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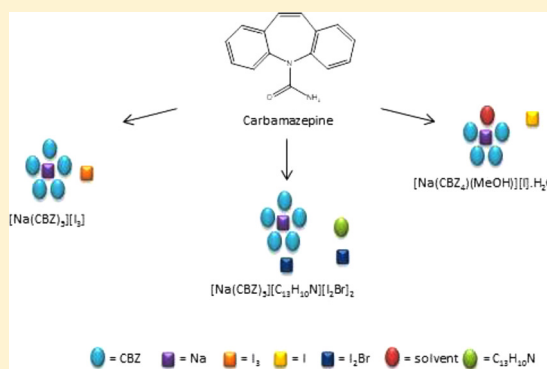
1 Ionic Cocrystals of Pharmaceutical Compounds: Sodium Complexes 2 of Carbamazepine

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6 **S** Supporting Information

7 **ABSTRACT:** Three inorganic cocrystal (ICC) forms of carbamazepine
8 (CBZ) have been synthesized, and their crystal structures are described.
9 $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$, $[\text{Na}(\text{CBZ})_5][\text{I}_3]$, and $[\text{Na}(\text{CBZ})_5]$ -
10 $[\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]$ are the first CBZ structures that contain metal
11 cations, and the latter example also contains acridinium, which is a
12 known metabolite of CBZ. All three Na complexes have distorted square
13 pyramidal NaO_5 coordination geometries but different conformations of
14 the four basal ligands and different hydrogen bonding interactions for
15 the apical ligand. The hydrogen bonded synthons that have been
16 identified for other species that contain neutral CBZ molecules are
17 absent in all these Na containing ICC phases and are replaced by Na–O
18 dative bonds. However, previously identified nonpolar supramolecular
19 constructs in the form of stacks and dimers are shared with other CBZ
20 containing structures.



21 ■ INTRODUCTION

22 Carbamazepine (CBZ) is the anticonvulsant drug used in the
23 treatment of epilepsy that has become one of the best known
24 model compounds used in solid state form identification and
25 characterization studies. It is attractive because it is a
26 molecularly simple active pharmaceutical ingredient (API)
27 with a nonpolar backbone and a single polar amide
28 functionality that is available for hydrogen bonding. Such
29 studies have led to date to five polymorphic crystalline phases
30 of CBZ being described,^{1–3} together with the structures of over
31 50 cocrystalline or solvate forms. Approximately half of the
32 crystal cofomers used with CBZ are neutral carboxylic acids^{4–7}
33 with organic solvates making up the next biggest grouping.^{7–10}
34 Supramolecular structural similarities throughout these species
35 have been described by Gelbrich and Hursthouse and further
36 commented on by others.^{4,11} Although numerous, most of the
37 known phases of CBZ are thus somewhat homogeneous with
38 respect to general chemical type. Some alternative formulations
39 have been attempted. For instance, although amide function-
40 alities are traditionally thought of as being nonionizable under
41 normal chemical conditions,¹² salt forms of CBZ with
42 protonation at the amide O atom have recently been reported.
43 Perumalla and Sun described a hydrochloride salt form,¹³
44 Frampton and co-workers described the methanesulfonate salt
45 form,¹⁴ and we have described a series of five $[\text{CBZ}(\text{H})][\text{X}]\cdot$
46 $n\text{H}_2\text{O}$ ($\text{X} = \text{Cl}$ or Br , $n = 0$ or 1) salts.¹⁵ This latter work also
47 described how exposing carbamazepine hydrochloride to
48 atmospheric water led to the formation of a hydronium salt,
49 $[\text{H}_3\text{O}][\text{Cl}]\cdot 2\text{CBZ}\cdot 2\text{H}_2\text{O}$. Although this can be described as a
50 salt form, it contains neutral CBZ rather than protonated

51 CBZ(H) and can thus perhaps be best thought of as a cocrystal
52 of hydronium chloride and CBZ. Recently the term ionic
53 cocrystal (ICC) has been popularized for such formulations to
54 differentiate them from the more usual API cocrystal case
55 where both the cofomers are neutral organic molecules.^{16,17}
56 Structurally similar species with neutral organic molecules
57 cocrystallized with cations and anions are of course well-known
58 in metal coordination chemistry and elsewhere, where they are
59 typically referred to as dipole (or solvent) separated ion pair
60 complexes.^{18–22} Similar species are also known with
61 ammonium ions replacing metal ions.^{23–25} The novelty of
62 the ICC terminology lies in the context of typically
63 pharmaceutically active organic species and the deliberate
64 crystal engineering of their structures to replace organic to
65 organic intermolecular interactions with ionic contacts. Despite
66 the recent coining of the term, such API-based ICC species can
67 be found in the historical literature, including a structural report
68 on two forms of CBZ, namely $[\text{NH}_4][\text{X}][\text{CBZ}]$ where $\text{X} = \text{Cl}$
69 or Br .²⁶ With ammonium and hydronium halide complexes of
70 CBZ being known and with the well-known occurrence of
71 donor separated ion pair species throughout main group metal
72 coordination chemistry, we decided to investigate the
73 possibility of forming ICC forms of CBZ with s-block metal
74 salts. Described herein is the synthesis and characterization of
75 three such species, $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$, $[\text{Na}(\text{CBZ})_5][\text{I}_3]$,
76 and $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]$.

