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Ionic Cocrystals of Pharmaceutical Compounds: Sodium Complexes of Carbamazepine

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Supporting Information

ABSTRACT: Three inorganic cocrystal (ICC) forms of carbamazepine (CBZ) have been synthesized, and their crystal structures are described. [Na(CBZ)$_2$](MeOH)$_2$][I$\cdot$H$_2$O $\cdot$[Na(CBZ)$_3$][I$_3$] and [Na(CBZ)$_4$]$_2$[C$_{11}$H$_{20}$N][IBr$_2$] are the first CBZ structures that contain metal cations, and the latter example also contains acridinium, which is a known metabolite of CBZ. All three Na complexes have distorted square pyramidal NaO$_4$ coordination geometries but different conformations of the four basal ligands and different hydrogen bonding interactions for the apical ligand. The hydrogen bonded synthons that have been identified for other species that contain neutral CBZ molecules are absent in all these Na containing ICC phases and are replaced by Na$\cdot$O$\cdot$CBZ dative bonds. However, previously identified nonpolar supramolecular constructs in the form of stacks and dimers are shared with other CBZ containing structures.

INTRODUCTION

Carbamazepine (CBZ) is the anticonvulsant drug used in the treatment of epilepsy that has become one of the best known model compounds used in solid state form identification and characterization studies. It is attractive because it is a molecularly simple active pharmaceutical ingredient (API) with a nonpolar backbone and a single polar amide functionality that is available for hydrogen bonding. Such studies have led to date to five polymorphic crystalline phases of CBZ being described, together with the structures of over 50 cocrystalline or solvate forms. Approximately half of the crystal coformers used with CBZ are neutral carboxylic acids with organic solvates making up the next biggest grouping.

Supramolecular structural similarities throughout these species have been described by Gelbrich and Hursthouse and further commented on by others. Although numerous, most of the known phases of CBZ are thus somewhat homogeneous with respect to general chemical type. Some alternative formulations have been attempted. For instance, although amide functionalities are traditionally thought of as being nonionizable under normal chemical conditions, salt forms of CBZ with protonation at the amide O atom have recently been reported.

Perumalla and Sun described a hydrochloride salt form, and Frampton and co-workers described the methanesulfonate salt form, and we have described a series of five CBZ(H)$\cdot$[X].nH$_2$O (X = Cl or Br, n = 0 or 1) salts. This latter work also described how exposing carbamazepine hydrochloride to atmospheric water led to the formation of a hydronium salt, [H$_2$O][Cl$\cdot$2CBZ$\cdot$H$_2$O. Although this can be described as a salt form, it contains neutral CBZ rather than protonated CBZ(H) and can thus perhaps be best thought of as a cocrystal of hydronium chloride and CBZ. Recently the term ionic cocrystal (ICC) has been popularized for such formulations to differentiate them from the more usual API cocrystal case where both the coformers are neutral organic molecules.

Structurally similar species with neutral organic molecules cocrystallized with cations and anions are of course well-known in metal coordination chemistry and elsewhere, where they are typically referred to as dipole (or solvent) separated ion pair complexes. Similar species are also known with ammonium ions replacing metal ions. The novelty of the ICC terminology lies in the context of typically pharmaceutically active organic species and the deliberate crystal engineering of their structures to replace organic with organic intermolecular interactions with ionic contacts. Despite the recent coining of the term, such API-based ICC species can be found in the historical literature, including a structural report on two forms of CBZ, namely [NH$_4$][X][CBZ] where X = Cl or Br. With ammonium and hydronium halide complexes of CBZ being known and with the well-known occurrence of donor separated ion pair species throughout main group metal coordination chemistry, we decided to investigate the possibility of forming ICC forms of CBZ with s-block metal salts. Described herein is the synthesis and characterization of three such species, [Na(CBZ)$_2$](MeOH)$\cdot$[I$\cdot$H$_2$O, [Na- (CBZ)$_3$][I$_3$], and [Na(CBZ)$_4$][C$_{11}$H$_{20}$N][IBr$_2$]$.  

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Table 1. Selected Crystallographic and Refinement Parameters for Na Complexes

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Synthesis of [Na(CBZ)][I]: A large excess (5.515 g, 36.8 mmol) of sodium iodide and 0.246 g (1.04 mmol) of carbamazepine were dissolved in 8 cm^3 of ethanol. The solution was heated in a water bath until both the carbamazepine and sodium iodide had dissolved. Once the solution had cooled to room temperature, 1 cm^3 of acetyl bromide was slowly added. A vigorous reaction was observed, and an inorganic solid precipitated. This was removed by filtration, and the solution was left in a narrow tube for approximately 1 month, after which time suitable crystals had formed. IR ν_max 3463, 3434, 3411, 2666, 3194, 1652, 1569, 1489, 1418, 1394, 808, 763 cm^-1. 

