Making crystals from crystals: a green route to crystal engineering and polymorphism†

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Supramolecular reactions between crystalline materials as well as reactions between a crystalline material and a vapour can be used to generate new crystalline substances. These solvent-free processes can be exploited to prepare both hydrogen-bonded co-crystals and coordination networks. Solid–vapour reactions do not differ from solid–vapour uptake/release processes, and can also be used to prepare polymorphs and solvates. It is argued that solvent-less reactions involving molecular crystals represent a green route to supramolecular solid-state chemistry and crystal engineering.

Introduction

Making crystals by design is the paradigm of crystal engineering.[1] The goal of this field of research is that of assembling functionalised molecular and ionic components into a target network of supramolecular interactions.[2] Such "bottom-up" process generates *collective* supramolecular properties (*e.g.* magnetism, non-linear optics, conductivity, nano-porosity, *etc.*) from the convolution of the physical and chemical properties of the individual building blocks with the periodicity and symmetry operators of the crystal (see Fig. 1).[3]

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The research work of many groups worldwide follows two main directions: coordination networks[4] and molecular materials,[5] with many relevant crossing points in between. The engineering of coordination networks can be described as *periodical coordination chemistry*,[6] because the use of *divergent polydentate ligand–metal coordination*, as opposed to the more traditional *convergent coordination* chemistry of chelating ligands, extends coordination chemistry through space in 1-D, 2-D and 3-D architectures (see Fig. 2). Even though periodical coordination chemistry is at present dominating the field, in terms of scientific output and of number of groups involved, the roots of crystal engineering are in molecular organic solid-state chemistry.[7]

In molecular crystal engineering, on the other hand, the interactions of interest are mainly of the non-covalent type, *e.g.* van der Waals,[8] hydrogen bonds,[9] π-stacking[10] *etc.* and their convolution with ionic interactions.[11]

What is a molecular crystal,[12] then? An operative "crystal engineering" definition of a molecular crystal can be based on
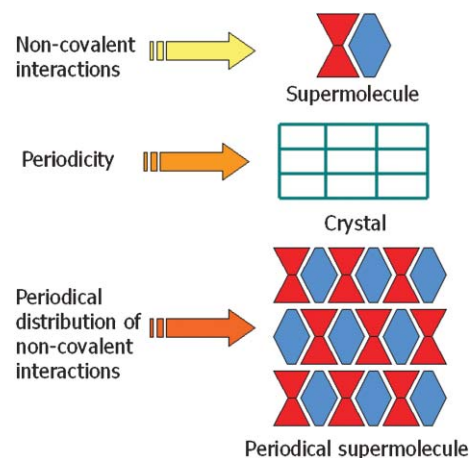

Fig. 1 From molecules to periodical supermolecules: the collective properties of molecular crystals result from the convolution of the properties of the individual molecular/ionic building blocks with the periodical distribution of intermolecular non-covalent bonding of the crystal.
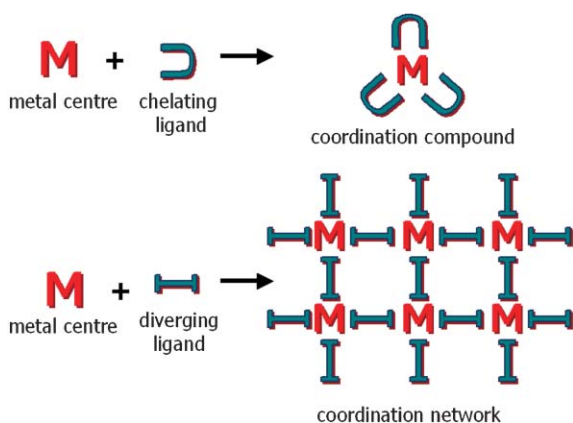
Fig. 2 Schematic representation of the relationship between molecular (top) and periodical (bottom) coordination chemistry: the use of bidentate ligand spacers allows construction of *periodical* coordination complexes.

the energy ranking of the bonding interactions: *the components of a molecular crystal are held together by intermolecular links that are weaker than the covalent chemical bonds within the individual components, whether molecules or molecular ions.* Hence, building blocks will retain, in general, their chemical and physical identity once evaporated or dissolved.

This definition encompasses also the possibility of obtaining *different crystal structures from the same building blocks, viz.* crystal polymorphism (see Fig. 3),[13] by choosing different sets of non-covalent (supramolecular) bonds. We remind the reader that differences in supramolecular bonding may generate relevant differences in physical and chemical properties, such as solubility, melting point, density, *etc.*,[14] as well as different behaviours under mechanical or thermal stress, with relevant consequences on packaging and tableting,[15] hence on processing and marketing of commercial crystalline solids, such as pigments and drugs.[16] A further element of variability to consider when dealing with molecular crystals and polymorphs is the co-crystallization[17] of guest molecules, usually provided by the solvents of crystallization. Solvate crystals of a given chemical species, for which the unsolvated crystal is known, are also referred to (and not without controversy[13b,18]) as pseudo-polymorphs.
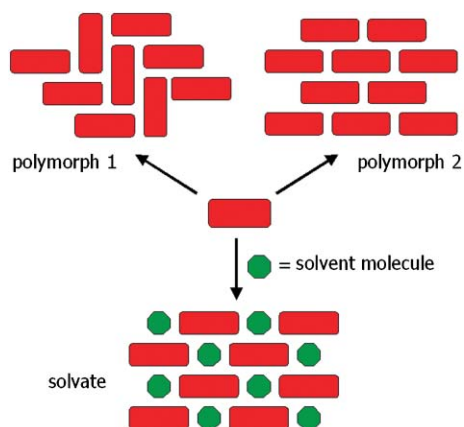
Fig. 3 From the same building block to polymorphs and to solvates

In this feature article we will focus on the idea that reactions between crystalline solids and between crystalline solids and vapours represent viable alternative methods to prepare new crystalline materials, *i.e. to make crystals from crystals.*

Our approach encompasses both the possibility of *reacting* a given crystalline material with another substance (which can be another crystalline materials, or a gas) and that of *transforming* a given crystalline material in a different one *via* a phase transition or *via* a loss of molecules (desolvation). Importantly, these "non-solution" approaches can be used not only to prepare new materials but also to generate new polymorphic or solvate modifications of the same substance.[19]

Making crystals from crystals

Crystal engineers are crystal *makers*. The ultimate step of a crystal engineering exercise is that of obtaining crystals, preferably single crystals of reasonable size that will allow to enjoy the speed and accuracy of single-crystal X-ray diffraction experiments. Even though amorphous molecular materials can be extremely interesting[22] and constitute a serious problem in studies of polymorphism, in crystal engineering studies the desired materials need to be – *by definition* – in the crystalline form.

