

Mechanochemical preparation and solid state characterization of 1:1 and 2:1 ionic cocrystals of cyanuric acid with alkali halides.

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7 Mechanochemical preparation and solid-state
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10 characterization of 1:1 and 2:1 ionic cocrystals of
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15 cyanuric acid with alkali halides.
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33 **ABSTRACT.** Mechanochemical mixing of cyanuric acid and alkali halides, which show
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36 extreme differences in solubility, is a viable, solvent-free method to quantitatively prepare
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39 ionic cocrystals (ICCs) of cyanuric acid (CA) with halide salts of alkali metals. In this paper we
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42 report the preparation and structural characterization of a series of new compounds, namely
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45 $CA_2 \cdot MCl$ (M= Rb, Cs), $CA \cdot MBr$ (M= Na, K, Rb, Cs), $CA \cdot RbI$, and of the two hydrates
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48 $CA \cdot NaBr \cdot 2H_2O$ and $CA \cdot KI \cdot H_2O$. Crystal structures were determined directly from X-ray
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55 powder diffraction data in all cases with the exception of $CA \cdot KI \cdot H_2O$, for which single crystals
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3 were obtained. The effect of the cation size on the stoichiometry as well as on the architecture
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7 of the ICCs has been discussed.
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11 **INTRODUCTION.** Mechanochemistry refers to reactions that use mechanical energy to
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13 facilitate chemical transformations. Mechanochemical approaches are being widely applied
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15 across diverse areas of chemical science,¹ since reactions can be promoted quickly and
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17 quantitatively either without solvent or with only tiny quantities.² In the past,
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19 mechanochemistry has been considered a lesser method for chemical synthesis with respect
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21 to solution-based approaches. However, the quest for sustainable alternatives to classical
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23 synthetic protocols has led to the discovery of new chemical reactions and to the
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25 development of a vast series of solvent-free processes.²
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41 In the crystal engineering field mechanochemistry is arguably the most common approach
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43 to the synthesis of cocrystals, i.e. of crystalline materials formed by two or more components
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45 that are separately solid at ambient conditions.³⁻¹⁰ Grinding and ball-milling of the solid
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47 reactants, whether in “wet” (liquid assisted grinding, also called kneading) or dry conditions,
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51 allow to overcome some of the limitations of other cocrystallization techniques. For instance,
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3 the commonly used cocrystallization by slow solvent evaporation often fails because of
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6 differences in solubility of the components in a given solvent; analogously, large differences
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10 between melting points or the tendency to sublime of one of the components limit the
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13 application of cocrystallization by co-melting. On the other hand, the main drawback of
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16 mechanochemical preparation of cocrystals is often the difficulty in determining the structural
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19 features of the mechanochemical product, because of the obvious lack of crystals suitable for
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22 structure determination via X-ray single crystal diffraction. Therefore, to elucidate the crystal
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25 structure of the mechanically prepared cocrystals, one can either attempt recrystallization
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28 from solution or structure determination directly from powder data. In the former case,
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31 however, as mentioned above, the difference in solubility of the components in a given
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34 solvent must be taken into account, as dissolution of the cocrystal often implies separation of
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37 the components with very different solubility profiles.¹¹⁻¹⁶ This is especially true in the case of
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40 ionic cocrystals (ICCs), composed of an organic moiety and of inorganic salts or complexes,
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43 where the difference in solubility in water or organic solvents is usually very large. In all these
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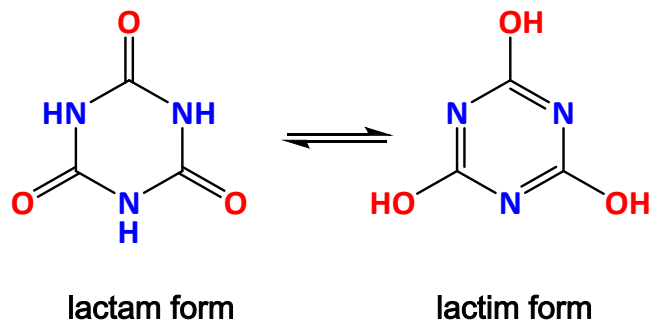
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3 cases the best option to determine the nature of the ICC is the structure determination directly
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7 from X-ray powder diffraction (XRPD) data.
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11 As a matter of fact, one of the reasons of interest for the ionic cocrystals described herein is
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13 precisely the huge difference in solubility and dissolution rate in water of the organic moiety
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15 (cyanuric acid, 1,3,5-triazinane-2,4,6-trione, $H_3C_3N_3O_3$, CA hereafter) and of the inorganic
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17 salts, as well demonstrated by the two cases previously communicated (CA·LiCl, CA·NaCl).¹⁷
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25 In this paper we expand the investigation of the products of mechanochemical reaction of CA
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28 with other MX alkali salts (M = Na, K, Rb, Cs, X = Cl, Br, I).
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33 Cyanuric acid was first synthesized by Friedrich Wöhler in 1829 by thermal decomposition of
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35 urea and uric acid,¹⁸ and its crystal structure was determined by Wiebenga in 1952.¹⁹ CA is a
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37 highly symmetrical molecule and is often mentioned as a perfect example of lactam-lactim
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39 tautomerism (see Scheme 1).
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48 **Scheme 1.** Lactam-lactim tautomerism of cyanuric acid.
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19 The lactim form structure is prevalent in solution,²⁰ whereas the lactam form, also referred
20 to as isocyanuric acid, is the thermodynamically stable form in the solid state.²¹ Both forms,
21 however, are commonly called “cyanuric acid”.²² In view of its highly symmetrical structure,
22 with three hydrogen bonding C=O acceptor sites and three hydrogen bonding N-H donor
23 sites, CA has been employed in a number of structural and crystal engineering studies, often
24 in conjunction with melamine, as the two molecules possess total complementarity of donor
25 and acceptor groups for the formation of NH...N and NH...O hydrogen bonds.²³⁻²⁵

