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Organic-inorganic ionic co-crystals: A new class of multipurpose compounds

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Organic–inorganic ionic co-crystals: a new class of multipurpose compounds

Dario Braga, * Fabrizia Grepioni and Oleksii Shemchuk

In this highlight, the reasons for the widespread interest generated by ionic co-crystals, namely those formed by a neutral molecule and a salt, are addressed. In particular, the class of compounds obtained by co-crystallization of neutral organic molecules and inorganic salts (*e.g.* alkali and alkaline earth halides, sulfates, phosphates *etc.*) is discussed with the focus on their applications in diverse areas, such as pharmaceuticals, food and fertilizers, and also in chiral resolution. It is argued that, in terms of structure and intermolecular bonding features, these compounds do not differ from classical coordination compounds (complexes) and that their popularity arises from the effectiveness of the organic–inorganic assembly to enhance thermal stability, improve particle size and morphology and change significantly the solubility and dissolution rate with respect to those of the pure active ingredients.

If *making crystals with a purpose* is the paradigm of crystal engineering, then the synthesis of co-crystals fulfills this objective.[1] Co-crystals are presently one of the major targets in the quest for new materials with novel or improved supramolecular properties.

Margaret Etter perceived long ago the importance of combining in the solid state the properties and characteristics of different molecules, to obtain not their mere sum, but entirely new collective properties.[2] Fig. 1 shows the assembly, prepared and characterized by Etter, of six cyclohexanedione molecules around a benzene molecule. This aggregate was chosen as the first logo of this journal in 1998.[3]

Since benzene is not solid at room temperature, Etter's cyclamer should be described as a solvate (see below); the crystal packing organization is dictated by the arrangement of six dione molecules around a single benzene molecule, trapped by a web of C–H···O hydrogen bonds. In broad terms, however, Etter's cyclamer can also be regarded as a pseudo co-crystal that provides a good example of supramolecular recognition and assembly in the solid state.

The definition of co-crystals is not straightforward and has been addressed by various authors.[4] It is nowadays generally assumed that co-crystals are formed by two or more components that form stable solid aggregates on their own at

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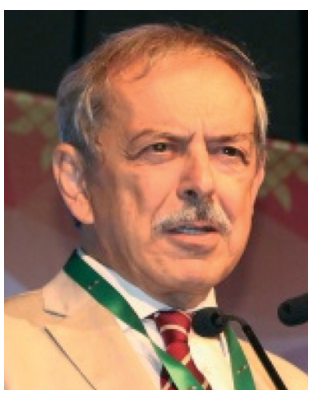

Dario Braga

Dario Braga is a full professor of chemistry. He is the author or co-author of about 500 publications on solid state chemistry and crystal engineering; he was the first scientific editor of CrystEngComm. His current interests include the study of hybrid organic–inorganic molecular and ionic cocrystals, polymorphs and hydrates. In 2005, together with his group, he founded the spinoff company PolyCrystalLine spA. He is Director of the Institute of Advanced Study of the University of Bologna.

Fabrizia Grepioni

Fabrizia Grepioni is a full professor of chemistry at the University of Bologna. She spent some years in the industry before getting a PhD at the University of Bologna, and for six years she was an associate professor at the University of Sassari. She has published about 350 papers on solid state chemistry and crystal engineering. Her major interests involve the study of multiple crystals forms of organic/inorganic solids, and of photoactive molecular materials.

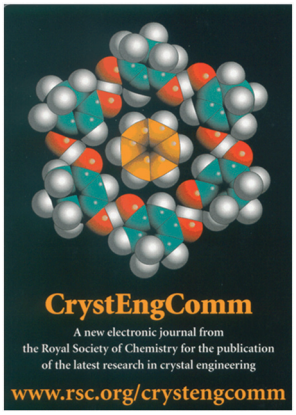

Fig. 1 The assembly of six cyclohexanedione molecules around a benzene used as a logo of the postcard announcement of *CrystEngComm* in 1998.

room temperature.[5] This is also, at least in the opinion of these authors, the most useful definition of a co-crystal, as it allows the discussion of the changes in crystalline properties afforded by co-crystallization with direct reference to those of the separate components under TPS conditions. This is particularly relevant when dealing with active pharmaceutical ingredients (APIs). Co-crystals offer new ways to design or to alter the properties of solid active species (*vide infra*).

The number of possible combinations between active molecules and ancillary co-formers or other active molecules is, in principle, without limit. For this reason, co-crystals have become attractive research objects in all areas dealing with molecular crystals (*e.g.* food, pharma, high energy materials, fertilizers, *etc.*).[6–12] Ternary co-crystals have also been reported.[13] A recent RSC book was dedicated exclusively to pharmaceutical co-crystals[14] while a comprehensive view and update on polymorphism occurrence for multicomponent systems, including co-crystals, has been provided recently.[15] Co-crystallization has also proven to be instrumental to extend intellectual property rights for drugs with expiring patent protection.[16] The FDA periodically publishes updated guidelines to cover the co-crystal definition and evaluation, the most recent dating February 2018.[17]

In terms of preparative routes, undoubtedly, mechanochemical methods (*e.g.* grinding, kneading, wet compression, *etc.*) have proved their efficacy in the often quantitative synthesis of new co-crystalline materials.[18] Crystallization from solution is also of paramount importance, often requiring an accurate definition of the solubility profiles of the active ingredient and of the co-former in a series of solvents in order to optimize the co-crystallization conditions.[19]

This highlight is focused on the small, but steadily growing, in terms of importance and impact, class of "ionic" co-crystals.

