

1

Applications of Crystal Engineering Strategies in Solvent-free Reactions: Toward a Supramolecular Green Chemistry

DARIO BRAGA, DANIELA D'ADDARIO, LUCIA MAINI, MARCO POLITO, STEFANO GIAFFREDA, KATIA RUBINI and FABRIZIA GREPIONI

Dipartimento di Chimica G. Ciamician, University of Bologna, Via Selmi 2, 40126 Bologna, Italy.

1. INTRODUCTION

Making crystals by design is the paradigm of crystal engineering [1]. The goal of this field of research is that of assembling functionalized molecular and ionic components into a target network of supramolecular interactions [2]. This “bottom-up” process generates *collective* supramolecular properties from the convolution of the physical and chemical properties of the individual building blocks with the periodicity and symmetry operators of the crystal (Figure 1) [3].

One can envisage two main subareas of crystal engineering, namely, those of coordination networks [4] and of molecular materials [5], even though all possible intermediate situations are possible. The preparation of coordination networks or polymers can be appropriately described as *periodical coordination chemistry* and exploits the possibility of *divergent ligand-metal coordination*, as opposed to the more traditional *convergent coordination chemistry* operated by chelating polydentate ligands [6] (Figure 2).

The possibility of exploiting engineered coordination networks for practical applications (such as absorption of molecules, reactions in cavities, etc.) very much depends on whether the networks contain large empty spaces (channels, cavities, etc.) [7] or whether the network is close packed because of interpenetration and self-entanglement [8]. The

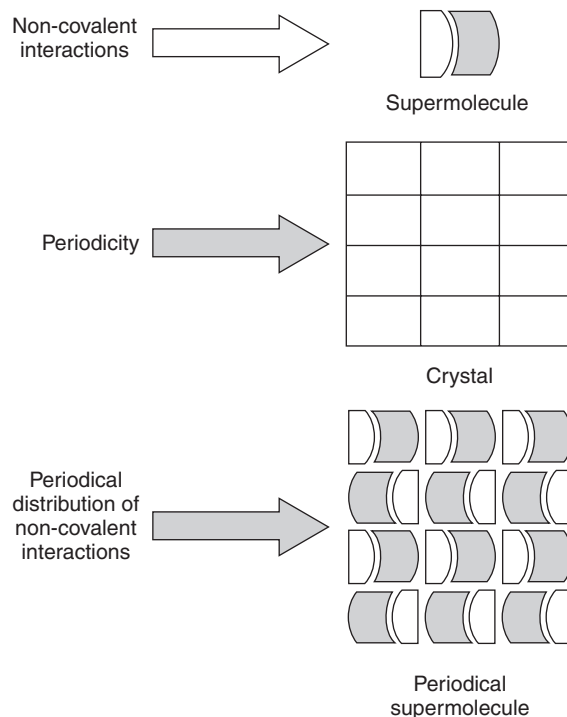


Figure 1. From molecules to periodical supermolecules: the collective properties of molecular crystals result from the convolution of the properties of the individual molecular/ionic building blocks with the periodical distribution of intermolecular non-covalent bonding of the crystal. Reproduced from Ref. 6 by permission of The Royal Society of Chemistry.

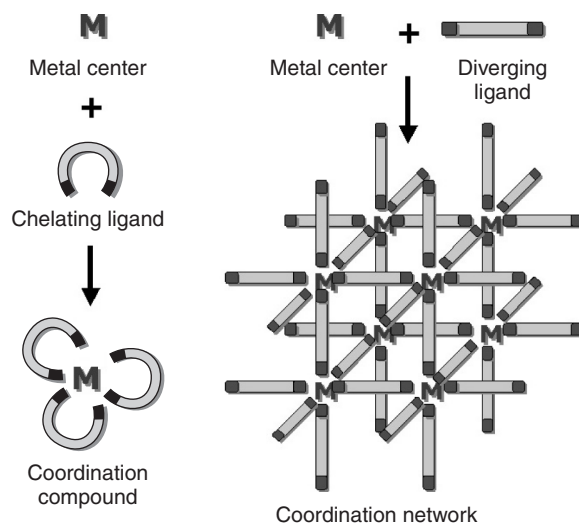


Figure 2. The relationship between molecular (left) and periodical (right) coordination chemistry: the use of bidentate ligand spacers allows construction of *periodical* coordination complexes. Reproduced from Ref. 6 by permission of The Royal Society of Chemistry.

possibility of sponge-like behavior by which the network can change, that is, swell/shrink to accommodate/release guest molecules, should also be taken into account [9].