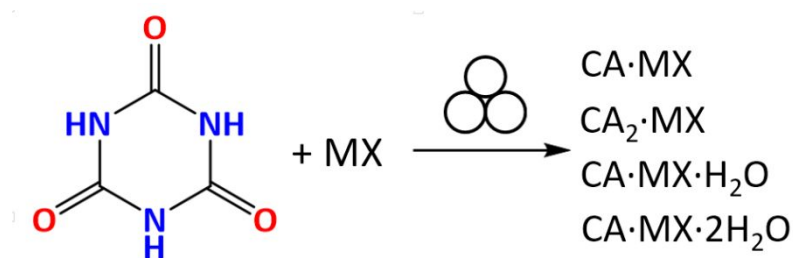
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45 In view of the analogy with the structure of barbituric acid,²⁶ which we have previously
46 shown to form stable ionic cocrystals with inorganic salts, we explored and reported on the
47 preparation and properties of ICCs of CA with LiCl and NaCl.¹⁷ Interestingly, CA•LiCl has
48 been recently investigated as a promising solar-blind nonlinear optical material in NLO
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3 technology.²⁷ The study represents an important development, within ionic cocrystal
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6 engineering strategies, with respect to the use of cyanurate salts,²⁸⁻³⁸ because it allows
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9 exploitation of the electronic properties of neutral cyanuric acid in the presence of alkali
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12 cations. These findings provided further motivation to expand the family of ICCs of cyanuric
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15 acid by cocrystallization with alkali halides of a general formula MX, where M = Na, K, Rb, Cs
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18 and X = Cl, Br, I, beyond the initial results obtained with LiCl and NaCl.
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25 It is worth recalling that CA•LiCl and CA•NaCl possess highly symmetrical arrangements of
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28 the organic moiety around the alkali cations.¹⁷ The architectures are sustained by direct
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31 O···M⁺ interactions of the CA molecules with the alkali cations, and of N-H···Cl⁻ hydrogen
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34 bonds with the chloride anions. These are the types of interactions operating in solution of
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37 protic solvents, e.g. water, so that these ICCs can also be regarded as special types of solid
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40 state solvates; cocrystallization of CA with NaCl significantly improves the solubility of CA in
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43 water and increases the intrinsic dissolution rate of CA, simultaneously decreasing the
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46 solubility of NaCl of an order of magnitude.¹⁷
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Beside testing thoroughly the mechanochemical reaction $CA + MX$ ($M = Na, K, Rb, Cs$, and $X = Cl, Br, I$) we also hoped to gain insight on the factors controlling the crystal structure stability and whether the formation of 1:1 or 2:1 cocrystals could be attributed to the relationship between cation and anion sizes and the formation of ICCs. The results are grouped in Table 1. In all cases discussed herein the ICCs were prepared by mechanical mixing^{2, 3} of CA with the inorganic salts via kneading with a few drops of solvent (water, ethanol or methanol), which is the only viable route to their synthesis (see Scheme 2).

Scheme 2. General scheme for the mechanochemical reaction of cyanuric acid with alkali metal halides [$M = Na, K, Rb, Cs$; $X = Cl, Br, I$].



As a matter of fact, in all the cocrystallization approaches mediated by slurry (in both H_2O and MeOH) unreacted CA was recovered. Similarly, crystallization/ recrystallization from H_2O or MeOH invariably led to a separate crystallization of the components. The only exception

was the recrystallization of CA with KI, which produced a small number of single crystals suitable for X-ray diffraction, while the majority of the solid recovered was a mixture of the starting materials. Structural determination directly from powder data was thus essential, in view of the polycrystalline nature of the product and of the difficulty in growing single crystals from solution.

Table 1. Ionic cocrystals of cyanuric acid and alkali halides discussed herein.

CA	Cl	Br	I
Li	CA·LiCl ¹⁷	a	a
Na	CA·NaCl ¹⁷	CA·NaBr, CA·NaBr·2H ₂ O	a
K	b	CA·KBr	CA·KI·H ₂ O
Rb	CA ₂ ·RbCl	CA·RbBr	CA·RbI
Cs	CA ₂ ·CsCl	CA·CsBr	b

(a) Deliquescent product. (b) Physical mixture of the reagents.

EXPERIMENTAL PART

Materials and instrumentation

All reagents and solvents used in this work were purchased from Sigma-Aldrich and used without further purification.

Solid State Synthesis

All the ICCs were obtained by kneading with ethanol, methanol or water. CA (1 mmol) and the corresponding coformer (1 mmol or 0.5 mmol for both RbCl and CsCl) were kneaded for 60 min with a Retsch MM200 ball miller operated at the frequency of 25 Hz, using stainless steel jars (5 mL) and two 3-mm balls, with the addition of a drop of solvent. CA•KI•H₂O crystals suitable for single crystal X-ray diffraction analysis were obtained by slow evaporation of a methanol saturated solution of the kneading product.