"*Natura non facit saltus*"

When dealing with ionic co-crystals, a preliminary distinction needs to be made. When hydrogen bonds between components are involved, the position of the proton within an acid–base pair system (for example the hydrogen bond between a carboxylic group and an amine) depends on the relative acid–base strength and, obviously, on the temperature. In this respect, the distinction between a fully "molecular" co-crystal system, *e.g.* XH···Y with no proton transfer from the acidic (proton donor) group to the basic (proton acceptor) group to an "ionic" system, *e.g.* $X^{(-)}\cdots HY^{(+)}$, with the anion and cation resulting from proton transfer from the acid to the base, can be rather semantic and may depend on the experimental conditions.

We observed long ago, in a combined X-ray and solid state NMR spectroscopy study, that bulk properties (such as melting point and solubility) often do not correlate with the proton position along the X–H···Y bond. In the systems under investigation, the correlation was with the odd–even alternation of aliphatic chain lengths, rather than with the molecular or salt nature of the co-crystal.[20] Similar observations made by others have led to the understanding of the "*salt-co-crystal continuum*" when dealing with hydrogen bonded co-crystals.[21] It has been pointed out that salts are usually observed when $\Delta pK_a = pK_a(\text{acid}) - pK_a(\text{base})$ is greater than 2 or 3, while a co-crystal is usually formed if $\Delta pK_a < 0$.[21] The first type of ionic co-crystal is therefore made of a neutral molecule A hydrogen bonded to a salt formed by its anion (or cation) and an inorganic cation (or anion) *viz.* $(nA)A^-B^+$ (or $(nA)A^+B^-$). A good example of this type is provided by the co-crystal formed by benzoic acid and sodium benzoate[22] (see Fig. 2). With the same scheme in mind, one can also conceive a ternary system, *e.g.* $(nA)C^+B^-$, where a neutral molecule is hydrogen bonded to a salt between a molecular ion and a metal cation. An example of this second type of ionic co-crystal is shown in Fig. 3, where the structure of the co-crystal between neutral

Oleksii Shemchuk

Oleksii Shemchuk earned his master's degree in Pharmacy in 2011 from the National University of Pharmacy (Ukraine), where he worked as a chief laboratory assistant in the Department of Pharmaceutical Chemistry until 2013. He won an Erasmus Mundus Masters Scholarship and in 2015 he obtained a second master's degree – in chemistry – from the University of Bologna. He is currently a PhD student in the Crystal Engineering group at the University of Bologna under the supervision of Prof. Grepioni. His current research interests focus on the field of multiple crystal forms, molecular and ionic co-crystals, chirality and solid solutions.

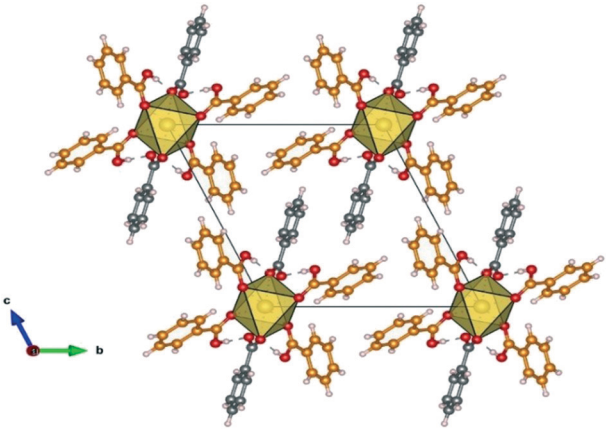

Fig. 2 The co-crystal formed by benzoic acid and sodium benzoate (QQQGMA0) is an example of a "molecular" ionic co-crystal made of a neutral molecule and its salt with an inorganic cation, *viz.* (nA)A^-B^+.

4-dimethylamino benzoic acid and the salt K^+ 3,5-dinitrobenzoate is reported.[23]

The third type of ionic co-crystal is the organic–inorganic aggregate between an organic molecule and an inorganic salt (whether constituted of monoatomic or polynuclear ions), *viz.* (nA)·M^+X^-. In these organic–inorganic systems, the principal interactions are those established by the organic moiety with the metal cations on the one hand and the inorganic anions on the other. Usually, oxygen or nitrogen atoms donate electrons towards the metal cation, while hydrogen bonds are formed between the hydrogen donor groups on the organic moiety and the anions, most often halides, but also PF_6^-, BF_4^- $H_2PO_4^-$, HSO_4^-, *etc.* As pointed out in one of our early reports,[24] the interactions between the organic molecule and the ions resemble those that solvent molecules establish with ions in solution or in solid solvates. These types of ionic co-crystals can also be viewed as a complex between organic type ligands and metal cations. The effects of ionicity in salts, solvates, co-crystals, and ionic co-crystals with respect to ionic liquids have also been analysed.[25]

An example of an ionic co-crystal of the type (nA)·M^+X^- formed by an organic ingredient and an alkali halide is shown in Fig. 4, where the structure of the co-crystal between barbituric acid and KBr is shown.