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Table 1. Selected Crystallographic and Refinement Parameters for Na Complexes

compound	[Na(CBZ) ₄ (MeOH)][I]·H ₂ O	[Na(CBZ) ₅][I ₃]	[Na(CBZ) ₅][C ₁₃ H ₁₀ N] [IBr ₂] ₂
formula	C ₆₁ H ₅₄ IN ₈ NaO ₆	C ₇₅ H ₆₀ I ₃ N ₁₀ NaO ₅	C ₈₈ H ₇₀ Br ₄ I ₂ N ₁₁ NaO ₅
formula wt	1145.01	1585.02	1957.98
cryst syst	monoclinic	monoclinic	triclinic
space group	C ₂	P ₂ ₁ /n	P $\bar{1}$
λ , Å	1.5418	0.71073	0.71073
<i>a</i> , Å	27.3789(19)	16.1230(6)	10.2171(5)
<i>b</i> , Å	6.8157(2)	11.2270(4)	14.4369(6)
<i>c</i> , Å	20.8598(14)	36.8726(16)	27.5476(12)
α , deg	90	90	91.841(3)
β , deg	134.626 (12)	91.165(3)	96.689(4)
γ , deg	90	90	90.972(4)
vol, Å ³	2770.4(3)	6673.0(4)	4032.7(3)
temp, K	123(2)	153(2)	123(20)
Z	2	4	2
reflns collected	5761	32950	28299
2 θ max, deg	146.1	54.0	50.0
reflns unique	4078	13309	14166
reflns obsd	4037	7205	8248
R _{int}	0.0267	0.0732	0.0708
GOF	1.078	1.029	1.075
R[<i>I</i> > 2 σ (<i>I</i>)], <i>F</i>	0.0364	0.0612	0.0847
R _w , <i>F</i> ²	0.0957	0.1019	0.2027
max/min electron density, e Å ⁻³	1.581/−0.685	0.646/−0.750	1.351/−1.168

77 ■ EXPERIMENTAL SECTION

78 Single crystal X-ray diffraction (SXD) measurements on the acridine
79 I₂Br salt were carried out by the National Crystallography Service.²⁷
80 All other crystallographic measurements were performed locally using
81 Oxford Diffraction instruments. Structural solution and refinement
82 against *F*² to convergence were performed using programs from the
83 SHELX suite.²⁸ Hydrogen atoms bound to carbon were placed in
84 idealized positions and refined in riding modes. Where possible, H
85 atoms bound to nitrogen or oxygen were placed as found in difference
86 Fourier syntheses and refined isotropically but with N–H bond length
87 restraints for CBZ containing species. For the structure of [Na-
88 (CBZ)₅][C₁₃H₁₀N][IBr₂]₂, poor crystal quality and a disordered CBZ
89 ligand resulted in a relatively low quality structure. Here all H atoms
90 were generated in idealized positions and allowed to ride on their
91 parent atoms. Selected crystallographic and refinement parameters are
92 given in Table 1 for the Na containing species and in the Supporting
93 Information for the others.

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

96 **Synthesis of [Na(CBZ)₄(MeOH)][I]·H₂O, Method 1.** A large
97 excess (5.010 g, 33.4 mmol) of sodium iodide and 0.216 g (0.91
98 mmol) of carbamazepine were dissolved in 8 cm³ of methanol. The
99 solution was heated in a water bath until the carbamazepine and
100 sodium iodide had dissolved. Once the solution had cooled to room
101 temperature, 1 cm³ of acetyl chloride was slowly added. A vigorous
102 reaction was observed, and NaI precipitated. This was removed by
103 filtration, and the filtrate was poured into a narrow tube and sealed
104 with parafilm. Small holes were made in the parafilm to aid
105 evaporation. Suitable crystals grew after approximately 7 days. IR
106 ν_{\max} 3458, 3323, 3266, 3197, 1652, 1575, 1490, 1418, 806, 764 cm⁻¹.

107 **Synthesis of [Na(CBZ)₄(MeOH)][I]·H₂O, Method 2.** A large
108 excess (5.306 g, 35.4 mmol) of sodium iodide and 0.264 g (1.12
109 mmol) of carbamazepine were dissolved in 8 cm³ of methanol. The
110 solution was heated in a water bath until both the carbamazepine and
111 sodium iodide had dissolved. The test tube was sealed with parafilm
112 and left to cool to room temperature. Small holes were made in the
113 parafilm to aid evaporation. Suitable crystals grew after approximately
114 2 days. SXD and IR spectroscopy showed these to be identical to the
115 product isolated by method 1.

