From unexpected reactions to a new family of *ionic co-crystals*: the case of barbituric acid with alkali bromides and caesium iodide

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Electronic Supplementary Information

(8 pages)

EXPERIMENTAL

All reagents and solvents were purchased from Sigma-Aldrich and used without further purification. The commercial barbituric acid was characterized by X-ray powder diffraction as the anhydrous Form II of barbituric acid.

Solid-state syntheses

BA·MBr·2H_2O. BA (1 mmol) and MBr (M= Li, Na, K, Rb) (1 mmol) were manually kneaded in an agate mortar for 5 minutes with a drop of methanol to help in obtaining the product quantitatively; no solvent was necessary in the reaction of BA with LiBr, due to the high hygroscopicity of LiBr.

BA·MBr and BA·CsI. BA (1 mmol) and MBr (M= Rb, Cs) (1 mmol) were manually ground in an agate mortar for 5 minutes.

Solution syntheses

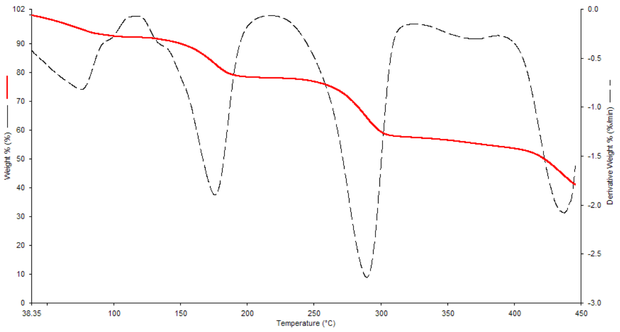
BA·MBr·2H_2O (M= Li, Na, K, Rb) were obtained by dissolution of BA (1 mmol) and MBr (M= Li, Na, K, Rb) (1 mmol) in 20 mL of hot absolute methanol; the solution was left to evaporate at room temperature and crystals suitable for X-ray single crystal diffraction were obtained.

BA·MBr (M= Rb, Cs) and **BA·CsI** were obtained by dissolution of BA (1 mmol) and MBr or CsI (1 mmol) in 20 mL of hot absolute ethanol; the solution was left to evaporate at room temperature and crystals suitable for X-ray single crystal diffraction were obtained.

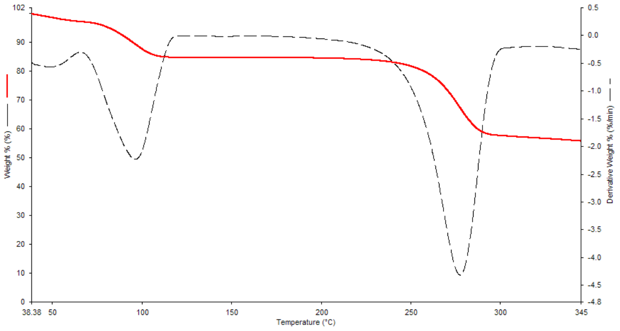
Vapour digestion

All the hydrated co-crystals were also obtained by vapour digestion. Exposure to methanol vapours was achieved by placing a glass sample holder, containing the powder of barbituric acid and MBr (M= Li, Na, K, Rb), in a cylindrical weighing bottle containing 5 mL of methanol: in this way the powder mixture, previously ground, and the solvent were not in direct contact; the reaction took place in a closed system at room temperature. In all cases higly crystalline powders were obtained.

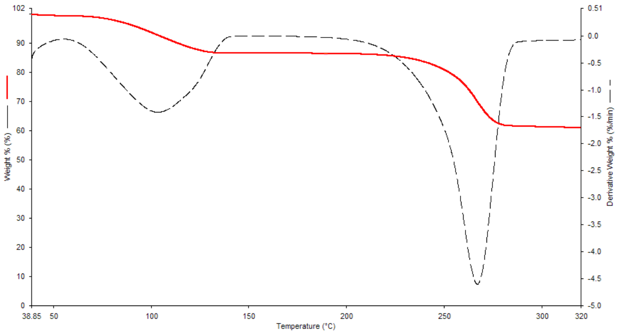
Thermogravimetric analysis (TGA) . TGA measurements were performed using a Perkin Elmer TGA7 in the temperature range 30-310°C under N_2 gas flow; heating was carried out at 5°C min^{-1}.