There are numerous examples of complexes of alkali and alkaline earth metal cations in the CSD,[26] as there is almost a continuum of structural analogies between these complexes and coordination complexes with transition metals. Indeed, *natura non facit saltus*. A discussion of these aspects is, however, beyond the scope of this highlight. We touched upon this point only in order to stress that the *ionic co-crystal* definition has entered the field, following the need to identify the utilitarian objective of preparing, on purpose, organic–inorganic materials by using inorganic salts to alter the solid-state properties of the active ingredients. In the following, we will provide examples of how organic–inorganic co-crystals have found applications in a variety of areas of applied crystal engineering.

Pharmaceutical ICCs

Altering the solid-state properties of active pharmaceutical ingredients has been one of the first goals of "crystal makers" since the beginning of the crystal engineering era. This is one of the reasons that explain why the co-crystal route has been taken by many researchers.[1,27]

A wide range of solid state properties (see Table 1) can be modified or generated by co-crystallization of organic active ingredients with inorganic co-formers. One of the early examples of the co-crystallization of active ingredients with inorganic salts was indeed the result of an attempt to improve lithium therapeutics of lithium salicylate and nicotinate by forming co-crystals with the amino acid L-proline.[28] These ionic co-crystals, especially lithium salicylate (Fig. 5), appeared to afford a better safety profile when compared with lithium carbonate (Li_2CO_3), which is FDA-approved.

Another good example is provided by 2-oxo-1-pyrrolidine acetamide, known as piracetam, first synthesized in 1964 at

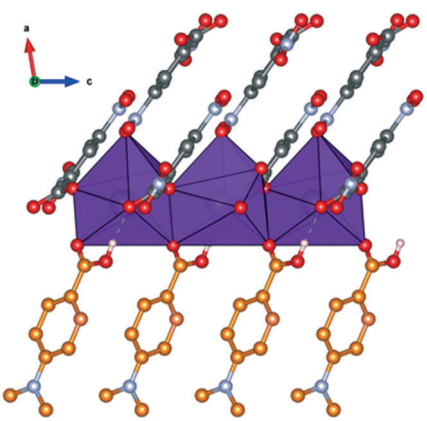

Fig. 3 The 1:1:1 co-crystal between neutral 4-dimethylamino benzoic acid and the salt K^+ 3,5-dinitrobenzoate. Hydrogen atoms are omitted for clarity.

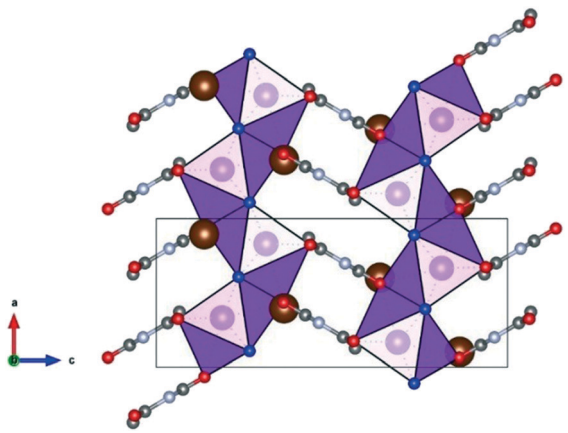

Fig. 4 The ionic co-crystal formed by barbituric acid and KBr is an example of an organic–inorganic ionic co-crystal (nA)·M^+X^-. Hydrogen atoms are omitted for clarity.

Table 1 Solid state properties that can be affected, with respect to the active ingredient, by the formation of ionic co-crystals

- Solubility in apolar solvents
- Solubility in water and other polar solvents
- Intrinsic dissolution rate
- Melting points
- Thermal and photo stability
- Colour
- Hygroscopicity
- Spontaneous chiral resolution
- Biological activity (co-drug)
- Morphology
- Particle size distribution

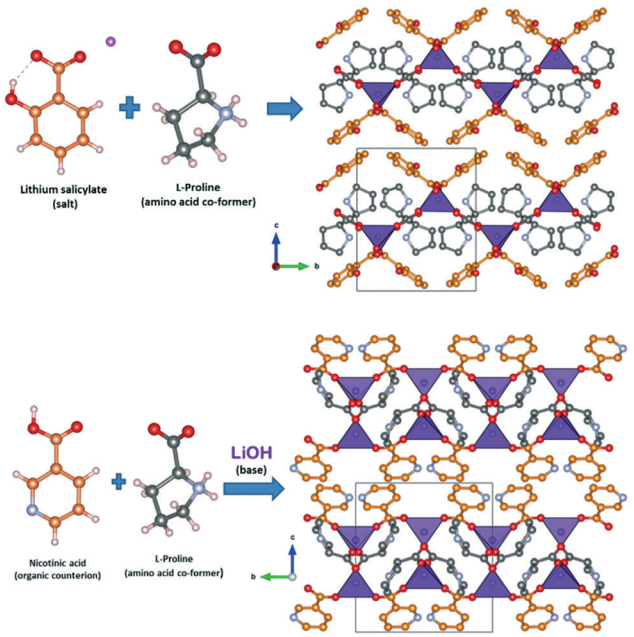

Fig. 5 The ionic co-crystal obtained by reacting L-proline with lithium salicylate (top) and with nicotinic acid and LiOH (bottom) (see ref. 28); hydrogen atoms are omitted for the sake of clarity.

