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

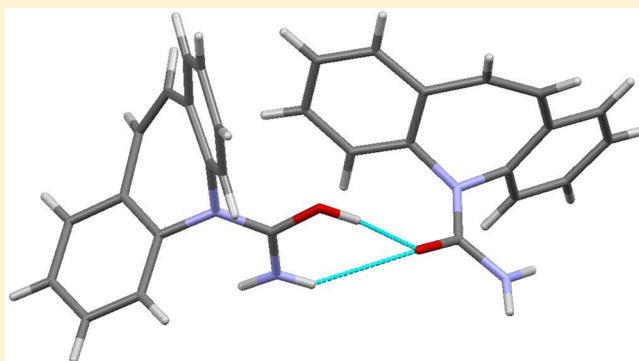
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S Supporting Information

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 $[\text{CBZ}(\text{H})][\text{Cl}]\cdot\text{H}_2\text{O}$. Reactions with other mineral acids (HI and HBF_4) gave ionic cocrystalline (ICC) forms $\text{CBZ}\cdot[\text{acridinium}][\text{I}_3]\cdot 2.5\text{I}_2$ and $\text{CBZ}\cdot[\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25}\cdot\text{H}_2\text{O}$ as well as the salt form $\text{CBZ}\cdot[\text{CBZ}(\text{H})][\text{BF}_4]\cdot 0.5\text{H}_2\text{O}$. Reaction of CBZ with a series of sulfonic acids also gave salt forms, namely, $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_5]$, $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]\cdot 0.5\text{H}_2\text{O}$, $[\text{CBZ}(\text{H})]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$, and $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]\cdot\text{H}_2\text{O}$. CBZ and protonated $\text{CBZ}(\text{H})$ 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 nonpolar 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.^{1–11} A much smaller body of work exists on other classes of solid-state forms. Ionic cocrystalline (ICC) forms of CBZ with NH_4 , OH_3 , and Na cations have been structurally described,^{12–14} as, recently, have salt forms which feature protonation of CBZ at the amide O atom.^{14–16} 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 nonpolar supramolecular constructs first described by Gelbrich and Hursthouse.¹⁷ This change in intermolecular bonding may in turn result in useful differences in material properties.^{13–15,18,19}

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-ionizable” API.^{20,21} 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.²² Perumalla and Sun’s original preparation of the salt $[\text{CBZ}(\text{H})][\text{Cl}]$ utilized *in situ* generation of HCl in nonaqueous solvents.¹⁵ 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.¹⁴ The original Perumalla and Sun work specified that this approach with nonaqueous conditions was necessary as H^+ generated in organic solution was more active than the solvated species (e.g., H_3O^+) 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”.¹⁵ Later reports have led us to reinvestigate the use of aqueous acids. Notable prompts were Frampton and co-workers’ isolation of $[\text{CBZ}(\text{H})][\text{MeSO}_3]$ from a reaction of CBZ with what was described as “neat” methanesulfonic acid ($\text{p}K_a$, approximately -2.6) and, perhaps even more interestingly, their characterization of the product formed by reaction of CBZ with trifluoroethanoic acid ($\text{p}K_a$, approximately -0.26)

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Table 1. Selected Crystallographic and Refinement Parameters