We have argued[23] that crystalline materials interesting for crystal engineering studies can also be obtained by reacting and transforming preformed crystals. This may be achieved by means of solvent-less processes,[24] such as those occurring between solids or between a solid and a vapour. Since processes of this type do not require recovery, storage and disposal of solvents, they are of interest in the field of "green chemistry".[25] In our approach reactions between molecular crystals and gases or other crystals are regarded as *supramolecular reactions*, whereby interactions, including coordination bonds, between reactants are broken while those of the product are being formed.[19] Solvent-free methods, however, still require that molecules are brought in contact for reaction. In general, fast and quantitative reactions can be achieved when finely ground powders (the large surface area helps molecular diffusion) are exposed to gaseous substances or co-ground with another powder. The two solvent-free processes are distinct but conceptually related, as depicted in the top part of Fig. 4.

In order to set the scope of this contribution, we should point out that "single crystal" and "polycrystalline powder" are relative definitions, which only express the size of the crystals *with respect to the technique in use.* A polycrystalline material is composed of small single crystals, typically too small for single-crystal X-ray diffraction experiments; on the other hand, crystals suitable for X-ray diffraction are often too small for neutron diffraction and so forth. In the context of this article the term "making crystals from crystals" will be used mainly to indicate processes involving polycrystalline powders. We should warn the reader that we will not discuss intra-solid reactions,[19] such as topochemical reactions of the type explored by Schmid[7b] in the early days of crystal engineering.[7] These reactions are now experiencing a wave of renewed interest.[20] We shall also not discuss reactions involving single crystals.[21]
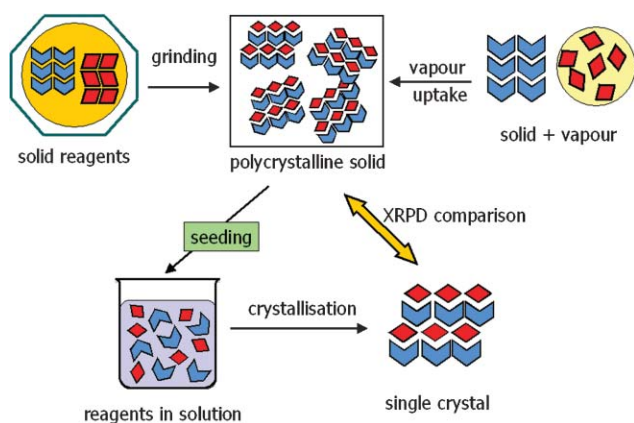
Fig. 4 Schematic representation of the solid–solid and solid–vapour processes and the strategy to obtain single crystals by recrystallisation *via seeding*.

Grinding, milling, kneading, seeding

Pioneering studies of reactions between molecular crystals were carried out by Rastogi *et al.* about forty years ago,[26] and extended by Curtin and Paul in the 1970s.[27] Etter and collaborators investigated formation of hydrogen-bonded co-crystals by grinding of the solid components,[28a] even in the presence of a third solid component.[28b] In the case of 2-aminobenzoic acid, Etter also showed grinding could determine polymorph interconversion.[28c]

In spite of these early suggestive results methods based on (manual) *grinding* or (electromechanical) *ball milling*[29] are not very popular in academic chemistry labs, and are often dismissed as "non-chemical", even though they are commonly used at industrial level mainly with inorganic solids and materials.[30] Another industrially relevant process that can be applied on a small-scale research lab is the so called *kneading*,[31] *i.e.* the use of small amounts of solvent or of a liquid reactant to accelerate (when not make altogether possible) the solid-state reactions carried out by grinding or milling.[32] *Kneading* has been described as a sort of "solvent catalysis" of the solid-state process, whereby the small amount of solvent provides a *lubricant* for molecular diffusion.[19a] The method is commonly employed, for example, in the preparation of cyclodextrin inclusion compounds.[33]

Whether a *kneaded* reaction between two solid phases can be regarded as a *bona fide* solid-state process is doubtful, as it is often the case with other mechanochemical reactions, because of the difficulty in controlling exact reaction conditions such as grinding time, temperature, pressure exerted by the operator, *etc.*. Even though a discussion of these extremely relevant aspects is beyond the scope of this article, one should consider, for example, that the heat generated in the course of a mechanochemical process can induce local melting of crystals or melting at the interface between the different crystals, so that the reaction takes place in the liquid phase even though solid products are ultimately recovered. The same reasoning applies to formation of eutectic phases[19e,f] and to reactions occurring with a minimal amount of solvent (*kneading*).

Another point to consider is that the polycrystalline nature of mechanochemical products makes impossible the use of

straightforward single-crystal diffraction methods, which are indispensable for a precise description of the structure of the crystal (the ultimate product of a crystal engineering experiment). Beside *ab initio* structure determination from powder diffraction data,[34] which is not yet of widespread application, one has to resort to the *a posteriori* preparation of single crystals starting from the powdered product. In some cases, single crystals can be grown from solution by *seeding*, *i.e.* by using a small portion of the polycrystalline sample to "instruct" the crystallization process. Once the single-crystal structure is known, an X-ray powder pattern can be calculated and compared with the measured powder patterns of products obtained from subsequent preparations (see bottom part of Fig. 4). As for *grinding* and *kneading*, *seeding* procedures are commonly employed in industries to guarantee crystallization/precipitation of the desired crystal form. *Seeds* of isostructural or *quasi*-isostructural species that crystallise well can also been employed to induce crystallisation of unyielding materials (*heteromolecular seeding*).[35] Of course, unintentional *seeding* may also alter the crystallization process in an undesired manner.[36]

These aspects will be developed by means of examples, taken mainly from our own work, organized in the following four sections:

