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# UNIVERSITÀ DEGLI STUDI DI TORINO

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# From molecular crystals to salt co-crystals of barbituric acid via the carbonate ion and an improvement of the solid state properties†

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Co-crystals formed by neutral barbituric acid (HBA) molecules and alkaline barbiturate salts have been prepared by solvent-free mechanochemical treatment of solid HBA and alkaline carbonates or bicarbonates. During the reaction the carbonate salts release CO<sub>2</sub> and H<sub>2</sub>O, affording the corresponding barbiturate salts which then co-crystallize with the neutral molecule. These “salt co-crystals” have general formula M<sup>x+</sup>(BA<sup>-</sup>)<sub>x</sub>·HBA·nH<sub>2</sub>O with (M= Na and K). The compounds can be obtained in a single step, by directly grinding HBA with M<sub>2</sub>CO<sub>3</sub> (4:1 ratio) or MHCO<sub>3</sub> (2:1 ratio), or, alternatively, in two steps: the preparation of the BA salt followed by a further grinding process or crystallization of the resulting salts with a stoichiometric amount of neutral HBA. All compounds have been characterized by means of single-crystal and powder XRD, solid-state NMR (<sup>1</sup>H MAS, <sup>13</sup>C and <sup>15</sup>N CPMAS), vibrational spectroscopies and thermal methods (DSC and TGA). A series of BA<sup>-</sup> salts (either hydrated or anhydrous) of formula M<sup>x+</sup>(BA<sup>-</sup>)<sub>x</sub>·nH<sub>2</sub>O (M= Na, K, Mg and Ca) have also been prepared and reported for comparison.

## Introduction

Tuning physicochemical properties of a molecular solid is of paramount importance in the solid-state chemistry as well as in several application fields such as pharmaceutical, explosives, agrochemicals, food industry, pigments, etc. This is basically the paradigm of the crystal engineering, which aims to the rational design of crystalline materials with desired properties<sup>1</sup>.

In the pharmaceutical field several methods have been reported for modulating the properties (in particular bioavailability and stability) of an active pharmaceutical ingredient (API). Among others polymorph screening,<sup>2</sup> dispersion in polymers,<sup>3</sup> inclusion in guest compounds or materials,<sup>4</sup> grinding,<sup>5</sup> etc. In this context, the co-crystal formation represents an effective approach because the properties of the solid can be substantially changed by an adequate choice of the co-former, which would require the optimization of an entirely new set of intermolecular interactions, from strong and weak hydrogen bond interactions,<sup>6</sup> to halogen bonds<sup>7</sup> and London dispersion forces. This leads to new chemical formulations associated to new crystal packings, hence to new properties (thermal stability, solubility, dissolution rate, color, processability etc.). Usually co-formers are organic molecules chosen on the basis of their ability to form supramolecular aggregates with the main component<sup>8</sup> or charge transfer complexes.<sup>9</sup> On the contrary, electrostatic interactions, such as those present in alkaline salts, have been only rarely employed.<sup>10</sup>

The design of co-crystals where an inorganic salt is used as a co-former has been reported by us in the cases of barbituric acid (HBA) with alkali salts,<sup>11</sup> of several APIs with alkaline earth<sup>12</sup> and more recently with piracetam.<sup>13</sup> In all cases the effect of co-crystal formation has led to improved properties in terms of thermal stability.

Herein we report a different strategy to obtain new crystal forms of barbituric acid. The general idea, recently put forward by Brittain,<sup>14a</sup> is that of ionizing a molecule (an acid or a base) to produce a molecular salt, which in turn can be used as a co-former in the preparation of a “salt co-crystal”<sup>14a</sup> of the original molecule. The molecular packing will be driven by the formation of hydrogen bonds and electrostatic interactions. This approach can represent a promising methodology for the pharmaceutical field, as it is possible to design new co-crystals with improved properties,<sup>14</sup> with the additional advantage that *in solution* both the starting molecule and the co-former are essentially the same chemical entity.

Barbituric acid, HBA, is the lead structure of the 5,5-substituted barbiturates, dominating group of sedative/hypnotic drugs during the first half of the 20th century. It is used as a precursor in the synthesis of numerous compounds such as polymers,<sup>14</sup> pigments,<sup>15</sup> dyes,<sup>16</sup> and Vitamin B2.<sup>17</sup> Four forms (I-IV) of HBA are known. The structures of form III (the high-temperature phase, HT-form)<sup>18</sup> and form IV (the thermodynamic phase)<sup>19</sup> have been solved, only recently, by combining diffraction (both

X-ray and neutron) and solid-state NMR (SSNMR) data. All polymorphs are characterized by molecules in the keto tautomeric form but form IV consisting of molecules in the enol form stabilized by a higher number of hydrogen bonds.

Here we present a strategy for obtaining a new class of salt co-crystals of HBA. As the target molecule is an acid, the corresponding salt can be obtained by reaction with carbonate salts, with the advantage that the carbonate anion is eliminated via CO<sub>2</sub> formation. This results in the presence of a BA<sup>-</sup> salt (salt co-former) and an HBA molecule together in the same lattice, i.e. in a salt co-crystal of general formula M<sup>x+</sup>(BA<sup>-</sup>)<sub>x</sub>·HBA·nH<sub>2</sub>O, with (M= Na and K). A series of BA<sup>-</sup> salts (either hydrate or anhydrous) of formula M<sup>x+</sup>(BA<sup>-</sup>)<sub>x</sub>·nH<sub>2</sub>O (M= Na, K, Mg and Ca) are also prepared for comparison.