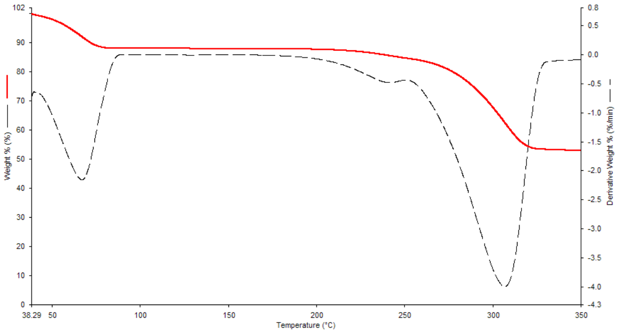
ESI Fig.1. *TGA trace for BA·LiBr·3*H_2O*.*



ESI Fig.2. *TGA trace for BAc·NaBr·2*H_2O*.*

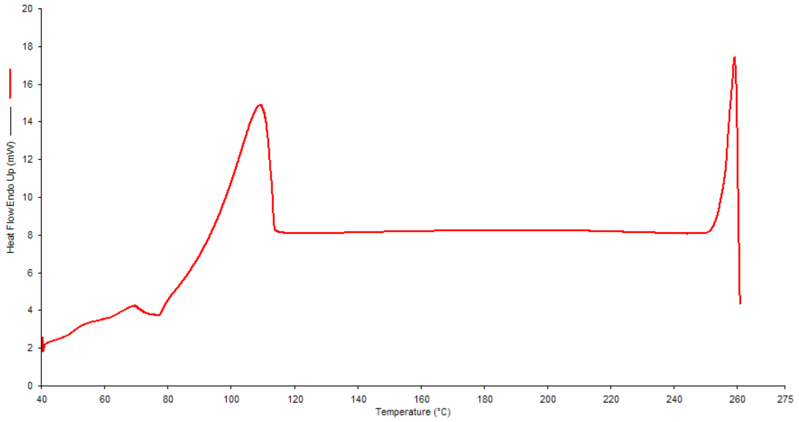


ESI Fig.3. *TGA trace for BAc·KBr·2*H_2O*.*

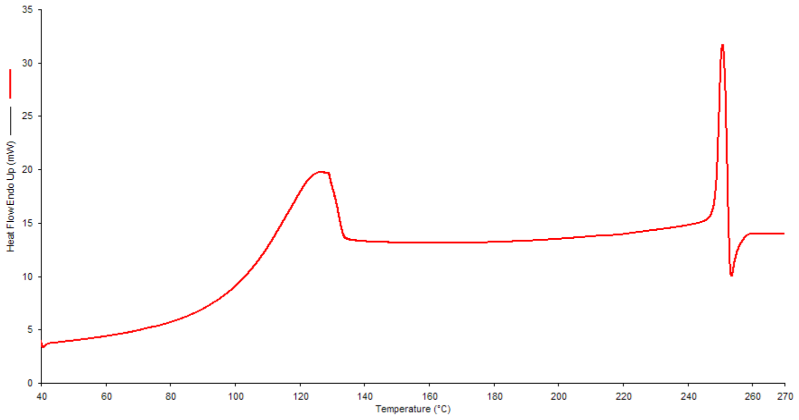


ESI Fig.4. *TGA trace for BA·RbBr·2*H_2O*.*

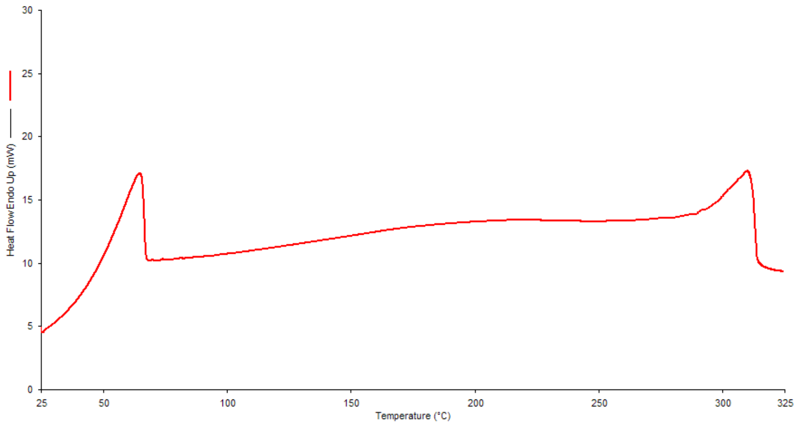
Differential Scanning Calorimetry (DSC): DSC thermograms were recorded on a Perkin Elmer Diamond equipped with a model ULSP90 intracooler. The samples (3-5 