While in periodical coordination chemistry it is useful to focus on the *knots* and *spacers* in order to describe the topology of the network, when dealing with molecular materials what matters most are the characteristics of the component molecules or ions and the type of interactions holding these building blocks together. These interactions are mainly of the non-covalent type (van der Waals, hydrogen bonds, π -stacking, ionic interactions, ion pairs, etc.) [10–12]. The intermolecular links will be weaker than the covalent chemical bonds within the individual components, which, in general, will retain their chemical and physical identity once evaporated or dissolved. This is not so for coordination networks that usually cannot be reversibly assembled and disassembled.

1.1. Making Crystals by *Smashing* Crystals?

Since the focus of crystal engineering is *making* crystals with a purpose, crystal *makers* invariably (and inevitably) end up facing the problem of obtaining crystals, possibly single crystals of reasonable size, in order to benefit from the speed and accuracy of single-crystal x-ray diffraction experiments. Even though amorphous materials can be extremely interesting, and certainly are so in the biological world and are providing inspiration to scientists [13], in crystal engineering studies, the desired materials need to be *by definition* in the crystalline form and will be obtained by a crystallization method, whether from solution, melt or vapor or from more forceful hydrothermal syntheses.

In this chapter, we will provide evidence that reactions between solids and between solids and vapors offer alternative ways to prepare crystals, both of the coordination network and of the molecular crystal type [14]. It may be useful to stress that, since reactions involving solid reactants or occurring between solids and gases do not generally require recovery, storage and disposal of solvents, they are of interest in the field of “green chemistry”, where environmentally friendly processes are actively sought [15]. Furthermore, solvent-less reactions often lead to very pure products and reduce the formation of solvate species [16].

In the following, we will discuss two types of solvent-free processes: those involving gas uptake by a molecular crystal to form a new crystalline solid and those involving reactions between molecular crystals or between a molecular and an ionic crystal to yield new crystalline materials [17]. Since the “Bolognese” crystal engineering laboratory has been traditionally interested in using organometallic building blocks, the vast majority of cases discussed throughout this chapter will show the utilization of organometallic building blocks [18].

In previous papers, we have argued that reactions of molecular crystals with gases or other crystals ought to be regarded as *supramolecular reactions* whereby non-covalent interactions (including coordination bonds) between guest and the host are broken and formed. The two types of processes are depicted in Figure 3.

The absence of solvent requires that other means be used to bring molecules into contact for the formation of supramolecular bonds. Since our reactants are, in general, molecular crystals, the utilization of finely ground powders favors reactions with vapors because of the large surface area. On the other hand, the reactions between two molecular crystals (as shown in Figure 3) often require co-grinding to obtain intercrystal reactions. Hence, in both types of reactions, crystals need to be ground, a condition that may appear