Synthesis of [Na(CBZ)₅][I₃]. A large excess (5.515 g, 36.8 mmol) 116
of sodium iodide and 0.246 g (1.04 mmol) of carbamazepine were 117
dissolved in 8 cm³ of ethanol. The solution was heated in a water bath 118
until both the carbamazepine and sodium iodide had dissolved. Once 119
the solution had cooled to room temperature, 1 cm³ of acetyl bromide 120
was slowly added. A vigorous reaction was observed, and an inorganic 121
solid precipitated. This was removed by filtration, and the solution was 122
left in a narrow tube for approximately 1 month, after which time 123
suitable crystals had formed. IR ν_{\max} 3463, 3434, 3411, 3266, 3194, 124
1652, 1569, 1489, 1418, 1394, 808, 763 cm⁻¹. 125

Synthesis of Carbamazepine Ammonium Bromide. Ammo- 126
nium bromide (0.043 g, 0.44 mmol) and 0.209 g (0.88 mmol) of 127
carbamazepine were dissolved in 4 cm³ of methanol. The solution was 128
heated in a water bath until both ammonium bromide and 129
carbamazepine had dissolved. Once the solution had cooled to room 130
temperature, 1 cm³ of acetyl bromide was slowly added. A vigorous 131
reaction was observed. The test tube was sealed with parafilm. Small 132
holes were made in the parafilm to aid evaporation. After 23 days, 133
crystals had formed and were collected for SXD analysis. 134

**Synthesis of Acridinium I₂X Species, [C₁₃H₁₀N][I₂X], X = Cl or 135
Br.** Potassium iodide (0.078 g, 0.47 mmol) and 0.221 g (0.94 mmol) 136
of carbamazepine were dissolved in 8 cm³ of methanol. The solution 137
was heated in a water bath until both the potassium iodide and 138
carbamazepine had dissolved. Once the solution had cooled to room 139
temperature, 1 cm³ of acetyl chloride was slowly added. A vigorous 140
reaction was observed, and a solid formed, which was removed by 141
filtration. After slow evaporation overnight, colorless crystals of 142
carbamazepine hydrochloride form II were obtained.¹⁵ Leaving the 143
solution for a further 3 days resulted in darkening of the solution and 144
the deposition of red crystals. These have been characterized as 145
[acridinium][I₂Cl]. The same acridinium species was obtained when 146
CsI was used in place of KI. Replacing MI with NH₄I and using acetyl 147
bromide rather than acetyl chloride gave dark blue crystals of 148
[acridinium][I₂Br]. 149

Synthesis of [Na(CBZ)₅][C₁₃H₁₀N] [IBr₂]₂. Sodium iodide (0.071 150
g, 0.43 mmol) and 0.224 g (0.95 mmol) of carbamazepine were 151
dissolved in 4 cm³ of methanol. The solution was heated in a water 152
bath until both sodium iodide and carbamazepine had dissolved. Once 153
the solution had cooled to room temperature, 1 cm³ of hydrobromic 154
acid was added. The test tube was sealed with parafilm. Small holes 155
were made in the parafilm to aid evaporation. Yellow crystalline 156

157 material was deposited after approximately 4 days. IR ν_{\max} 3421, 3315,
158 1601, 1567, 1487, 1455, 1435, 804, 769, 746, 726 cm^{-1} .