(i) mechanochemical preparation of hydrogen-bonded adducts and cages

(ii) mechanochemical preparation of coordination networks

(iii) solid–vapour reactions involving hydrogen-bonded crystals

(iv) induced polymorphism and solvate formation

Mechanochemical preparation of hydrogen-bonded adducts

Hydrogen-bonding interactions play a central role in molecular crystal engineering as witnessed by the vast literature on hydrogen-bonded crystals.[37]

We have recently exploited inter-solid reactions between molecular crystals to prepare hydrogen-bonded adducts of organic and organometallic molecules. For example, crystals of the ferrocenyl dicarboxylic acid complex [Fe(η^5-$C_5H_4COOH)_2$] react with solid nitrogen-containing bases, such as 1,4-diazabicyclo[2.2.2]octane, 1,4-phenylenediamine, piperazine, *trans*-1,4-cyclohexanediamine and guanidinium carbonate, generating quantitatively the corresponding organic–organometallic adducts.[38] The case of the adduct [N($CH_2CH_2)_3$NH][Fe(η^5-C_5H_4COOH)(η^5-C_5H_4COO)] (see Fig. 5) is particularly noteworthy because the same product can be obtained in three different ways: (i) by reaction of solid [Fe(η^5-$C_5H_4COOH)_2$] with vapours of 1,4-diazabicyclo[2.2.2]octane (which possesses a small but significant vapour pressure), (ii) by reaction of solid [Fe(η^5-$C_5H_4COOH)_2$] with solid 1,4-diazabicyclo[2.2.2]octane, $C_6H_{12}N_2$, *i.e.* by co-grinding of the two crystalline powders, and by reaction in MeOH solution of the two reactants. The fastest process is the solid–solid reaction. The base can be removed by mild thermal treatment, and the structure of the starting dicarboxylic acid is regenerated. The processes imply breaking and reassembling of hydrogen-bonded networks,
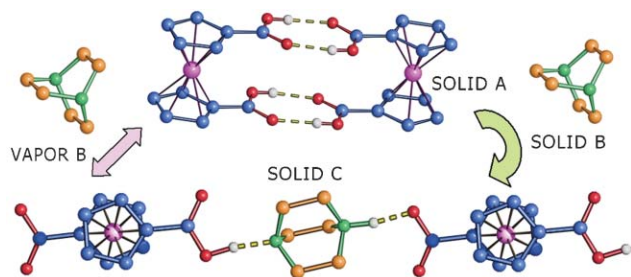
Fig. 5 The solid–vapour and solid–solid reactions involving 1,4-diazabicyclo[2.2.2]octane with formation of a linear chain of hydrogen-bonded $[Fe(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]^-$ anions and monoprotonated $[N(CH_2CH_2)_3NH]^+$ cations. (Reprinted from ref. 35a with permission.)

conformational change from *cis* to *trans* of the –COO/–COOH groups on the ferrocene diacid, and proton transfer from acid to base.

In the organic chemistry area, the mechanochemical formation of hydrogen-bonded co-crystals between sulfonamide (4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide) and aromatic carboxylic acids has been investigated by Caira *et al.*[39]

Mechanical mixing of solid dicarboxylic acids $HOOC(CH_2)_nCOOH$ ($n = 1–7$) of variable chain length together with the solid base 1,4-diazabicyclo[2.2.2]octane, $[N(CH_2CH_2)_3N]$, generates the corresponding salts or co-crystals of formula $[N(CH_2CH_2)_3N]–H–[OOC(CH_2)_nCOOH]$ ($n = 1–7$) (see Fig. 6).[40] The reactions imply transformation of inter-acid O–H···O bonds into hydrogen bonds of the O–H···N type between acid and base. The nature (whether neutral O–H···N or charged $^{(-)}$O···H–N$^{(+)}$) of the hydrogen bond was established by means of solid-state NMR measurement.
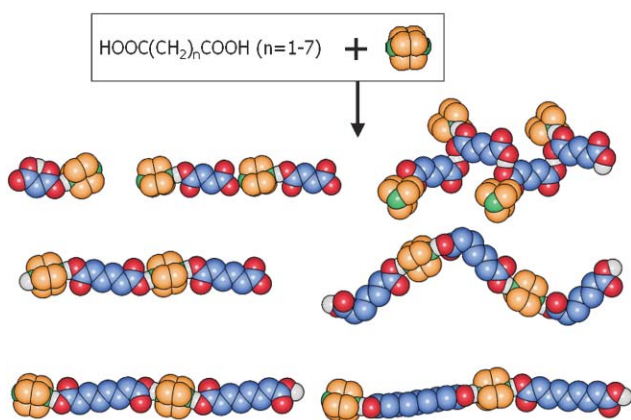

Fig. 6 The reaction of solid dicarboxylic acids $HOOC(CH_2)_nCOOH$ ($n = 1–7$) with the solid base 1,4-diazabicyclo[2.2.2]octane, $[N(CH_2CH_2)_3N]$, generates the corresponding salts or co-crystals of formula $[N(CH_2CH_2)_3N]–H–[OOC(CH_2)_nCOOH]$ ($n = 1–7$). The O–H···O hydrogen bonds present in the solid acid are replaced by neutral O–H···N and charged $^{(-)}$O···H–N$^{(+)}$ interactions, with formation of dimeric units ($n = 1$) or infinite chains ($n = 2–7$) (H_{CH} atoms not shown for clarity).