compound	CBZ·[C ₁₃ H ₁₀ N][I ₃]·2.5I ₂	CBZ·[CBZ(H)][BF ₄]·0.5H ₂ O	CBZ·[H ₅ O ₂] _{0.25} [BF ₄] _{0.25} ·H ₂ O	
formula	C ₂₈ H ₂₂ I ₈ N ₃ O	C ₃₀ H ₂₆ BF ₄ N ₄ O _{2.5}	C ₁₅ H _{15.25} B _{0.25} FN ₂ O _{2.5}	
fw	1431.69	569.36	285.24	
cryst syst	monoclinic	monoclinic	monoclinic	
space group	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2	<i>C</i> 2/ <i>c</i>	
λ, Å	0.71073	0.71073	0.71073	
<i>a</i> , Å	17.7346(16)	26.8750(3)	29.788(2)	
<i>b</i> , Å	9.2416(7)	8.9636(7)	5.1199(2)	
<i>c</i> , Å	22.5168(15)	11.7505(13)	21.1130(16)	
α, deg	90	90	90	
β, deg	99.498(7)	104.459(12)	120.804(10)	
γ, deg	90	90	90	
vol, Å ³	3639.8(5)	2741.0(4)	2765.7(3)	
temp, K	123(2)	123(2)	123(2)	
<i>Z</i>	4	4	8	
reflcs collcd	14505	4949	6940	
2θ max, deg	50.0	57.6	58.8	
unique reflcs	6390	4121	3340	
obsd reflcs	3321	3053	2515	
<i>R</i> _{int}	0.0982	0.0312	0.0234	
goodness of fit	0.950	1.011	1.092	
<i>R</i> [<i>I</i> > 2 <i>s</i> (<i>I</i>)], <i>F</i>	0.0595	0.0454	0.0479	
<i>R</i> _w <i>F</i> ²	0.1298	0.1032	0.1115	
max/min electron density, e Å ⁻³	1.461/−1.216	0.197/−0.212	0.219/−0.255	
compound	[CBZ(H)][O ₃ SC ₆ H ₅]	[CBZ(H)] ₂ [O ₃ SCH ₂ CH ₂ SO ₃]	[CBZ(H)][O ₃ SC ₆ H ₅ (OH)(COOH)]·H ₂ O	[CBZ(H)][O ₃ SC ₆ H ₄ (OH)]·0.5H ₂ O
formula	C ₂₁ H ₁₈ N ₂ O ₄ S	C ₃₂ H ₃₀ N ₄ O ₈ S ₂	C ₂₂ H ₂₀ N ₂ O ₈ S	C ₂₁ H ₁₉ N ₂ O _{5.5} S
fw	394.43	662.72	472.46	419.44
cryst syst	monoclinic	triclinic	triclinic	monoclinic
space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> <i>n</i>
λ, Å	0.71073	0.71073	0.71073	0.71073
<i>a</i> , Å	10.5380(3)	7.3746(7)	7.1788(4)	12.5378(9)
<i>b</i> , Å	15.4546(4)	8.6949(10)	12.3752(6)	12.2352(7)
<i>c</i> , Å	12.0765(3)	12.9832(11)	13.2726(7)	13.5144(11)
α, deg	90	92.746(8)	114.329(5)	90
β, deg	109.358(3)	98.386(7)	93.133(4)	109.876(9)
γ, deg	90	104.180(9)	97.161(4)	90
vol, Å ³	1855.59(9)	795.46(14)	1058.68(10)	1949.6(3)
temp, K	123(2)	123(2)	123(2)	123(2)
<i>Z</i>	4	1	2	4
reflcs collcd	8881	7642	9988	8477
2θ max, deg	59.1	55.9	58.0	54.0
unique reflcs	4509	3436	5069	5421
obsd reflcs	3461	2699	3801	4306
<i>R</i> _{int}	0.0234	0.0411	0.0323	0.0341
goodness of fit	1.025	1.073	1.045	1.059
<i>R</i> [<i>I</i> > 2 <i>s</i> (<i>I</i>)], <i>F</i>	0.0433	0.0616	0.0537	0.0494
<i>R</i> _w <i>F</i> ²	0.1001	0.1578	0.1403	0.1089
max/min electron density, e Å ⁻³	0.298/−0.388	0.770/−0.360	0.744/−0.361	0.533/−0.439

as an intermediate or equilibrium species with a partial ionized, salt nature and a partial neutral, cocrystal nature.¹⁶ Thus, protonation of CBZ seems to be possible with species that have *pK_a* values that are higher than would be expected for say concentrated aqueous HCl. Finally, while our own work showed that adding drops of water to solid [CBZ(H)][Cl] did indeed lead to a reversion to CBZ dihydrate,¹⁴ it also showed that slow addition of water to [CBZ(H)][X] (*X* = Br or Cl) through exposure to air gave [CBZ(H)][Br]·H₂O and [CBZ]₂[H₃O][Cl] thus showing that the presence of water was not incompatible with the existence of ionic phases of CBZ.¹⁴ Reported herein is a structural investigation of salt and

ICC forms of CBZ derived from reactions of CBZ with strong aqueous acids.