159 ■ RESULTS AND DISCUSSION

160 The structures of two types of species that can be described as
161 ICC complexes are known for CBZ, the ammonium containing
162 isostructural species $[\text{NH}_4][\text{X}][\text{CBZ}]$ where X = Cl or Br and
163 the hydronium $[\text{H}_3\text{O}][\text{Cl}]\cdot 2\text{CBZ}\cdot 2\text{H}_2\text{O}$.^{15,26} Neither type
164 contains a metal ion, so the initial goal of this work was to
165 introduce a pharmaceutically acceptable metal cation such as
166 Na^+ . The known CBZ ICC species were not prepared by
167 straightforward cocrystallization of the salt with CBZ. The
168 ammonium species were prepared by Reck and Thiel in the
169 presence of a surfactant,²⁶ while the hydronium species
170 originated from slow addition of atmospheric water to a
171 reactive salt form of CBZ, namely, the oxygen protonated salt
172 $[\text{CBZ}(\text{H})][\text{Cl}]$.¹⁵ Initially, we attempted to form CBZ ICC
173 complexes by simply cocrystallizing methanolic solutions of
174 CBZ with aqueous solutions of a wide variety of simple s-block
175 metal salts. None of these attempts were successful; nor was a
176 similar attempt to prepare $[\text{NH}_4][\text{X}][\text{CBZ}]$ in the absence of
177 surfactant. It was thus decided to attempt an adaptation of the
178 route that gave the hydronium species. This involved addition
179 of acetyl halide to methanol solutions of the API to give *in situ*
180 generation of nonaqueous HCl or HBr. In the absence of other
181 ions, this is known to give protonated CBZ, which crystallizes
182 as halide salts.^{13,15} However, herein the methanolic CBZ
183 solutions also contained additional simple salts (usually iodides
184 because these were found to be more soluble than other
185 halides) initially in very high concentrations in an attempt to
186 force the inclusion of ions in the final product. This approach
187 allowed the isolation of two ICC forms of CBZ with Na. Single
188 crystal diffraction showed these to be $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot$
189 H_2O and $[\text{Na}(\text{CBZ})_5][\text{I}_3]$, see Experimental Section for
190 preparative details. Despite the great efforts previously
191 expended on preparing novel forms of CBZ, there are no
192 structural reports of CBZ species that contain metal ions in the
193 CCDC.²⁹ A similar approach utilizing acetyl bromide also
194 allowed $[\text{NH}_4][\text{Br}][\text{CBZ}]$ to be isolated and analyzed without
195 the use of surfactant.

196 The structure of $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$ has crystallo-
197 graphically imposed C_2 symmetry, and both $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$
198 and $[\text{Na}(\text{CBZ})_5][\text{I}_3]$ feature dis-
199 torted square pyramidal NaO_5 cores ($\tau = 0.41$ and 0.28 for
200 $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$ and $[\text{Na}(\text{CBZ})_5][\text{I}_3]$, respec-
201 tively, where $\tau = 0$ indicates ideal square pyramidal geometry
202 and $\tau = 1$ corresponds to trigonal bipyramidal),³⁰ see Figures 1
203 and 2. In both cases, the Na ion is raised slightly above the basal
204 plane described by the four O donor atoms from the CBZ
205 ligands (by $0.453(3)$ and $0.574(3)$ Å, respectively), with the
206 apical coordination site being occupied by a disordered MeOH
207 ligand in $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$ and by a fifth CBZ
208 ligand in $[\text{Na}(\text{CBZ})_5][\text{I}_3]$. Na–O bond lengths in the more
209 sterically crowded $[\text{Na}(\text{CBZ})_5]$ cation are somewhat elongated
210 compared with those of the $[\text{Na}(\text{CBZ})_4(\text{MeOH})]$ ion. The
211 range of basal Na–O distances is thus $2.326(4)$ to $2.403(4)$ Å
212 for $[\text{Na}(\text{CBZ})_5]$ and $2.317(3)$ to $2.366(3)$ Å for $[\text{Na}(\text{CBZ})_4(\text{MeOH})]$.
213 In both species, the apical Na–O bond is
214 the shortest, with this being a more significant difference for the
215 coordinated MeOH ($2.307(4)$ and $2.258(9)$ Å for $[\text{Na}(\text{CBZ})_5]$
216 and $[\text{Na}(\text{CBZ})_4(\text{MeOH})]$, respectively). All four CBZ ligands
217 of the $[\text{Na}(\text{CBZ})_4(\text{MeOH})]$ ion are orientated so that their
218 azepine rings lie below the complex's basal plane, with one *trans*

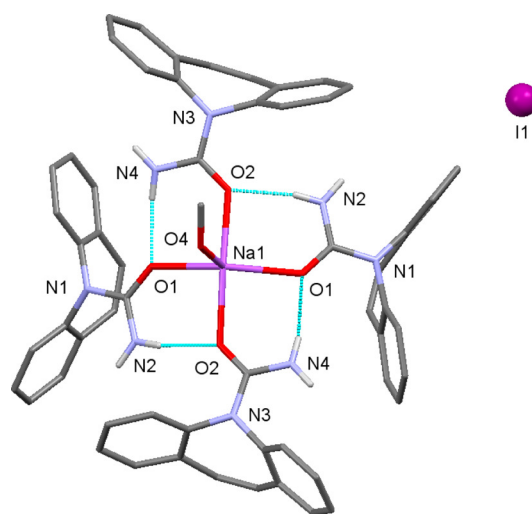


Figure 1. Molecular structure of $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$. Disorder in the solvent and all nonamide hydrogen atoms have been omitted for clarity. Here and elsewhere, hydrogen bonds are shown as light blue lines.