We have also exploited the great versatility of the organometallic zwitterion $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]$[41a] in the preparation of hybrid organometallic-inorganic salts, by reacting the solid complex with a number of M^+X^- salts ($M^+ = K^+$, Rb^+, Cs^+, NH_4^+; $X^- = Cl^-$, Br^-, I^-, PF_6^-) and obtaining compounds of general formula $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]_2\cdot M^+X^-$.[41b] In some cases ($M^+ = Rb^+$, Cs^+, $X = Cl^-$, Br^-, I^-) it has been necessary to resort to *kneading* by adding a few drops of water to the solid mixture in order to obtain the desired product. The polycrystalline products have been characterized by powder- and single crystal-X-ray diffraction as well as by a combination of solution and solid-state NMR methods. This class of compounds is characterized by the presence of a supramolecular cage formed by four zwitterionic molecules encapsulating the alkali or ammonium cations *via* O···M$^+$ or O···H–N interactions. The cage is sustained by O–H···O hydrogen bonds between carboxylic –COOH and carboxylate –COO$^{(-)}$ groups, and by C–H···O bonds between –CH$_{Cp}$ and –CO groups, while the anions are layered in between the cationic complexes, as shown in Fig. 7 in the case of $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]_2\cdot Cs^+I^-$. It is fascinating to think of this inter-solid reaction as a sort of sophisticated solid-state "solvation" process of the cations by the organometallic complex.[41c]

## Mechanochemical preparation of coordination networks

Another relevant topic of crystal engineering is the preparation of coordination networks (the literature is growing
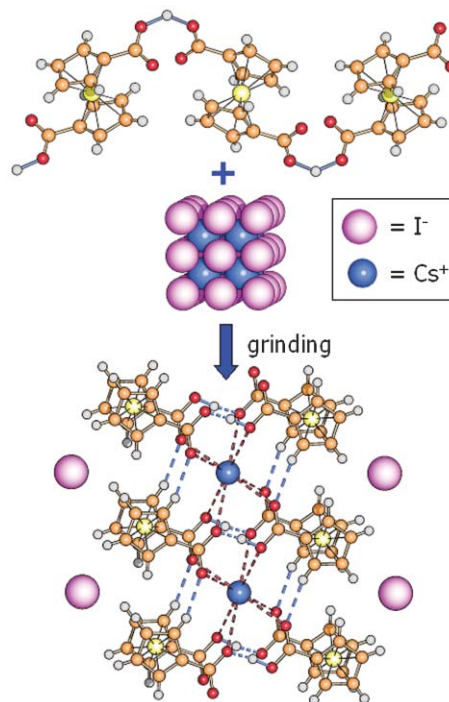
Fig. 7 A pictorial representation of the process leading from $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]$ and CsI to $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]_2\cdot Cs^+I^-$.

exponentially).[42] In our lab, we have begun to explore the mechanochemical preparation of coordination networks by using bidentate nitrogen bases.[43] The coordination polymer Ag[N(CH$_2$CH$_2$)$_3$N]$_2$[CH$_3$COO]·5H$_2$O has been obtained by co-grinding in the solid state and in the air of silver acetate and [N(CH$_2$CH$_2$)$_3$N] in 1:2 ratio (see Fig. 8(a)). The preparation of single crystals of Ag[N(CH$_2$CH$_2$)$_3$N]$_2$[CH$_3$COO]·5H$_2$O was obviously indispensable for the determination of the exact nature of the co-grinding product. One could thus establish that the coordination network in Ag[N-(CH$_2$CH$_2$)$_3$N]$_2$[CH$_3$COO]·5H$_2$O is based on chains of Ag$^+$···[N(CH$_2$CH$_2$)$_3$N]···Ag$^+$···[N(CH$_2$CH$_2$)$_3$N]···Ag$^+$, with each silver atom carrying an extra pendant [N(CH$_2$CH$_2$)$_3$N] ligand and a coordinated water molecule in tetrahedral coordination geometry. When ZnCl$_2$ is used instead of AgCH$_3$COO in the equimolar reaction with [N(CH$_2$CH$_2$)$_3$N], different products are obtained from solution and solid-state reactions, respectively. Fig. 8(b) shows that the structure of Zn[N(CH$_2$CH$_2$)$_3$N]Cl$_2$, crystallized from solution, is based on a one-dimensional *zigzag* coordination network constituted of alternating [N(CH$_2$CH$_2$)$_3$N] and ZnCl$_2$ units, joined by Zn–N bonds. Crystals of the product obtained by grinding have not been obtained and the details of this compound remain unknown. However, we have been able to demonstrate that the phase obtained by co-grinding can be transformed into the known anhydrous phase Zn[N(CH$_2$CH$_2$)$_3$N]Cl$_2$ by prolonged manual grinding.

Other examples of mechanochemical preparation of coordination complexes are known. Steed and Raston and co-workers have explored the use of mechanochemistry in the synthesis of extended supramolecular arrays.[44] Grinding of Ni(NO$_3$)$_2$ with 1,10-phenanthroline (phen) resulted in the facile preparation of [Ni(phen)$_3$]$^{2+}$ accompanied by a dramatic and rapid colour change. Addition of the solid sodium salt of tetrasulfonatocalix[4]arene (tsc) gives two porous π-stacked supramolecular arrays [Ni(phen)$_3$]$_2$[tsc^{4-}]·nH$_2$O and the related [Na(H$_2$O)$_4$(phen)][Ni(phen)$_3$]$_4$[tsc^{4-}][tsc^{5-}]·nH$_2$O depending on stoichiometry. It has also been reported that the co-grinding of copper(II) acetate hydrate with 1,3-di(4-pyridyl)propane (dpp) gives a gradual colour change from blue to blue–green over *ca.* 15 min. The resulting material was
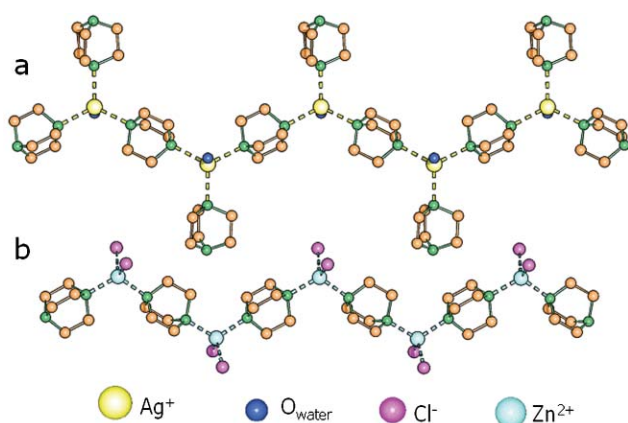
shown by solid-state NMR spectroscopy to comprise a 1D coordination polymer with water-filled pores. The same host structure, [{Cu(OAc)$_2$}$_2$(μ-dpp)]$_n$, could be obtained from solution containing methanol, acetic acid or ethylene glycol guest species.[45]
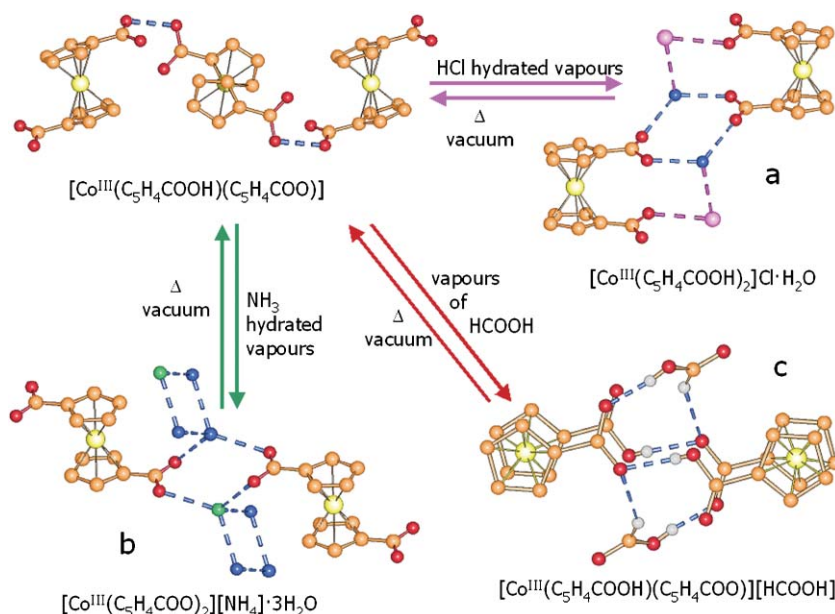
Solid–vapour reactions involving hydrogen-bonded crystals