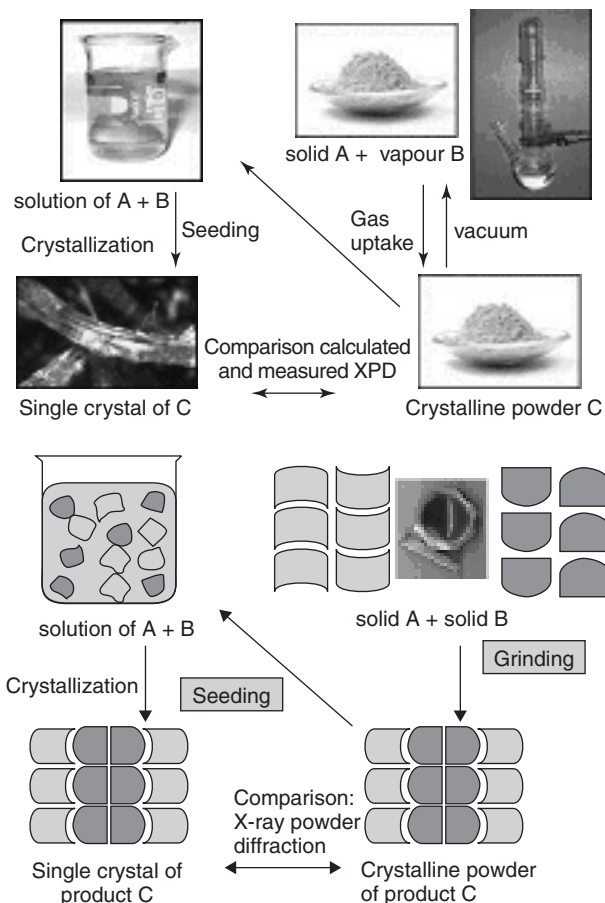


Figure 3. The solid–gas (top) and solid–solid (bottom) processes and the strategy to obtain single crystals by recrystallization of the solid reaction product in the presence of *seeds* of the desired crystals.

to contradict the *single-crystal dogma*, as the vast majority of crystal engineering studies are based on the type of structural knowledge provided by single-crystal x-ray diffraction experiments. This is also true for the cases discussed herein. The characterization of the products of both solid–gas and solid–solid strategies rely on the possibility of obtaining single crystals of the desired product, either by direct crystallization from solution or via *seeding*, in order to be able to compare the powder diffractograms measured on the product of the solvent-free process with that calculated on the basis of the single crystal structures. This aspect of the work will be briefly expanded upon in the next section.

1.2. Milling, Grinding, Kneading and Seeding

As mentioned in the previous section, the size of the crystals will dictate the experimental method of choice. Unless one resorts to high-intensity synchrotron radiation, microcrystals

will allow only powder diffraction experiments, which only rarely can be used for *ab initio* structure determination in order to get those precise structural information that are so essential to the crystal engineer. Clearly, the solvent-less reactions of a crystalline powder with a vapor or that between two crystalline powder are, generally speaking, not compatible with the formation of large single crystals, since it will generally produce a material in the form of a powder.

Nonsolution methods to obtain new products require the chemist, or crystal engineer, to explore/exploit methods that are not routinely used in chemical laboratories. Reactions of the type described herein require broadening the view of typical chemical processes. Beside the conventional “academic” chemical reaction procedures (typically Schlenk techniques, if air-sensitive organometallic molecules are synthesized as building blocks), one has to resolve to methods, such as *grinding* and *milling*, that are less popular – when they are not dismissed as nonchemical – in research laboratories. These methods are related to the mechanochemical activation of reactions occurring between solids and to the control exerted on the crystallization process [19, 20].

Grinding and milling

Typical mechanochemical reactions are those activated by co-grinding or milling of powder materials, usually carried out either manually, in an agate mortar, or electro-mechanically, as in ball milling. In both cases, the main difficulty is in controlling reaction conditions: grinding time, temperature, pressure exerted by the operator, and so on. Furthermore, the heat generated in the course of the 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. One should also keep in mind that mechanical stress, by fracturing the crystals, increases surface area and facilitates interpenetration and reaction depending on the ability of molecules to diffuse through the crystal surfaces. With this viewpoint, intersolid reactions between molecular crystals can be conceptually related to the uptake of a vapor from a molecular solid to form a new crystalline solid.

Mechanochemical processes, and more generally solid-state reactions, though little exploited at the level of academic research, are commonly used at industrial level, mainly with inorganic solids and materials [21].

Kneading

Even though the discussion of the role of solvent in a chapter devoted to solvent-free reactions may seem contradictory, it is useful to remind the reader that, in some cases, the use of a small quantity of solvent can accelerate solid-state reactions carried out by grinding or milling [22]. The method of the grinding of powdered reactants in the presence of a small amount of solvent, also known as *kneading*, is commonly exploited, for instance, in the preparation of cyclodextrin inclusion compounds. Studies of *kneading* and development of laboratory/industry *kneaders* (mainly of pharmaceutical powders) have been carried out [23].

