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Steps towards a nature inspired inorganic crystal engineering

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This Perspective outlines the results obtained at the University of Bologna by applying crystal engineering strategies to develop nature inspired organic–inorganic materials to tackle challenges in the health and environment sectors. It is shown by means of a number of examples that co-crystallization of inorganic salts, such as alkali and transition metal halides, with organic compounds, such as amino acids, urea, thiourea and quaternary ammonium salts, can be successfully used for (i) chiral resolution and conglomerate formation from racemic compounds, (ii) inhibition of soil enzyme activity in order to reduce urea decomposition and environmental pollution, and (iii) preparation of novel agents to tackle antimicrobial resistance. All materials described in this Perspective have been obtained by mechanochemical solvent-free or slurry methods and characterized by solid state techniques. The fundamental idea is that a crystal engineering approach based on the choice of intermolecular interactions (coordination and hydrogen bonds) between organic and inorganic compounds allows obtaining materials with collective properties that are different, and often very much superior to those of the separate components. It is also demonstrated that the success of this strategy depends crucially on cross-disciplinary synergistic exchange with expert scientists in the areas of bioinorganics, microbiology, and chirality application-oriented developments of these novel materials.

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Introduction

Crystal engineering has been defined as the synthesis of functional solid-state structures from neutral or ionic building blocks, using intermolecular interactions in the design strategy.[1] It is a dynamic discipline in continuous, rapid evolution, being a way to approach solid state issues, rather than an ensemble of techniques, a sequence of steps, a recipe or a computational model. Actually, modern crystal engineering is all of this together and allows tackling problems in many diverse fields of application/utilization of solid materials.[2,3]

There is a vast literature available to the reader interested in revisiting the evolutionary steps of the discipline, an *ad hoc* entry point being the landmark 1989 book by Gautam Desiraju "Crystal Engineering: The Design of Molecular Solid".[4]

Crystal engineering, though born in the organic chemistry field, rapidly expanded across all sub-fields of chemistry, as well as outside the domain of chemistry.[5,6] Here we focus on some developments in the inorganic chemistry area. An interesting entry point in time is represented by the Dalton Discussion on "Inorganic Crystal Engineering" held at the University of Bologna in 2000.[7] The meeting saw a great variety of contributions on coordination polymers, metal organic frameworks, networks, molecular complexes and polymorphs. The working definition of inorganic crystal engineering was "modelling, synthesis and evaluation of the properties of crystalline materials obtained from inorganic, organometallic and bioinorganic building blocks".

In two decades the field has expanded beyond expectations. The success is certainly due to the enormous possibilities of innovation generated by the hybridization of the supramolecular approach (the chemistry beyond the molecule)[8] with the utilitarian objectives of materials chemistry, in order to tackle high impact issues of our times, as environmental cleansing,[9] gas storage,[10] CO_2 trapping,[11] new drug delivery systems,[12] and more efficient catalysts,[13] among others.

The progress in experimental and computational techniques and the almost combinatorial possibilities offered by the convolution of transition metal properties (coordination geometry, charge, spin, *etc.*) with the library of organic

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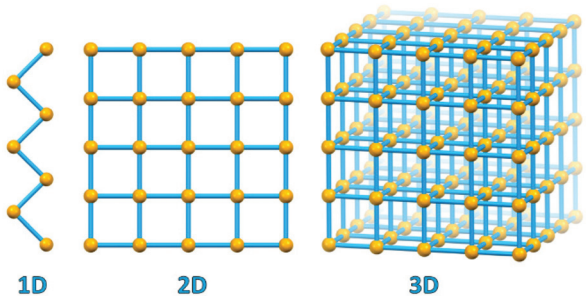


Fig. 1 1D coordination polymer, 2D coordination network and 3D MOF geometries. Metal-based nodes in yellow, connectors/polydentate ligands in light blue.

ligands, each with its own specific supramolecular bonding capacities, were also responsible for the expansion of the area.

A fundamental evolutionary step took place in the area of coordination chemistry with the substitution of "convergent" ligand polydentation on a same metal, so typical of 0-D coordination complexes, by "divergent" polydentation on different metal atoms, which led to the development of coordination polymers, coordination networks and metal organic frameworks (see Fig. 1).[14]

The quest for porous materials for gas uptake/trapping/release, *etc*. was and is one of the main drivers for the interest in MOFs.[10,11,15,16]

More recently, research in this direction was paralleled by the systematic preparation of analogous porous compounds obtained from organic building blocks capable of 1-, 2- and 3-strong hydrogen bonding interactions. Organic hydrogen bonded frameworks (HOFs), analogous to MOFs, are being investigated.[17,18]

In terms of relevance and impact in the field, the counterpart of porous materials, whether based on organic or metallo-

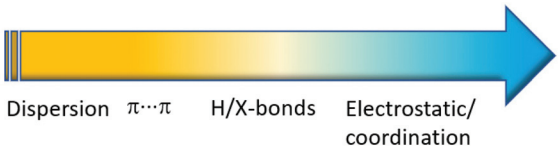


Fig. 2 Interactions and corresponding energies (increasing from yellow to blue) at work between neutral molecules and ions in a supramolecular context.

organic building blocks, is certainly represented by co-crystals.[19] Co-crystals engineering relies on the use of supramolecular interactions (hydrogen bonds,[20] halogen and chalcogen bonds,[21] weak π-interactions[22] *etc*.) to aggregate in the solid state two or more molecular components so as to attain collective properties that the separate components do not possess or to alter specific physico-chemical properties (solubility, dissolution rate, melting *etc*.) of an active ingredient by association with a coformer.[23,24]

Crystal engineering involving co-crystals owns its unquestionable success to the possibility of applying this approach to a great variety of crystalline aggregates, such as drugs,[25] agrochemicals,[26] fertilizers,[27] food ingredients,[28] organic semiconductors,[29] and energetic materials,[30] among others. In this respect, if coordination bonds are included (see Fig. 2) in the portfolio of supramolecular interactions available to devise crystalline materials, with collective properties resulting from the convolution of those of metal complexes and those of organic molecules, the distinction between coordination compounds and co-crystals becomes a matter of context.