Solid–vapour reactions are another solvent-free route to new materials. Reactions of this type have been extensively investigated in the organic field and nowadays hundreds of quantitative processes are known.[46] Applications to organometallic cases are less popular.[47]

We have investigated the reactivity towards vapours of acids and bases of the organometallic zwitterion [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)], because the presence of one –COOH group, which can react with bases, and one –COO$^{(−)}$ group, which can react with acids, confers to this species a useful amphoteric behaviour. The reaction between a solid acid and a basic vapour was first investigated by the Italian scientist Pellizzari as early as in 1884.[48] In the 1970s Paul and Curtin, beside studying solid–solid reactions, investigated solid–vapour reactions in a series of elegant studies.[49]

The zwitterion [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)] undergoes fully reversible heterogeneous reactions with the hydrated vapours of a variety of acids (*e.g.* HCl,[50a] CF$_3$COOH,[50b] HBF$_4$[50b]) and bases (*e.g.* NH$_3$, NMe$_3$, NH$_2$Me[47a]), with formation of the corresponding salts.[50] Formation of the salts in the heterogeneous reactions was assessed by comparing observed X-ray powder diffraction patterns with those calculated on the basis of the single-crystal structures determined from crystals obtained from solution. In the case of vapours of aqueous HCl complete conversion of the neutral crystalline zwitterion into the crystalline chloride salt [Co^{III}(η^5-C$_5$H$_4$COOH)$_2$]Cl·H$_2$O is attained in few minutes of exposure.[50a] The polycrystalline product can be converted back to neutral [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)] by heating the sample under low pressure (see Fig. 9(a)). The behaviour of [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)] towards NH$_3$ is similar: exposure to vapours of wet ammonia quantitatively transforms the neutral complex into the hydrated ammonium salt [Co^{III}(η^5-C$_5$H$_4$COO)$_2$]-[NH$_4$]·3H$_2$O.[50a] Absorption of ammonia is also fully reversible: upon thermal treatment the salts convert quantitatively into the neutral zwitterion (see Fig. 9(b)). Analogously [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)] reversibly reacts with CF$_3$COOH,[50b] CH$_2$ClCOOH,[50c] CHF$_2$COOH,[50c] HBF$_4$ and HCOOH,[50d] without decomposition or detectable formation of amorphous material. The materials are robust and stable and can be cycled through release/absorption without decomposition. The reactions of [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)] with HCl and CF$_3$COOH were also investigated by AFM on single crystals.[50e]

The adduct with formic acid[50d] deserves a closer look, because upon crystal formation proton transfer does not take place, and the product [Co^{III}(η^5-C$_5$H$_4$COOH)(η^5-C$_5$H$_4$COO)][HCOOH] is a co-crystal rather than a salt

Fig. 8 The coordination network in Ag[N(CH$_2$CH$_2$)$_3$N]$_2$[CH$_3$COO]·5H$_2$O (a) and in Zn[N(CH$_2$CH$_2$)$_3$N]Cl$_2$ (b).

Legend: Ag$^+$, O$_{water}$, Cl$^-$, Zn^{2+}

Fig. 9 The reversible reactions between anhydrous $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$ and HCl (a), NH$_3$ (b), and HCOOH (c) leading to formation of $[Co^{III}(\eta^5\text{-}C_5H_4COOH)_2]Cl\cdot H_2O$, $[Co^{III}(\eta^5\text{-}C_5H_4COO)_2][NH_4]\cdot 3H_2O$, and $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)][HCOOH]$, respectively.

(Fig. 9(c)), as shown by both X-ray and CPMAS NMR spectroscopy.

In summary, the zwitterion $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$ can be said to behave as a solid amphoteric trap towards vapours of both acids and bases. Since the solid–vapour reactions occur with wet vapours, one may be brought to suppose that the reactions occur *via* a process of dissolution and recrystallisation, as the vapours are adsorbed by the crystalline powder. The reverse process, *i.e.* reconstruction of the zwitterion crystals, is more difficult to explain as it implies proton removal from the cationic acid. Moreover, the TGA experiments show that water of hydration is always released first, while the acid and the base come off only subsequently. Hence the participation in the reverse process of an intermediate liquid phase is unlike.