Synthesis of Carbamazepine Ammonium Bromide: Ammonium bromide (0.043 g, 0.44 mmol) and 0.209 g (0.88 mmol) of carbamazepine were dissolved in 4 cm^3 of methanol. The solution was heated in a water bath until both ammonium bromide and carbamazepine had dissolved. Once the solution had cooled to room temperature, 1 cm^3 of acetyl bromide was slowly added. A vigorous reaction was observed. The test tube was sealed with parafilm. Small holes were made in the parafilm to aid evaporation. After 23 days, crystals had formed and were collected for SXD analysis.

Synthesis of Acridinium I/X Species: [C_6H_4(CH_3)_2N_2][I][Cl] or Br. Potassium iodide (0.078 g, 0.47 mmol) and 0.221 g (0.94 mmol) of carbamazepine were dissolved in 8 cm^3 of methanol. The solution was heated in a water bath until both the potassium iodide and carbamazepine had dissolved. Once the solution had cooled to room temperature, 1 cm^3 of acetyl chloride was slowly added. A vigorous reaction was observed, and a solid formed, which was removed by filtration. After slow evaporation overnight, colorless crystals of carbamazepine hydrochloride form II were obtained. Leaving the solution for a further 3 days resulted in darkening of the solution and the deposition of red crystals. These have been characterized as [acridinium][I][Cl]. The same acridinium species was obtained when CsI was used in place of KI. Replacing MI with NH_3 resulted in a relatively low quality structure. Here all H atoms bound to nitrogen or oxygen were placed as found in diamond. Selected crystallographic and refinement parameters are given in Table 1 for the Na containing species and in the Supporting Information for the others.

FTIR measurements were made on crushed solid samples and with an A_2 Technologies ATR instrument.

Synthesis of [Na(CBZ)_2(MeOH)][I][H_2O], Method 1. A large excess (5.010 g, 33.4 mmol) of sodium iodide and 0.43 mmol) and 0.224 g (0.95 mmol) of carbamazepine were dissolved in 8 cm^3 of methanol. The solution had cooled to room temperature, 1 cm^3 of acetyl chloride was slowly added. A vigorous reaction was observed, and an inorganic solid precipitated. This was removed by filtration, and the solution was left in a narrow tube for approximately 1 month, after which time suitable crystals had formed. IR ν_max 3463, 3434, 3411, 2666, 3194, 1652, 1569, 1489, 1418, 1394, 808, 763 cm^-1.
The structures of two types of species that can be described as ICC complexes are known for CBZ, the ammonium containing isostructural species [NH$_4$][X][CBZ] where X = Cl or Br and the hydronium [H$_2$O][Cl]-2CBZ·2H$_2$O. Neither type contains a metal ion, so the initial goal of this work was to introduce a pharmaceutically acceptable metal cation such as Na$^+$. The known CBZ ICC species were not prepared by straightforward cocrystallization of the salt with CBZ. The ammonium species were prepared by Reck and Thiel in the presence of a surfactant, while the hydronium species originated from slow addition of atmospheric water to a reactive salt form of CBZ, namely, the oxygen protonated salt [CBZ(H)][Cl]. Initially, we attempted to form CBZ ICC complexes by simply cocrystallizing methanolic solutions of CBZ with aqueous solutions of a wide variety of simple s-block metal salts. None of these attempts were successful; nor was a similar attempt to prepare [NH$_4$][X][CBZ] in the absence of surfactant. It was thus decided to attempt an adaptation of the route that gave the hydronium species. This involved addition of acetyl halide to methanol solutions of the API to give in situ generation of nonaqueous HCl or HBr. In the absence of other ions, this is known to give protonated CBZ, which crystallizes as halide salts. However, herein the methanolic CBZ solutions also contained additional simple salts (usually iodides because these were found to be more soluble than other halides) initially in very high concentrations in an attempt to force the inclusion of ions in the final product. This approach allowed the isolation of two ICC forms of CBZ with Na. Single crystal diffraction showed these to be [Na(CBZ)$_2$(MeOH)][I]·H$_2$O and [Na(CBZ)$_2$][I$_2$], see Experimental Section for preparative details. Despite the great efforts previously expended on preparing novel forms of CBZ, there are no structural reports of CBZ species that contain metal ions in the CCDC. A similar approach utilizing acetyl bromide also allowed [NH$_4$][Br][CBZ] to be isolated and analyzed without the use of surfactant.