For this reason, in this Perspective, as in other related studies, the term co-crystallization has been used purposely to underline the fact that crystalline materials with specific application-oriented properties have been prepared by direct mixing

Dario Braga, Fabrizia Grepioni, Lucia Casali, Cecilia Fiore, Renren Sun, Oleksii Shemchuk and Luca Mazzei (from left to right).

Prof. Dario Braga and Prof. Fabrizia Grepioni lead the group of Molecular Crystal Engineering at the University of Bologna. The research of the group focuses on crystal engineering applied to multiple crystal forms (molecular and ionic co-crystals, polymorphs, solvates, inorganic/organic metal complexes) to tackle pharmaceutical, agrochemical and environmental issues related to solid-state chemistry. Dr Lucia Casali (PostDoc), Cecilia Fiore (PhD student) and Renren Sun (visiting PhD student) are all active members. Dr Oleksii Shemchuk has been part of the group for six years, and is currently an FNRS postdoctoral researcher at the Institute of Condensed Matter and Nanosciences, University of Louvain-la-Neuve, working on chiral systems and chiral resolution in the Molecular Chemistry, Materials and Catalysis group of Prof. Tom Leyssens. Dr Luca Mazzei is a Junior assistant professor at the Department of Pharmacy and Biotechnology, University of Bologna, working in the group of Prof. Stefano Ciurli in the Bioinorganic Chemistry field; his research involves characterization of metal-dependent proteins responsible for medical and agro-environmental issues, including the elucidation of their structure–function relationships.

of compounds that separately form stable crystalline phases at ambient conditions, which, incidentally, is an operative definition of co-crystals.[19c] It will also be seen that the preparative methods are mainly based on solvent-free mechanochemical approaches.[31] Direct mixing of the solid reactants has been amply demonstrated to be well suited for the preparation of co-crystals whether these are molecular co-crystals (*i.e.* neutral molecules interacting in the solid state only *via* non-covalent bonds), ionic co-crystals (*i.e.* co-crystals formed by inorganic salts and neutral organic molecules) or complexes (formed *via* co-crystallization of organic molecules with transition metal salts).

Attention will be focused on the utilization of the principles outlined above towards three specific areas of nature inspired crystal engineering, namely chiral resolution of amino acids and drugs, soil enzyme inhibition and antimicrobial activity enhancement *via* co-crystallization. All results discussed herein originate from the collaborations between the molecular crystal engineering group of the University of Bologna and other groups of scientists in Italy and abroad and depend critically on synergistic interactions between different branches of science.

Co-crystallization with inorganic salts and chiral resolution

Chiral resolution of enantiomeric pairs is one of the "perpetual" challenges of applied chemistry. This is not only because chiral molecules are ubiquitous in nature but also, and very importantly, because enantiomers of a biologically active compound may exert very different pharmacological activity. Regulatory authorities, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), require independent pharmacological tests for each enantiomer, as well as an assessment of their combined effects, before authorizing administration of active principles in the form of racemic mixtures or compounds.[32] Hence, methods to separate enantiomers are of great interest, and their applications are not limited to the pharmaceutical field.

As mentioned above, co-crystallization of active pharmaceutical ingredients and/or molecules of pharmaceutical interest has proven useful to modify the physicochemical properties of a target molecule.[25–28] One such application of the co-crystallization approach can indeed be in the direction of separating enantiomers in racemic compounds. To this goal, crystal engineering has introduced new approaches for chiral separation in addition to commonly used methods (*e.g.* chiral chromatography,[33] kinetic resolution,[34] diastereoisomeric salt formation,[35] and preferential crystallization[36,37]). These approaches are based on (i) chiral resolution *via* enantiospecific co-crystal formation,[38–41] *i.e.* co-crystallization of a racemic compound with either an enantiopure coformer, and (ii) the use of an achiral co-crystallizing agent, whereby the role of co-crystallization is that of transforming a racemic compound into a conglomerate.[42,43]

Somewhat serendipitously we have found a third way to utilize achiral coformers to obtain chiral resolution and conglomerate formation starting from a racemic compound.[44] In the course of the preparation of ionic co-crystals[45] of the racemic amino acid histidine with lithium halides LiX (X = Cl, Br, I) we have observed that the Li^+ cation selectively coordinates molecules of the same handedness, regardless of whether the crystalline product is racemic or a conglomerate.[46] Depending on the type of halide, the crystalline materials may result in either a racemic crystal but composed of separate chains of the same chirality, or, in the case of X = I, separate out as a conglomerate (Fig. 3).

In both the conglomerate and the racemic crystals the Li^+ cations are coordinated to the amino acid of the same chirality (Fig. 4).

It is useful to stress that, while chiral selection *via* co-crystallization of a racemic compound by means of an enantiopure coformer is predictable, the resolution of enantiomeric pairs *via* coordination to a small cation favouring tetrahedral coordination could not be anticipated.

