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)][I]·H₂O, [Na(CBZ)₃][I]₃, and [Na(CBZ)₄][C₁₃H₁₀N][IBr₂]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 NaO₅ 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–O 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,¹–³ together with the structures of over 50 cocrystalline or solvate forms. Approximately half of the crystal coformers used with CBZ are neutral carboxylic acids⁴–⁷ with organic solvates making up the next biggest grouping.⁷ Supramolecular structural similarities throughout these species have been described by Gelbrich and Hursthouse and further commented on by others.⁴,¹¹ 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,¹² salt forms of CBZ with protonation at the amide O atom have recently been reported. Perumalla and Sun described a hydrochloride salt form,¹³ Frampton and co-workers described the methanesulfonate salt form,¹⁴ and we have described a series of [CBZ(H)]ₓ[X]·nH₂O (X = Cl or Br, n = 0 or 1) salts.¹⁵ This latter work also described how exposing carbamazepine hydrochloride to atmospheric water led to the formation of a hydronium salt, [H₂O][Cl]·2CBZ·2H₂O. 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.¹⁶,¹⁷ 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.¹⁸–²² Similar species are also known with ammonium ions replacing metal ions.²³–²⁵ The novelty of the ICC terminology lies in the context of typically pharmacologically active organic species and the deliberate crystal engineering of their structures to replace organic dative bonds. However, previously identified nonpolar supramolecular constructs in the form of stacks and dimers are shared with other CBZ containing structures.

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Table 1. Selected Crystallographic and Refinement Parameters for Na Complexes

<table>
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<th>compound</th>
<th>formula</th>
<th>formula wt</th>
<th>cryst syst</th>
<th>space group</th>
<th>$\lambda$, Å</th>
<th>$a$, Å</th>
<th>$b$, Å</th>
<th>$c$, Å</th>
<th>$\alpha$, deg</th>
<th>$\beta$, deg</th>
<th>$\gamma$, deg</th>
<th>vol, Å³</th>
<th>$Z$</th>
<th>reflns collected</th>
<th>$R_{\text{fl}}$, $0.750$</th>
<th>$R_{\text{fl}}$, $1.000$</th>
<th>$R_{\text{fl}}$, $1.500$</th>
<th>$R_{\text{fl}}$, $2.000$</th>
<th>$R_{\text{fl}}$, $3.000$</th>
<th>$\rho_{\text{calc}}$, e Å⁻³</th>
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<tr>
<td>[Na(CBZ)₄(MeOH)][I]·H₂O</td>
<td>Na₆H₂₀I₄N₈NaO₆</td>
<td>1145.01</td>
<td>monoclinic</td>
<td>C₁</td>
<td>1.5418</td>
<td>27.3789(19)</td>
<td>6.8157(2)</td>
<td>20.8598(14)</td>
<td>90</td>
<td>91.626 (12)</td>
<td>90</td>
<td>2770.4(3)</td>
<td>2</td>
<td>5761</td>
<td>0.0267</td>
<td>0.0364</td>
<td>0.0957</td>
<td>1.581/−0.685</td>
<td>0.646/−0.750</td>
<td>1.351/−1.168</td>
</tr>
<tr>
<td>[Na(CBZ)₅]·[I₃]</td>
<td>Na₈H₆I₅O₅</td>
<td>1585.02</td>
<td>monoclinic</td>
<td>$P_2_1/n$</td>
<td>16.1230(6)</td>
<td>11.2270(4)</td>
<td>36.8726(16)</td>
<td>90</td>
<td>91.165 (3)</td>
<td>90</td>
<td>6673.0(4)</td>
<td>153(2)</td>
<td>2</td>
<td>32950</td>
<td>0.0732</td>
<td>0.0612</td>
<td>0.1019</td>
<td>2.8299</td>
<td>1.4166</td>
<td>0.8047</td>
</tr>
<tr>
<td>[Na(CBZ)₅]·[C₈H₇Br₂]</td>
<td>Na₈H₇Br₄I₄N₈NaO₆</td>
<td>1957.98</td>
<td>triclinic</td>
<td>$P$</td>
<td>0.71073</td>
<td>10.2171(5)</td>
<td>14.4369(6)</td>
<td>27.5476(12)</td>
<td>91.841 (3)</td>
<td>90.972 (4)</td>
<td>4032.7(3)</td>
<td>123(20)</td>
<td>2</td>
<td>54.0</td>
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<td>1.075</td>
<td>2.027</td>
<td>50.0</td>
<td>8248</td>
<td>0.8847</td>
</tr>
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</table>

**EXPERIMENTAL SECTION**

Single crystal X-ray diffraction (SXD) measurements on the acridine $I$Br salt were carried out by the National Crystallography Service. All other crystallographic measurements were performed locally using Oxford Diffraction instruments. Structural solution and refinement were against $F^2$ to convergence were performed using programs from the SHELX suite. 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 diatomic syntheses and refined isotropically but with N−H bond length restraints for CBZ containing species. For the structure of [Na(CBZ)₅]·[C₈H₇Br₂]·poor crystal quality and a disordered CBZ ligand resulted in a relatively low quality structure. Here all H atoms were generated in idealized positions and allowed to ride on their parent atoms. Selected crystallographic and refinement parameters are given in Table 1 for the Na containing species and in the Supporting Information for the others.