■ EXPERIMENTAL SECTION

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.²³ 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·[C₁₃H₁₀N][I₃]·2.5I₂ 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 in the Supporting Information. See also CCDC 1419992–1419998.

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 α 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 θ . Data were analyzed using TOPAS.²⁴ Diffraction patterns are given in the Supporting Information.

FTIR measurements were made on crushed, solid samples and with an A₂ Technologies ATR instrument.

Reactions of CBZ with Aqueous HCl. A 10 mL aliquot 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 min, 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 [CBZ(H)][Cl]·H₂O: [CBZ(H)][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 10 days gave a small number of colorless crystals. SXD and IR analyses showed that the previously known hydronium species [CBZ]₂[H₃O][Cl] had formed.¹⁴

A 0.242 g (1.02 mmol) amount 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 [CBZ]₂[H₃O][Cl].

Reactions of CBZ with Aqueous HBr. A 10 mL aliquot 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 min, 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 [CBZ(H)][Br]·H₂O: [CBZ(H)][Br] (form II).

A 0.204 g (0.86 mmol) amount 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 [CBZ(H)][Br]·H₂O.

Reaction of CBZ with Aqueous HI. A 1 mL aliquot 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 min, 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 CBZ·[C₁₃H₁₀N][I₃]·2.5I₂.

Reactions of CBZ with Aqueous HBF₄. A 4 mL aliquot 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 later text. No CBZ containing material was isolated from the filtrate.

A 0.239 g (1.01 mmol) amount 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 CBZ·[H₃O]₂[BF₄]_{0.25}·H₂O, while orange crystals were CBZ·[CBZ(H)]·[BF₄]_{0.5}·H₂O.

Synthesis of [CBZ(H)][O₃SC₆H₄(OH)]·0.5H₂O. 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 [CBZ(H)][O₃SC₆H₅]. A 0.20 g (0.85 mmol) amount 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 [CBZ(H)][O₃SC₆H₃(OH)(COOH)]·H₂O. A 0.20 g (0.85 mmol) amount 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 [CBZ(H)][O₃SC₆H₃(OH)(COOH)]·H₂O; these were analyzed by SXD.

Synthesis of [CBZ(H)]₂[O₃SCH₂CH₂SO₃]. A 0.202 g (0.86 mmol) amount of CBZ and 0.269 g (1.42 mmol) of 1,2-ethanedithiolic acid hydrate were dissolved in 4 mL of ethanol. The solution was heated in a water bath until both the CBZ and ethanedithiolic 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 [CBZ(H)][X] with the CBZ(H) cation formed by protonation at the amide O atom of CBZ.^{14,15} 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, [CBZ(H)][Br]·H₂O, but for the chloride there is a partial loss of HCl and a proton transfer from CBZ(H) to water to give the solid-state hydronium species [CBZ]₂[H₃O][Cl].¹⁴ 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.¹³

Our initial attempts to form salt forms of CBZ using aqueous acids simply involved adding concentrated strong acids (HCl, HBr, HI, and HBF₄) 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.¹⁵ 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 [CBZ(H)][X], X = Cl or Br, spectra see ref 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 [CBZ(H)]-

[Cl] was identified, the remaining peaks were indexed to a unit cell ($a = 5.0341(3) \text{ \AA}$, $b = 11.1488(8) \text{ \AA}$, $c = 25.7824(15) \text{ \AA}$, $\beta = 91.251(3)^\circ$, $V = 1446.68(15) \text{ \AA}^3$, $P2_1/n$, and $T = 293 \text{ K}$) that closely matched that of the known species $[\text{CBZ}(\text{H})][\text{Br}] \cdot \text{H}_2\text{O}$,¹⁴ 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