As an example of a laboratory scale preparation, one could mention the preparation by *kneading* of binary β -cyclodextrin-bifonazole [24], and of β -cyclodextrin inclusion compounds of ketoprofen [25a], ketoconazole [25b], and carbaryl [25c].

Clearly, the objection whether a *kneaded* reaction between two solid phases can be regarded as a *bona fide* solid-state process is justified. However, in the context of this work, our interest lies more in the methods used to make new crystalline materials rather than in the mechanisms. *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.

Seeding

Another apparent contradiction of the utilization of “noncrystallization” methods to prepare new crystalline materials arises from the fact that the products of grinding, milling and kneading processes are usually in the form of a powdered material, while single crystals would be desirable or indispensable for the characterization of the reaction product. Crystallization by *seeding*, that is, crystallization in the presence of microcrystals of the desired materials, is one way to control the growth of a given polycrystalline powder to a size adequate for single-crystal x-ray diffraction experiments.

Seeding procedures are commonly employed in pharmaceutical industries to make sure that the desired crystal form is always obtained from a preparative process, a relevant problem when different polymorphic modifications can be obtained [26]. It is also important to appreciate that *seeding* often prevents formation of kinetically favored products and allows those thermodynamically favored.

Seeds of isostructural or *quasi*-isostructural species that crystallize well can also be employed to induce crystallization of unyielding materials, a process that may be termed *heteromolecular seeding* [27, 28]. For instance, chiral co-crystals of tryptamine and hydrocinnamic acid have also been prepared by crystallization in the presence of seeds of different chiral crystals [29]. Of course, unintentional *seeding* may also alter the crystallization process in an undesired manner [30].

The use of these methods will now be discussed mainly on the basis of examples taken from our recent work.

2. MECHANOCHEMICAL PREPARATION OF HYDROGEN-BONDED ADDUCTS

Manual grinding of the ferrocenyl dicarboxylic acid complex $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ with solid nitrogen-containing bases, namely, 1,4-diazabicyclo[2.2.2]octane, 1,4-phenylenediamine, piperazine, *trans*-1,4-cyclohexanediamine and guanidinium carbonate, generates quantitatively the corresponding organic-organometallic adducts [31] (Figure 4a). The case of the adduct $[\text{HC}_6\text{N}_2\text{H}_{12}][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ (Figure 4b) is particularly noteworthy because the same product can be obtained in three different ways: (i) by reaction of solid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ with vapors of 1,4-diazabicyclo[2.2.2]octane (which possesses a small but significant vapor pressure), (ii) by reaction of solid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ with solid 1,4-diazabicyclo[2.2.2]octane, that is, by co-grinding of the two crystalline powders, and by reaction of the two reactants in MeOH solution. Clearly, the fastest process is the solid–solid reaction. It is also interesting to note that the base can be removed by mild treatment regenerating the structure of the starting dicarboxylic acid. The processes imply breaking and reassembling of hydrogen-bonded networks, conformational change from *cis* to *trans* of the $-\text{COO}/-\text{COOH}$ groups on the ferrocene diacid, and