UCB and belonging to the family of nootropic cognitive enhancing medicines, marketed also for the treatment of vertigo and events associated with ageing. It is currently approved in over 100 countries as Nootropil®. Organic–inorganic ionic co-crystals of piracetam can easily be prepared by mechanical treatment of piracetam with lithium salts, such as LiCl (see Fig. 6) and LiBr.[29]

The ICC between piracetam and LiCl is a proof of concept of the purposeful combination in the solid state of the properties of diverse materials, because both piracetam and LiCl are utilized in neuroscience. As a matter of fact, the lithium ion is used medically in patients affected by bipolar disorder and also in conjunction with antidepressants. For this reason, the co-crystal can also be seen as a potential co-drug.

Another example of the use of ICCs to address specific drug handling problems is provided by the co-crystal between glucose and LiCl.[30] The organic molecule was used as a co-former to increase the stability of the lithium halide towards

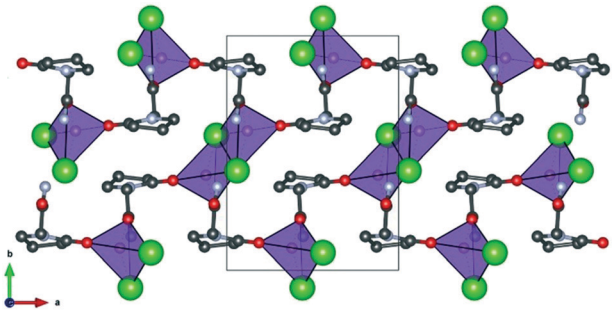

Fig. 6 The organic–inorganic ionic co-crystal prepared by mechanochemical reaction of the active pharmaceutical ingredient piracetam with LiCl. Hydrogen atoms are omitted for clarity.

moisture uptake. The idea was to use co-crystallization as a tool to improve the stability of lithium salts towards humidity. However, blood and brain pharmacokinetics experiments showed no significant difference between the ICC and lithium chloride itself, indicating that the co-crystal dissociated before reaching its site of action. The structure of the ICC with LiCl could not be determined. Fig. 7 shows the structure of the LiBr analogue (FOWVIY).

Ionic co-crystals of carbamazepine (CBZ) of the formula $[Na(CBZ)_4(MeOH)][I]\cdot H_2O$, $[Na(CBZ)_5][I_3]$, have also been reported as an example of a carbamazepine compound containing metal cations.[31] The interest stems from the possibility of using ICCs in drug selection. The active ingredients brivaracetam and seletracetam, also prepared and patented by UCB, have been utilized in the preparation of ionic co-crystals. Besides the interest in preparing LiCl derivatives as co-drugs,[32] the formation of co-crystals with the inorganic salts $MgCl_2$ and $CaCl_2$ (see Fig. 8 for the structure of $SEL_2\cdot MgCl_2\cdot 4H_2O$)[33] has been used to improve thermal stability, hygroscopicity, and crystal morphology with respect to pure drugs. In the case of seletracetam, it was possible to change from the tiny needles formed by the pure drug, to the larger, well-shaped, triangular crystals obtained as ICCs with $MgCl_2$, while co-crystallization of brivaracetam with $CaCl_2$ produces rectangular rod-like crystals.

ICCs in agriculture

The ICC technology has recently been applied in the field of agriculture and fertilizers, opening up a field of great interest. Jonas Baltrusaitis and collaborators have reported[34] that

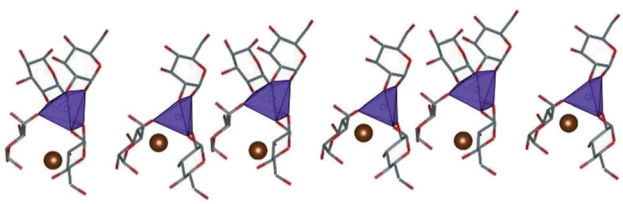

Fig. 7 The structure of the ICC between glucose and LiBr (FOWVIY). Hydrogen atoms are omitted for clarity.