## Experimental Part

Barbituric acid (HBA) (2, 4, 6 (*1H*, *3H*, *5H*)-Pyrimidinetrione), M<sub>2</sub>CO<sub>3</sub>, MHCO<sub>3</sub> (M= Na and K) and MCO<sub>3</sub> (M= Mg and Ca) were purchased from Sigma-Aldrich and used without purifications. The HBA commercial batch was characterized by SSNMR analysis as pure Form II (tri-carbonyl isomer). All K and Na derivatives (salts and co-crystals) were obtained using both bicarbonates and carbonates by following the appropriate stoichiometry.

Even though only the use of carbonates is reported, all salt co-crystals and salts can be achieved in the same way by using either carbonates or bicarbonates according to the corresponding stoichiometry. All preparations are summarized in Table 1.

- NaBA·1H<sub>2</sub>O (salt) was obtained by kneading (water) BA<sup>-</sup> and Na<sub>2</sub>CO<sub>3</sub> in 2:1 ratio for 5 minutes.

- NaBA·HBA·2H<sub>2</sub>O (salt co-crystal) was obtained by kneading (water) HBA and NaBA·1H<sub>2</sub>O in 1:1 ratio for 10 minutes. The sample was also obtained by directly kneading of HBA and Na<sub>2</sub>CO<sub>3</sub> in 4:1 ratio. Crystals for single crystal X-ray analysis were isolated by slowly cooling a hot water solution.

- KBA (salt) was obtained by kneading (water) HBA and K<sub>2</sub>CO<sub>3</sub> in 2:1 ratio for 5 minutes.

- KBA·HBA·2H<sub>2</sub>O (salt co-crystal) was collected after 2 days as a second fraction of a crystallization in water of HBA and KBA in 1:1 ratio. The first fraction was characterized as HBA hydrate. The co-crystal forms colorless rods. Direct crystallization of HBA and K<sub>2</sub>CO<sub>3</sub> results in the precipitation of a larger amount of HBA hydrate. Kneading (water) of HBA and K<sub>2</sub>CO<sub>3</sub> leads to a mixture of KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O.

- KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O (salt co-crystal) was obtained as third fraction of the crystallization for obtaining KBA·HBA·2H<sub>2</sub>O left at 4°C for further 7 days. The co-crystal forms agglomerates of yellow needles.

- CaBA<sub>2</sub>·3H<sub>2</sub>O (salt) was obtained by kneading (water) HBA and CaCO<sub>3</sub> in 2:1 ratio for 30 minutes.

- MgBA<sub>2</sub>·2H<sub>2</sub>O (salt) was obtained by grinding with several water drops HBA and MgCO<sub>3</sub> in 2:1 ratio for 5 minutes. It spontaneously converts (about 2-3 weeks) to a mixture of hydrates.

- MgBA<sub>2</sub> (salt) was obtained by dehydration of MgBA<sub>2</sub>·2H<sub>2</sub>O at 170°C for 4 hours.

All products were characterized by: single crystal (co-crystals only) and powder X-Ray diffraction (XRPD), SSNMR, IR (ATR)

and Raman spectroscopies, DSC and TGA calorimetric analyses and IDR.

All crystal data were collected on an Oxford Xcalibur S instrument with MoK<sub>α</sub> radiation (λ=0.71073 Å) and graphite monochromator at room temperature. Crystal data and details of measurements for NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O are summarized in Table 2. SHELX97<sup>20</sup> was used for structure solution and refinement based on F<sup>2</sup>. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms bound to carbon and nitrogen atoms were added in calculated positions. Hydrogen atoms bound to oxygen atoms were located from a Fourier map and their position refined.

X-ray powder diffractograms were collected on a Panalytical X'Pert PRO automated diffractometer with CuK<sub>α</sub> radiation and a X'Celerator detector. Mercury (CSD) was used for the calculation of X-ray powder patterns on the basis of single-crystal data. All powder X-Ray diffractogram are reported in the ESI†.

All SSNMR spectra were recorded on a Bruker Avance II 400 instrument operating at 400.23, 100.65 and 40.55 MHz for <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N nuclei, respectively. For <sup>13</sup>C and <sup>15</sup>N CPMAS spectra, cylindrical 4 mm o.d. zirconia rotors with a sample volume of 80 μL were employed. Samples were spun at 12 and 9 kHz for <sup>13</sup>C and <sup>15</sup>N, respectively. A ramp cross-polarization pulse sequence was used with contact times of 2-4 (<sup>13</sup>C) or 4 ms (<sup>15</sup>N), a <sup>1</sup>H 90° pulse of 3 μs, recycle delays of 5-15 s and 76-426 transients for <sup>13</sup>C and 390-15700 transients for <sup>15</sup>N. <sup>1</sup>H MAS experiments were performed on a 2.5 mm Bruker probe at a spinning speed of 32 kHz. The <sup>1</sup>H MAS spectra were acquired with the DEPTH sequence (π/2-π-π) for suppressing the probe background signal.<sup>21</sup> For all samples, the <sup>1</sup>H 90° pulse length was set to 3 μs and the recycle delay to 5-15 s. 16-64 transients were averaged. <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N chemical shifts were referenced via the resonance of solid adamantane (<sup>1</sup>H signal at 1.87 ppm), HMB (<sup>13</sup>C methyl signal at 17.4 ppm) and (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> (<sup>15</sup>N signal at -355.8 ppm with respect to CH<sub>3</sub>NO<sub>2</sub>).