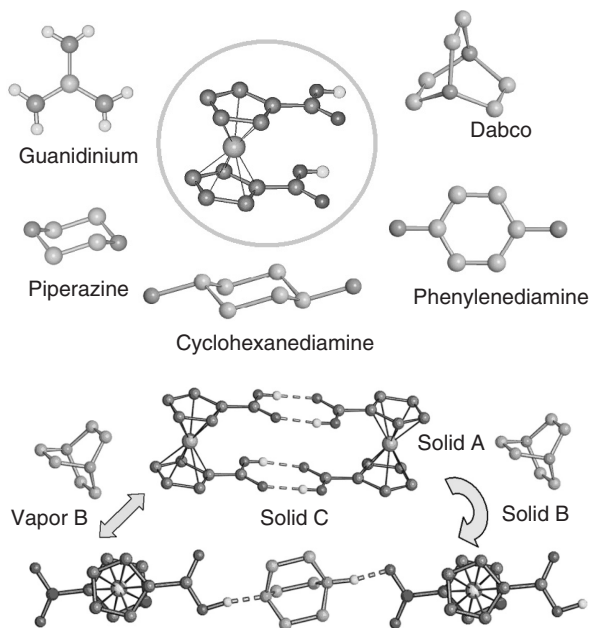


Figure 4. (a) Grinding of the organometallic complex $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ (top center) as a solid polycrystalline material with the solid bases 1,4-diazabicyclo[2.2.2]octane, $\text{C}_6\text{H}_{12}\text{N}_2$ (top right), guanidinium carbonate, $[\text{C}(\text{NH}_2)_3]_2[\text{CO}_3]$ (top left – only cation is shown), 1,4-phenylenediamine, $p\text{-(NH}_2)_2\text{C}_6\text{H}_4$, (bottom right), piperazine, $\text{HN}(\text{C}_2\text{H}_4)_2\text{NH}$, (bottom left) and *trans*-1,4-cyclohexanediamine, $p\text{-(NH}_2)_2\text{C}_6\text{H}_{10}$, (bottom center) generates quantitatively the corresponding adducts $[\text{HC}_6\text{H}_{12}\text{N}_2][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$, $[\text{C}(\text{NH}_2)_3]_2[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]\cdot 2\text{H}_2\text{O}$, $[\text{HC}_6\text{H}_8\text{N}_2][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$, $[\text{H}_2\text{C}_4\text{H}_{10}\text{N}_2][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]$, and $[\text{H}_2\text{C}_6\text{H}_{14}\text{N}_2][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]\cdot 2\text{H}_2\text{O}$, and (b) the solid–gas and solid–solid reactions involving 1,4-diazabicyclo[2.2.2]octane with formation of the linear chain.

proton transfer from acid to base. As mentioned above, in some cases, it was necessary to resolve to *seeding*, that is, to the use of a tiny amount of power of the desired compound, to grow crystals suitable for single-crystal x-ray experiments.

The effect of mechanical mixing of solid dicarboxylic acids $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ ($n = 1-7$) of variable chain length together with the solid base 1,4-diazabicyclo[2.2.2]octane, $\text{C}_6\text{H}_{12}\text{N}_2$, to generate the corresponding salts or co-crystals of formula $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{-H}[\text{OOC}(\text{CH}_2)_n\text{COOH}]$ ($n = 1-7$) has also been investigated [32]. The reactions implied transformation of interacid $\text{O-H}\cdots\text{O}$ bonds into hydrogen bonds of the $\text{O-H}\cdots\text{N}$ type between acid and base, an example is shown in Figure 5. The nature (whether neutral $\text{O-H}\cdots\text{N}$ or charged $(^-)\text{O}\cdots\text{H-N}^{(+)}$) of the hydrogen bond was established by means of solid-state NMR measurement, the chemical shift tensors of the compounds obtained with chain length from 3 to 7 [32].

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.* [33].

In a related study [34], it has been shown that the reaction of $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ with malonic acid $[\text{HOOC}(\text{CH}_2)\text{COOH}]$ in the molar 1:2 ratio yields two different crystal forms

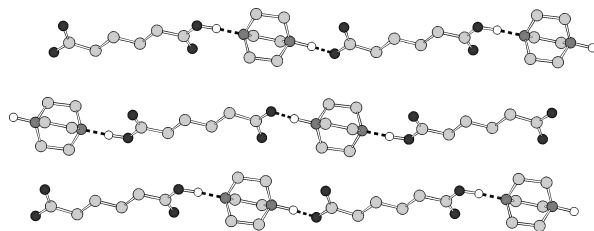


Figure 5. The product of the reaction of the solid base 1,4-diazabicyclo[2.2.2]octane, $C_6H_{12}N_2$, with solid adipic acid generates a chain structure of formula $[N(CH_2CH_2)_3N]-H-[OOC(CH_2)_4-COOH]$. Note how the $O-H-O$ hydrogen-bonds present in the solid acid are replaced by neutral $O-H\cdots N$ and charged $^{(-)}$ $O-H\cdots N^{(+)}$ upon transfer of one proton from the acid to the base.