Stimulated by this unexpected observation we decided to test the chiral selectivity and conglomerate formation[34] for a number of amino acid racemic compounds[44] (see Table 1). In the cases of the LiCl ionic co-crystals with valine, leucine, histidine and proline it was also possible to obtain both the racemic compound and the conglomerate, both types of crystals containing amino acids of the same chirality coordinating the Li^+ cation. Coordination to Zn^{2+} does not lead to conglomerate formation. In most cases, however, the Zn^{2+} ions directly

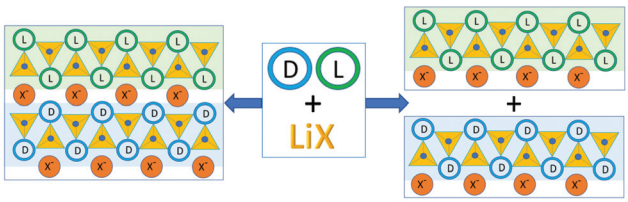


Fig. 3 Co-crystallization of the investigated racemic amino acids with lithium halides. "L" and "D" stay for the L- and D-amino acid molecules respectively; small blue spheres represent water oxygens.[46]

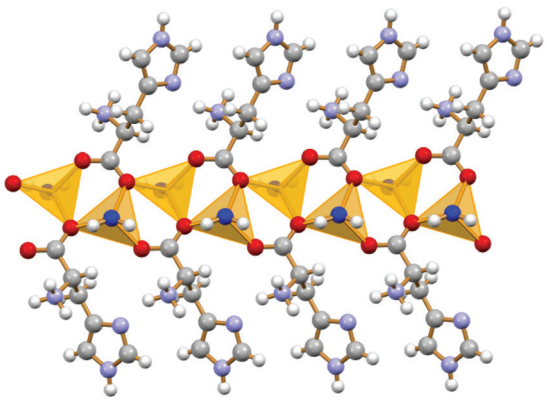


Fig. 4 Homochiral chain observed in both conglomerate and racemic ICC of histidine with lithium chloride.[46]

Table 1 Co-crystallization products obtained from the reaction of racemic amino acids and metal salts mentioned in this Perspective

Amino acid	LiX[46–48] Racemate	Conglomerate	$ZnCl_2$[49] Racemate
DL-Alanine	DL-Ala·LiCl·H_2O	—	DL-Ala_2·$ZnCl_2$
DL-Valine	DL-Val·LiCl·H_2O	D-/L-Val·LiCl·H_2O	DL-Val_2·$ZnCl_2$
DL-Leucine	DL-Leu·LiCl·1.5H_2O	L-Leu·LiCl·H_2O	—
DL-Isoleucine	—	D-/L-Ile·LiCl·H_2O	DL-Ile_2·$ZnCl_2$
DL-Histidine	DL-His·LiCl·H_2O		
DL-His·LiBr·1.5H_2O	D-/L-His·LiI·1.5H_2O	—	
DL-Proline	DL-Pro·LiCl·H_2O		
DL-Pro·LiI·H_2O			
DL-Pro·LiBr			
DL-Pro·LiI	D-/L-Pro·LiCl·H_2O		
D-/L-Pro·LiBr·H_2O			
D-/L-Pro·LiCl			
	DL-Pro_2·$ZnCl_2$		
DL-Pro_2·$ZnCl_2$			
DL-Serine	—	—	DL-Ser_2·$ZnCl_2$
DL-Threonine	—	—	DL-Thr_2·$ZnCl_2$·Thr
DL-Asparagine	—	—	DL-Asn_2·$ZnCl_2$
DL-Tyrosine	—	—	DL-Tyr·$ZnCl_2$
DL-Glutamic acid	—	—	DL-Glu_2·$ZnCl_2$

interact with amino acids of the same chirality, hence forming homochiral complexes within racemic crystals. It may be useful to focus on those cases where the enantiomeric selection by tetrahedral coordination is not observed, *i.e.* the family of Zn^{2+} complexes of the amino acids alanine, valine, proline, isoleucine, serine, asparagine, tyrosine, and threonine.[49]

The question then arose on whether the "tetrahedral selectivity" towards homochiral molecules could be observed also with other small metals favoring tetrahedral coordination. To this end, racemic amino acids were mechanochemically reacted with $ZnCl_2$; the results are shown in Table 1.

With the exception of threonine, which crystallizes out as *meso*-threonine$_2$$ZnCl_2$, all other amino acids as their racemic compounds under different preparative conditions (manual grinding, liquid assisted grinding (LAG), ball milling *etc.*) generally leads to crystals of *rac*-(amino acid)$_2$$ZnCl_2$, formed by 0D homochiral complexes of formula L-(amino acid)$_2$$ZnCl_2$ and D-(amino acid)$_2$$ZnCl_2$, respectively (see Fig. 5).

With DL-proline both the known racemic[50] and the new *meso*-proline$_2$$ZnCl_2$ solids have been obtained (see Fig. 6).

Formation of 1D coordination polymers has been observed in the cases of DL-asparagine and DL-tyrosine, with alternating D- and L-amino acids along the polymeric chain, as shown in Fig. 7.

After discovering the potential of co-crystallization of lithium and zinc halides with the racemic amino acids in terms of chiral resolution, we decided to switch from model compounds to APIs. In close collaboration with the research

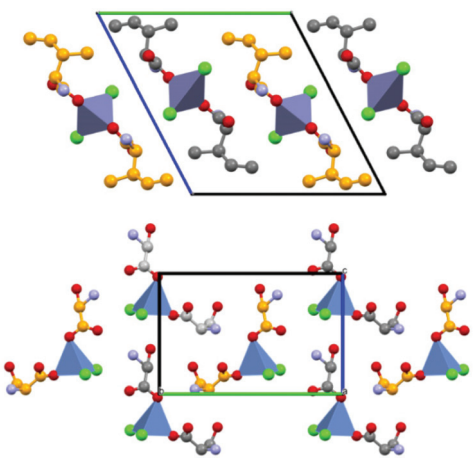


Fig. 5 0D homochiral complexes of formula L-(amino acid)$_2$$ZnCl_2$ (top) and D-(amino acid)$_2$$ZnCl_2$ (bottom), respectively. Reproduced from ref. 49 with permission from the Royal Society of Chemistry.