Synthesis of [Na(CBZ)₅]·[I₃]. 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 cm³ of methanol. 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 cm³ 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 $\nu$ 3463, 3434, 3411, 3266, 3194, 1652, 1569, 1489, 1418, 1394, 808, 763 cm⁻¹.

Synthesis of [Na(CBZ)₄(MeOH)][I]·H₂O, Method 1. A large excess (5.010 g, 33.4 mmol) of sodium iodide and 0.216 g (0.91 mmol) of carbamazepine were dissolved in 8 cm³ of methanol. 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 cm³ of acetyl chloride was slowly added. A vigorous reaction was observed, and NaI precipitated. This was removed by filtration, and the filtrate was poured into a narrow tube and sealed with paraffin. Small holes were made in the paraffin to aid evaporation. Suitable crystals grew after approximately 7 days. IR $\nu$ 3458, 3323, 3266, 3197, 1652, 1575, 1490, 1418, 806, 764 cm⁻¹.

Synthesis of [Na(CBZ)₄(MeOH)][I]·H₂O, Method 2. A large excess (5.306 g, 35.4 mmol) of sodium iodide and 0.264 g (1.12 mmol) of carbamazepine were dissolved in 8 cm³ of methanol. The solution was heated in a water bath until both the carbamazepine and sodium iodide had dissolved. The test tube was sealed with paraffin and left to cool to room temperature. Small holes were made in the paraffin to aid evaporation. Suitable crystals grew after approximately 2 days. SXD and IR spectroscopy showed these to be identical to the product isolated by method 1.

Synthesis of [Na(CBZ)₅]·[C₈H₇Br₂]·I. Sodium iodide (0.071 g, 0.43 mmol) and 0.221 g (0.94 mmol) of carbamazepine were dissolved in 4 cm³ 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 cm³ of acetyl bromide was slowly added. A vigorous reaction was observed. The test tube was sealed with paraffin. Small holes were made in the paraffin to aid evaporation. After 23 days, crystals had formed and were collected for SXD analysis.
RESULTS AND DISCUSSION

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]$\cdot$2CBZ$\cdot$2H$_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)$_5$](MeOH)[$\cdot$I]. H$_2$O and [Na(CBZ)$_5$][$\cdot$I], 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)$_5$(MeOH)]($\cdot$I)$\cdot$H$_2$O has crystallographically imposed $C_2$ symmetry, and both [Na(CBZ)$_5$(MeOH)]($\cdot$I)$\cdot$H$_2$O and [Na(CBZ)$_5$][$\cdot$I] feature distorted square pyramidal Na$_2$O cores ($\tau = 0.41$ and 0.28 for [Na(CBZ)$_5$(MeOH)]($\cdot$I)$\cdot$H$_2$O and [Na(CBZ)$_5$][$\cdot$I], 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$_2$O 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)$_5$(MeOH)]($\cdot$I)$\cdot$H$_2$O and by a fifth CBZ ligand in [Na(CBZ)$_5$][$\cdot$I]. Na$\rightarrow$O bond lengths in the more sterically crowded [Na(CBZ)$_5$] cation are somewhat elongated compared with those of the [Na(CBZ)$_5$(MeOH)] ion. The range of basal Na$\rightarrow$O distances is thus 2.326(4) to 2.403(4) Å for [Na(CBZ)$_5$] and 2.317(3) to 2.366(3) Å for [Na(CBZ)$_5$(MeOH)]. In both species, the apical Na$\rightarrow$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)$_5$] and [Na(CBZ)$_5$(MeOH)], respectively). All four CBZ ligands of the [Na(CBZ)$_5$(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 O$\rightarrow$Na$\rightarrow$O and O$\rightarrow$Na$\rightarrow$O$, \; ') = 1 - x, y, 1 - z).