Thermogravimetric Analysis (TGA)

TGA measurements (Figures SI-11 to SI-18) for all compounds were performed with a Perkin-Elmer TGA7 in the temperature range 30-400 °C, under an N₂ gas flow, at the heating rate of 5 °C min⁻¹.

X-ray powder diffraction measurements

Room temperature X-ray powder diffraction (XRPD) patterns were collected on a PANalytical X'Pert PRO automated diffractometer, equipped with an X'celerator detector, in

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3 the 2θ range 3–50° (step size 0.0334, time/step 30.480 s, VxA 40x40). Data analyses were
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7 carried out using the PANalytical X'pert Highscore Plus program.
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10 **Structural Characterization from powder data**

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14 Powder diffraction data were analysed with the software X'Pert HighScore Plus. 10-20
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17 peaks were chosen in the 2θ range 3-50°, and unit cell parameters were found using the
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20 DICVOL4 algorithm. The structures were initially solved by simulated annealing performed
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23 with EXPO2014,³⁹ using one metal ion, halogen atoms and one or two molecules of cyanuric
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26 acid. Ten runs for simulated annealing trial were set, and a cooling rate (defined as the ratio
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29 T_n/T_{n-1}) of 0.95 was used. Platon⁴⁰ ADDSYMM SHELX command was consequently applied
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32 to find the space group with the highest reasonable symmetry. Afterwards the best solutions
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35 were used for Rietveld refinements, performed with the software TOPAS5.0.⁴¹ Structural data
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38 for all compounds investigated in this work are listed in table SI-1.
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45 **Single Crystal X-ray Diffraction**

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48 Single-crystal data for $CA \cdot KI \cdot H_2O$ were collected at RT on an Oxford X'Calibur S CCD
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51 diffractometer equipped with a graphite monochromator (Mo-K α radiation, $\lambda = 0.71073\text{\AA}$).
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3 Data collection and refinement details are listed in table SI-1. The structure was solved by the
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7 Intrinsic Phasing methods and refined by least squares methods against F^2 using SHELXT-
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10 2018⁴² and SHELXL-2018⁴² with Olex2 interface.⁴³ Non-hydrogen atoms were refined
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13 anisotropically. H_{OH} and H_{NH} atoms were either located from a Fourier map or added in
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17 calculated positions and refined riding on their respective nitrogen or oxygen atoms. The
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21 software Mercury 4.0⁴⁴ was used for graphical representations and for powder pattern
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24 simulation on the basis of single crystal data.
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29 Crystal data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html
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32 (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ,
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36 UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk). CCDC numbers 1997990-
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48 RESULTS AND DISCUSSION

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3 As shown in Table 1, mechanical mixing of CA with MX salts (M = Na, K, Rb, Cs, and X =
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6 Cl, Br, I) yielded a series of ICCs, analogous to the ICCs CA·LiCl and CA·NaCl, discussed
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10 previously.¹⁷ Reactions were carried out by kneading (also called liquid assisted grinding,
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13 LAG²) with the addition of a small quantity of solvent to a physical mixture of the reactants in
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17 adequate stoichiometric ratios. In all cases recrystallization from water, methanol and ethanol
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21 was attempted with the aim of obtaining single crystals suitable for X-ray diffraction. In view of
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25 the large differences in solubilities mentioned above, all attempts proved unsuccessful, and
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28 only starting materials were recovered. At variance with this behavior, the ICC between CA
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31 and KI yielded a small number of single crystals, which turned out to be the monohydrate
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34 CA·KI·H₂O. For all the other ICCs, therefore, structures had to be determined from X-ray
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38 powder diffraction data, which revealed, inter alia, that most ICCs discussed here are
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42 anhydrous. The formation of anhydrous compounds of alkali salts is per se rather unusual,
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45 since the majority of ICCs of alkali halides prepared this far^{11, 14, 15} tends to form hydrates,
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49 while anhydrous forms can be only obtained, in some cases, by subsequent dehydration
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53 processes, and are, in general, highly hygroscopic. We attribute this difference to the peculiar
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3 structure of CA, i.e. to its small size and highly symmetrical shape, a combination that affords
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7 optimal packings with spherical ions, as it will be apparent in the following.
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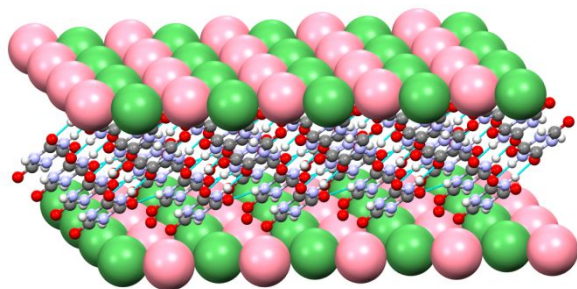
10 11 **Ionic cocrystals of CA with MCl (M = Li, Na, K, Rb, Cs)** 12 13