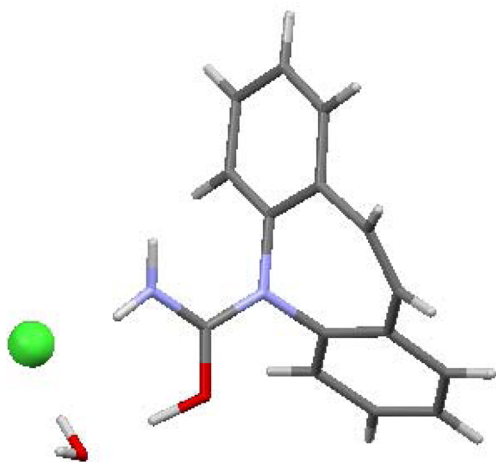


Figure 1. Structure of $[\text{CBZ}(\text{H})][\text{Cl}] \cdot \text{H}_2\text{O}$ as determined by PXRD. Protonation of CBZ is at the O atom of the amide group, and this group donates a short $\text{O}-\text{H} \cdots \text{O}$ hydrogen bond to the water molecule ($\text{O} \cdots \text{O}$, 2.520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

on this cell and that of form II of $[\text{CBZ}(\text{H})][\text{Cl}]$, gave an excellent fit ($R_{\text{wp}} = 3.26$, $6-70^\circ 2\theta$) to the PXRD data. A two-phase rigid-body Rietveld refinement ($R_{\text{wp}} = 5.25$, $6-70^\circ 2\theta$) 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 the Supporting Information for refinement details.

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, $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$.¹⁴ 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, $[\text{CBZ}]_2[\text{H}_3\text{O}][\text{Cl}]$.¹⁴

Reaction of CBZ with concentrated aqueous HBr followed a pattern similar 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, $5-65^\circ 2\theta$) showed it to be composed of 90% $[\text{CBZ}(\text{H})][\text{Br}] \cdot \text{H}_2\text{O}$ and 10% form II $[\text{CBZ}(\text{H})][\text{Br}]$; see Supporting Information. Reaction of an ethanol solution of CBZ with concentrated aqueous HBr yielded crystals only of the hydrated salt. To summarize, 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 colored 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

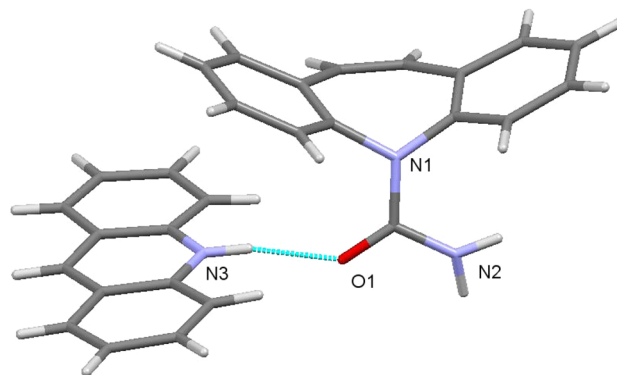


Figure 2. Hydrogen bonded CBZ/acridinium pair from the crystal structure of $\text{CBZ} \cdot [\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3] \cdot 2.5\text{I}_2$.

been formed with the final product containing neutral CBZ molecules, cationic acridinium, and a polyiodide array that can be best rationalized as one I_3 anion and 2.5 neutral 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 Br , have previously been described.^{12,13} 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.²⁵⁻²⁷ It has also previously been trapped during the crystallization of CBZ in the presence of NaI and HBr as the ICC complex $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]_2$.¹³ 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, so the resulting crystal structure has a relatively low resolution especially with respect to the light atom organic components. It can be seen though that the acridinium cation forms a single $\text{N}-\text{H} \cdots \text{O}$ 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 centers; indeed the I centers form only $\text{I} \cdots \text{I}$ 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 I_3 and I_2 species occupying layers parallel to the ab plane but with a single crystallographically independent I_2 molecule lying within the otherwise wholly organic ab layer.

