankland,<sup>‡</sup> and Mark J. Spillman<sup>‡</sup>

#### **Contents**

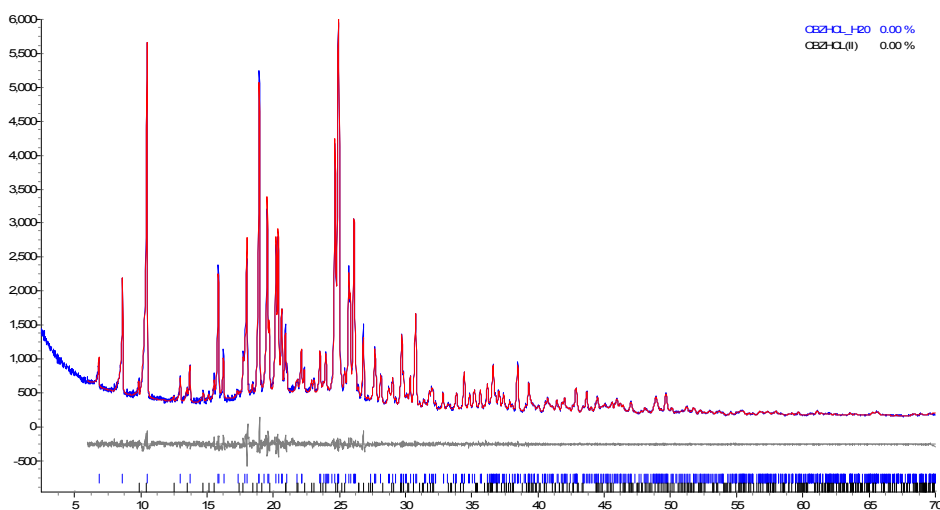
- 1a. Pawley fit data for reaction with HCl.
- 1b. Rieveld fit data for reaction with HCl.
- 2a. Pawley fit data for reaction with HBr.
- 2b. Rieveld fit data for reaction with HBr.

NB. All “known” phases were originally described in Buist, A. R.; Kennedy, A. R.; Shankland, K.; Shankland, N.; Spillman, M. J. *Cryst. Growth Des.* **2013**, *13*, 5121.



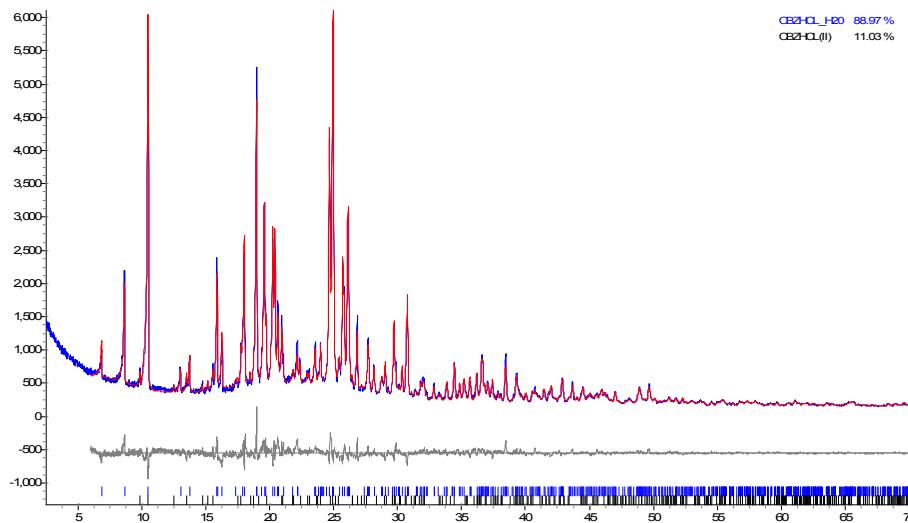
1. PXRD of solid isolated from reaction of CBZ with concentrated aqueous HCl.
  - a. Two phase Pawley fit.  
Rwp 3.260, 6 – 70 degrees.