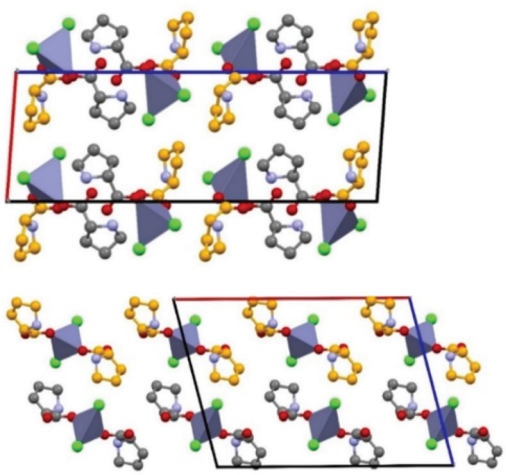


Fig. 6 Comparison between crystal packings for homochiral (top) and heterochiral (bottom) DL-pro$_2$·$ZnCl_2$. Grey and orange spheres for carbons refer to proline molecules with opposite chirality; Zn^{2+} coordination polyhedra in blue-grey; chloride ions in lime green; H atoms omitted for clarity. Reproduced from ref. 49 with permission from the Royal Society of Chemistry.

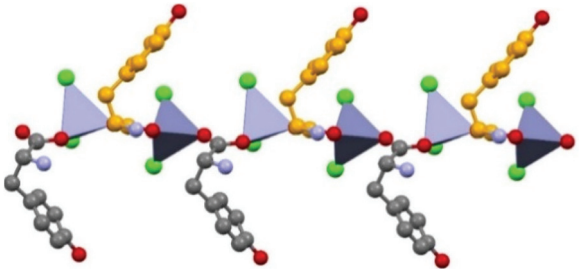


Fig. 7 1-D coordination polymer observed in the case of crystalline *catena*-[(μ_2-DL-tyrosine)$ZnCl_2$]. Reproduced from ref. 49 with permission from the Royal Society of Chemistry.

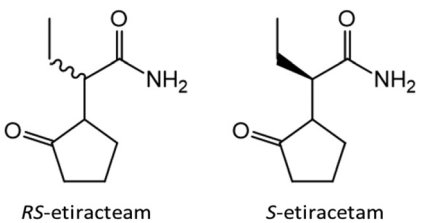
group of Professor Tom Leyssens at the Catholic University of Louvain we have investigated the possibility to achieve chiral resolution of RS-etiracetam[51] (ETI, Scheme 1, left) – the racemate of the antiepileptic drug levetiracetam (S-etiracetam, Scheme 1, right).

Based on the co-crystallization results obtained for amino acids, lithium halides seemed to be the most promising coformers in terms of potential conglomerate formation. However, all the co-crystallization experiments with etiracetam were unsuccessful. Consequently, we turned to different inorganic salts, and the most obvious choice was zinc chloride. Even though no conglomerate formation had been observed with amino acids,[49] its homochiral preference increased the chances that complexes with etiracetam would crystallize as conglomerates. Unfortunately, the complexation of racemic etiracetam with $ZnCl_2$ resulted in racemic *RS*-$ETI_2{\cdot}ZnCl_2$: as expected, zinc cations were coordinated by etiracetam molecules of one chirality, forming distinct layers of *R*-$ETI_2{\cdot}ZnCl_2$ and of *S*-$ETI_2{\cdot}ZnCl_2$ in the overall racemic compound, but no chiral resolution was achieved (see Fig. 8).

Interestingly, a subsequent increase of the amount of zinc chloride with respect to *RS*-etiracetam led to disruption of the racemic compound, with formation of the stable conglomerate *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ (Scheme 2).

Organic–inorganic adducts for soil enzyme inhibition

In this section we describe our inorganic crystal engineering approach to tackle an important agro-environmental and economic issue related to the global nitrogen (N) cycle (Fig. 9), namely the urgent need to ensure sustainable soil fertilization



RS-etiracteam *S*-etiracetam

Scheme 1 Chemical structures of *RS*-etiracetam (ETI) and levetiracetam (*S*-etiracetam).

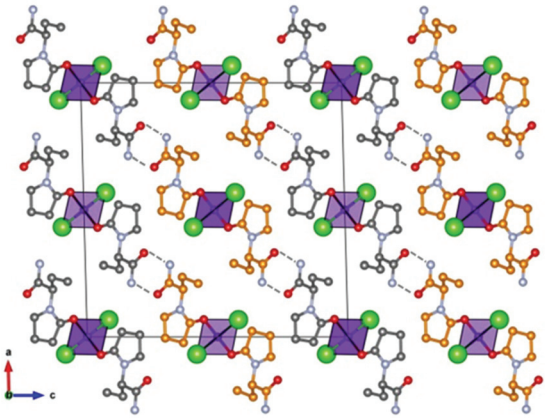
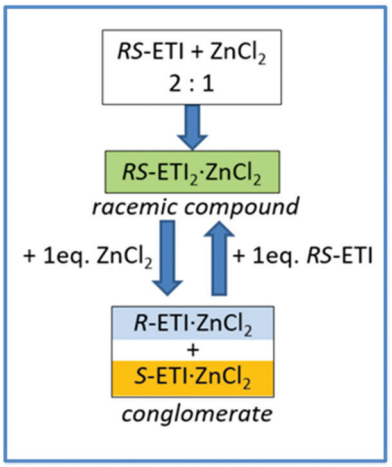


Fig. 8 Crystalline *RS*-$ETI_2{\cdot}ZnCl_2$: Projection in the *ac*-plane, showing the hydrogen bonds between the amido groups of etiracetam molecules of opposite chirality (coloured in grey and orange for clarity). "Orange" and "grey" layers of *R*-$ETI_2{\cdot}ZnCl_2$ and *S*-$ETI_2{\cdot}ZnCl_2$ can be seen in projection, parallel to the *a*-axis. Reproduced from ref. 51 with permission from the Royal Society of Chemistry.