mg) were placed into different kinds of pans: open, sealed or pinholed Al-pans. Temperature and enthalpy calibrations were performed using high purity standards (n-decane, benzene and indium). All measurements were conducted in the range 30-400 °C at a heating rate of 5°C/min, up to decomposition.



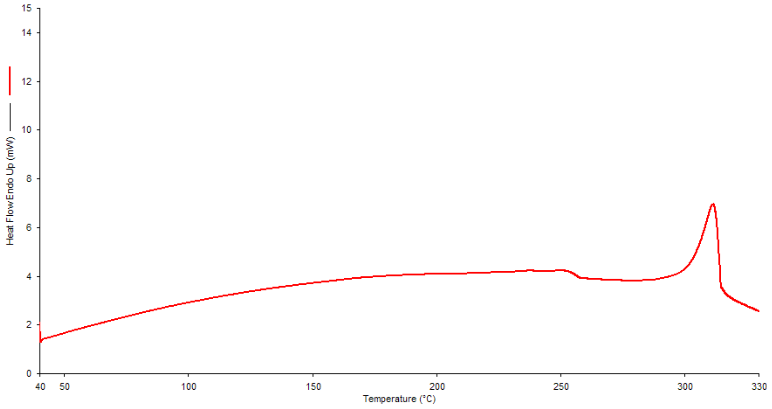
ESI Fig.5. *DSC curve for BA·NaBr·2*H_2O *in a pinholed pan.*



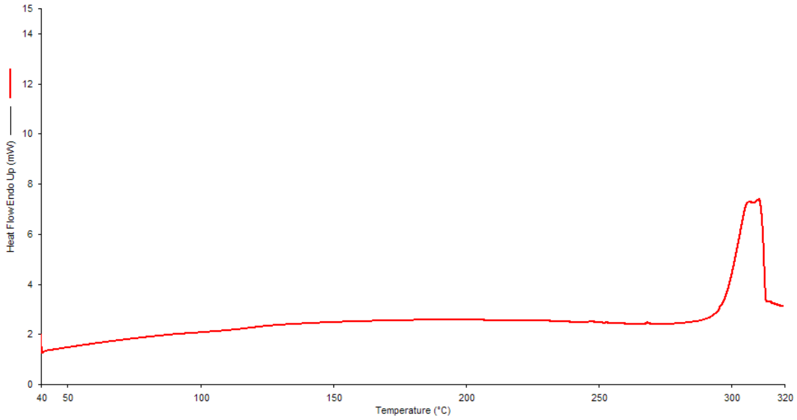
ESI Fig.6 *DSC curve for BA·KBr·2*H_2O *in a pinholed pan.*