IR and Raman spectroscopies were instrumental only for the screening of products and for monitoring preparations. In particular to discriminate between the different forms, attention was focused on the regions from 3500 to 3300 cm<sup>-1</sup> (NH and OH stretching), 3100 and 3000 cm<sup>-1</sup> (CH and CH<sub>2</sub> stretching) and 1700-1600 cm<sup>-1</sup> (C=O stretching). All IR and Raman spectra are reported in the ESI†. IR spectra were collected directly on the sample using a Harrick MVP2 ATR cell with Bruker FT-IR Equinox 55 equipped with KBr optics and a DLaTGS detector. The spectra were acquired at 2 cm<sup>-1</sup> resolution for 32-64 scans. Raman spectra were measured on a Bruker Vertex 70 spectrometer equipped with a RAM II using a 1064 nm Nd:YAG source and a Ge diode detector (laser power 50 mW, spectral resolution 4 cm<sup>-1</sup>).

Calorimetric measurements (Differential Scanning Calorimetry, DSC) were performed with a TA instrument Q200. The samples (5-10 mg) were placed in closed aluminium pans and heated with a ramp of 10 °C min<sup>-1</sup> in the temperature range from 25 to 600 °C. Thermogravimetric (TGA) measurements were performed under N<sub>2</sub> flow (ramp, 10°Cmin<sup>-1</sup>) by a TA instrument Q600 SDT Simultaneous DSC-TGA heatflow analyser. The samples (5-10 mg) were placed in alumina pans.

**Table 1** Starting co-formers, preparation, class of product, formula and sample form.

Co-Formers		Preparation	Class	Formula	Sample Form
HBA	K <sub>2</sub> CO <sub>3</sub> / KHCO <sub>3</sub>	kneading	salt	KBA	white powder
HBA	KBA	crystallization	salt co-crystal	KBA·HBA·2H <sub>2</sub> O	colorless rods
HBA	KBA	crystallization	salt co-crystal	KBA·HBA <sub>0.5</sub> ·1.5H <sub>2</sub> O	yellow needle
HBA	Na <sub>2</sub> CO <sub>3</sub> / NaHCO <sub>3</sub>	kneading	salt	NaBA·1H <sub>2</sub> O	white powder
HBA	NaBA·1H <sub>2</sub> O	kneading and crystallization	salt co-crystal	NaBA·HBA·2H <sub>2</sub> O	Colorless rods
HBA	CaCO <sub>3</sub>	kneading	salt	CaBA <sub>2</sub> ·3H <sub>2</sub> O	white powder
HBA	MgCO <sub>3</sub>	kneading	salt	MgBA <sub>2</sub> ·2H <sub>2</sub> O	
	MgBA <sub>2</sub> ·2H <sub>2</sub> O	heating	salt	MgBA <sub>2</sub>	

**Table 2** Crystal data for salt co-crystals of formula BA·NaBA·2H<sub>2</sub>O, BA·KBA·2H<sub>2</sub>O and BA·KBA·1.5H<sub>2</sub>O.

	NaBA·HBA·2H <sub>2</sub> O	KBA·HBA·2H <sub>2</sub> O	KBA·HBA <sub>0.5</sub> ·1.5H <sub>2</sub> O
formula	C <sub>8</sub> H <sub>11</sub> N <sub>4</sub> NaO <sub>8</sub>	C <sub>8</sub> H <sub>11</sub> N <sub>4</sub> KO <sub>8</sub>	C <sub>12</sub> H <sub>16</sub> N <sub>6</sub> K <sub>2</sub> O <sub>12</sub>
symmetry	Triclinic	Monoclinic	Monoclinic
space group	P -1	C 2/c	C 2/m
a	6.419(1)	51.935(7)	14.686(5)
b	10.026(2)	11.829(4)	16.190(2)
c	10.326(2)	12.781(3)	10.926(3)
α	69.67(2)	90	90
β	80.22(2)	91.881(15)	131.41(5)
γ	80.44(1)	90	90
V (Å <sup>3</sup> )	609.922	7847.14	1948.42
Z,Z'	Z:2 Z':1	Z:8 Z':3	Z:4 Z':1
R%	7.02	6.23	5.52

## Results and discussion

The salt co-crystals can be obtained by directly grinding HBA and carbonate or bicarbonate in a 4:1 or 2:1 ratio, respectively. An alternative way is based on the following sequence of steps: 1) preparation of the BA<sup>-</sup> salt by kneading HBA with carbonates (M<sub>n</sub>CO<sub>3</sub> with M= Na, K, Mg and Ca, n= 1 or 2 depending on M) and 2) the use of the resulting salt as co-former in a grinding process or in a crystallization with a stoichiometric amount of HBA.

Advantages of using carbonates are related to the release of CO<sub>2</sub> and H<sub>2</sub>O, while grinding, that avoids the presence of carbonate residues in the products. In any case, for pharmaceutical applications, possible traces of carbonates would be harmless thanks to their high body tolerance (they are present in the Pharmacopoeia).

The resulting compounds are five BA<sup>-</sup> salts (NaBA·1H<sub>2</sub>O, KBA, MgBA<sub>2</sub>, MgBA<sub>2</sub>·2H<sub>2</sub>O and CaBA<sub>2</sub>·3H<sub>2</sub>O) and three salt co-crystals NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O. Results are summarized in Table 1.

Unfortunately, it was not possible to produce salt co-crystals of Mg and Ca.