Scheme 2 Graphic representation of the *RS*-ETI:$ZnCl_2$ system in the solid-state, and the role of stoichiometry in the racemic compound/conglomerate switch mechanism. Reproduced from ref. 51 with permission from the Royal Society of Chemistry.

and crop productivity by minimizing N losses upon the use of N-containing plant fertilizers. Urea is the most widely used plant fertilizer, accounting for about 60% of the global nitrogen fertilizer used in the World.[52] Upon its deposition in the soil, urea is degraded by urease (urea amidohydrolase, EC 3.5.1.5), a nickel-dependent enzyme widely spread in soils both inside living cells of plants and microorganisms (*i.e. Sporosarcina pasteurii*) and in an extracellular form adsorbed onto soil components.[53a] Urease catalyzes rapid hydrolysis of urea into hydrogen carbonate (HCO_3^-) and ammonium (NH_4^+), the latter serving as a nutrient to plants, at a rate 10^{15} times faster than in the non-catalyzed reaction[53b] and an overall pH increase is observed that leads to the formation of

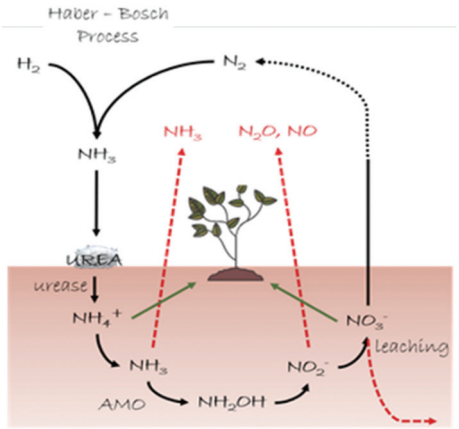


Fig. 9 Schematic representation of the N cycle (black arrows). Loss pathways of the reactive N are shown with red arrows, while green arrows indicate the N species available for plants.

gaseous ammonia (NH_3).[53a,c] Along with urease, the copper-dependent enzyme ammonia monooxygenase (AMO) present in ammonia-oxidizing microorganisms (*i.e. Nitrosomonas europaea*) catalyzes the oxidation of nascent ammonia into hydroxylamine (NH_2OH),[54] that is further oxidized to nitrite (NO_2^-) and nitrate (NO_3^-); NO_3^- is used as an available N form by plants, but it concomitantly undergoes leaching phenomena in soils. Moreover, both NO_2^- and NO_3^- act as precursors of gaseous species responsible for the greenhouse effect. As a consequence of this complex reactions network, a large amount (*ca.* 50%) of nitrogen fertilizer applied to soils as urea is lost, while the environment is polluted.[55]

To the present day, two main methods have been employed to tackle this problem: (i) coating/encapsulation of urea and (ii) amendment of urea-based fertilizers with inhibitors. The first approach is aimed to reduce the water solubility/dissolution rate of urea while the second directly modulates the reaction rates of urease and AMO, responsible for the ammonification and nitrification processes, thus enhancing N uptake by plant roots.

More recently, it has been shown that urea based ionic co-crystals with inorganic compounds can successfully be used to slow down urea decomposition, hence ammonia release. Good examples are provided by urea·$MgSO_4$ co-crystals,[56] as well as by co-crystals with Ca^{2+} salts obtained *via* mechanochemistry using the appropriate minerals.[57] Beside co-crystals, inorganic salts such as $Ca(NH_4)_2(HPO_4)_2{\cdot}H_2O$ and $Mg(NH_4)_2(HPO_4)_2{\cdot}$ 4H2O as well as their struvite equivalents $Ca(NH_4)(PO_4){\cdot}H_2O$ and $Mg(NH_4)(PO_4){\cdot}6H_2O$ have been utilized.[58]

In our efforts to apply crystal engineering strategies to address this important nature inspired problem, we have joined strengths with the groups of Professor Baltrusaitis at the University of Leigh and of Professor Ciurli at the University of Bologna in the quest for hybrid organic–inorganic co-crystals capable to reconcile both the above-mentioned aspects, *i.e.* to improve the chemical–physical properties of urea by reducing its water solubility/dissolution rate and to exert an inhibition activity towards the enzymes urease and/or AMO, yet still providing nutrients and fertilizers to the soil.

We have found[59] that when urea is co-crystallized with the inorganic metal salts KCl and $ZnCl_2$, crystalline urea·$ZnCl_2$·KCl (ZnKU) is obtained quantitatively in a simple, solvent free and scalable manner. It is worth mentioning that the compound is known in two polymorphic modifications depending on the preparation conditions (Fig. 10a).

We have found[59] that when urea is co-crystallized with the inorganic metal salts KCl and $ZnCl_2$, crystalline urea·$ZnCl_2$·KCl is obtained quantitatively in a simple, solvent free and scalable manner. It is worth mentioning that the compound is known in two polymorphic modifications depending on the preparation conditions (Fig. 10a).

The compound obtained from aqueous solution at 80 °C is a metastable form, since it converts by slurry at RT into the stable form, which can be obtained by ball milling or crystallization at RT.[27] The known ability of Zn(II) to act as a urease inhibitor[60a] prompted us to determine the inhibitory potency of increasing concentrations of ZnKU in its stable crystal form on enzyme activity (as shown in Fig. 10b), demonstrating a strong inhibition effect. Beside acting as an efficient modulator of urease activity, the co-crystal provides a nutrient component (KCl) together with the urea fertilizer.