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16 The structural features of the LiCl and NaCl cocrystals with CA have been described
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19 previously and need not to be discussed here in details.¹⁷ The interaction of CA with alkali
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22 chloride salts formed by the smallest cations of the group resulted into formation of materials
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26 in 1:1 stoichiometry.
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31 On increasing the size of the cations, passing from Li⁺ and Na⁺ to Rb⁺ and Cs⁺, a change in
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34 stoichiometry is observed, resulting in the formation of the isomorphous pair CA₂•RbCl and
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37 CA₂•CsCl (see below). When the reaction of CA with KCl was attempted, however, no ICC
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41 could be obtained, irrespective of stoichiometry or method employed (kneading with ethanol,
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44 H₂O and methanol, etc.). This might indicate that the K⁺ cation is either too large to form a
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48 stable 1:1 ICC with CA, and too small to form a stable 2:1 ICC. In order to circumvent this
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52 problem, attempts were made to prepare ICCs as solid solutions via mechanochemistry. The
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55 stoichiometric ratios 1:0.5:0.5 and 1:0.8:0.2 were chosen for CA:NaCl:KCl mixtures, while
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3 2:0.5:0.5 and 2:0.8:0.2 were chosen for CA:RbCl:KCl mixtures. The idea was that of exploring
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7 the possibility of accommodating a smaller quantity of K^+ cations within the lattices of
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10 CA•NaCl or CA_2 •RbCl. The experiment, however, proved unsuccessful, and in all cases a
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14 physical mixture of the reagents was obtained.
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18 The ICCs CA_2 •RbCl and CA_2 •CsCl are isomorphous. Figure 1 shows the main packing
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21 features for the rubidium ICC. This is a typical example of non-standard coordination found
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24 with large alkali metal cations: the number of contacts involving the Rb^+ ion and the
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27 surrounding CA oxygens and chloride anions is large, and no regular polyhedron can be
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30 drawn around the cation. The crystal is better described as a layered structure with alternating
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33 "RbCl" or "CsCl" and double CA sheets (Figure 1, top), with CA molecules interacting to each
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38 other via N-H...O hydrogen bonds, and directing one third of the N-H and C=O groups
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42 towards the anions and the cations, respectively (Figure 1, bottom).
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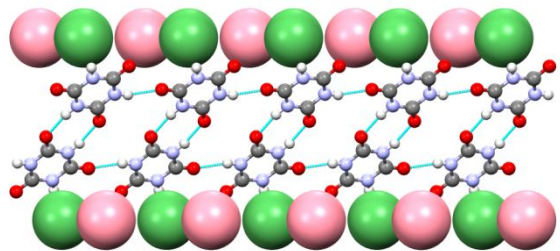


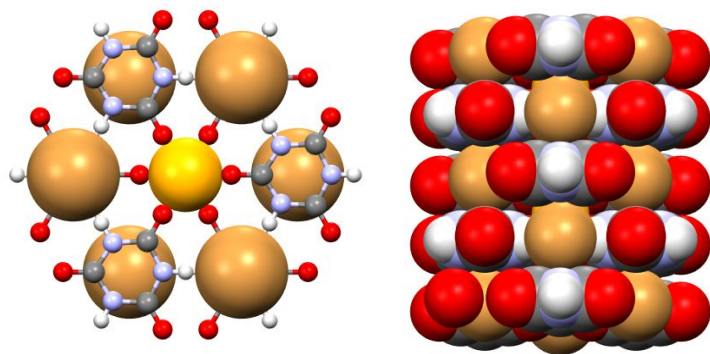
Figure 1. (Top) The layered structure of $\text{CA}_2 \cdot \text{RbCl}$ ($\text{CA}_2 \cdot \text{CsCl}$ is isomorphous); (bottom) CA molecules are "sandwiched" in between "RbCl" 2D-layers, and interact to each other via hydrogen bonds of the $\text{NH} \cdots \text{O}$ type (light blue). Pink: Rb^+ cations; green: Cl^- anions.

The two ICCs, $\text{CA}_2 \cdot \text{RbCl}$ and $\text{CA}_2 \cdot \text{CsCl}$, although isomorphous show a markedly different behavior towards moisture. The former ICC is stable if exposed to air at room temperature, whereas the latter is highly hygroscopic, readily adsorbing water from the atmosphere and becoming a sticky solid. A change in the XRPD pattern is observed for $\text{CA}_2 \cdot \text{CsCl}$ upon hydration, but the initial anhydrous pattern is restored upon heating.

Ionic cocrystals of CA with MBr (M = Li, Na, K, Rb, Cs)

The ICCs obtained with NaBr, KBr and RbBr are all characterized by a 1:1 stoichiometry. So far, preparation of $\text{CA} \cdot \text{LiBr}$ has proven unsuccessful, yielding unreacted material often together with some unidentified solids. The mechanochemical reaction of CA with alkali

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3 bromides proceeds to completion in a shorter time with respect to the analogous chlorides
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7 salts; as an example, the reaction of a mixture NaCl and NaBr with CA yielded quantitatively
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10 CA·NaBr within 15 minutes, while after that time CA and NaCl were still unreacted.