The failure in the preparation of salt co-crystals of HBA with alkali earth salts can be taken as indicative of a difference in relative crystal lattice energies. Co-crystal formation always requires that the association of two or more molecular (or ionic) units in the solid state is more thermodynamically stable than the separate crystals. It would appear that the larger Madelung effect due to the presence of di-positive charges and the consequent different stoichiometric ratio in alkali earth salts with respect to alkali salts has a larger effect on the lattice energy so that the salt forms preferentially with respect to the prospected co-crystal.

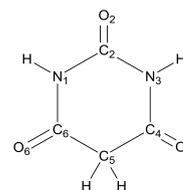
Single crystals suitable for X-ray diffraction analysis have been obtained only for the salt co-crystals NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O. The other compounds have been characterized by XRPD, SSNMR (<sup>1</sup>H MAS and <sup>13</sup>C and <sup>15</sup>N CPMAS), IR (ATR) and Raman spectroscopies, the complementary information provided by the different techniques give insight on the structures of the final products.<sup>22</sup> DSC, TGA and IDR measurements complete the sample characterization with the aim of evaluating the effects of crystal form (molecular packing, weak interactions, conformations...) on the macroscopic properties (thermal stability and bioavailability through the melting point and the IDR, respectively).

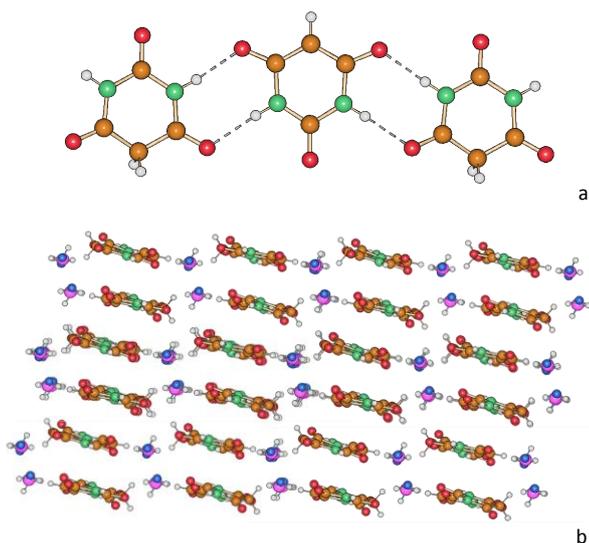
### Single Crystal X-Ray Diffraction.

Crystals of NaBA·HBA·2H<sub>2</sub>O are obtained by slow evaporation of a hot water solution of HBA and Na<sub>2</sub>CO<sub>3</sub> (ratio 2:1). Two hydrated forms KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O are obtained by crystallizing HBA and KBA in water: crystals of the former are collected after about 2 days, while the latter is achieved by slowly evaporation at 4°C of the same solution after other 7 days.

NaBA·HBA·2H<sub>2</sub>O crystallizes as triclinic P-1 and the asymmetric unit contains one HBA, one BA<sup>-</sup>, two water molecules and one sodium cation.

The structure of NaBA·HBA·2H<sub>2</sub>O is characterized by the presence of chains of alternating HBA and BA<sup>-</sup> as shown in Fig. 1a. The O4 and O6 atoms (see Scheme 1 for labelling) are involved in N-H...O interaction and form the R2,2 (8) hydrogen bond pattern while the O2 is mainly coordinating the cations. The interactions characterize all achieved salt co-crystals presented in the work. The hydrogen bond pattern allows the formation of linear organic ribbons which run parallel to one another. The water molecules are in the coordination sphere of the metal atoms. The overall structure can be described by alternation of organic and inorganic layers (Fig. 1b).

**Scheme 1** Labels used for describing the HBA and BA<sup>-</sup>.



**Fig. 1** a) Hydrogen bond pattern between HBA and BA<sup>-</sup>; b) overall packing, view along (0 1 -1). Water molecules are in blue and sodium cations in magenta.

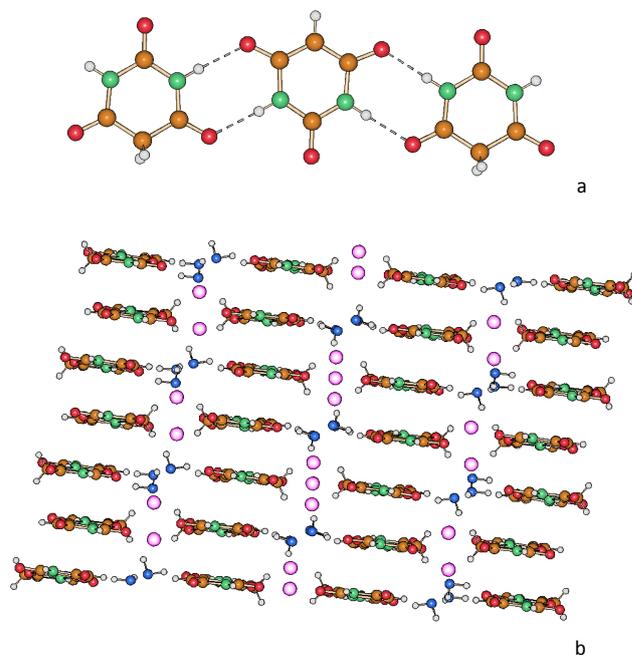
The KBA·HBA·2H<sub>2</sub>O crystallizes as orthorhombic C2/c and it is characterized by an asymmetric unit consisting of 3 HBA molecules, 3 BA<sup>-</sup>, 2 potassium cations in general position with full occupancy, one potassium cation in general position with half occupancy and one potassium cation on a two fold axes. The organic molecules form chains of alternating HBA and BA<sup>-</sup> as shown in Fig. 2a based on the R2,2 (8) hydrogen bond pattern involving the O4 and O6 atoms. Two independent inorganic layers are present in the structure and one of them is characterized by the disorder position of the potassium cation. Although KBA·HBA·2H<sub>2</sub>O and NaBA·HBA·2H<sub>2</sub>O are not isomorphic they show a similar packing (see Fig. 2b).

KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O crystallizes as orthorhombic C2/m; the asymmetric unit consists of two sodium positions with occupancy 0.5 lying on the mirror plane, a BA<sup>-</sup>, half HBA and three water molecules on special positions (two molecules on the mirror plane and one on the two-fold rotation axes). HBA and BA<sup>-</sup> form chains with the sequence HBA...BA<sup>-</sup>...BA<sup>-</sup>...HBA as shown in Fig. 3a. These linear ribbons stack one upon the other as observed in the other structures to form alternating organic and inorganic stacks along the *c* axes (Fig. 3b).

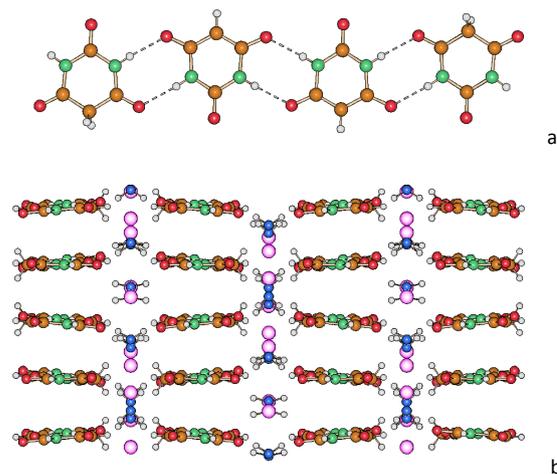
### Solid-state NMR characterization

All SSNMR data (<sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N) with assignments are listed in Table 3. The SSNMR spectra of the salt co-crystals perfectly agree with the XRD structures, thus their discussion is reported in the ESI†.

<sup>13</sup>C and <sup>15</sup>N CPMAS spectra (Fig. 4 and 5) give information concerning asymmetric unit, phase purity, crystallinity, local environment, short range structure and hydrogen bond (for <sup>15</sup>N especially).<sup>23</sup> In particular, from <sup>13</sup>C CPMAS spectra it is straightforward to distinguish between HBA molecules and BA<sup>-</sup> ions since they differ for the C5 resonance which falls around 39 (CH<sub>2</sub>) and 80 (CH) ppm, respectively. Interestingly, the CH signal of the neutral tautomeric BA polymorph (form IV) falls at 79.5 ppm a similar value to that of BA<sup>-</sup>.<sup>24</sup> <sup>1</sup>H MAS NMR



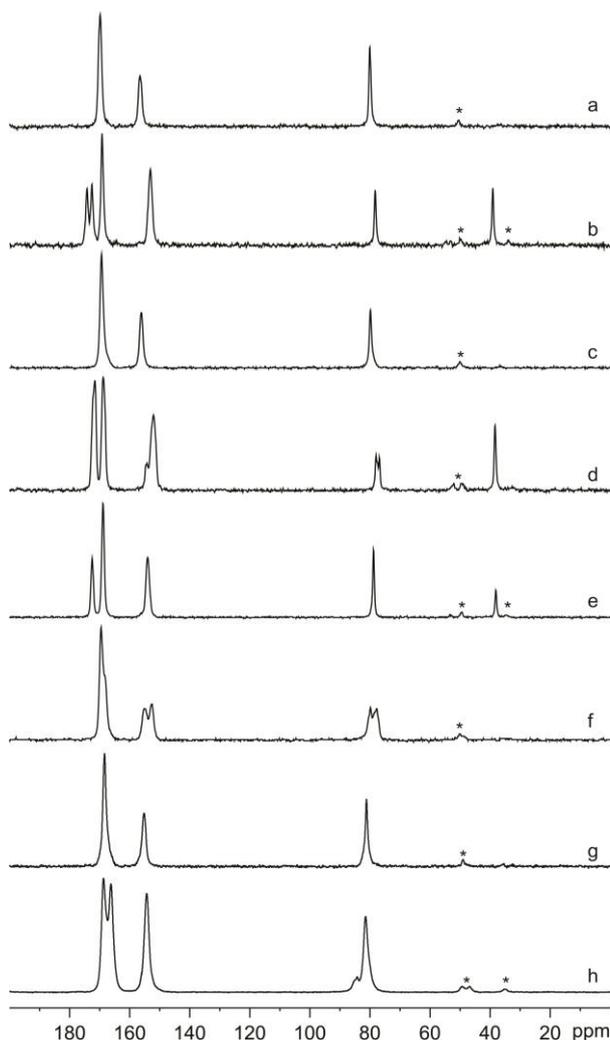
**Fig. 2** a) Hydrogen bond pattern between HBA and BA<sup>-</sup>; b) overall packing, water molecules are in blue and potassium cations in magenta.