We have also reported that co-crystallization of urea and thiourea (a known inhibitor of ammonia oxidation process by AMO[60b] with $ZnCl_2$ produces the mixed system

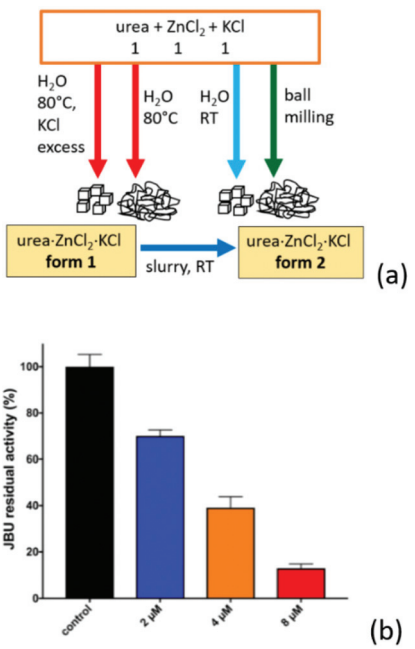


Fig. 10 (a) Urea·Zn·KCl forms **1** and **2** obtained by reacting urea, $ZnCl_2$ and KCl in 1 : 1 : 1 stoichiometric ratio. (b) Residual percentage activity of jack bean urease (JBU), referred to 100% (control, black bar) in the presence of increasing concentrations of ZnKU form **2**, at pH 7.5. The blue, orange and red bars correspond to 2, 4 and 8 μM of inhibitor, respectively. Reproduced from ref. 10 with permission from the Royal Society of Chemistry.

[$ZnCl_2$(thiourea)(urea)] (ZnTU).[60c,d] This compound, besides providing the urea fertilizer, is able to act as a dual inhibitor. In particular, measurements carried out on bacterial cultures containing either *S. pasteurii* or *N. europaea*, as well as in tandem experiments in the presence of both the microorganisms, provide evidence that ZnTU is selectively effective in lowering the ammonification and oxygen consumption *via* the Zn^{2+} and thiourea components, respectively. By carrying the urea fertilizer and simultaneously inhibiting these two N cycle key enzymes, hence ZnTU is able to thus increasing N fertilization efficiency (see Fig. 11).

As a third example of application of crystal engineering and solid state strategies to investigate compounds with potentials in the agrochemical field is the recently reported *in situ* monitoring of the mechanochemical reaction between the AMO inhibitor dicyandiamide and inorganic salts of the urease inhibitor copper(II) [CuX_2, where X = Cl^-, NO_3^-].[61] By getting a better understanding of the mechanochemical experimental conditions to obtain the new adducts it was possible to drive the reactions towards the desired compounds and to suggest a methodology to explore new compounds of agrochemical interest. A similar approach has been discussed by Friscic *et al.*[62]

Targeting antimicrobial resistance with organic–inorganic co-crystals and complexes

This section deals with a third nature inspired application of the crystal engineering. Herein we discuss our efforts in the quest for new materials to tackle another high-impact problem of our times, namely antimicrobial resistance.[63] Crystal engineering approaches utilizing metal complexes and coordination networks with antimicrobial properties have been gaining popularity as a new means to deal with this challenge.[64] As a matter of fact, metals have been used as antimicrobials[65] long before the discovery of antibiotics and before their utilization to treat human, animal and plant diseases became such a widespread practice. However, it is the abuse of antibiotics that accelerates the development of antimicrobial resistance in microorganisms.

In close collaboration with the group of Professor Ray Turner at the University of Calgary, we have investigated the co-crystallization of a series of metal complexes with active organic principles in the quest for new antimicrobial agents. While in the previous section we use co-crystallization techniques with the aim of obtaining materials able to inhibit enzyme activity, here the goal is quite the opposite: co-crystallization methods are used to prepare new compounds with old drugs to see if the antimicrobial activity can be enhanced.

More specifically, we have concentrated our efforts on a well-known disinfectant-bacteriostatic organic molecule belonging to the class of quaternary-cation compounds (QCC),[66] namely proflavine,[67] *e.g.* (acridine-3,6-diamine). Proflavine (PF) and its protonated proflavinium cation (HPF^+) shown in Scheme 3 have been used in the preparation and evaluation of a series of co-crystals obtained by reacting proflavine with salts and complexes of Cu, Zn, Ag and Ga.

Compounds were obtained in most cases by mechanochemical mixing of the solid reactants or by slurry mediated reactions; this last method yielded higher purity target products, which were subsequently utilized for the investigation of the antimicrobial activity against three bacteria strains, namely *Pseudomonas aeruginosa* ATCC27853, *Staphylococcus aureus* ATCC25923, and *Escherichia coli* ATCC25922.

An example is shown in Fig. 12, where the structure of the copper(I) chloride co-crystal PF·CuCl is shown,[68] formed by a

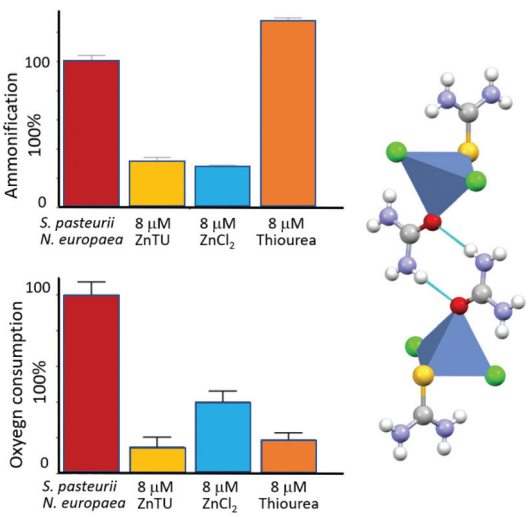
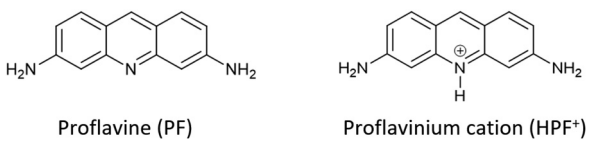


Fig. 11 Inhibition activity of [Zn(thiourea)(urea)Cl_2] (ZnTU) towards a mixture of *S. pasteurii* and *N. europaea* cells: residual ammonification (top left) and oxygen consumption (bottom left) in the absence (red bar) and in the presence of 8 μM ZnTU (yellow bars) are compared to the effect provided by stoichiometric amounts of $ZnCl_2$ (light blue bars) and thiourea (orange bars), reported as controls. The structure of ZnTU is shown on the right.[60]



Scheme 3 Neutral proflavine PF and the proflavinium cation HPF+.