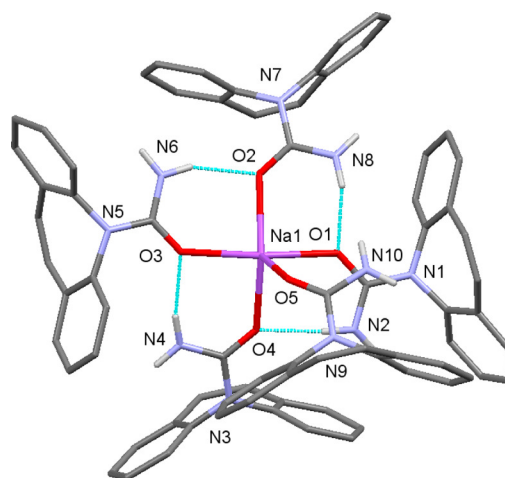


Figure 2. Molecular structure of the cation in $[\text{Na}(\text{CBZ})_5][\text{I}_3]$. Nonamide hydrogen atoms have been omitted for clarity.

pair of ligands significantly more below the plane than the other 219
mutually *trans* pair (compare $145.33(19)^\circ$ and $170.0(2)^\circ$ for 220
 $\text{O1}-\text{Na1}-\text{O1}'$ and $\text{O2}-\text{Na1}-\text{O2}'$ respectively, $' = 1 - x, y, 1$ 221
 $- z$). 222

The four basal CBZ ligands of the $[\text{Na}(\text{CBZ})_5]$ ion adopt a 223
different conformation, with three azepine rings below the basal 224
plane and one (that containing N1) above the plane, see Figure 225
3. Despite this conformational difference, intramolecular 226
hydrogen bonding between the four basal CBZ ligands is 227
similar for the two complexes, Figures 1 and 2. In each 228
complex, each of the amide NH_2 groups of the four basal CBZ 229
ligands donates a single intramolecular hydrogen bond to the 230
amide O atom acceptor of the neighboring basal CBZ ligand. 231
The second H atom of these four NH_2 groups does not form a 232
hydrogen bonding interaction. The apical CBZ ligand of the 233
 $[\text{Na}(\text{CBZ})_5]$ cation does not take part in any classical hydrogen 234
bonds, but its NH_2 group is orientated toward the olefin 235
backbone of the unique azepine ring that lies above the basal 236
plane (H to C=C centroid is 2.80 Å). In contrast, the apical 237
MeOH ligand of $[\text{Na}(\text{CBZ})_4(\text{MeOH})]$ simply donates a O– 238

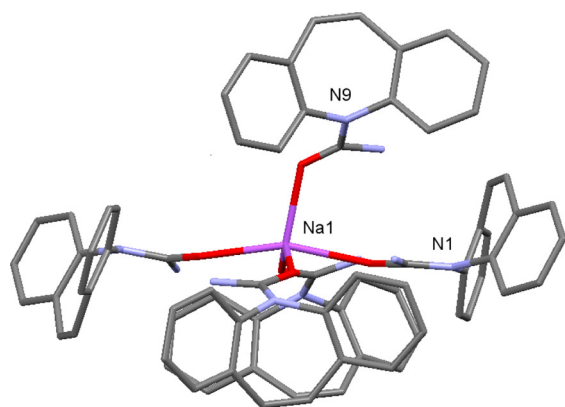


Figure 3. Cation of $[\text{Na}(\text{CBZ})_5][\text{I}_3]$ drawn so as to emphasize the three down, one up conformation of the apezine rings of the four basal ligands. The ligand containing N9 is the fifth, apical ligand.

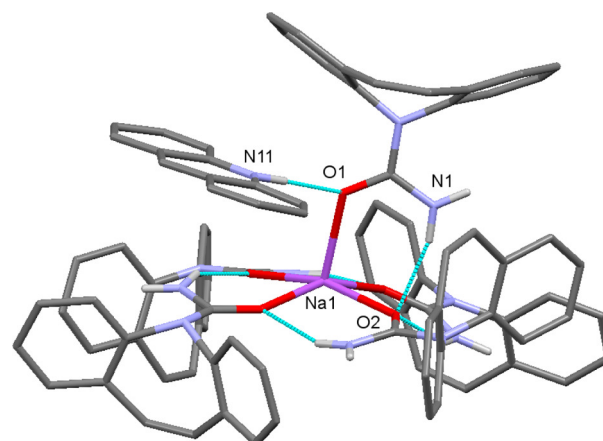


Figure 4. Hydrogen bonded $[\text{Na}(\text{CBZ})_5]$ and acridinium cation pair found in the structure of $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]_2$. H atoms bound to C are omitted for clarity.