The structure of [Na(CBZ)$_2$(MeOH)][I]·H$_2$O has crystallographically imposed C$_2$ symmetry, and both [Na$_2$- (CBZ)$_2$(MeOH)][I]·H$_2$O and [Na(CBZ)$_2$][I$_2$] feature distorted square pyramidal Na$_2$O$_4$ cores ($\tau = 0.41$ and 0.28 for [Na(CBZ)$_2$(MeOH)][I]·H$_2$O and [Na(CBZ)$_2$][I$_2$], respectively, where $\tau = 0$ indicates ideal square pyramidal geometry and $\tau = 1$ corresponds to trigonal bipyramidal), see Figures 1 and 2. In both cases, the Na ion is raised slightly above the basal plane described by the four O donor atoms from the CBZ ligands (by 0.453(3) and 0.574(3) Å, respectively), with the apical coordination site being occupied by a disordered MeOH ligand in [Na(CBZ)$_2$(MeOH)][I]·H$_2$O and by a fifth CBZ ligand in [Na(CBZ)$_2$][I$_2$]. Na–O bond lengths in the more sterically crowded [Na(CBZ)$_2$][I$_2$] cation are somewhat elongated compared with those of the [Na(CBZ)$_2$(MeOH)] ion. The range of basal Na–O distances is thus 2.326(4) to 2.403(4) Å for [Na(CBZ)$_2$] and 2.317(3) to 2.366(3) Å for Na–(CBZ)$_2$(MeOH). In both species, the apical Na–O bond is the shortest, with this being a more significant difference for the coordinated MeOH (2.307(4) and 2.258(9) Å for [Na(CBZ)$_2$]) and [Na(CBZ)$_2$(MeOH)], respectively). All four CBZ ligands of the [Na(CBZ)$_2$(MeOH)] ion are orientated so that their azepine rings lie below the complex's basal plane, with one trans pair of ligands significantly more below the plane than the other mutually trans pair (compare 145.33(19)$^\circ$ and 170.0(2)$^\circ$ for O1–Na1–O1' and O2–Na1–O2' respectively, $' = 1 - x, y, 1$).

The four basal CBZ ligands of the [Na(CBZ)$_2$] ion adopt a different conformation, with three azepine rings below the basal plane and one (that containing N1) above the plane, see Figure 3. Despite this conformational difference, intramolecular hydrogen bonding between the four basal CBZ ligands is similar for the two complexes, Figures 1 and 2. In each complex, each of the amide NH$_2$ groups of the four basal CBZ ligands donates a single intramolecular hydrogen bond to the amide O atom acceptor of the neighboring basal CBZ ligand. The second H atom of these four NH$_2$ groups does not form a hydrogen bonding interaction. The apical CBZ ligand of the [Na(CBZ)$_2$] cation does not take part in any classical hydrogen bonds, but its NH$_2$ group is orientated toward the olefinic backbone of the unique azepine ring that lies above the basal plane (H to C=C centroid is 2.80 Å). In contrast, the apical MeOH ligand of [Na(CBZ)$_2$(MeOH)] simply donates a O...H bond to another MeOH ligand of another complex.

**Figure 1.** Molecular structure of [Na(CBZ)$_2$(MeOH)][I]·H$_2$O. Disorder in the solvent and all nonamide hydrogen atoms have been omitted for clarity. Here and elsewhere, hydrogen bonds are shown as light blue lines.

**Figure 2.** Molecular structure of the cation in [Na(CBZ)$_2$][I$_2$]. Nonamide hydrogen atoms have been omitted for clarity.

**RESULTS AND DISCUSSION**

Material was deposited after approximately 4 days. IR $\nu_{\max}$ 3421, 3315, 1601, 1567, 1487, 1455, 1435, 804, 797, 746, 726 cm$^{-1}$. 
Figure 3. Cation of [Na(CBZ)$_5$][I$_3$] drawn so as to emphasize the three down, one up conformation of the azepine rings of the four basal ligands. The ligand containing N9 is the fifth, apical ligand.