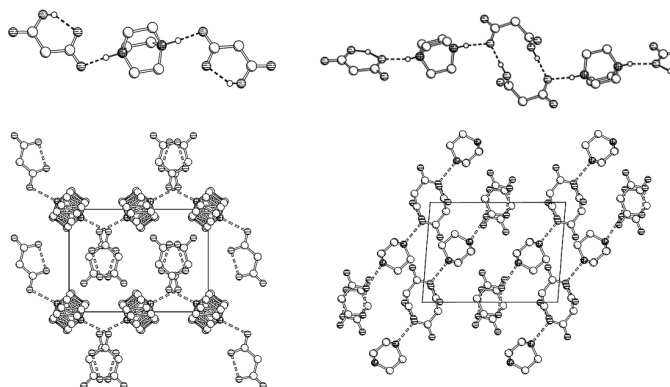


Figure 6. Form I (right) and II (left) of $[HN(CH_2CH_2)_3NH][OOC(CH_2)COOH]_2$ and their respective crystal packings. Form I is obtained by solid-state co-grinding or by rapid crystallization while form II is obtained by slow crystallization.

of the salt $[HN(CH_2CH_2)_3NH][OOC(CH_2)COOH]_2$ (Figure 6) depending on the preparation technique and crystallization speed: the less dense form I, containing mono-hydrogen malonate anions forming conventional intramolecular hydrogen bonds between hydrogen malonate anions, is obtained by solid-state co-grinding or by rapid crystallization, while a denser form II, containing intermolecular hydrogen bonds is obtained by slow crystallization. Forms I and II do not interconvert, while form I undergoes an order-disorder phase transition on cooling. These observations led the authors to wonder whether the two forms could be treated as *bona fide* polymorphs or should be regarded more appropriately as hydrogen-bond isomers of the same *solid supermolecule*.

3. MECHANICALLY INDUCED FORMATION OF COVALENT BONDS

While the reactions described in the previous section can be regarded as supramolecular reactions since only hydrogen-bond breaking and forming are implied, in this section we will discuss examples of mechanochemical formation of covalent bonds for the preparation of building blocks. Bis-substituted pyridine/pyrimidine ferrocenyl complexes have

been obtained by mechanically induced Suzuki-coupling reaction [35] in the solid state starting from the complex ferrocene-1,1'-diboronic acid, $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-B}(\text{OH})_2)_2]$. It is worth recalling that boronic esters and acids are thermally stable, relatively un-reactive to both oxygen and water, and thus easily handled without special precautions. It has been reported that the use of an alumina/potassium fluoride mixture without solvent is very effective in palladium-catalyzed reactions, in particular in the Suzuki coupling of phenyl iodides with phenylboronic acids [36] and in the synthesis of thiophene oligomers *via* Suzuki coupling [36d]. The use of KF/alumina as a solid-phase support for solvent-less Suzuki reactions offers a convenient, environmentally friendly, route to the synthesis of mono- and bis-substituted pyridine and pyrimidine ferrocenyl derivatives (Figure 8), as an alternative to the preparation in solution. In the case of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]$, the solvent-less process is much faster, and more selective than the same reaction carried out in solution. However, the reactions in Figure 7 appear to be facilitated by the addition of tiny amounts of MeOH and, as discussed above, cannot be considered entirely solvent-less.

All reactions depicted in Figure 8 were carried out in air at room temperature. In the Suzuki reaction, the yield depends critically on having a good dispersion of the palladium catalyst on the $\text{KF-Al}_2\text{O}_3$. This dispersion was obtained by grinding the palladium catalyst with $\text{KF-Al}_2\text{O}_3$ before the reaction and, later, by adding to the mixture of Al_2O_3 /reagents/catalyst a few drops (0.1–0.2 ml) of methanol, which was subsequently evaporated under reduced pressure.

Beside shorter reaction times, less workup, higher yield and the absence of solvents, the solid-state reaction affords the possibility of combining different synthetic steps in order to obtain homo- and hetero-ligand ferrocenyl complexes.