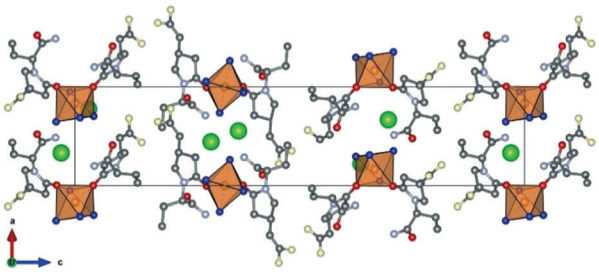

Fig. 8 The structure of the ICC between the API seletracetam and $MgCl_2$ ($SEL_2{\cdot}MgCl_2{\cdot}4H_2O$). Water oxygen atoms are in blue; hydrogens atoms are omitted for clarity.

mechanochemical treatment of urea with Mg^{2+} and Ca^{2+} salts results in the facile synthesis of ionic co-crystals as fertilizer materials, able to enhance nitrogen cycle sustainability by decreasing NH_3 emissions.

It has been reported that urea ICCs such as $CaSO_4{\cdot}4CO(NH_2)_2$, $Ca(H_2PO_4)_2{\cdot}4CO(NH_2)_2$, $Ca(NO_3)_2{\cdot}4CO(NH_2)_2$, $MgSO_4{\cdot}6CO(NH_2)_2{\cdot}0.5H_2O$, $Mg(H_2PO_4)_2{\cdot}4CO(NH_2)_2$ and $Mg(NO_3)_2{\cdot}4CO(NH_2)_2{\cdot}xH_2O$ can be prepared with a clean, synthetic procedure based on solid state reactions. In the case of $CaSO_4{\cdot}4CO(NH_2)_2$, the conversion of the parent materials into the co-crystals was reported to be complete within 10 min of milling. Nitrogen release from urea *via* natural decomposition of $CaSO_4{\cdot}4CO(NH_2)_2$ to yield NH_3 was demonstrated to be significantly inhibited,[34] but the actual physical basis or underlying mechanisms of this inhibition – biological or physicochemical – are not known and should serve as fruitful areas of further research. This discovery has major implications for the global nitrogen management cycle.[35] Fig. 9 (left) shows the structure of the calcium sulfate ionic co-crystal $CaSO_4{\cdot}4CO(NH_2)_2$ as determined by Boeyens *et al.*,[36] while Fig. 9 (right) shows the effect of ammonia release over time with respect to uncomplexed urea. The same authors have also reported applications of the same reasoning to diurea sulfates and to urea phosphate $CO(NH_2)_2{\cdot}H_3PO_4$.[37]

Cyanuric acid is also employed in agriculture as a source of nitrogen[38] although, because of its poor solubility in water and of its toxicity, is usually applied weeks in advance of planting.[39] The co-crystals of NaCl with cyanuric acid show a

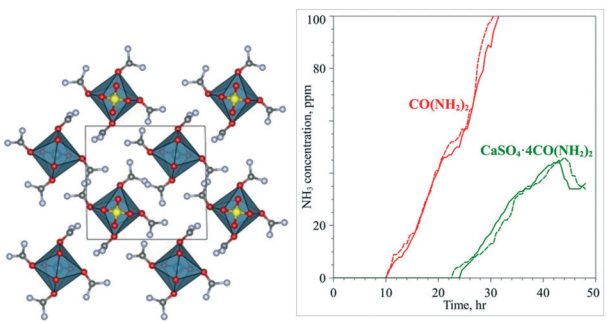

Fig. 9 The structure of the urea co-crystal $CaSO_4{\cdot}4CO(NH_2)_2$ (left), and a plot of the NH_3 emission testing (right). Hydrogen atoms are omitted for clarity (adapted from ref. 34 with permission from ACS).

significant increase in solubility and also in intrinsic dissolution rate.[40] Fig. 10 shows the structure of the co-crystal of cyanuric acid with NaCl and a comparison of the IDRs.

ICCs in food

The preparation of compounds based on the association of sugars with inorganic salts dates back more than a century. Since the subject of ionic co-crystals with carbohydrates has been recently reviewed by Oertling,[41] we only need to recall, in the context of this highlight, a few significant examples. Fig. 11 shows a number of carbohydrates that have been found to form stable co-crystals with salts, in particular pentoses (*e.g.* ribose, arabinose and xylose), hexoses (*e.g.* glucose, fructose, galactose and mannose), and disaccharides (*e.g.* sucrose, lactose and trehalose). Since combining NaCl with carbohydrates allows introduction of a combined source of sodium and calories, the idea of ionic co-crystals with sugars is rather interesting from a nutraceutical point of view.

The preparation of a compound of glucose and sodium chloride in a 2 : 1 ratio, an ionic co-crystal *ante litteram*, was first described in 1825 by Calloud.[42a] The same compound was later cited in 1843,[42b] but it was only in 1927 that the exact composition, together with the phase diagram of the water–glucose–sodium chloride system, was established.[42c,d] It is also worth mentioning that Pasteur found this compound in the urine of diabetics in 1851.[42e] The structure, determined in 1991 by Ferguson *et al.*,[43] is shown in Fig. 12.