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a @ 5.03414`_0.00027  
b @ 11.14877`_0.00080  
c @ 25.78240`_0.00152  
al 90  
be @ 91.25143`_0.00287  
ga 90  
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phase_name "CBZHCL(II)"  
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b @ 9.60052`_0.00153  
c @ 17.94263`_0.00305  
al 90  
be 90  
ga 90  
volume 1326.22116`_0.323484258  
space_group "P212121"
```



Blue = novel [CBZ(H)][Cl].H<sub>2</sub>O phase. Black = known phase II of anhydrous [CBZ(H)][Cl].

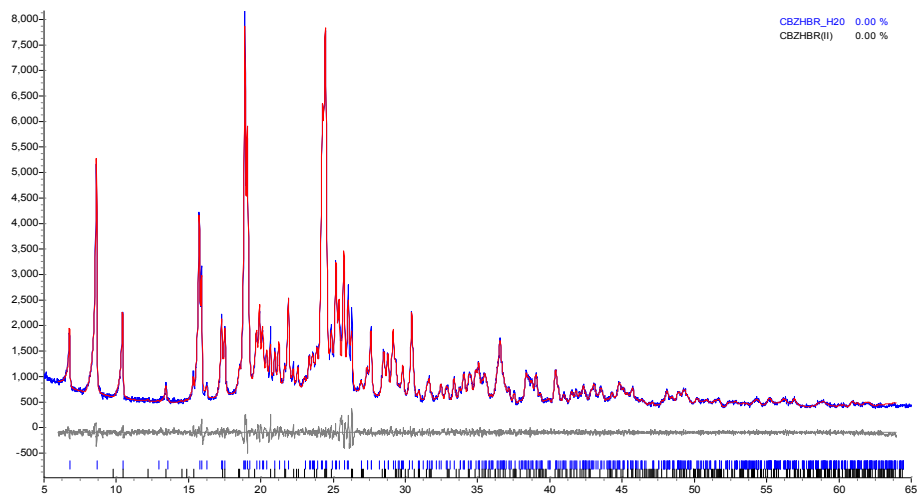
1. PXRD of solid isolated from reaction of CBZ with concentrated aqueous HCl.
  - b. Two phase Rietveld fit.  
Rwp, 5.250 for 6 to 70 degrees.  
89.0(2) % [CBZ(H)][Cl].H<sub>2</sub>O to 11.0(2) % for phase II [CBZ(H)][Cl].



Blue = novel [CBZ(H)][Cl].H<sub>2</sub>O phase. Black = known phase II of anhydrous [CBZ(H)][Cl].

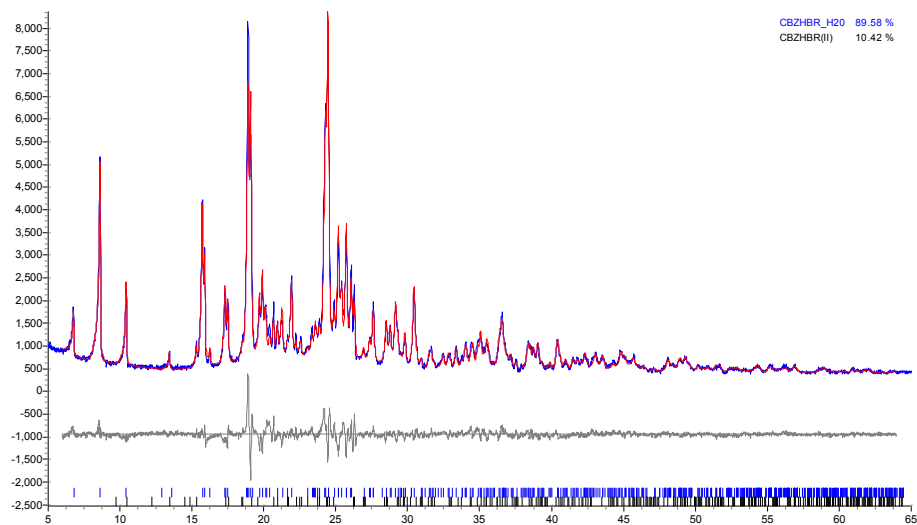
2. PXRD of solid isolated from reaction of CBZ with concentrated aqueous HBr.  
a. Two phase Pawley fit. Rwp 4.75, 6 – 64 degrees.

```
phase_name "CBZHBR_H2O"  
  a @ 5.18827`_0.00051  
  b @ 11.13533`_0.00097  
  c @ 26.08000`_0.00201  
  al 90.00  
  be @ 91.33556`_0.01068  
  ga 90.00  
volume 1506.31287`_0.229865654  
space_group "P21/n"  
phase_name "CBZHBR(II)"  
  a @ 7.89578`_0.00274  
  b @ 9.56420`_0.00231  
  c @ 18.14549`_0.00481  
  
al 90  
be 90  
ga 90  
volume 1370.2892`_0.683430069  
space_group "P212121"
```



Blue = known [CBZ(H)][Br].H<sub>2</sub>O phase. Black = known phase II of anhydrous [CBZ(H)][Br].

2. PXRD of solid isolated from reaction of CBZ with concentrated aqueous HBr.
- b. Two phase Rietveld fit.
- Rwp, 7.30 for 6 to 64 degrees.
- 89.6(2) % [CBZ(H)][Br].H<sub>2</sub>O to 10.4(2) % for phase II [CBZ(H)][Br].



Blue = known [CBZ(H)][Br].H<sub>2</sub>O phase. Black = known phase II of anhydrous [CBZ(H)][Br].