**Fig. 3** a) Hydrogen bond pattern between HBA and BA<sup>-</sup>, in this case the sequence is HBA...BA<sup>-</sup>...BA<sup>-</sup>...HBA. b) overall packing, water molecules are in blue and potassium cations in magenta.

experiments (Fig. 6) provide information on HB presence and strength. Large high-frequency shifts, up to 14-20 ppm, are normally associated to strong hydrogen bonds, whereas lower chemical shift values (around 10 ppm) are related to weak contacts.<sup>25</sup> All samples are characterized by hydrogen-bonded proton chemical shift values around 12-14 ppm, suggesting the presence of medium-weak interactions. In particular, the salt co-crystals are characterized by stronger HBs consistent with the short heavy atom distances observed in the structures (around 2.7-2.8 Å). <sup>1</sup>H MAS NMR spectra, combined with TGA data, are also helpful to the evaluation of the hydration degree through the deconvolution of signals around 3-6 ppm.

The <sup>13</sup>C CPMAS spectra of all salts are characterized by the C5



**Fig. 4**  $^{13}\text{C}$  (100 MHz) CPMAS spectra of samples NaBA·1H<sub>2</sub>O (a), NaBA·HBA·2H<sub>2</sub>O (b), KBA (c), KBA·HBA·2H<sub>2</sub>O (d), KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O (e), CaBA<sub>2</sub>·3H<sub>2</sub>O (f), MgBA<sub>2</sub>·2H<sub>2</sub>O (g) and MgBA<sub>2</sub> (h) recorded with a spinning speed of 12 kHz. Asterisks represent spinning sidebands.

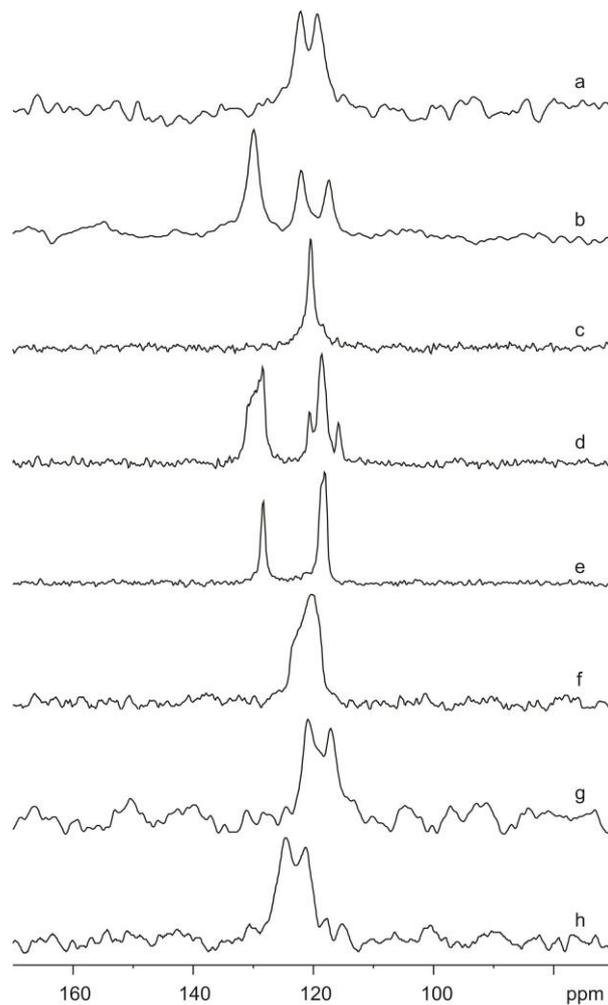
resonance, around 80 ppm, typical of BA<sup>-</sup>.

NaBA·1H<sub>2</sub>O is characterized by one BA<sup>-</sup> and Na<sup>+</sup> in the asymmetric unit as confirmed by the single set of signals in both  $^{13}\text{C}$  and  $^{15}\text{N}$  CPMAS spectra. One water molecule is also present as observed from the  $^1\text{H}$  MAS spectrum and TGA data. Two hydrogen bond environments for the nitrogen atoms are presumable from the presence of two  $^{15}\text{N}$  peaks (119.3 and 122.1 ppm).

KBA is an anhydrous salt ( $^1\text{H}$  MAS spectrum and TGA curves) characterized by half BA<sup>-</sup> in the asymmetric unit owing to the single set of  $^{13}\text{C}$  signals (C4 and C6 169.9 ppm, C2 156.7 ppm and C5 80.5 ppm) and to the single  $^{15}\text{N}$  peak (120.2 ppm).

The  $^{13}\text{C}$  CPMAS spectrum of MgBA<sub>2</sub>·2H<sub>2</sub>O shows a single set of resonances suggesting the presence of one independent BA<sup>-</sup> and half Mg<sup>2+</sup> in the unit cell. The two  $^{15}\text{N}$  peaks (120.9 and 117.1 ppm) indicate the asymmetry of the BA<sup>-</sup> ion due to the different environments of the nitrogen atoms. The number of water molecule from  $^1\text{H}$  integral values is 2 while from TGA data is 3.

In the case of Ca(BA)<sub>2</sub>·3H<sub>2</sub>O, five independent BA<sup>-</sup> ions are