Another interesting example is provided by the co-crystal of sucrose with sodium chloride, which was first obtained in 1839 (ref. 44) by simple evaporation of table salt and sugar

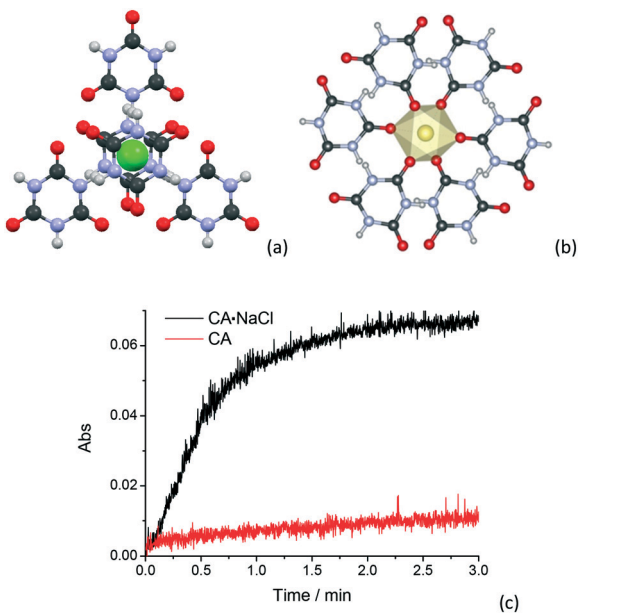

Fig. 10 Ball-and-stick representation of the chloride (a) and sodium (b) ion first coordination spheres in the ICC between cyanuric acid and NaCl; (c) graph representing the intrinsic dissolution rate of CA·NaCl (black curve) and CA (red curve) in water at 298 K (reprinted with permission from RSC).

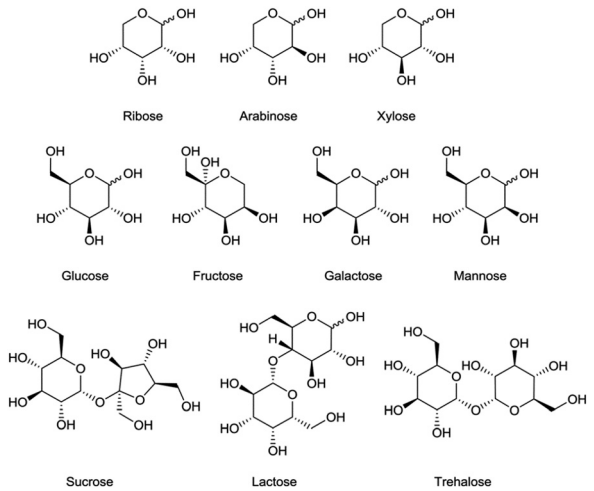

Fig. 11 Carbohydrates that have been found to form stable co-crystals with salts (reprinted with permission from RSC).

from an aqueous solution. The compound is deliquescent, and the structure has not been fully determined yet, while the composition of the bromide analogue was determined to be sucrose·NaBr·$2H_2O$ (ref. 45) (see Fig. 13).

In a more recent report, the ionic co-crystals of sodium chloride with three different carbohydrates, together with the optimization of the process on a multigram, semitechnical scale, have been described.[46] The main feature in common between the structures of D-(−)-ribose·NaCl and D-(+)-sucrose ·NaCl·$2H_2O$ (see Fig. 14) is the presence of a sodium chloride "ion pair".

An even more remarkable situation has been observed in the co-crystal of cyanuric acid with LiCl,[40] where a Li^+Cl^- ion pair is completely encapsulated in an organic shell of cyanuric acid molecules (see Fig. 15).

ICCs and chirality

The use of co-crystallization as an instrument to resolve enantiomers from a racemate has been successfully employed in a number of cases.[47,48] The basic idea is that an enantiopure co-former ought to interact selectively and differently with the enantiomers, leading to the formation of different "supramolecular diastereomers" with the enantiomers of opposite chirality. Co-crystals of enantiopure (homochiral) and

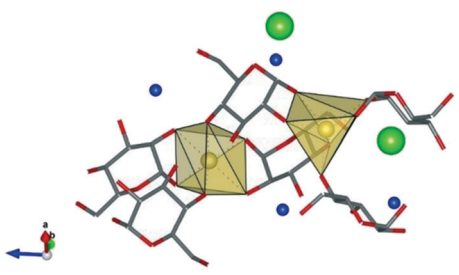

Fig. 12 Representation of the crystal structure of (α-D-glucose)$_2$·NaCl ·H_2O (VEGLOI01). Hydrogen atoms are omitted for clarity.

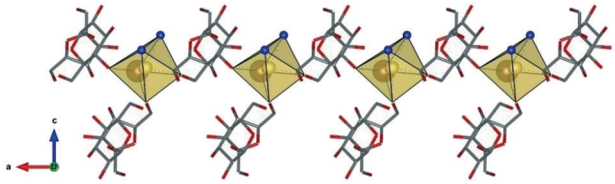

Fig. 13 Crystal structure representation of the ionic co-crystal sucrose·NaBr·$2H_2O$ (DINYOO10). Hydrogen atoms are omitted for clarity.

achiral amino acid zwitterions with Li^+ and Cl^- or NO_3^- counterions have also been reported.[49]

Leyssens *et al.* have shown enantioselective co-crystal formation in the case of 2-(2-oxopyrrodin-1-yl)butanamide (etiracetam) with *S*-mandelic and *S*-tartaric acid (see Fig. 16), while co-crystals are not formed with the *R*-etiracetam enantiomer.[50] Conglomerate formation was also reported as a result of crystallization from a racemate *via* formation of molecular co-crystals.[51,52]