239 $\text{H}\cdots\text{O}$ hydrogen bond to the water solvate. Both MeOH and
 240 water positions are disordered about the crystallographic 2-fold
 241 rotation axis, and thus discussion of the geometric details of
 242 these groups is not warranted. This difference in hydrogen
 243 bonding between the two species may contribute to the
 244 different conformations of the basal $\text{Na}(\text{CBZ})_4$ units.
 245 Examination of the bond lengths of the amide groups and
 246 comparison with literature compilations of equivalent data
 247 shows that all the CBZ ligands of these two Na complexes have
 248 $\text{C}=\text{O}$ and $\text{C}-\text{N}$ bond lengths that lie within the ranges
 249 normally seen for neutral CBZ species.^{14,15} This indicates that
 250 complexation to Na does not greatly alter the ligands' internal
 251 geometries. However, the geometry of the apical CBZ ligand of
 252 the $[\text{Na}(\text{CBZ})_5]$ cation does differ subtly from the geometries
 253 of the other coordinated CBZ ligands. The $\text{C}=\text{O}$ length of the
 254 apical ligand is somewhat shorter than the others (compare
 255 1.223(7) with a range of 1.240(6)–1.251(6) Å) and both $\text{C}-\text{N}$
 256 distances of the apical ligand are somewhat longer than those of
 257 the other ligands (compare 1.370(8) and 1.378(7) Å for $\text{C}-$
 258 NH_2 and $\text{C}-\text{NR}_2$ with ranges of 1.335(7)–1.344(8) and
 259 1.354(7)–1.369(7) Å).

260 Most of the cocrystallization experiments attempted simply
 261 returned the starting materials or CBZ dihydrate or previously
 262 known hydrogen halide salts of CBZ as the sole products. The
 263 color of some experiments, especially those with low pH, was
 264 observed to darken with time. Similar darkening of samples
 265 with time was seen in solutions of protonated CBZ(H) salt
 266 forms.¹⁵ This was attributed to the decomposition of CBZ to
 267 acridine, and this is now confirmed by the isolation and crystal
 268 structure determination of two acridinium salt species,
 269 $[\text{C}_{13}\text{H}_{10}\text{N}][\text{I}_2\text{X}]$, $\text{X} = \text{Cl}$ or Br . The structures are included in
 270 the Supporting Information as rare examples of crystallo-
 271 graphically well ordered $[\text{I}_2\text{X}]_n$ species.^{31–33} Although the
 272 transformation from CBZ to acridine is rather unintuitive, a
 273 variety of experimental conditions have been reported to induce
 274 this decomposition. Indeed acridine is a known metabolite of
 275 CBZ.^{34–37} On attempting to replace in situ generation of acid
 276 with a simple addition of aqueous HBr, a third Na ICC
 277 complex was obtained, $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]_2$. That
 278 this species contains both CBZ and acridinium makes it of
 279 enhanced interest, see Figure 4.

280 The $[\text{Na}(\text{CBZ})_5]$ cation in $[\text{Na}(\text{CBZ})_5][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]_2$ is
 281 similar to that in $[\text{Na}(\text{CBZ})_5][\text{I}_3]$ in that the NaO_5 core has a
 282 near square pyramidal geometry ($\tau = 0.11$, Na1 raised 0.395(5)
 283 Å from the plane defined by the four basal O atoms). Another

similarity is that one of the four basal CBZ ligands is again 284
 orientated with its apezine ring above the basal plane defined by 285
 the four O atoms and the other three apezine rings lie below 286
 this plane. However, one of these basal CBZ ligands is 287
 disordered such that a minor conformation is also present in 288
 the crystal, and this has two apezine rings above the basal plane 289
 and two below it. As with both the other Na complexes, the 290
 amide groups of the four basal CBZ ligands form intra- 291
 molecular $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds with their neighboring 292
 CBZ ligands. The NH_2 group of the fifth apical CBZ ligand 293
 behaves differently from that in $[\text{Na}(\text{CBZ})_5][\text{I}_3]$. Rather than a 294
 weak interaction with the π system of the apezine ring that is 295
 raised above the basal plane, here the amine group forms a 296
 classical $\text{N}-\text{H}\cdots\text{O}$ interaction with the O atom of the raised 297
 ligand. Meanwhile, the O atom of the apical CBZ ligand is 298
 involved in a strong hydrogen bond with the formally positively 299
 charged $\text{N}-\text{H}$ group of the acridinium cation. Thus, the two 300
 cations $[\text{Na}(\text{CBZ})_5]$ and $[\text{C}_{13}\text{H}_{10}\text{N}]$ are bound tightly together. 301
 None of the anions in any of the three Na species described 302
 interact with polar groups of the cations. In all cases, only $\text{C}-$ 303
 $\text{H}\cdots\text{X}$ ($\text{X} = \text{I}$ or Br) interactions are observed. For 304
 $[\text{Na}(\text{CBZ})_5][\text{I}_3]$ none of these interactions are shorter than 305
 the sum of van der Waals distances while the other two species 306
 each make four $\text{C}-\text{H}\cdots\text{X}$ interactions shorter than van der 307
 Waals distances. Inorganic coordination chemists would thus 308
 classify all three species as dipole separated ion pair 309
 complexes.^{18–22} 310