The di-substituted ferrocenyl derivatives can be utilized to prepare “complexes of complexes” [37]. In particular, novel mixed-metal macrocyclic complexes were obtained by reacting $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]$ with metal salts, such as AgNO_3 , $\text{Cd}(\text{NO}_3)_2$, $\text{Cu}(\text{CH}_3\text{COO})_2$, $\text{Zn}(\text{CH}_3\text{COO})_2$, and ZnCl_2 [38]. A family of hetero-bimetallic metalla-macrocycles was obtained and characterized: $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]_2\text{Ag}_2(\text{NO}_3)_2 \cdot 1.5\text{H}_2\text{O}$, $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]_2\text{Cu}_2(\text{CH}_3\text{COO})_4 \cdot 3\text{H}_2\text{O}$, $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]_2\text{Cd}_2(\text{NO}_3)_4 \cdot \text{CH}_3\text{OH} \cdot 0.5\text{C}_6\text{H}_6$, $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]_2\text{Zn}_2(\text{CH}_3\text{COO})_4$ and $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]_2\text{Zn}_2\text{Cl}_4$ (Figure 8). Beside the metalla-macrocycles, the reaction of mechanochemically prepared $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]$ with the ferrocenyl dicarboxylic acid complex $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ has led to the supramolecular adduct $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$. However, in these cases, mechanochemical mixing leads to formation of an amorphous material.

As a matter of fact, there are not yet many examples of the utilization of mechanochemical procedures in coordination chemistry. Balema *et al.* have shown, for instance, that the cis-platinum complexes *cis*-(Ph_3P) $_2$ PtCl $_2$ and *cis*-(Ph_3P) $_2$ PtCO $_3$ can be prepared mechanochemically from solid reactants in the absence of solvent [39]. Orita *et al.*, on the other hand, have reported that the reaction of (ethylenediamine) Pt(NO $_3$) $_2$ with 4,4'-bipyridine, which takes as long as 4 weeks at 100 °C to form metalla-macrocycles molecular squares, is brought to completion within 10 min at room temperature by mixing reactants without solvents [40]. Similar reaction acceleration has also been observed with triazine-based ligands. Double helix formation under solvent-free conditions has also been achieved by reacting chiral oligo(bipyridine) copper complexes with $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6$. The progress