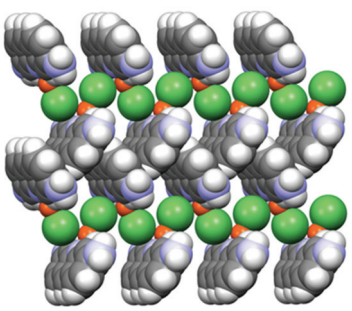


Fig. 12 $(CuCl\cdots CuCl\cdots)_n$ chains and herring-bone arrangement of proflavine molecules in the proflavine·CuCl co-crystal. Reproduced from ref. 68 with permission from the Royal Society of Chemistry.

1-D polymer of CuCl monomers and by neutral proflavine molecules arranged in herring-bone fashion.

The PF·$AgNO_3$ and PF·CuCl compounds were subjected to microbiological assays against *S. aureus*, *P. auriginosa* and *E. coli*. Both compounds perform better than proflavine and the inorganic salts separately (see Fig. 13). We took this as a proof of concept for the possibility of using hybrid inorganic salts and active molecules to generate new materials for applications, for example, in surface coating.

With the same rationale, we then attempted preparation of analogous derivatives of $ZnCl_2$.[69] The nature of the products obtained by mechanochemical and solution methods varied depending on the Zn-proflavine stoichiometric ratio and on the experimental conditions. Two compounds were isolated and fully characterized as [HPF]$ZnCl_3$ and as the monohydrate $[HPF]_2[ZnCl_4]\cdot H_2O$, respectively. Contrary to the copper and silver complexes both compounds contain proflavine as its proflavinium cation $(HPF)^+$.

The structures of the two compounds are compared in Fig. 14. The most noteworthy feature of these two materials is the stacking of the proflavinium cations. The same interaction is predominant in the crystal structures of neutral proflavine (PF) and of the salt $[HPF]Cl\cdot 2H_2O$.

When tested against the pathogen indicator strains the compounds showed a 50–125% enhancement of the antimicrobial activity with respect to $AgNO_3$ used as a reference standard. The increase in antimicrobial activity is slightly less pronounced when compared to the physical mixture of the separate components, but it is still noteworthy, see Fig. 15. In summary, the association of proflavine, as its proflavinium cation, with Zn increases the antimicrobial efficacy of proflavine itself.

More recently,[70] we have extended the quest for novel proflavine-based co-crystals by using as a preformed building block, the gallium oxalate complex $[Ga(ox)_3]^{3-}$, in order to prepare the molecular salt $[HPF]_3[Ga(ox)_3]\cdot 4H_2O$ (see Fig. 16). The proflavinium cations envelope the $[Ga(ox)_3]^{3-}$ anions forming the stackings of proflavine cations similar to those observed in the neutral co-crystals discussed above.

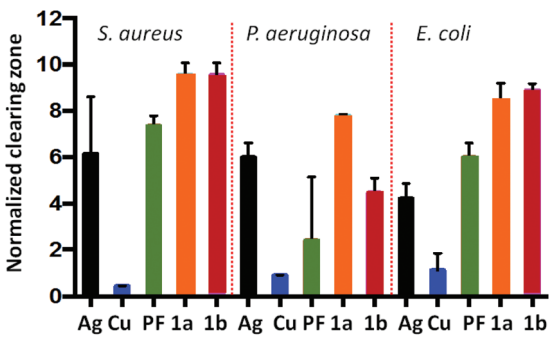


Fig. 13 Efficacy of PF based compounds: Normalized zones of growth inhibition utilizing compound impregnated disks [Ag = $AgNO_3$, PF = proflavine, Cu = CuCl, 1a = PF·CuCl, 1b = PF·$AgNO_3$]. Reproduced from ref. 68 with permission from the Royal Society of Chemistry.

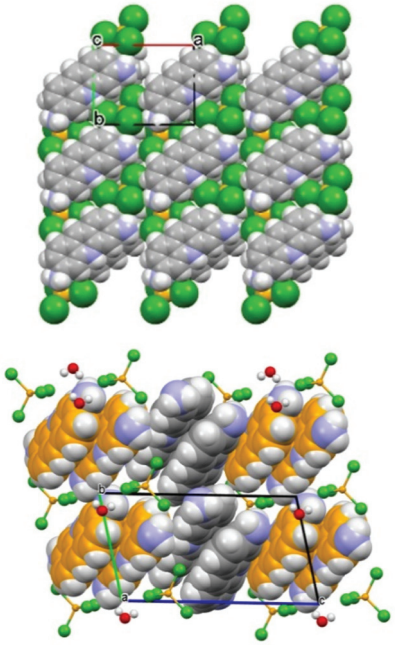


Fig. 14 (Top) Projection in the *ab*-plane of crystalline $ZnCl_3$(HPF) in which the molecules are arranged in piles along the *c*-axis direction. (Bottom) Projection down the crystallographic *b*-axis of crystalline $[HPF]_2[ZnCl_4]\cdot H_2O$, showing the herring-bone pattern of HPF^+ cationic pairs. Reproduced from ref. 69 with permission from the Royal Society of Chemistry.