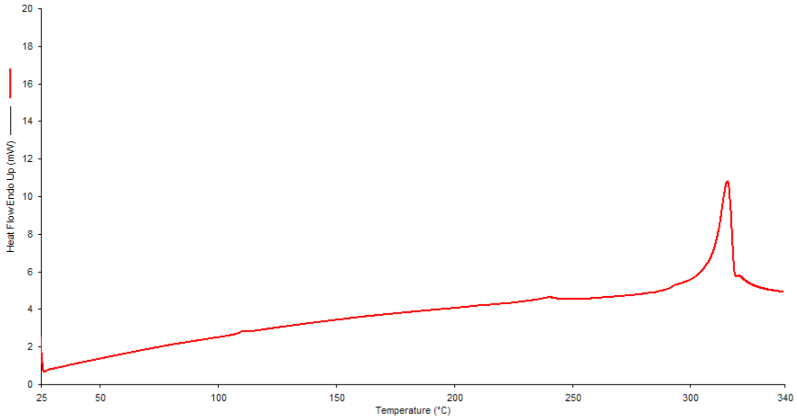
ESI Fig.7 *DSC curve for BA·RbBr·2*H_2O *in an open pan.*



ESI Fig.8 *DSC curve for BA·RbBr in a pinholed pan.*



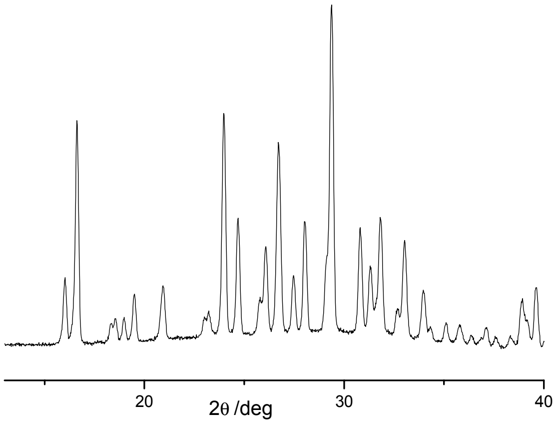
ESI Fig.9 *DSC curve for BA·CsBr in a pinholed pan.*



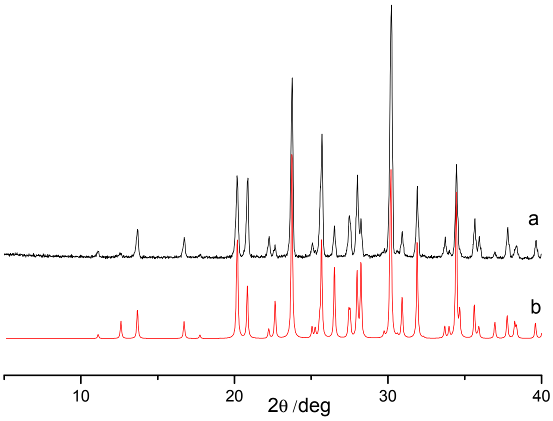
ESI Fig.10 *DSC curve for BA·CsI in a pinholed pan.*

X-Ray powder diffraction measurements.

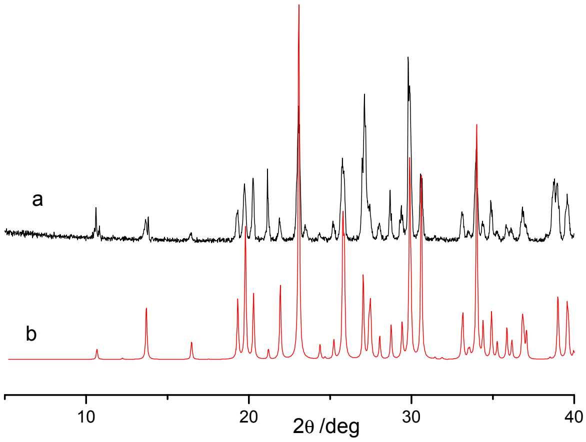
X-ray diffraction patterns were collected on a Panalytical X'Pert PRO automated diffractometer with Cu-Kα radiation and X'Celerator detector without a monocromator, equipped with Anton Paar TTK 450 for measurements at controlled temperature.