Mechanochemical methods have been used to prepare ICCs of L- and DL-histidine with lithium halides LiX (X = Cl, Br, and I).[53] It was found that conglomerate co-crystals of the L- and DL-histidine separate enantiomers can be obtained in the case of LiI, with spontaneous chiral resolution and formation of enantiopure crystals L-His·LiI·1.5H_2O and D-His·LiI ·1.5H_2O, while, in the cases of LiCl and LiBr, the racemic compounds DL-His·LiCl·1.5H_2O and DL-His·LiBr·1.5H_2O were obtained. The somewhat surprising aspect of this result was the fact that the chiral preference shown by the formation of a conglomerate with LiI was, somewhat, maintained also in the racemic crystals. Crystals of the DL-His·LiCl·1.5H_2O and DL-His·LiBr·1.5H_2O racemic compounds are in fact constituted of separate layers of enantiopure L-His·LiCl/Br·H_2O and D-His ·LiCl/Br·H_2O joined by water bridges (see Fig. 17).

On discussing lithium coordination in ICCs, it is worth recalling the early observations made by Margaret Etter in the preparation of a series of succinimide co-crystals with lithium salts, which all showed the same type of tetrahedral coordination.[54] Interestingly, a series of negative results in the preparation of co-crystals (NaF, NaCl, NaBr, NaI, $NaPF_6$, KCl, KBr, KI, $MgBr_2$, $MgSO_4$, $CaBr_2$) were also described in

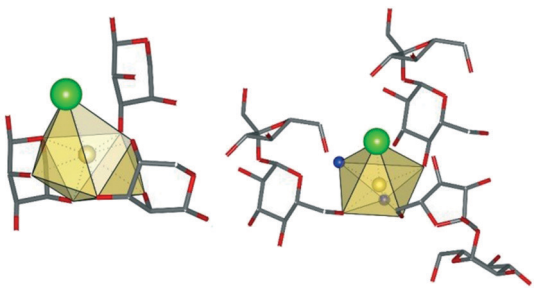

Fig. 14 The structures of (left) D-(−)-ribose·NaCl and (right) D-(+)-sucrose·NaCl·$2H_2O$. Note the presence of distinct Na^+Cl^- ion pairs in both crystals. Hydrogen atoms are omitted for clarity.

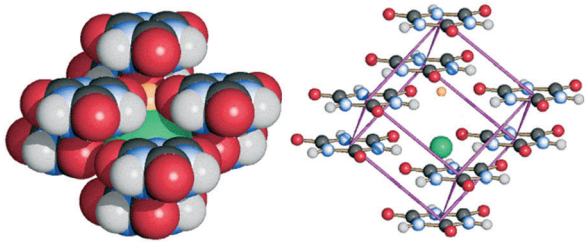

Fig. 15 The co-crystal of cyanuric acid with LiCl, where a Li^+Cl^- ion pair is encapsulated in a shell of cyanuric acid molecules (reprinted with permission from RSC).

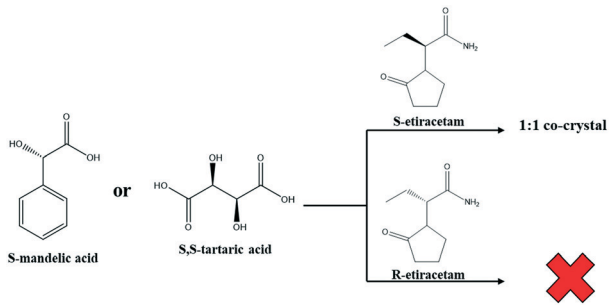

Fig. 16 The enantioselective co-crystal formation in the case of the *S*-enantiomer of 2-(2-oxopyrrodin-1-yl)butanamide (*S*-etiracetam) with *S*-mandelic and *S*-tartaric acid. The same reaction with *R*-etiracetam does not lead to co-crystal formation.

the same paper, and the reason for the lack of success was attributed to the difference in ionic radii. Indeed, the mechanochemical reaction of D- and L-histidine and of DL-histidine with CaX_2 salts has yielded different results from those described above with LiX salts, because of the preference of the calcium cation for higher coordination numbers.[55] The octahedral coordination around the calcium cations did not lead to chiral discrimination of the type observed with the tetrahedral coordination of the lithium cation, but rather generated

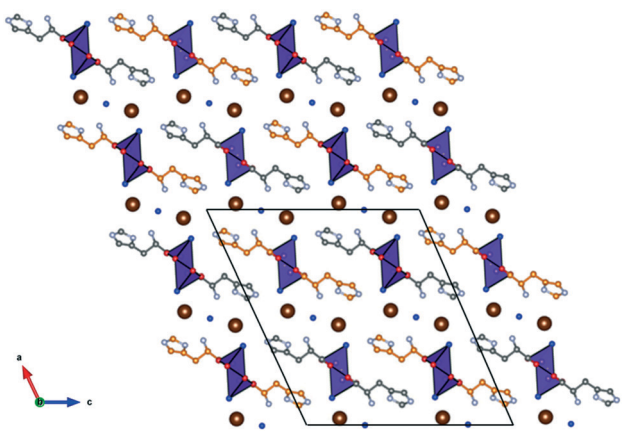

Fig. 17 The co-crystal formed by the enantiopure chains of L-histidine and *R*-histidine coordinated to the Li cations in the crystal of racemic DL-His·LiCl/Br·1.5H_2O. The different colors assigned to histidine mark the segregation of the two enantiomers in chains extending along the *b*-axis. Hydrogen atoms are omitted for clarity.