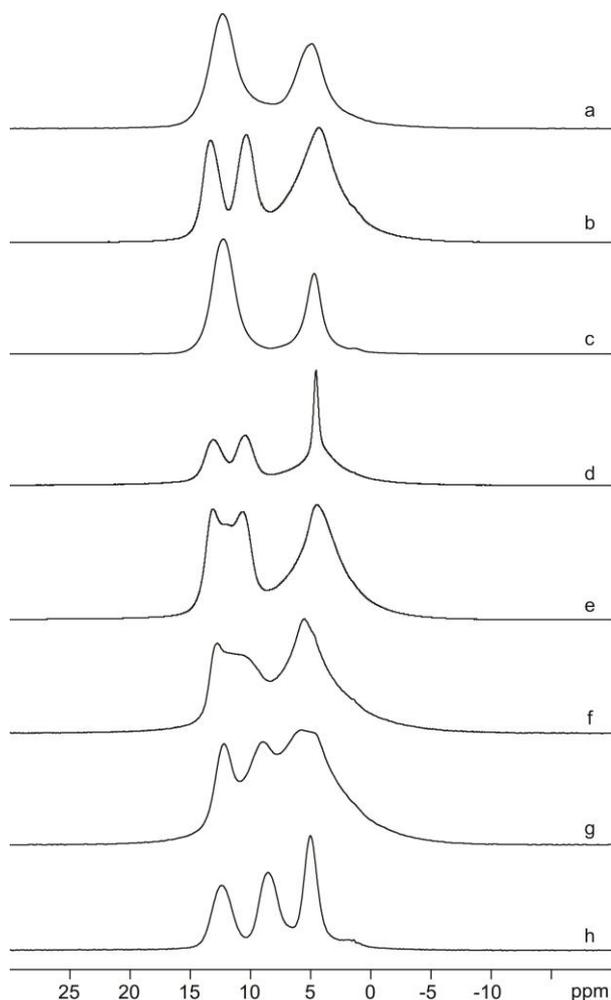
**Fig. 5**  $^{15}\text{N}$  (40 MHz) CPMAS spectra of samples NaBA·1H<sub>2</sub>O (a), NaBA·HBA·2H<sub>2</sub>O (b), KBA (c), KBA·HBA·2H<sub>2</sub>O (d), KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O (e), CaBA<sub>2</sub>·3H<sub>2</sub>O (f), MgBA<sub>2</sub>·2H<sub>2</sub>O (g) and MgBA<sub>2</sub> (h) recorded with a spinning speed of 9 kHz.

expected in the unit cell as highlighted by the splitting of the C5 resonance (77.9 sh, 78.4, 79.2 sh, 80.5 and 81.1 sh ppm). The N-H environments are all similar giving rise to a single very broad (~210 Hz)  $^{15}\text{N}$  peak at 120.2 ppm with a shoulder at 122.3 ppm. The  $^1\text{H}$  MAS combined with TGA data predicts about three water molecules in the asymmetric unit.

#### Dehydration/hydration processes

**Differential Scanning Calorimetry (DSC) and Thermogravimetric (TGA) Analyses.** Calorimetric data of salts and co-crystals are reported in Table 4 while the thermograms are presented in ESI†.

Weight loss in the first 60-70° degrees in TGA curves (data not shown) suggests that all salts are hygroscopic. This agrees with the narrow  $^1\text{H}$  water peak around 4-5 ppm observed in the  $^1\text{H}$  MAS spectra of freshly synthesized samples (spectra not shown). This resonance disappears by heating the sample at 60°C for 30 minutes. Presumably, the adsorbed water molecules arise either from the CO<sub>3</sub><sup>2-</sup> dissociation to CO<sub>2</sub> and H<sub>2</sub>O or water used for



**Fig. 6**  $^1\text{H}$  (400 MHz) MAS spectra of samples NaBA·1H<sub>2</sub>O (a), NaBA·HBA·2H<sub>2</sub>O (b), KBA (c), KBA·HBA·2H<sub>2</sub>O (d), KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O (e), CaBA<sub>2</sub>·3H<sub>2</sub>O (f), MgBA<sub>2</sub>·2H<sub>2</sub>O (g) and MgBA<sub>2</sub> (h) recorded with a spinning speed of 32 kHz.

kneading.

In the case of hydrate compounds, the structural water molecules are removed between 70 and 165°C. In all cases, the dehydration process leads to mixtures of unidentifiable anhydrous phases but for MgBA<sub>2</sub>·2H<sub>2</sub>O. Indeed, a crystalline phase MgBA<sub>2</sub> has been obtained and characterized by two independent BA<sup>-</sup> as highlighted by four signals in the  $^{15}\text{N}$  spectrum (124.8, 123.6, 121.5 and 120.9 ppm) (Fig. 5). Its rehydration leads to a mixture of hydrate phases achievable also by kneading BA and MgCO<sub>3</sub> for more than 30 minutes.

In the salt co-crystals the neutral BA molecule is removed around 230-250°C. Its release leads, in all cases, to amorphous anhydrous salts different from those achieved by grinding BA with carbonates.

Melting, which corresponds also to decomposition, occurs around 380-450°C. It is worth noting that the formation of salts and salt co-crystals leads to an increase of the BA thermal stability of about 200°C.

**Table 3**  $^{13}\text{C}$ ,  $^{15}\text{N}$  and  $^1\text{H}$  chemical shifts (ppm) of the salts NaBA·1H<sub>2</sub>O, KBA, MgBA<sub>2</sub>, MgBA<sub>2</sub>·2H<sub>2</sub>O and CaBA<sub>2</sub>·3H<sub>2</sub>O and of the salt co-crystals NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O.