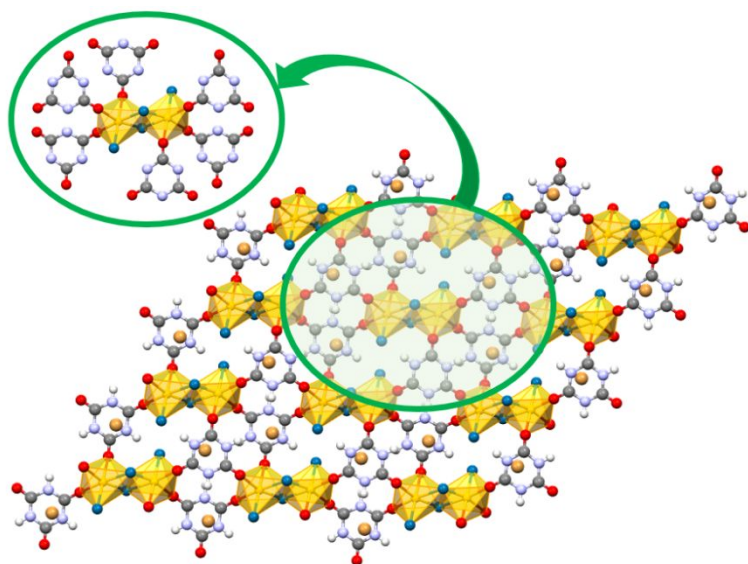


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28 **Figure 2.** The octahedral coordination around Na⁺ in CA·NaBr (left). The compound is
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31 isostructural with CA·NaCl.²⁰ A lateral view (right) showing the intercalation of bromide anions
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35 with CA molecules along the c-axis. Yellow: Na⁺ cations; brown: Br⁻ anions.

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40 Mechanochemical reaction of NaBr with CA in 1:1 stoichiometric ratio resulted in different
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43 products, depending on the solvent used in the kneading process: when a few drops of
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46 methanol or ethanol were added to the reagents mixture, the anhydrous ICC of formula
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49 CA·NaBr was obtained, which is isomorphous with CA·NaCl.¹⁷ When the same experiment
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3 was performed using drops of water, however, the hydrated ICC of formula $\text{CA}\cdot\text{NaBr}\cdot 2\text{H}_2\text{O}$
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7 was obtained (see Figure 2).
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11 In the hydrated ICC $\text{CA}\cdot\text{NaBr}\cdot 2\text{H}_2\text{O}$ three water molecules enter the coordination sphere of
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13 the cations, taking the place of three CA molecules: as the stoichiometric ratio $\text{CA}\cdot\text{NaBr}$ is still
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15 1:1, two water molecules act as bridges between pairs of Na^+ cations (see Figure 3).
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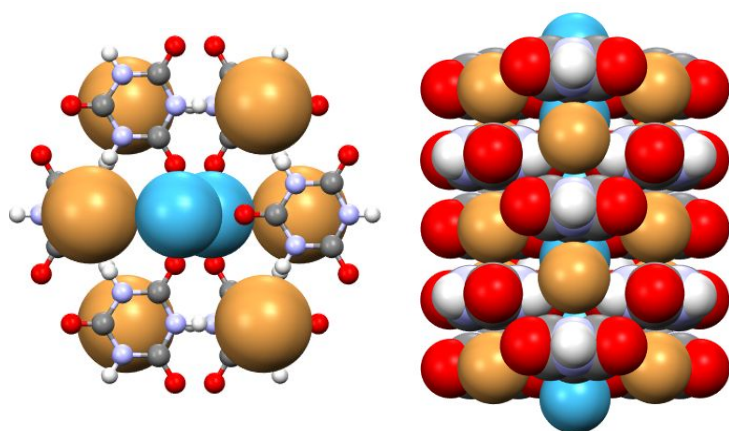


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42 **Figure 3.** Pairs of sodium cations in $\text{CA}\cdot\text{NaBr}\cdot 2\text{H}_2\text{O}$ (view in the 110 plane) are bridged by
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44 water molecules (in blue), which are part of the octahedral coordination spheres.
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50 On passing to the larger cations K^+ , Rb^+ and Cs^+ , we see again formation of anhydrous
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54 ICCs. In the case of the potassium the resulting ICC is quasi-isostructural with the sodium
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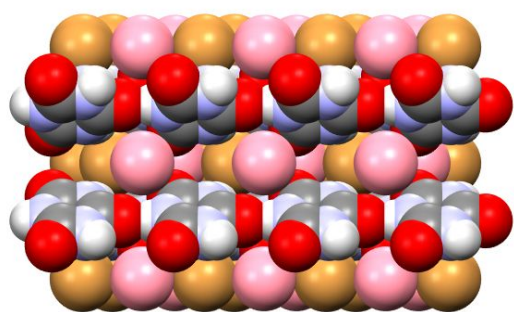
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3 chloride ICC, with each potassium surrounded by six CA molecules, which are intercalated
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7 between anions along the a-axis in channel-like fashion, as shown in figure 4b (compare with
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10 Figure 2).