The final concentrated mineral acid reacted with CBZ was HBF_4 . There were similarities to the HCl and HBr reactions in that treating solid CBZ with the concentrated acid did not give any apparent dissolution of the CBZ. Analyzing the powder recovered from the acid by IR spectroscopy indicated that it contained both CBZ and BF_4 anions; however, PXRD of this material was inconclusive as we were unable to index the

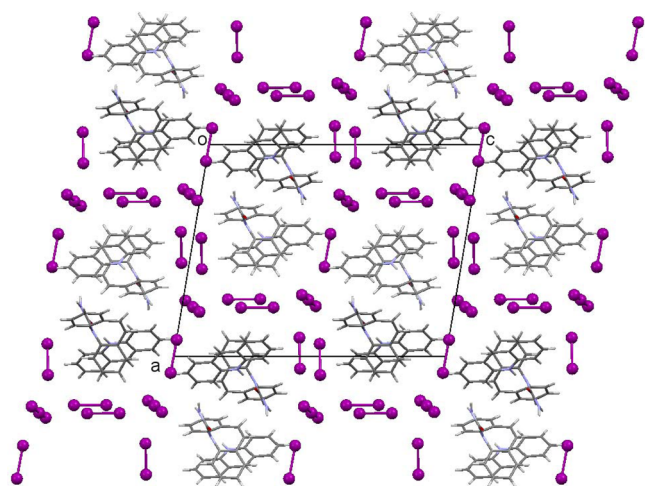


Figure 3. Packed structure of the ICC species $\text{CBZ}\cdot[\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_3]\cdot 2.5\text{I}_2$ with view down the b axis.

pattern. It is likely to consist of a mixture of phases. In an attempt to grow crystals suitable for SXD analysis, concentrated 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 CBZ(H) and analyzed 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.¹⁴ Furthermore, the presence of (partial) BF_4 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 $\text{C}=\text{O}$ bond accompanied by shortening of the $\text{C}-\text{N}$ bonds.^{14,16} 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 cofomer such as a carboxylic acid.^{4,7,17} In the structure of $\text{CBZ}\cdot[\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25}\cdot\text{H}_2\text{O}$ 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.¹⁴

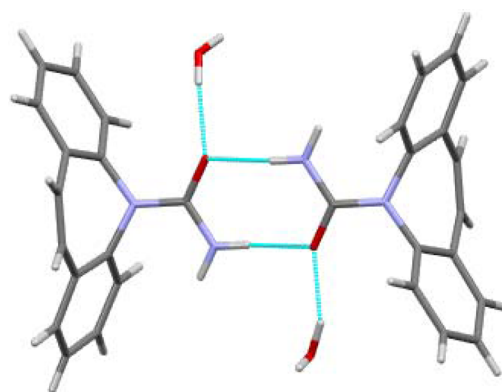


Figure 4. Hydrogen bonded solvated CBZ homodimer from the structure of the hydronium ion species $\text{CBZ}\cdot[\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25}\cdot\text{H}_2\text{O}$. This supramolecular motif is common in other structures that also contain neutral CBZ.

The orange crystals isolated from the same reaction of CBZ and 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 CF_3COO 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.^{14,16} The $\text{C}=\text{O}$ and $\text{C}-\text{N}$ 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 $\text{O}-\text{H}$ proton being situated between the O atoms of CBZ and CBZ(H); see Figure 5. Despite this arrangement and the short

Table 2. Amide Group Bond Lengths for Protonated and Neutral CBZ

	$\text{C}=\text{O}$ (Å)	$\text{C}-\text{NH}_2$ (Å)	$\text{C}-\text{N}_{\text{ring}}$ (Å)
neutral CBZ ^a	1.242	1.342	1.373
cationic CBZ(H) ^b	1.299–1.312	1.304–1.326	1.323–1.338
$\text{CBZ}\cdot[\text{H}_5\text{O}_2]_{0.25}[\text{BF}_4]_{0.25}\cdot\text{H}_2\text{O}$	1.2471(18)	1.340(2)	1.369(2)
$\text{CBZ}\cdot[\text{CBZ}(\text{H})][\text{BF}_4]\cdot 0.5\text{H}_2\text{O}$	1.249(4)	1.364(4)	1.360(4)
$\text{CBZ}\cdot[\text{CBZ}(\text{H})][\text{BF}_4]\cdot 0.5\text{H}_2\text{O}$	1.295(4)	1.313(4)	1.348(4)
$[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_5]$	1.2918(19)	1.318(2)	1.340(2)
$[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]$	1.290(6)	1.306(6)	1.342(5)
$[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]'$	1.285(5)	1.322(5)	1.334(5)
$[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]$	1.287(3)	1.326(3)	1.336(3)
$[\text{CBZ}(\text{H})]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$	1.309(3)	1.308(3)	1.342(3)

^aAverage values from 47 nondisordered, well-modeled, SXD determined molecules present in the CSD.²⁸ ^bRange of values found for the five forms described as being solely of salt character in refs 14 and 16.