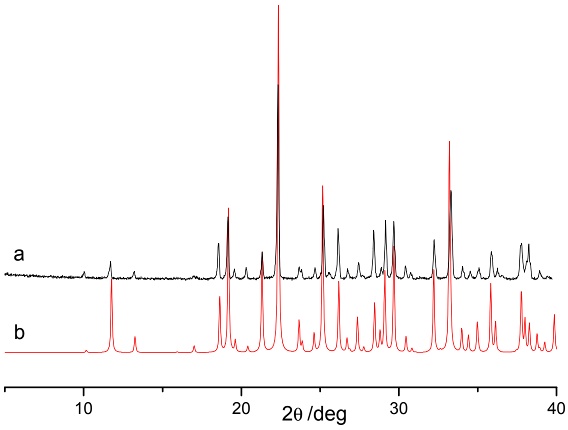
ESI Fig.11 *BA·LiBr·3H_2O: experimental pattern for the product of the grinding process.*



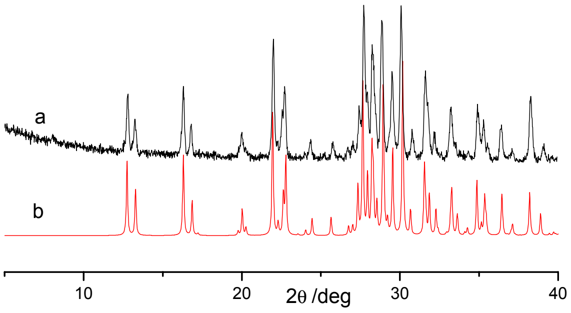
ESI Fig.12 *BA·NaBr·2H_2O: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*



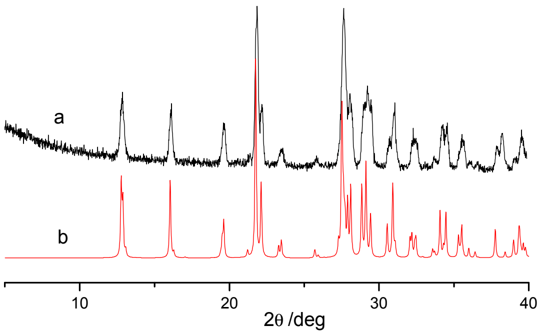
ESI Fig.13 *BA·KBr·2H_2O: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*



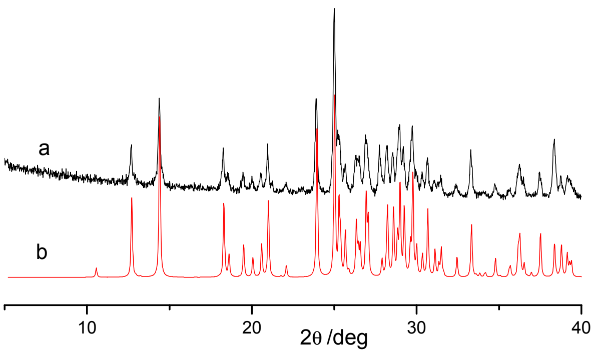
ESI Fig.14 *BA·RbBr·2H$_2$O: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*



ESI Fig.15 *BA·RbBr: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*



ESI Fig.16 *BA·CsBr: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*



ESI Fig.17 *BA·CsI: comparison between the experimental (a, product of the grinding process) and calculated (b, single crystal) X-ray diffraction patterns.*

Crystal structure determination: All crystal data were collected on an Oxford Xcalibur S with Mo-Kα radiation, λ = 0.71073 Å and monochromator graphite at 293(2)K. Crystal data and details of measurements are summarized in ESI Tables 1 and 2. SHELX97[ESI-1] was used for structure solution and refinement based on F^2. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms bound to carbon atoms were added in calculated positions. Hydrogen atoms bound to nitrogen and oxygen atoms were located from a Fourier map and their position refined. Mercury[ESI-2]and Schakal[ESI-3] were used for the graphical representation of the results. The program PLATON[ESI-4] was used to calculate hydrogen bond distances and packing parameters.