On closing this section we would like to emphasize that heterogeneous solid–vapour reactions represent an alternative to nanoporosity (*i.e.* to zeolitic behaviour) for the controlled uptake and release of small molecules[47] and are being actively investigated in the quest for solid-state sensors, reservoirs, filters and sieves for detecting or trapping small molecules.[51]

Induced polymorphism and solvate formation

The paradigm of crystal engineering is the possibility of obtaining an ordered and periodical organization of molecules or ions through space from the self-assembly of building blocks (see Fig. 1). The control of the assembly process depends on our capacity of *instructing* molecules or molecular ions how to recognize each other and form stable crystal nuclei, that eventually lead to the desired crystalline material. Clearly, if the instructions are not very precise and/or if other (uncontrolled or less controlled) external factors affect the process, the result can be unpredictable or admit multiple solutions, *i.e.* serendipitous polymorphism. The problem is further complicated by the possibility of obtaining different solvate forms. One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to *predict* whether a new species may crystallizes from solution with one or more molecules of solvent. However, while serendipitous polymorphism and solvate formation are very common ("it happens" to crystallize the same substance as different crystals or solvates), intentional polymorphism is more difficult, as it requires the purposed investigation of the conditions to obtain different crystals for the same species.[13,52]

Thus far we have provided evidence that the solvent-free *reaction* of a molecular crystal with a vapour can be exploited to make new crystalline supramolecular aggregates. A useful notion is that the same approach can be used to prepare a new *polymorph or solvate*.[53] This section of the *Feature Article* will expand on this idea. We will show how mechanical treatment, vapour uptake and release and seeding can all be used to obtain new crystal forms. We will also discuss the useful possibility of obtaining interconversion of crystal forms as a function of pressure and temperature.

We have come across a case of relationship between polymorphism and pseudo-polymorphism during the initial preparation of the zwitterion $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$.[38a] Single crystals of this molecule could be obtained by *seeding* a water solution obtained by dissolving the trihydrate $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]\cdot 3H_2O$ with *seeds* prepared by step-wise dehydration of the hydrated species.[38b] A thermogravimetric experiment showed that $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]\cdot 3H_2O$ reversibly releases one water molecule at 378 K, while the loss of the two remaining water molecules occurs at *ca.* 506 K and is immediately followed by a phase transition. Subsequent

comparison of the calculated and measured powder diffractograms of the anhydrous phase confirms that the powder obtained at 506 K and the single crystals precipitated at room temperature after *seeding* possess the same structure. Importantly, crystallization in the absence of seeds of $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]$ yields the initial trihydrate form $[Co^{III}(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]\cdot3H_2O$.

In a similar process, crystals of $[Ru(\eta^6-C_6H_6)_2][BF_4]_2$ can be crystallized from nitromethane as the solvate form $[Ru(\eta^6-C_6H_6)_2][BF_4]_2\cdot MeNO_2$. These solvate crystals, if exposed to air, rapidly convert to the unsolvate form $[Ru(\eta^6-C_6H_6)_2][BF_4]_2$. The nature of this latter compound was established from single crystals obtained from water in the presence of seeds of the powder material obtained from desolvated crystals $[Ru(\eta^6-C_6H_6)_2][BF_4]_2\cdot MeNO_2$.[54]

The opposite process, namely solvent uptake, can often be activated by mechanical treatment of unsolvated crystals. There are several reports on that even gentle grinding of a powder product to prepare a sample for powder diffraction may lead to the formation of a hydrated product.[55] In our lab, we have seen that the hydrated salt $[Co(\eta^5-C_5H_5)_2]^+[Fe(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]^-\cdot H_2O$ is obtained by simply grinding in the air the crystalline powder of $[Co(\eta^5-C_5H_5)_2]^+[Fe(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]^-$ that precipitates from THF or nitromethane on reacting $[Co(\eta^5-c_5H_5)_2]$ with $[Fe(\eta^5-C_5H_4COOH)_2]$.[56a] Once $[Co(\eta^5-C_5H_5)_2]^+[Fe(\eta^5-C_5H_4COOH)(\eta^5-C_5H_4COO)]^-\cdot H_2O$ has been obtained by grinding, *its single crystals* can be grown from water or nitromethane, while crystals of the anhydrous form are no longer observed. However, on heating, the hydrated form loses water at 373 K and reverts to the starting material.

A related situation has been observed on reacting solid $[N(CH_2CH_2)_3N]$ with solid malonic acid $[HOOC(CH_2)COOH]$ in the molar 1:2 ratio.[56b] Two different crystal forms of the salt $[HN(CH_2CH_2)_3NH][OOC(CH_2)COOH]_2$ are obtained depending on preparation technique (grinding or solution) and crystallization speed. Form I, containing mono-hydrogen malonate anions forming conventional intramolecular O–H⋯O hydrogen bonds and inter-ionic N–H⋯O hydrogen bonds, is obtained by solid-state co-grinding or by rapid crystallization, while form II, containing *both* intermolecular and intramolecular O–H⋯O hydrogen bonds, is obtained by slow crystallization (see Fig. 10). Form I and II do not interconvert, while form I undergoes an order–disorder phase transition on cooling. One can envisage the two crystalline forms as *hydrogen-bond isomers* of the same *solid supermolecule*.

Proton transfer along a hydrogen bond poses an interesting question about polymorph definition. In fact, proton mobility along a hydrogen bond (say from O–H⋯N to $^{(-)}$O⋯H–N$^{(+)}$) may not be associated with a phase transition, even though it implies the formal transformation of a molecular crystal into a molecular salt. This situation has been observed, for instance, for the proton migration along an O–H⋯O bond in a co-crystal of urea–phosphoric acid (1:1) as a function of temperature.[57a] Mootz and Wiechert, on the other hand, have isolated two co-crystals of pyridine and formic acid: in the 1:1 co-crystal proton transfer from formic acid to pyridine does not take place, while in the 1:4 co-crystal N–H$^{(+)}$⋯O$^{(-)}$
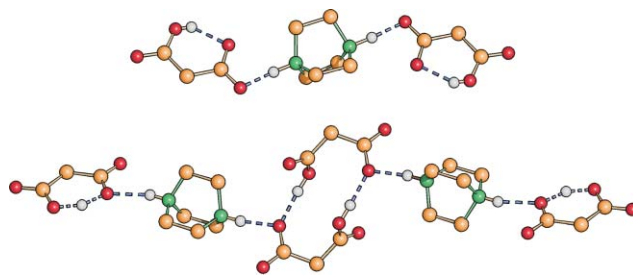
**Fig. 10** Form I (top) and II (bottom) of $[HN(CH_2CH_2)_3NH][OOC(CH_2)COOH]_2$ and the hydrogen-bonded anion⋯cation chains present in their crystals. Form I is obtained by solid-state co-grinding or by rapid crystallization, while form II is obtained by slow crystallization.

interactions are present.[57b] Examples of this kind are rare, but serve to stress how the phenomenon of polymorphism can be, at times, full of ambiguity.