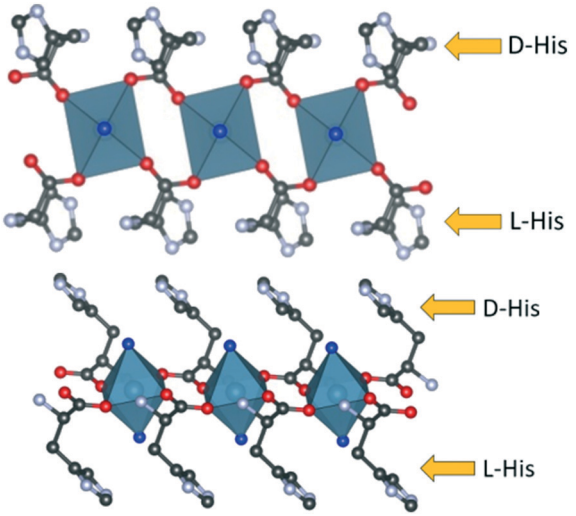

Fig. 18 Ribbons of histidine bridged calcium cations in crystalline (DL-His)$_2$·$CaCl_2$·3H_2O. Histidine ligands of opposite chirality are linked on the opposite rims. Hydrogen atoms are omitted for clarity.

coordination polymers with enantiopure edges, *i.e.* with a ligand of the same chirality on the same side of the calcium octahedral coordination (see Fig. 18).

It is worth mentioning here that in the last few decades, in the search for novel nonlinear optical active (NLO) systems, ionic cocrystals of enantiopure amino acids with alkali metal halides have been investigated, synthesized and grown in large crystals of optical quality under the name "semiorganic materials" (as opposed to purely organic crystals).[56] They have shown good mechanical and thermal properties and possess high nonlinearity, a wide transmission range, high conversion efficiency and high laser damage threshold.[56]

Conclusions

In this highlight, we have focused on the design, preparation and evaluation of co-crystals formed by organic molecules and inorganic salts. We have argued that this special type of ionic co-crystal possesses features that make it a worthwhile target for research in diverse areas of crystal engineering, from pharmaceutical to food, from fertilizers to chirality, *etc.*

Crystal formed between organic and inorganic systems have been known for long but only recently have they been considered as materials with bulk properties that could be "tuned" by engineering aggregates that would not simply add, but combine the physico-chemical properties of the individual components. Indeed, one of the main motivations to research co-crystals is the possibility of altering the physico-chemical properties of a given crystalline molecular material, by forming a different crystalline solid with the same molecules of choice. A similar conceptual frame is used to compare the properties of solvates or hydrates with the corresponding unsolvate/anhydrous compounds. It appears, from the examples provided above, that co-crystallization with inorganic salts can have an

even higher impact on the properties of the molecular materials for a diversity of applications (drugs, fertilizers, aliments, racemates, and NLO active systems).

In terms of preparative methods, besides conventional crystallization from solution, mechanochemical mixing, whether dry or wet grinding,[18] has most certainly proved to be the method of choice. Direct reaction between an active ingredient and inorganic salts is easy to carry out, easily scalable from manual mixing in an agate mortar or ball milling to large scale facilities, besides being economically convenient (save on solvents), environmentally friendly (solvent disposal), *etc.* It is also important to point out that the progress in co-crystal solid state chemistry has undoubtedly been assisted by the developments in computational and instrumental facilities and in the increasing capacity to determine the structure of molecular materials directly from powder diffraction. Unless one is successful in growing single crystals (perhaps *via* seeding of a solution obtained from the powdered sample), the structure of a product obtained mechanochemically is not easily accessible. A significant step forward has been made possible by the increasing capacity to solve structures from powder diffraction data. We should also mention that significant step forwards have been made in high resolution solid state NMR spectroscopy.

And yet we have shown that compounds that nowadays would be described as ionic co-crystals have been prepared and characterized long before. We have cited examples that date back almost two centuries. Nonetheless, the purposeful preparation of compounds in which not only the chemical, biological, and pharmaceutical, but also the magnetic, spectral and optoelectronic, chiral features of organic molecules are convoluted with the properties of inorganic salts results in a class of novel compounds on their own. What is novel is not their structure as much as the idea of exploiting the resulting properties in a diversity of applied fields.

We might as well conclude this highlight with the words of the Nobel laureate W. L. Bragg: "*the important thing in science is not so much to discover new facts as to discover new ways of thinking about them*".

Conflicts of interest

There are no conflicts to declare.

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