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15 In these cocrystals as well as in those of the CA•MI type (M = Na, K, Rb) (see below) there
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18 is a clear tendency for the anions to interact directly with the π -system of the cyanuric acid
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21 molecules. This type of anion- π interactions involving cyanuric acid has been the subject of a
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25 computational study by Frontera *et al.*⁴⁵
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45 **Figure 4.** The structure of CA•KBr viewed down the a-axis (left) and a side-view showing the
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47 alternation of bromide anions and CA molecules (right). Light blue: K⁺ cations; brown: Br
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49 anions.
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3 The ionic cocrystals $CA \cdot RbBr$ and $CA \cdot CsBr$ constitute an isomorphous pair (see Table SI-
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7 1). Again, as in the case of the isomorphous pair $CA_2 \cdot RbCl$ and $CA_2 \cdot CsCl$, the packing can be
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10 described as alternating sheets of cations/anions and, this time due to a 1:1 stoichiometry, of
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13 monolayers of CA molecules (see Figure 5).
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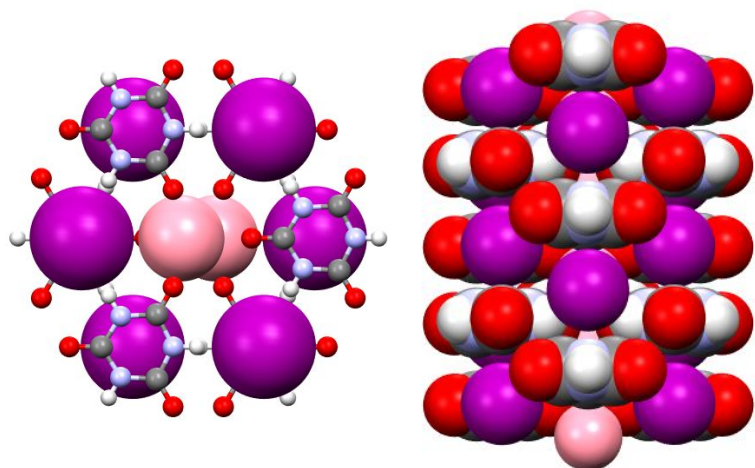


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30 **Figure 5.** The layered structure of $CA \cdot RbBr$ ($CA \cdot CsBr$ is isomorphous), with CA molecules
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33 sandwiched between layers of rubidium cations and bromide anions; layers are extending
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35 parallel to the *ab*-plane. Note the similarity with the layered structure of the 2:1 ICCs
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38 $CA_2 \cdot RbCl$ and $CA_2 \cdot CsCl$, although this time the CA molecules are arranged in monolayers
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44 (1:1 stoichiometry). Pink: Rb^+ cations; brown: Br^- anions.
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48 Ionic cocrystals with MI (M = Na, K, Rb)

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4 In this subset of ICCs we report the successful characterization of two compounds, namely
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7 the anhydrous $\text{CA}\cdot\text{RbI}$, which is isomorphous with $\text{CA}\cdot\text{KBr}$ (see Figure 6), and the
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10 monohydrate $\text{CA}\cdot\text{KI}\cdot\text{H}_2\text{O}$. All efforts to characterize the products of the mechanochemical
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13 reactions of CA with LiI, NaI and CsI were frustrated. In particular, the reaction with LiI
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16 resulted in the formation of a new phase, which was highly hygroscopic and unstable upon
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19 standing in the air at ambient conditions, turning into a deliquescent substance in a matter of
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22 minutes. Analogous behavior was observed for the products with NaI and CsI (see Table 1).
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28 In this respect, $\text{CA}\cdot\text{LiCl}$ appears to afford the only stable combination of size and
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31 stoichiometric ratio for an ICC of CA with the Li^+ cation.
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3 **Figure 6.** The arrangement of cations, anions and CA molecules, viewed down the
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7 crystallographic a -axis in crystalline CA·RbI (left), which is isomorphous with CA·KBr (see
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10 Figure 5), and a side-view showing the alternation of bromide anions and CA molecules
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14 (right). Pink: Rb⁺ cations; purple: I⁻ anions.
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21 As stated above, the two ICCs CA·KBr and CA·RbI are isomorphous (see Table S1): the
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24 Rb⁺ radius is larger than the one for K⁺, but the size of the anion also increases on passing
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27 from Br⁻ to I⁻; therefore a larger anion requires a larger cation. If the cation remains the same
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31 but we use a larger anion, as it is the case with KI, a water molecule is required per formula
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35 unit to "fill in" the extra volume left in the crystal. In this way the monohydrate CA·KI·H₂O is
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38 formed, for which structural determination from single crystal data was possible. CA·KI·H₂O
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42 was found to be quasi-isostructural with the ICCs CA·NaCl, CA·NaBr, CA·KBr and CA·RbI
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45 (see Figure 7): distortion of the packing arrangement is observed, accompanied by loss of
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49 symmetry from orthorhombic Pnma to monoclinic P2₁/c.
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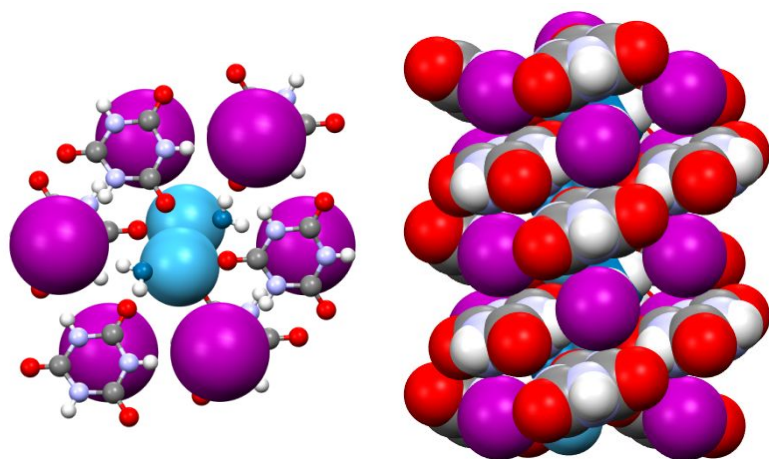


Figure 7. The main packing motif in the crystals structure of $\text{CA}\cdot\text{KI}\cdot\text{H}_2\text{O}$ (view down the b -axis). Note the similarity with the packing arrangement for $\text{CA}\cdot\text{NaBr}$, $\text{CA}\cdot\text{KBr}$ and $\text{CA}\cdot\text{RbI}$.