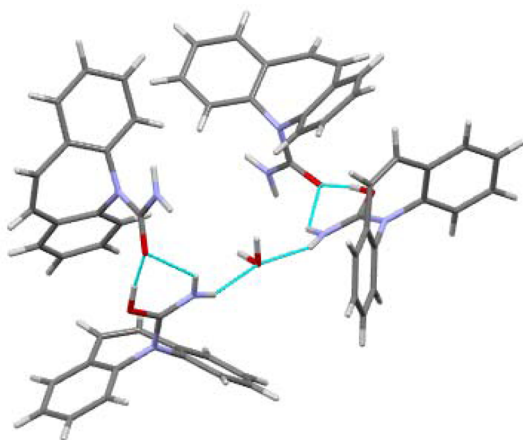


Figure 5. Two hydrogen bonded CBZ/CBZ(H) dimers connected through further hydrogen bonding to a shared water molecule to give a discrete tetrameric $(\text{CBZ}_2\cdot\text{CBZ(H)}_2\cdot\text{H}_2\text{O})$ unit.

$\text{O}\cdots\text{O}$ distance of 2.499(3) Å, the distinct $\text{C}=\text{O}$ and $\text{C}-\text{N}$ 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 $\text{N}-\text{H}$ to water hydrogen bonds to form discrete tetramers as shown in Figure 5. The geometry about the water molecule is completed by $\text{O}-\text{H}$ to BF_4 hydrogen bonds. The water molecule thus has a rather typical two donor, two acceptor nature.²⁹ 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 H_3O cations or, in the case of $[\text{CBZ(H)}][\text{Br}]\cdot\text{H}_2\text{O}$, a neutral water molecule that has a partial H_3O character due to proton dynamics.¹⁴ $\text{CBZ}\cdot[\text{CBZ(H)}][\text{BF}_4]\cdot 0.5\text{H}_2\text{O}$ is the first hydrated CBZ(H) species to feature no amide $\text{O}-\text{H}\cdots\text{water}$ interaction.

Reactions of CBZ with Sulfonic Acids. Four single crystal diffraction structures were obtained for $[\text{CBZ(H)}][\text{X}]$ 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, $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]\cdot 0.5\text{H}_2\text{O}$ was isolated from an entirely aqueous reaction mixture while 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 $[\text{CBZ(H)}][\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]\cdot\text{H}_2\text{O}$, 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 $\text{C}=\text{O}$ and $\text{C}-\text{N}$ 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 MeSO_3 salt¹⁶ and is equivalent to the R2,2(8) hydrogen bonded heterodimers commonly described for CBZ cocrystals with carboxylic acids,⁷ but with the obvious difference that here the acidic proton is placed on CBZ rather than on the acid coformer. In the benzenesulfonate, the $\text{N}-\text{H}$ moiety not used in dimer formation donates a hydrogen bond to the same sulfonate O atom that takes part in the $\text{O}-\text{H}\cdots\text{O}$ interaction. These interactions combine to give a one-dimensional hydrogen bonded chain that propagates parallel to the crystallographic c direction; see Figure 7. The

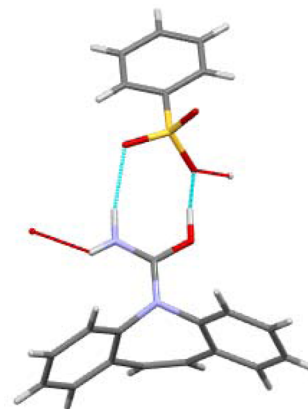


Figure 6. Heterodimer formed by hydrogen bonding between CBZ(H) cation and O_3SPh anion. See Figure 7 for the expanded polymeric motif.