An intriguing case of interconversion between unsolvate and solvate crystals is observed when $[N(CH_2CH_2)_3N]$ is reacted with maleic acid $[HOOC(HC=CH)COOH]$. The initial product is the anhydrous salt $[HN(CH_2CH_2)_3N][OOC(HC=CH)COOH]$, which contains chains of $^{(+)}$N–H⋯N$^{(+)}$ bonded cations $[HN(CH_2CH_2)_3N]^+$ and "isolated" $[OOC(HC=CH)COOH]^-$ anions.[58] Upon exposure to humidity the anhydrous salt converts within few hours into the hydrated form $[HN(CH_2CH_2)_3N][OOC(HC=CH)COOH]\cdot0.25H_2O$, which contains more conventional "charge-assisted" $^{(+)}$N–H⋯O$^{(-)}$ hydrogen bonds between anion and cation (see Fig. 11). This latter form can also be obtained by co-grinding.

The two isomorphous crystalline complexes $[M(\eta^5-C_5H_5)_2][PF_6]$ (M = Co, Fe) afford a textbook example of an enantiotropic system, *i.e.* of polymorphs that interconvert as a function of temperature.[59] The room temperature phases of these crystals have been shown, by variable-temperature X-ray diffraction experiments and differential scanning calorimetry (DSC), to undergo two reversible solid-to-solid phase changes
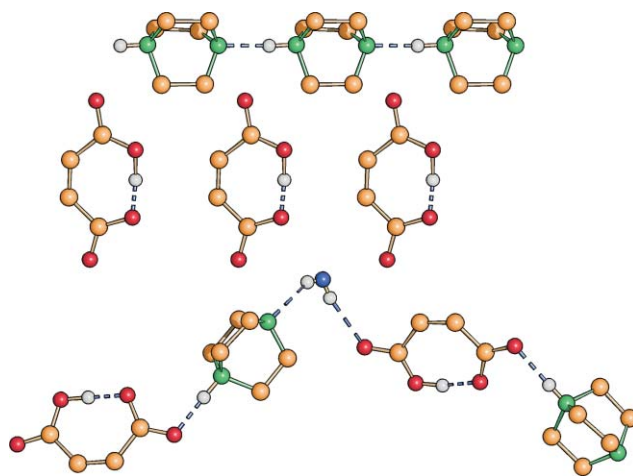
Fig. 11 Views of the packing and hydrogen bonding in the anhydrous salt $[HN(CH_2CH_2)_3N][OOC(HC=CH)COOH]$ (top) and of the hydrated salt $[HN(CH_2CH_2)_3N][OOC(HC=CH)COOH]\cdot H_2O_{0.25}$ (bottom).

towards a low-temperature monoclinic phase and a high-temperature cubic phase, respectively. The only difference between Co and Fe is in the temperatures of the transitions: M = Fe, *ca.* 213.1 and 347.1 K, M = Co, *ca.* 251.8 and 313.9 K measured in the heating cycles, respectively. Therefore, the range of thermal stability of the intermediate phase is *ca.* 62 K in the case of Co and *ca.* 134 K in the case of Fe. The phase transitions could be studied on the single-crystal X-ray diffractometer by collecting data sets on the same crystal specimen. While the room- and low-temperature phases are ordered, the high-temperature phase of $[Co(\eta^5-C_5H_5)_2][PF_6]$ contains ordered $[PF_6]^-$ anions and orientationally disordered $[Co(\eta^5-C_5H_5)_2]^+$ cations (see Fig. 12), while, in the case of $[Fe(\eta^5-C_5H_5)_2][PF_6]$, both cations and anions are disordered.

The close structural similarity between the two complexes $[M(\eta^5-C_5H_5)_2]^+$ (M = Co, Fe) prompted us to explore the possibility of *growing crystals from solutions containing mixtures of the two cations*. We have discovered that, in the solid state, the two cations are *fully miscible in the whole range of composition* and that the composition is the same as that of the *water solutions* from which the mixed-crystals are precipitated, *e.g.* the mixed salts can be formulated as $[Co_xFe_{1-x}(\eta^5-C_5H_5)_2][PF_6]$ (with $0 < x < 1$).[60] Moreover, *the phase transition behaviour depends linearly on the composition* (see Fig. 12). The temperatures at which the two solid-to-solid phase transitions occur vary regularly, as a direct function of the molar ratio, between the two extremes defined by the homo-cationic crystals.
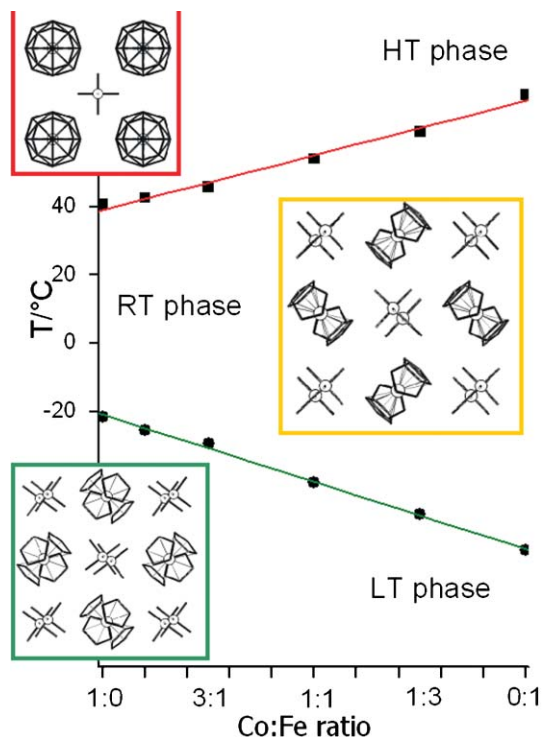

Fig. 12 Schematic representation of the relationship between the three structures of crystalline $[M(\eta^5-C_5H_5)_2][PF_6]$ (M = Co, Fe) and the dependence of the phase transition temperatures on the alloy composition, when $[Co(\eta^5-C_5H_5)_2]^+$ and $[Fe(\eta^5-C_5H_5)_2]^+$ are co-crystallized to give $[Co_xFe_{1-x}(\eta^5-C_5H_5)_2][PF_6]$ (with $0 < x < 1$).