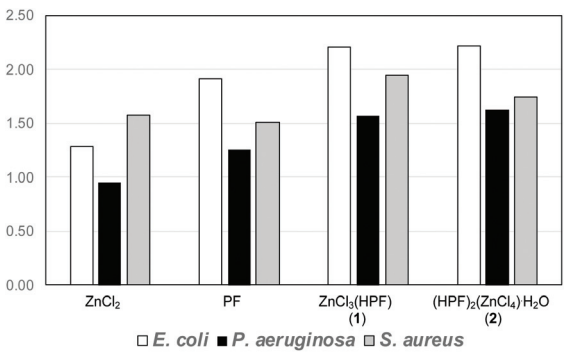


Fig. 15 Fold antimicrobial activity of proflavine, $ZnCl_3$(HPF) and $(HPF)_2(ZnCl_4)\cdot H_2O$ compared to the activity of $AgNO_3$ (the value of 1.00 is equal efficacy as silver nitrate). Reproduced from ref. 69 with permission from the Royal Society of Chemistry.

As in the cases discussed above, the antimicrobial performance has been evaluated by disk diffusion assays, showing that also the gallium compound can be a valuable antimicrobial. It is worth mentioning that, while $[HPF]_3[Ga(ox)_3]\cdot 4H_2O$ is effective against all three strains, the gallium oxalate salt $K_3[Ga(ox)_3]$ shows an impressive selectivity towards *P. aeruginosa*, with little to no antimicrobial activity against the other two organisms. This selectivity is *per se* remarkable and is being investigated further in its microbiological aspects.

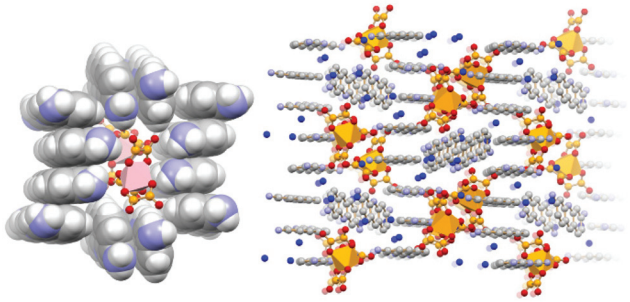


Fig. 16 π-stacking of $[HPF]^+$ cations in crystalline $[HPF]_3[Ga(ox)_3]\cdot 4H_2O$ (left); an envelope formed by proflavinium cations around two $[Ga(ox)_3]^{3-}$ anions (right)[70].

In summary, these results show that co-crystallization of a known QCC compound, *e.g.* proflavine, with metal salts, such as CuCl, $CuCl_2$ and $AgNO_3$, but also with a preformed coordination compound such as $[Ga(ox)_3]^{3-}$, *via* mechanochemical or slurry methods, is a viable, eco-friendly, and inexpensive way to obtain new materials with enhanced antimicrobial properties. All crystalline materials investigated thus far, namely PF·CuCl, PF·$AgNO_3$, $ZnCl_3$(HPF), $[HPF]_2[ZnCl_4]\cdot H_2O$ and $[HPF]_3[Ga(ox)_3]\cdot 4H_2O$ appear to perform better than PF and the metal salts separately. The antimicrobial performance of these compounds is noteworthy, even more so because the crystal mixtures by weight invariably contain less proflavine by moles.

These results ought to be looked at in the context of the work of other groups. The number of papers dealing with hybrid inorganic–organic materials to tackle antimicrobial resistance[71] and /or to find new, metal based ways for drug delivery[72] is rapidly increasing.

Conclusions and outlook

In closing the Dalton Trans. Perspective in 2000,[7] one of us wrote "It is the challenge for the future to demonstrate that crystal engineering is providing a new way of thinking Chemistry...". With hindsight, we might also add that crystal engineering was also providing a new way of thinking Crystallography, because many crystallographers realized that they could exploit their knowledge of supramolecular interactions in the solid state, combined with the experience in crystallization and solid-state characterization methods, to make their own solid materials, thanks also to a synergistic interaction with those expert in organic and inorganic synthesis. The transition from crystallography to crystal making has generated a bounty of results in all directions of solid-state chemistry, with important applications in very many diverse fields, causing an evolution from crystal making to crystal utility. Accordingly, we have chosen to apply the crystal engineering way of thinking to address some specific nature inspired societal challenges, such as antimicrobial resistance caused by the increasing use of antibiotics in humans, animals and agriculture, and the environmental and economic issues related to degradation of the most commonly used fertilizer, namely urea, by natural soil enzymes. To address these problems, as demonstrated by the papers presented in this Perspective, a multidisciplinary approach to problem solving is of paramount importance. Forces need to be joined with other scientists, in order to evaluate the performance of the materials produced by applying the crystal engineering paradigm, namely, going from molecules and complexes to supramolecular aggregates with collective solid state properties. The inorganic chemistry area offers plenty of opportunities and great diversity of physico-chemical and biological properties. During the two past decades, thanks to the possibility of providing new tools to tackle new and old problems, crystal engineering has overcome many disciplinary barriers, providing opportunities for new discoveries not only in terms of fundamental "blue sky" research, but also in terms of applied, industrially relevant, high impact research. A truly holistic science, as well pointed out by Desiraju.[1]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

As pointed out repeatedly in this Perspective, the work described here could only be done by virtue of a close synergistic interaction with other research groups. We gratefully acknowledge the fruitful collaboration with the groups of Professors Ray J. Turner (University of Calgary), Stefano Luciano Ciurli (University of Bologna), Jonas Baltrusaitis (University of Leigh), Tom Leyssens (University of Leuven), Franziska Emmerling (BAM, Berlin). The China Scholarship Council is acknowledged (Renren Sun) for a Visiting PhD Student State Scholarship. We also acknowledge financial support from MUR, project "Nature Inspired Crystal Engineering" (PRIN2020), and from the University of Bologna.

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