ICC forms are of generic interest because they present the 311
 possibility of generating API containing materials with different 312
 intermolecular bond types from those seen in organic systems, 313
 and this may allow the chemophysical properties of APIs to 314
 be modified.^{16,17} Intermolecular interactions and packing in 315
 CBZ polymorphs and cocrystals have been widely commented 316
 on in the literature. Two descriptive strands are often used. The 317
 first of these describes the various supramolecular synthons 318
 found in CBZ species, commonly such synthons are based on 319
 the hydrogen bonding modes of the amide group. The various 320
 structures of the CBZ polymorphs are based upon CBZ dimers. 321
 This dimeric arrangement is often contrasted with a theoretical 322
 chain structure predicted to be stable and similar to the motif 323
 found in related amides.^{38–41} In many cocrystalline forms of 324
 CBZ, the dimeric motif is retained, commonly with the addition 325
 of $\text{N}-\text{H}\cdots\text{A}$ hydrogen bonds as shown in Figure 5. An 326 65

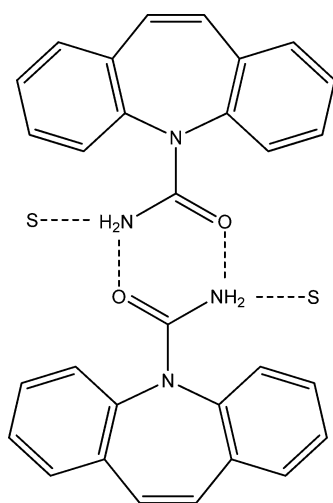


Figure 5. Representation of the CBZ hydrogen bonded dimer motif. When present, S is a hydrogen bond acceptor in the form of a solvent molecule or a cocrystal conformer.

327 alternative arrangement is found in phases where the cofomer
328 is a carboxylic acid. Here the commonly found motif is a
329 heterodimer with an amide to COOH contact.^{8,9} A second
330 strand of CBZ structural analysis has looked not just at
331 intermolecular bonding interactions but at supramolecular
332 constructs, that is at any packing motif that is repeated in
333 different CBZ phases no matter what the bonding nature of the
334 interaction might be. This approach identified two dimeric
335 constructs and two stacking constructs that appear in multiple
336 CBZ structures (including the hydrogen bonded dimer
337 discussed above).¹¹

338 Ammonium halide based ICC forms of CBZ have been
339 known for some time. These are the isostructural species
340 $[\text{NH}_4][\text{X}][\text{CBZ}]$ where $\text{X} = \text{Cl}$ and Br .²⁶ Because the available
341 database structures (VUBCAW and VUBCEA) do not contain
342 information on H atom positions, we have redetermined the
343 structure of $[\text{NH}_4][\text{Br}][\text{CBZ}]$ at low temperature. This
344 confirms that $[\text{NH}_4][\text{Br}][\text{CBZ}]$ has a CBZ hydrogen bonded
345 dimer motif with further hydrogen bonds from the dimer to
346 both cations and anions, see Figure 6. This is a simple variation
347 on the hydrogen bonding structure common to many organic

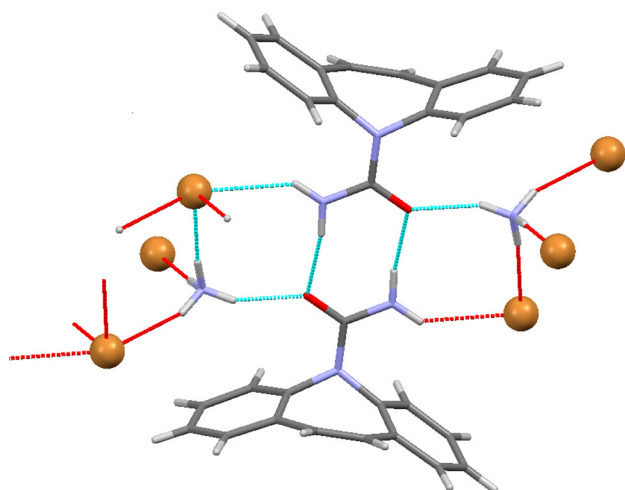


Figure 6. Part of the hydrogen bonding motif found in the structure of $[\text{NH}_4][\text{Br}][\text{CBZ}]$. Bromide ions drawn as brown spheres.