H⋯O hydrogen bond to the water solvate. Both MeOH and water positions are disordered about the crystallographic 2-fold rotation axis, and thus discussion of the geometric details of these groups is not warranted. This difference in hydrogen bonding between the two species may contribute to the different conformations of the basal Na(CBZ)$_3$ units. Examination of the bond lengths of the amide groups and comparison with literature compilations of equivalent data shows that all the CBZ ligands of these two Na complexes have C=O and C–N bond lengths that lie within the ranges normally seen for neutral CBZ species. This indicates that complexation to Na does not greatly alter the ligands of the other coordinated CBZ ligands. The C=O length of the apical ligand is somewhat shorter than the others (compare 1.223(7) with a range of 1.240(6)–1.251(6) Å) and both C–N distances of the apical ligand are somewhat longer than those of the other ligands (compare 1.370(8) and 1.378(7) Å for C–NH$_2$ and C–NR$_2$ with ranges of 1.335(7)–1.344(8) and 1.354(7)–1.369(7) Å).

Most of the cocystalization experiments attempted simply returned the starting materials or CBZ dihydrolyte or previously known hydrogen halide salts of CBZ as the sole products. The color of some experiments, especially those with low pH, was observed to darken with time. Similar darkening of samples with time was seen in solutions of protonated CBZ(H) salt forms. This was attributed to the decomposition of CBZ to acridine, and this is now confirmed by the isolation and crystal structure determination of two acridinium salt species, [CB$_2$H$_2$N][IX], X = Cl or Br. The structures are included in the Supporting Information as rare examples of crystallographically well ordered [IX]$_n$ species. Although the transformation from CBZ to acridine is rather unintuitive, a variety of experimental conditions have been reported to induce this decomposition. Indeed acridine is a known metabolite of CBZ.

On attempting to replace in situ generation of acid with a simple addition of aqueous HBr, a third Na ICC complex was obtained, [Na(CBZ)$_3$][C$_9$H$_7$N][IBr$_2$]. That this species contains both CBZ and acridinium makes it of enhanced interest, see Figure 4.

The [Na(CBZ)$_5$] cation in [Na(CBZ)$_5$][C$_9$H$_7$N][IBr$_2$] is similar to that in [Na(CBZ)$_5$][I$_3$] in that the NaO$_5$ core has a near square pyramidal geometry (τ = 0.11, Na1 raised 0.395 Å from the plane defined by the four basal O atoms). Another similarity is that one of the four basal CBZ ligands is again orientated with its azepine ring above the basal plane defined by the four O atoms and the other three azepine rings lie below this plane. However, one of these basal CBZ ligands is disordered such that a minor conformation is also present in the crystal, and this has two azepine rings above the basal plane and two below it. As with both the other Na complexes, the amide groups of the four basal CBZ ligands form intra-molecular N⋯H⋯O hydrogen bonds with their neighboring CBZ ligands. The NH$_2$ group of the fifth apical CBZ ligand behaves differently from that in [Na(CBZ)$_5$][I$_3$]. Rather than a weak interaction with the π-system of the azepine ring that is raised above the basal plane, here the amine group forms a classical N⋯H⋯O interaction with the O atom of the raised 297 ligand. Meanwhile, the O atom of the apical CBZ ligand is involved in a strong hydrogen bond with the formally positively charged N⋯H group of the acridinium cation. Thus, the two cations [Na(CBZ)$_5$] and [C$_9$H$_7$N] are bound tightly together. None of the anions in any of the three Na species described interact with polar groups of the cations. In all cases, only C⋯X (X = I or Br) interactions are observed. For [Na(CBZ)$_5$][I$_3$] none of these interactions are shorter than the sum of van der Waals distances while the other two species make four C⋯H⋯X interactions shorter than van der Waals distances. Inorganic coordination chemists would thus classify all three species as dipole separated ion pair complexes.