	$\delta^{13}\text{C}$	$\delta^{15}\text{N}$	$\delta^1\text{H}$
NaBA·1H <sub>2</sub> O	169.8	122.1	12.3
	156.4	119.3	4.9
	79.9		
NaBA·HBA·2H <sub>2</sub> O	174.8	129.7	13.3
	173.2		
	169.7		
	153.7		
	78.8		
BAK	169.9	120.2	12.3
	156.7		
	80.5		
KBA·HBA·2H <sub>2</sub> O	172.2	130.7sh	13.1
	169.4	130.1sh	10.4
	155.2		
	154.8	129.6	
	153.2sh		
	152.6	128.9	4.6
	78.6	128.4	
	78.1	120.6	
	77.5	118.6	
	39.1	115.8	
KBA·HBA <sub>0.5</sub> ·1.5H <sub>2</sub> O	173.0	128.2	13.7
	169.4	118.5sh	11.9
	154.6		10.7
	79.5	118.1	
	38.8		4.5
CaBA <sub>2</sub> ·3H <sub>2</sub> O	170.1	122,3sh	12.8
	168.8	120.2	10.3
	155.7		5.6sh
	155.3		
	153.3		
	81.1sh		
	80.5		4.7
	79.2sh		
	78.4		
77.9sh			
MgBA <sub>2</sub> ·2H <sub>2</sub> O	168.4	120.9	12.1
	155.2	117.1	9.0
	81.2		5.8
MgBA <sub>2</sub>	169.5	124.7	12.3
	166.9		8.5
	155.1	121.2	4.9
	82.3		

**Table 4** DSC and TGA data of the salts NaBA·1H<sub>2</sub>O, KBA, MgBA<sub>2</sub>, MgBA<sub>2</sub>·2H<sub>2</sub>O and CaBA<sub>2</sub>·3H<sub>2</sub>O and of the salt co-crystals NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O. T<sub>w</sub> = water release temperatures; T<sub>BA</sub> = BA release temperatures (only for salt co-crystals); T<sub>md</sub> = melting/decomposition temperatures. Onset temperatures are reported.

Samples	T <sub>w</sub> (°C)	T <sub>BA</sub> (°C)	T <sub>md</sub> (°C)
BA	--	--	245,0
NaBA·1H <sub>2</sub> O	91,7	--	404,8
NaBA·HBA·2H <sub>2</sub> O	116,7	230,0	437,9
KBA	--	--	390,5
KBA·HBA·2H <sub>2</sub> O	67,2	248,0	406,7
	128,7		
KBA·HBA <sub>0.5</sub> ·1.5H <sub>2</sub> O	107,7	248,9	401,9
CaBA <sub>2</sub> ·3H <sub>2</sub> O	112,2	--	458,5
MgBA <sub>2</sub> ·2H <sub>2</sub> O	145,9	--	446,9
MgBA <sub>2</sub>	--	--	441,6

## Slurry experiments

Slurry conversion/competition experiments were performed on the salt/salt co-crystal mixtures. The NaBA·HBA·2H<sub>2</sub>O: NaBA·H<sub>2</sub>O and KBA·HBA·2H<sub>2</sub>O: KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O mixtures (prepared in a salt:salt co-crystal stoichiometric ratio of 1:1) were allowed to equilibrate in a saturated aqueous solution for 3 days, in order to find out which form is least soluble. The resulting solids were analyzed via Raman spectroscopy.

In the case of the NaBA·HBA·2H<sub>2</sub>O: NaBA·H<sub>2</sub>O mixture the salt co-crystal signals were found unaltered, while signals corresponding to the salt were different both from (i) the original salt, (ii) HBA Form II, (iii) a tautomer of HBA (iv) and the hydrated form of HBA; it is possible that a different hydrated salt was obtained in this case. In the case of the KBA·HBA·2H<sub>2</sub>O: KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O mixture the solid obtained from the slurry experiment was found to be a mixture of hydrated HBA and KBA and of KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O. From this result we can surmise that the KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O is more stable than KBA·HBA·2H<sub>2</sub>O.

## Conclusions

In this paper we have reported the preparation and full structural and solid state spectroscopic characterization of three salt co-crystals obtained by direct solid-state reaction of HBA and alkali carbonates or bicarbonates, namely NaBA·HBA·2H<sub>2</sub>O, KBA·HBA·2H<sub>2</sub>O and KBA·HBA<sub>0.5</sub>·1.5H<sub>2</sub>O. Furthermore the same reaction with alkaline earth carbonates has been attempted resulting, however, only in a series of new molecular salts without evidence of co-crystal formation, namely NaBA·H<sub>2</sub>O, KBA, MgBA<sub>2</sub>, MgBA<sub>2</sub>·2H<sub>2</sub>O and CaBA<sub>2</sub>·3H<sub>2</sub>O. The use of carbonates presents several advantages, among them the release of CO<sub>2</sub> and H<sub>2</sub>O avoiding carbonate presence in the product. All compounds have been characterized by combining experimental techniques known to provide complementary information on powdered samples such as powder X-ray diffraction (XRPD), SSNMR (<sup>1</sup>H MAS and <sup>13</sup>C and <sup>15</sup>N CPMAS), IR (ATR) and Raman spectroscopies, DSC, TGA.

Although pure HBA is not pharmacologically active, we show that salt co-crystal formation can be exploited as a viable route to improve its thermal stability. This method, thanks to the possibility of choosing among many co-formers with different properties, shows larger opportunities than the polymorphism phenomenon or than the salt formation. These observations may have relevant implications in all areas where crystal forms are investigated and utilized and in particular with APIs. In particular we plan to explore the possibility of heterogeneous salt co-crystal formation by using a molecular salt as a partner in co-crystallization experiments with another, different, molecular systems. Clearly this method could be used with two different APIs or with many other combinations.

## Notes

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† Electronic Supplementary Information (ESI) available: discussion of the SSNMR characterization of the salt co-crystals, XRPD, Raman, IR (ATR), TGA, DSC, and IDR profiles. See DOI: 10.1039/b000000x

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