The close structural similarity between the two complexes $[M(\eta^5-C_5H_5)_2]^+$ (M = Co, Fe) prompted us to explore the possibility of growing crystals from solutions containing *mixtures of the two cations*. The resulting mixed salts $[Co_xFe_{1-x}(\eta^5-C_5H_5)_2][PF_6]$ (with $0 < x < 1$) show that the two cations are *fully miscible in the whole range of composition* and that the composition is the same as that of the water solutions from which the mixed-crystals are precipitated. Moreover, *the phase transition behaviour depends linearly on the composition*, *i.e.* the temperatures at which the two solid-to-solid phase transitions can be selected by choosing the molar ratio in solution. Thus, the mixed-crystal $[Co_xFe_{1-x}(\eta^5-C_5H_5)_2][PF_6]$, though composed of molecular ions and soluble in water, possesses the features of an alloy of the A_xB_{1-x} type.

The *seeding* procedure can also be exploited to attempt crystallization of unyielding materials if *seeds* of isostructural or *quasi*-isostructural species that crystallise well are available.[61] This sort of *heteromolecular seeding* has been instrumental to the separation of two concomitant polymorphs.[62] Precipitation of $[Fe(\eta^5-C_5H_5)_2]^+$ as its $[AsF_6]^-$ salt generates two concomitant crystal phases: a trigonal phase (Fe-T) and a monoclinic phase (Fe-M). In order to separate the two polymorphs two solutions were seeded with crystals of the trigonal phase of $[Co(\eta^5-C_5H_5)_2][AsF_6]$ and of the monoclinic phase of $[Fe(\eta^5-C_5H_5)_2][PF_6]$, yielding the corresponding trigonal and monoclinic forms of $[Fe(\eta^5-C_5H_5)_2][AsF_6]$, respectively. The seeding was successful and yielded good quality single crystals of Fe-T and Fe-M (see Fig. 13), which proved to be sufficiently robust to undergo a full cycle of four phase transitions directly on the diffractometer, (Fe-T → Fe-M → Fe-C (cubic phase) → Fe-M → Fe-T), a rather uncommon situation that permitted a whole rationalization of the phase transitional behaviour.

On closing the section devoted to polymorphism, we ought to point out that the ongoing intensive research on coordination network crystal engineering is opening new avenues to the investigation of polymorphs and solvates. As a matter of fact the same *divergent* ligand may yield topologically different coordination networks with the same metal, which will have
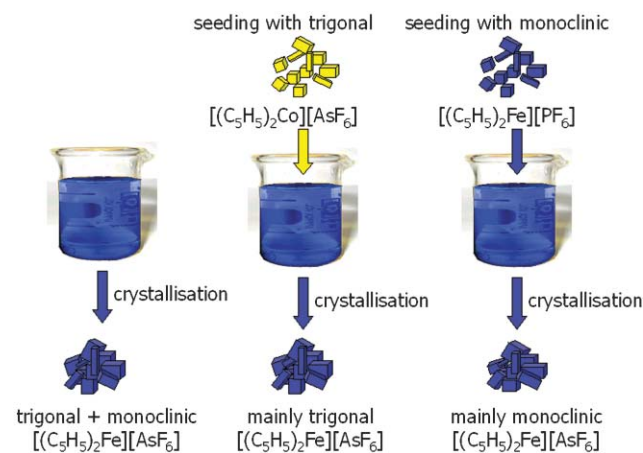
Fig. 13 The seeding procedure where crystals of trigonal $[Co(\eta^5-C_5H_5)_2][AsF_6]$ were used to grow the trigonal form of $[Fe(\eta^5-C_5H_5)_2][AsF_6]$, while crystals of monoclinic $[Fe(\eta^5-C_5H_5)_2][PF_6]$ were used to obtain the monoclinic form of $[Fe(\eta^5-C_5H_5)_2][AsF_6]$.

the same composition but different architecture (polymorphs or supramolecular isomers?). Moreover, the same network can co-crystallize with a different number and type of molecules in the voids and channels, and these molecules can be desorbed or substituted often without network destruction or reconstruction.[63] Solvent and/or guest dependent topological isomerism in coordination polymers has been recently reviewed.[4a]

Concluding remarks

In this *Feature Article* we have shown that "crystals can be made from crystals" by mechanical mixing of molecular and ionic crystals and by reacting crystals and vapours in solvent-free conditions. This awareness is useful in crystal engineering not only because it provides alternative routes to the synthesis of new crystalline materials but also because it can be exploited to obtain different forms of a given substance, *e.g.* crystal polymorphs or solvates. Polymorphism, with its high degree of serendipity, contrasts the ideas of control and reproducibility dear to the crystal engineer. Hence, for both scientific and utilitarian reasons, any step forward towards a higher degree of control of polymorphism and solvate formation is useful.

Solid–solid and solid–vapour reactions have been the subject of investigation for decades in the fields of organic and of inorganic chemistry and are commonly used in industrial processes. In spite of this, or – perhaps – because of this, these processes are not very popular in the field or organometallic and coordination chemistry. Clearly, the control on solid-state reactions, that can be used to trap environmentally dangerous or poisonous molecules, is an attractive goal for solid-state chemistry and crystal engineering. For instance, one may purposefully plan to assemble molecules that are capable of absorbing molecules from the gas phase and, possibly, to react with them. This implies *sensing* and could be exploited to detect molecules if there is a measurable response from the solid state. If the reaction is quantitative and reversible, the same processes (whether based on weak non-covalent bonding or on some type of covalent/ionic, high enthalpy, process) can be used to trap gases and deliver them where appropriate.

Since the solid–solid and solid–vapour reactions described in this article involve formation or disruption of non-covalent interactions, they can be looked at as *supramolecular reactions* between a two periodical supermolecules (crystals) or between a periodical supermolecule and a molecule in the gas phase. The concept can be stretched to encompass also solvation/desolvation processes, because the uptake/loss of solvent molecules requires supramolecular bond breaking and forming, as for the formation of a co-crystal or a supramolecular adduct.

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