The four basal CBZ ligands of the [Na(CBZ)$_5$] ion adopt a different conformation, with three azepine rings below the basal plane and one (that containing N1) above the plane, see Figure 2. 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)$_5$] cation does not take part in any classical hydrogen bonds, but its NH$_2$ group is oriented toward the olefin 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)$_5$(MeOH)] simply donates a O$\rightarrow$N$^\cdot$C$^\cdot$C bond.
enhanced interest, see Figure 4. This dimeric arrangement is often contrasted with a theoretical
framework of the CBZ polymorphs, commonly such synthons are based on
intermolecular bond types from those seen in organic systems,16,17 the possibility of generating API containing materials with di-
verse applications. However, one of these basal CBZ ligands is disordered such that a minor conformation is also present in the crystals, and this has two azepine rings above the basal plane and two below it. With both the other Na complexes, the remaining ligands of the four basal CBZ ligands form intra-
molecular N–H⋯O hydrogen bonds with their neighboring CBZ ligands. The NH3 group of the fifth apical CBZ ligand behaves differently from that in [Na(CBZ)5][I3]. 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 97 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 [C13H10N] 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–N–X (X = Cl or Br) interactions are observed. For [Na(CBZ)5][I3] none of these interactions are shorter than the sum of van der Waals distances while the other two species each make four C–H⋯X interactions shorter than van der Waals distances. Inorganic coordination chemists would thus classify all three species as dipoole separated ion pair complexes.18–22

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 chemophysical properties of APIs to be modified.16,17 Intermolecular interactions and packing in CBZ polymorphs and cocrystals 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.21 This dimeric arrangement is often contrasted with a theoretical chain structure predicted to be stable and similar to the motif found in related amides.28–41 In many cocrystalline forms of CBZ, the dimeric motif is retained, commonly with the addition of N–H⋯A hydrogen bonds as shown in Figure 5. An enhanced interest 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. With both the other Na complexes, the remaining ligands of the four basal CBZ ligands form intra-molecular N–H⋯O hydrogen bonds with their neighboring CBZ ligands. The NH3 group of the fifth apical CBZ ligand behaves differently from that in [Na(CBZ)5][I3]. 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 97 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 [C13H10N] 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–N–X (X = Cl or Br) interactions are observed. For [Na(CBZ)5][I3] none of these interactions are shorter than the sum of van der Waals distances while the other two species each 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.18–22

Figure 3. Cation of [Na(CBZ)5][I3] 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.

Figure 4. Hydrogen bonded [Na(CBZ)5] and acridinium cation pair found in the structure of [Na(CBZ)5][C13H10N][IBr2]2. H atoms bound to C are omitted for clarity.
alternative arrangement is found in phases where the coformer
is a carboxylic acid. Here the commonly found motif is a
deretermer with an amide to COOH contact.8,9 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).11
Ammonium halide based ICC forms of CBZ have been
known for some time. These are the isostructural species
[NH₄][X][CBZ] where X = Cl and Br.26 Because the available
database structures (VUBCAW and VUBCEA) do not contai
information on H atom positions, we have redetermined the
structure of [NH₄][Br][CBZ] at low temperature. This
confirms that [NH₄][Br][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, [H₃O][Cl]·2CBZ·2H₂O, also
retains the hydrogen bonded CBZ dimer although CBZ salt forms with O atom protonated amide groups do not.15
Furthermore, the [NH₄][X][CBZ] species were included in
Gelbrich and Hursthouse’s initial work on supramolecular
constructs in CBZ.11 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).11
Thus, despite containing charged ions, the ICC structures of
[NH₄][X][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.16
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;42–45 thus a situation where the “Na”10
species adopt structures akin to that of [NH₄][Br][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.11 Both trans-
lational stacks and dimeric examples can be identified, as
illustrated in Figures 7 and 8.

Figure 5. Representation of the CBZ hydrogen bonded dimer motif. When present, S is a hydrogen bond acceptor in the form of a solvent molecule or a cocrystal conformer.

Figure 6. Part of the hydrogen bonding motif found in the structure of [NH₄][Br][CBZ]. Bromide ions drawn as brown spheres.

Figure 7. Translational stack of CBZ molecules found in the structure of [Na(CBZ)₆(MeOH)]·[I]·H₂O. This is supramolecular construct A in ref 11. In this case, the translation is along the crystallographic b axis and hence along the Na–O(MeOH) molecular axis.

Figure 8. Close packed dimer of CBZ molecules found in the structure of [Na(CBZ)]·[I]₃. This is supramolecular construct B in ref 11. Similar interactions can be found in the structure of [Na(CBZ)]₆·
[C₆H₆N][IBr₂].
The first structures of metal containing forms of CBZ have been synthesized and crystallographically characterized. These three Na complexes can be described as ionic cocrystals. The authors thank the National Crystallography Service at the University of Southampton for data collection on the I\(_2\)Br salt of acridinium. The change in intermolecular hydrogen bonding and the high ratio of CBZ to coformer make these ICC forms interesting for the study of API form selection.

### 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 cocrystals. The authors thank the National Crystallography Service at the University of Southampton for data collection on the I\(_2\)Br salt of acridinium.

### ACKNOWLEDGMENTS

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### REFERENCES