Light blue: K^+ cations; violet: I^- anions; blue: water oxygens.

It is remarkable how these cocrystal structures can be rationalized according to a simple model based on the ratio between cation and anion sizes (see Table 3).⁴⁶ The ion relative dimensions appear to play a fundamental role in determining not only whether a given ICC of CA can or cannot be obtained but also the stable stoichiometry for the compounds.

Table 3. Shannon & Prewitt ionic radii, used here for ions size comparisons.⁴⁶

Cation	radius* (pm)	Anion	radius* (pm)
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Li ⁺	73		
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Na ⁺	116	Cl ⁻	167
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K ⁺	152	Br ⁻	182
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Rb ⁺	166	I ⁻	206
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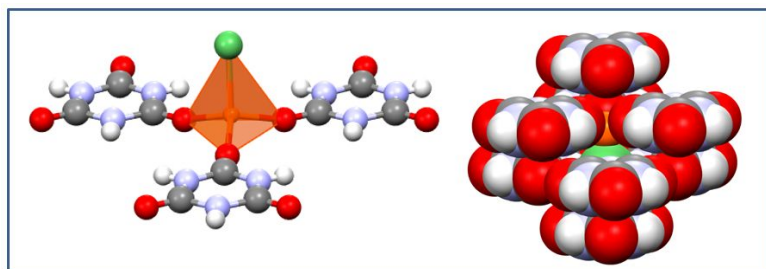
Cs ⁺	181		
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* Coordination number is 6 for all ions except lithium, for which the C.N. 4 is considered.

Three situations can be distinguished:

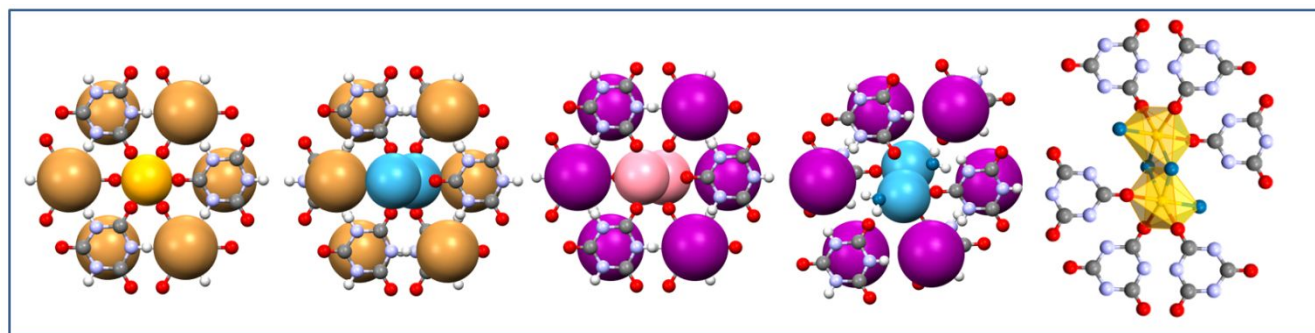
i) When the size of the cation is markedly smaller than the size of the anion, as in the case of LiCl (Scheme 3), the lithium cation is tetrahedrally coordinated by CA molecules and a chloride anion, but the ICC is better described as formed by Li⁺Cl⁻ "ionic pairs" surrounded by eight CA molecules in a cubic fashion;¹⁷ the CA:MX stoichiometric ratio is 1:1. Increasing the anion size further does not seem to allow stable packings, and crystalline CA·LiBr, CA·LiI are not obtained.

Scheme 3. The cation size is markedly smaller than the size of the anion: CA·LiCl.¹⁷



ii) When the size of the cation is smaller than the size of the anion (Scheme 4), ICCs with 1:1 stoichiometry are observed forming isomorphous (NaBr), isostructural (KBr, RbI) or quasi-isostructural (KI, with the presence of water) structures with respect to $CA \cdot NaCl$; in the case of NaBr water can be accommodated in the crystal, and a derivative structure with pairs of cations bridged by water molecules is also observed.

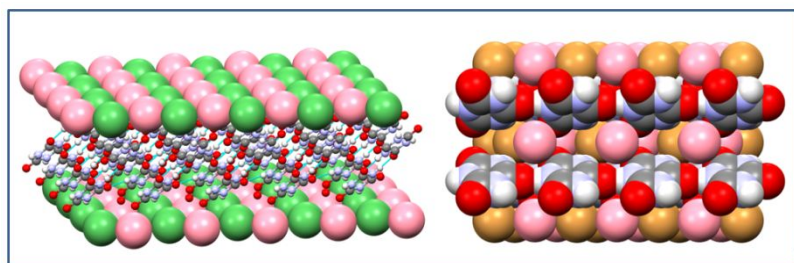
Scheme 4. The cation size is smaller than the size of the anion. From left to right: $CA \cdot NaBr$, $CA \cdot KBr$, $CA \cdot RbI$, $CA \cdot KI \cdot H_2O$, $CA \cdot NaBr \cdot 2H_2O$



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3 iii) When cation and anion have similar radii, layered structures are obtained (Scheme 5).