348 cocrystals of CBZ. The hydronium, $[\text{H}_3\text{O}][\text{Cl}]\cdot 2\text{CBZ}\cdot 2\text{H}_2\text{O}$,
349 also retains the hydrogen bonded CBZ dimer although CBZ
350 salt forms with O atom protonated amide groups do not.¹⁵
351 Furthermore, the $[\text{NH}_4][\text{X}][\text{CBZ}]$ species were included in
352 Gelbrich and Hursthouse's initial work on supramolecular
353 constructs in CBZ.¹¹ In this analysis, both have entirely
354 unexceptional packing features with structures that contain the
355 common "translational stack" motif as well as the hydrogen
356 bonded dimer (supramolecular constructs A and C in ref 11).
357 Thus, despite containing charged ions, the ICC structures of
358 $[\text{NH}_4][\text{X}][\text{CBZ}]$ are not obviously different from the
359 structures of nonionic CBZ cocrystals. However, the three Na
360 containing ICC forms of CBZ described herein do have
361 significant structural differences from the CBZ cocrystals
362 previously described. The hydrogen bonded CBZ dimer is
363 now absent. Complexation to the Na center requires the CBZ
364 ligands to point inward to the common center and constrains
365 the homoleptic CBZ $\text{NH}\cdots\text{O}$ interactions such that they
366 connect only to CBZ ligands bound to the shared Na center.
367 Note that although the observed structures do not contain CBZ
368 dimers, such an arrangement is entirely possible. The structures
369 of ammonium and alkali metal salts of the same anions are
370 often isostructural;^{42–45} thus a situation where the "NaI"
371 species adopt structures akin to that of $[\text{NH}_4][\text{Br}][\text{CBZ}]$ is
372 conceivable. Although the three Na complexes do not adopt the
373 same hydrogen bonded supramolecular synthons as other CBZ
374 species, they do adopt the nonpolar (or shape-based)
375 supramolecular constructs previously identified.¹¹ Both trans-
376 lational stacks and dimeric examples can be identified, as
377 1718

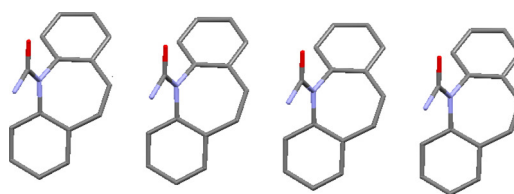


Figure 7. Translational stack of CBZ molecules found in the structure of $[\text{Na}(\text{CBZ})_4(\text{MeOH})][\text{I}]\cdot\text{H}_2\text{O}$. This is supramolecular construct A in ref 11. In this case, the translation is along the crystallographic b axis and hence along the $\text{Na}-\text{O}(\text{MeOH})$ molecular axis.

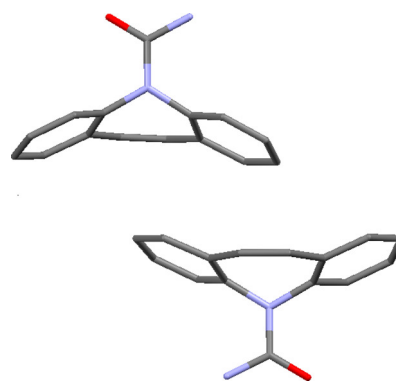


Figure 8. Close packed dimer of CBZ molecules found in the structure of $[\text{Na}(\text{CBZ})_3][\text{I}_3]$. This is supramolecular construct B in ref 11. Similar interactions can be found in the structure of $[\text{Na}(\text{CBZ})_3][\text{C}_{13}\text{H}_{10}\text{N}][\text{IBr}_2]_2$.

378 ■ CONCLUSION

379 The first structures of metal containing forms of CBZ have
380 been synthesized and crystallographically characterized. These
381 three Na complexes can be described as ionic cocrystals.
382 Synthesis at low pH was found to be advantageous. Unlike the
383 previously described ammonium halide and hydronium
384 chloride ICC forms of CBZ, these new structures do not
385 show the same intermolecular bonding motifs as other neutral-
386 CBZ containing phases. Instead dative bonds between Na and
387 the O atom of CBZ predominate and, because the halide based
388 anions make only relatively weak C–H...X contacts with the
389 cations, give dipole separated ion pair forms. CBZ to CBZ
390 hydrogen bonding interactions exist solely within the ligand
391 sets of single [Na(CBZ)₄(HOME)] or [Na(CBZ)₅] cations.
392 Despite the dramatic change in intermolecular bond type and
393 geometry, the three Na containing CBZ ICC phases still
394 present the previously identified nonpolar CBZ supramolecular
395 constructs, showing that here at least these shape-based packing
396 motifs are more robust than the polar hydrogen bonded
397 synthons. The change in intermolecular bonding and the high
398 ratio of CBZ to cofomer make these ICC forms interesting
399 materials for the study of API form selection.

400 ■ ASSOCIATED CONTENT

401 ● Supporting Information

402 X-ray crystallographic information for [NH₄][Br][CBZ] and
403 the acridinium salts with I₂Br and I₂Cl and crystallographic
404 information files (CIF) for all six structures. This material is
405 available free of charge via the Internet at <http://pubs.acs.org>.
406 Crystallographic information files are also available from the
407 Cambridge Crystallographic Data Center (CCDC) upon
408 request (<http://www.ccdc.cam.ac.uk>, CCDC deposition num-
409 bers 1023495 to 1023500).

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413 Notes

414 The authors declare no competing financial interest.

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