ESI Table 1. Crystal data and details of measurements for the hydrated co-crystals BA·MBr·2H$_2$O (M = Na, K, Rb) and the anhydrous co-crystals BA·MBr (M = Rb, Cs) and BA·CsI

	BA·NaBr·2H$_2$O	**BA·KBr·2H$_2$O**	**BA·RbBr·2H$_2$O**	**BA·RbBr**	**BA·CsBr**	**BA·CsI**
Formula	$C_4H_8BrN_2NaO_5$	$C_4H_8BrKN_2O_5$	$C_4H_8BrN_2O_5Rb$	$C_4H_4BrN_2O_3Rb$	$C_4H_4BrCsN_2O_3$	$C_4H_4CsIN_2O_3$
Mol wt	267.02	283.12	329.5	293.47	340.90	387.9
System	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Triclinic
Space group	Pnma	Pnma	Pnma	$P2_1/n$	$P2_1/n$	P-1
a (Å)	7.1308(3)	7.1114(3)	7.223(2)	8.984(5)	9.0870(5)	7.302(5)
b (Å)	7.8805(3)	8.1724(3)	8.3270(10)	8.756(5)	9.1380(4)	7.510(5)
c (Å)	16.0515(6)	16.9065(7)	17.384(3)	10.296(5)	10.4000(6)	9.400(5)
α (°)	90°	90°	90°	90	90	110.800(5)
β (°)	90°	90°	90°	92.949(5)	91.345(6)	101.329(5)
γ (°)	90°	90°	90°	90	90	94.472(5)
V (Å³)	902.00(6)	982.56(7)	1045.60(4)	808.90(8)	863.35(8)	466.30(5)
Z	4	4	4	4	4	2
Density (g cm^{-3})	1.966	1.914	2.093	2.410	2.623	2.763
F(000)	528	560	632	552	624	348
μ(MoKα) (mm^{-1})	4.598	4.601	8.551	11.021	8.879	7.246
Measured reflns	2595	3134	2641	3512	2502	14441
Unique reflns	1110	1233	1258	1843	1659	2323
Refined parameters	80	80	79	108	108	108
R(int)	0.0186	0.0143	0.0152	0.0273	0.0160	0.0242
GOF on F²	0.924	0.910	0.892	0.933	0.947	1.039
R_1 (on F, I >2s(I)	0.0328	0.0247	0.0331	0.0524	0.0254	0.0208
WR_2 (F², all data)	0.0715	0.0505	0.0719	0.1247	0.0523	0.0432

Intrinsic Dissolution Rate (IDR)

In order to measure the intrinsic dissolution rate we prepared for each compound ten pellets (200 mg, 13 mm diameter) using a pressure of 5 tons. We then measured the X-ray diffraction patterns of the pellets, and we noticed that: (i) the crystallinity of all solids is lower, with respect to the products of the solution or grinding experiments compounds are slightly less crystalline. This might be due to changes in the crystallites size as an effect of the applied pressure; (ii) more interestingly, the diffractogram for the BA·RbBr·2H_2O pellet shows the presence of anhydrous BA·RbBr, which must have formed via partial extrusion of water from the solid as a consequence of the applied pressure. It is reasonable to assume that this second event occurs also for the other hydrates, although – being they all more hygroscopic than the rubidium salt – we can also assume that re-hydration occurs immediately after pellet preparation.

For these reasons we choose to measure the intrinsic dissolution rate solubility only for the anhydrous systems.

We first prepared a calibration curve: four standard solutions (4×10^{-4}, 6×10^{-4}, 8×10^{-4} and 10×10^{-4}) were prepared diluting a mother solution of barbituric acid in water. We analyzed the dissolution rate in water at room temperature of barbituric acid (form II) and of the anhydrous ionic co-crystals BA·RbBr, BA·CsBr, BA·CsI.

Measurements were carried out with a Varian Cary 50 Spectrophotometer equipped with a fibre optic dip probe.

We measured the absorbance and used the linear part of the spectra between 0.1 and 0.5 min, its slope corresponding to the dissolution rate, in that interval of time, expressed in Abs/min. The Abs/min values were then interpolated in the calibration curve to find the rate of dissolution of the analytes expressed as conc/min.

References

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