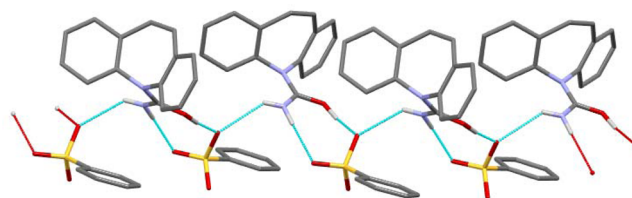


Figure 7. Cation/anion heterodimers as shown in Figure 6 connect through further $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds to give a one-dimensional polymer. Note that one O atom per sulfonate group is not involved in hydrogen bonding and this results in asymmetric chains with CBZ at one side and sulfonate anions on the other.

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.

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 $\text{O}-\text{H}$ hydrogen bond. This forms the three fragment R2,3(8) motif illustrated in Figure 9. The

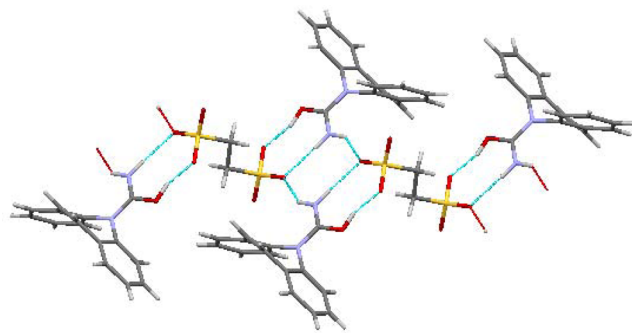


Figure 8. Hydrogen bonding in $[\text{CBZ(H)}]_2[\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3]$ illustrating the three fused hydrogen bonded rings and their connection through the two headed $\text{O}_3\text{SCH}_2\text{CH}_2\text{SO}_3$ anions.

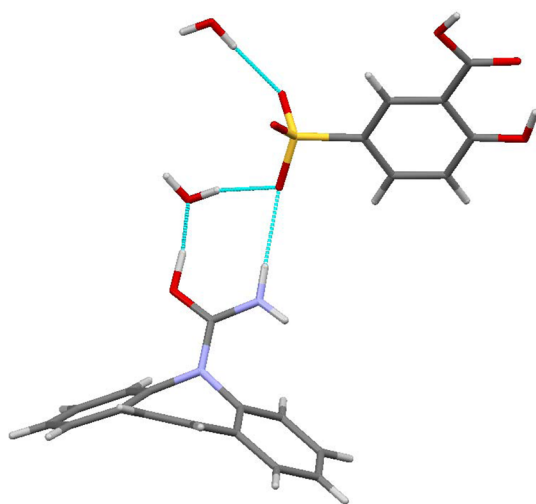


Figure 9. Cyclic hydrogen bonded motif in $[\text{CBZ}(\text{H})]\cdot[\text{O}_3\text{SC}_6\text{H}_3(\text{OH})(\text{COOH})]\cdot\text{H}_2\text{O}$ with a water molecule substituted into the R2,2(8) heterodimer pair seen in Figure 6.

similar motif involving both water and anion is formed by one of the two crystallographically independent CBZ(H) ions of $[\text{CBZ}(\text{H})][\text{O}_3\text{SC}_6\text{H}_4(\text{OH})]\cdot 0.5\text{H}_2\text{O}$ 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 nonaqueous 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 ($[\text{CBZ}(\text{H})][\text{X}]$, X = Cl or Br), hydrated salts ($[\text{CBZ}(\text{H})][\text{X}]\cdot n\text{H}_2\text{O}$, X = Cl, Br, $\text{O}_3\text{SC}_6\text{H}_4(\text{OH})$), mixed CBZ/CBZ(H) salts ($\text{CBZ}\cdot[\text{CBZ}(\text{H})]\cdot[\text{BF}_4]$), 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 13 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.^{14,16} 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) is 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).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b01223.

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 (PDF) Files for all new structures discussed (CIF)

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Notes

The authors declare no competing financial interest.

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