ICC forms are of generic interest because they present the possibility of generating API containing materials with different intermolecular bond types from those seen in organic systems, and this may allow the chemico-physical properties of APIs to be modified. Intermolecular interactions and packing in CBZ polymorphs and cocystalizations have been widely commented on in the literature. Two descriptive strands are often used. The first of these describes the various supramolecular synthons found in CBZ species, commonly such synthons are based on the hydrogen bonding modes of the amide group. The various structures of the CBZ polymorphs are based upon CBZ dimers. This dimeric arrangement is often contrasted with a theoretical chain structure predicted to be stable and similar to the motif found in related amides. In many cocystaline forms of CBZ, the dimeric motif is retained, commonly with the addition of N–H⋯A hydrogen bonds as shown in Figure 5.
alternative arrangement is found in phases where the coformer is a carboxylic acid. Here the commonly found motif is a heterodimer with an amide to COOH contact. A second strand of CBZ structural analysis has looked not just at intermolecular bonding interactions but at supramolecular constructs, that is at any packing motif that is repeated in different CBZ phases no matter what the bonding nature of the interaction might be. This approach identified two dimeric constructs and two stacking constructs that appear in multiple CBZ structures (including the hydrogen bonded dimer discussed above). Ammonium halide based ICC forms of CBZ have been known for some time. These are the isostructural species \([\text{NH}_4][X]\)[CBZ] where X = Cl and Br. Because the available database structures (VUBCAW and VUBCEA) do not contain information on H atom positions, we have redetermined the structure of \([\text{NH}_4][\text{Br}][\text{CBZ}]\) at low temperature. This confirms that \([\text{NH}_4][\text{Br}][\text{CBZ}]\) has a CBZ hydrogen bonded dimer motif with further hydrogen bonds from the dimer to both cations and anions, see Figure 6. This is a simple variation on the hydrogen bonding structure common to many organic cocrystals of CBZ. The hydronium, \([\text{H}_3\text{O}][\text{Cl}]:2\text{CBZ}:\text{H}_2\text{O}\), also retains the hydrogen bonded CBZ dimer although CBZ salt forms with O atom protonated amide groups do not. Furthermore, the \([\text{NH}_4][X][\text{CBZ}]\) species were included in Gelbrich and Hursthouse’s initial work on supramolecular constructs in CBZ. In this analysis, both have entirely unexceptional packing features with structures that contain the common “translational stack” motif as well as the hydrogen bonded dimer (supramolecular constructs A and C in ref 11). Thus, despite containing charged ions, the ICC structures of \([\text{NH}_4][X][\text{CBZ}]\) are not obviously different from the structures of nonionic CBZ cocrystals. However, the three Na containing ICC forms of CBZ described herein do have significant structural differences from the CBZ cocrystals previously described. The hydrogen bonded CBZ dimer is now absent. Complexation to the Na center requires the CBZ ligands to point inward to the common center and constrains the homoleptic CBZ NH...O interactions such that they connect only to CBZ ligands bound to the shared Na center. Note that although the observed structures do not contain CBZ dimers, such an arrangement is entirely possible. The structures of ammonium and alkali metal salts of the same anions are often isostructural; thus a situation where the “Na” species adopt structures akin to that of \([\text{NH}_4][\text{Br}][\text{CBZ}]\) is conceivable. Although the three Na complexes do not adopt the same hydrogen bonded supramolecular synthons as other CBZ species, they do adopt the nonpolar (or shape-based) supramolecular constructs previously identified. Both translational stacks and dimeric examples can be identified, as illustrated in Figures 7 and 8.
CONCLUSION

The first structures of metal containing forms of CBZ have been synthesized and crystallographically characterized. These three Na complexes can be described as ionic cocrysalts. Synthesis at low pH was found to be advantageous. Unlike the previously described ammonium halide and hydronium chloride ICC forms of CBZ, these new structures do not show the same intermolecular bonding motifs as other neutral-CBZ containing phases. Instead, native bonds between Na and the C atom of CBZ predominate and, because the halide based anions make only relatively weak contacts with the cations, give dipole separated ion pairs. CBZ to CBZ hydrogen bonding interactions exist solely within the ligand sets of single Na(CBZ)$_2$OHMe) or Na(CBZ)$_3$ cations. Despite the dramatic change in intermolecular bond type and geometry, the three Na containing CBZ ICC phases still present the previously identified nonpolar CBZ supramolecular constructs, showing that at least these shape-based packing motifs are more robust than the polar hydrogen bonded synths. The change in intermolecular bonding and the high ratio of CBZ to coformer make these ICC forms interesting materials for the study of API form selection.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic information for [NH$_4$][Br][CBZ] and the acridinium salts with I$_2$Br and I$_2$Cl and crystallographic information files (CIF) for all six structures. This material is available free of charge via the Internet at http://pubs.acs.org.

Crystallographic information files are also available from the Cambridge Crystallographic Data Center (CCDC) upon request (http://www.ccdc.cam.ac.uk, CCDC deposition numbers 1023495 to 1023500).

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Notes

The authors declare no competing financial interest.

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REFERENCES

(10) Fabbiani, F. P. A.; Byrne, L. T.; McKinnon, J. J.; Spackman, M. A. CrystEngComm 2007, 9, 728.