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7 The stoichiometry is 2:1 in the case of the chlorides RbCl and CsCl, and 1:1 for the bromides
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10 RbBr and CsBr.

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15 **Scheme 5.** The cation size is similar to the one of the anion. Left: $CA_2 \cdot RbCl$ (and
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17 isomorphous) $CA_2 \cdot CsCl$); right: $CA \cdot RbBr$ (and isomorphous $CA \cdot CsBr$)
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33 These trends are reminiscent of those relating structural types of crystalline alkali halides
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36 with the notable difference that, in these ICCs, it is the very stoichiometry of the product (1:1
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39 or 2:1) that is dictated by the need to obtain close packed crystal structures. In this respect we
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43 take as a negative counterproof that we have been unable to obtain ICCs with LiBr and LiI.
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47 Packings of the large anions with the very tiny Li^+ cation appears to lead to unstable
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51 arrangements. In fact, the products of the mechanochemical reactions are extremely
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55 hygroscopic and deliquescent materials that proved impossible to handle. Similarly, the
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3 passage from NaCl to RbCl and CsCl marks the “switch” in stoichiometry from 1:1 to 2:1 with
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7 the chlorides. In this respects, it is noteworthy that no ICC could be obtained with KCl,
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10 suggesting that the K^+ / Cl^- radius ratio is not optimal either in 1:1 or in 2:1 cocrystals
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14 structures.

18 CONCLUSIONS

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22 Mechanochemical mixing of solid reactants is not only a viable, solvent-free, alternative to
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25 solution methods for the preparation of new compounds and materials, but often it is the only
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28 way to overcome the problems caused by large differences in solubilities of the reactants.^{2,3}
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32 This is especially true in crystal engineering exercises aimed to the preparation of hybrid
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35 materials between organic fragments and inorganic salts or coordination compounds, e.g.
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38 ionic cocrystals.⁶ As a matter of fact, mechanochemical methods have been successfully
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41 applied in a number of cocrystal syntheses. For example, mechanical mixing of urea with Mg
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44 and Ca salts have been used to prepare ionic cocrystals with the aim to provide additional
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47 primary and secondary nutrients, such as P, Ca, Mg and S, in sustainable soil fertilization.⁴⁷⁻⁵⁰
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4 In this paper we have systematically applied grinding and ball-milling in both dry and wet
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7 conditions to prepare an entirely new series of ICCs of CA with alkali halides. Beside the
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10 interest in associating cyanuric acid with soluble alkali salts for its potential industrial
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13 applications^{22, 51} there is the attractive possibility of using stable crystalline solids containing
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16 neutral CA in solar-blind nonlinear optical material in NLO technology.²⁷
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22 The main problem to overcome in mechanochemical preparations is polycrystalline nature
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25 of the products that does not permit single crystal structure analysis. Furthermore, the
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28 extreme difference in solubility between cyanuric acid and the alkali salts prevents the
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31 recrystallization of the products as single crystals because when the polycrystalline product is
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34 dissolved in water immediate separation of the insoluble organic moiety from the soluble
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37 inorganic component is observed. It has been necessary to recur to systematic crystal
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40 structures determination directly from powder diffraction data allowing, inter alia, to rationalize
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43 the reasons for the absence of some ICCs and also to identify structural types and reasons
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46 for the switch from 1:1 to 2:1 stoichiometry on increasing cation and/or anion sizes.
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3 ASSOCIATED CONTENT
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8 **Supporting Information.** Crystallographic details and XRPD patterns are accessible for the
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11 structures reported. This material is available free of charge via the Internet at
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15 <http://pubs.acs.org>.
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31 **Author Contributions**
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35 The manuscript was written through contributions of all authors. All authors have given
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38 approval to the final version of the manuscript.
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50 assistance with TGA measurements.
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ABBREVIATIONS

CA cyanuric acid, XRPD X-ray powder diffraction.

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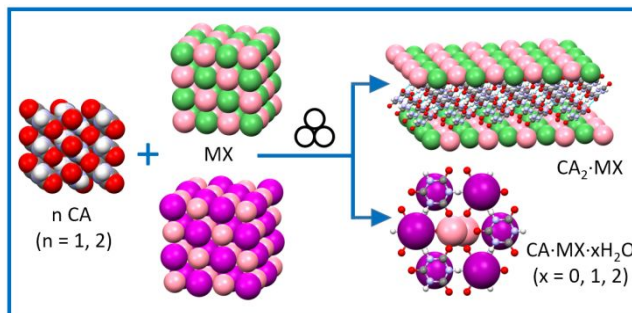
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Mechanochemical preparation and solid-state characterization of 1:1 and 2:1 ionic cocrystals of cyanuric acid with alkali halides.

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Synopsis

Mechanochemical mixing of cyanuric acid and alkali halides, which show extreme differences in solubility, is a viable, solvent-free method to prepare ionic cocrystals with potential industrial and technological applications.