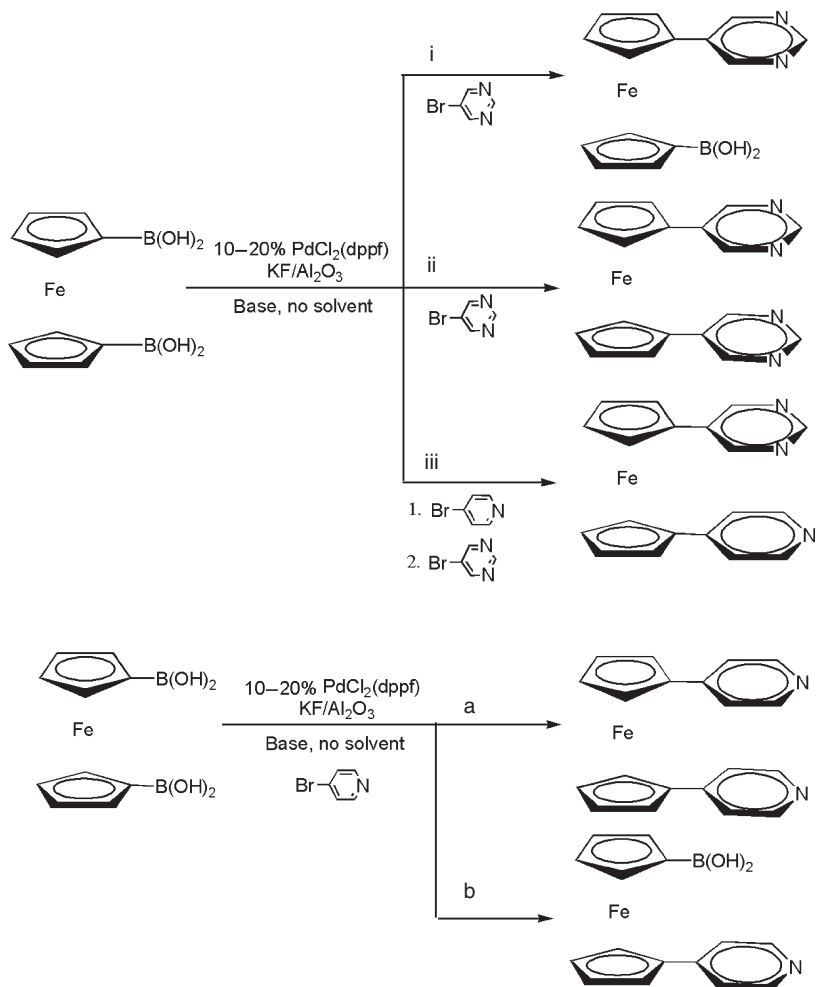


Figure 7. The solid-state synthesis of mono- and bis-substituted pyridine and pyrimidine ferrocenyl derivatives (i: stoichiometry (1:1); ii: stoichiometry (1:2); iii: stoichiometry (1:1:1); a: stoichiometry (1:2); b: stoichiometry (1:1)).

of the reaction was monitored by measuring solid-state CD-spectra showing that after grinding for 5 min the desired helicate had been obtained.

3.1. Mechanochemical Preparation of Coordination Networks

Even though the mechanochemical preparation of the metalla-macrocycles described in the previous section was not possible, coordination polymers with bidentate nitrogen bases can be prepared mechanochemically [41].

The coordination polymer Ag[N(CH₂CH₂)₃N]₂[CH₃COO]·5H₂O has been obtained by co-grinding in the solid state, and in air, of silver acetate and [N(CH₂CH₂)₃N] in a 1:2 ratio (Figure 9). Single crystals suitable for x-ray diffraction were obtained from a

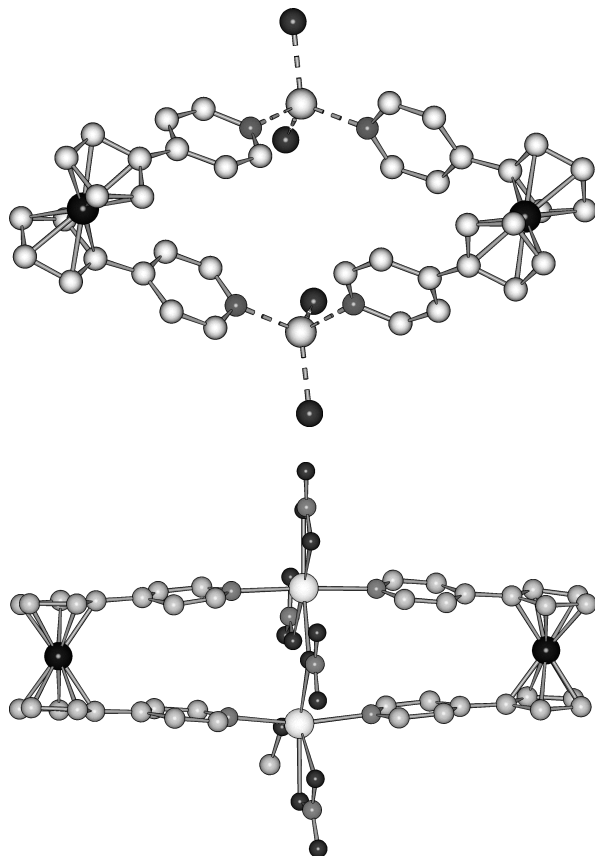


Figure 8. The metalla-macrocycles produced by reaction of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-1-C}_5\text{H}_4\text{N})_2]$ and the salts ZnCl_2 (a) and $\text{Cd}(\text{NO}_3)_2$ (b). The starting material has been obtained by Suzuki-coupling reaction in the solid-state starting from the complex ferrocene-1,1'-diboronic acid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{-B}(\text{OH})_2)_2]$.

water–methanol solution and used to compare calculated and experimental x-ray powder diffractograms. When ZnCl_2 is used instead of AgCH_3COO in the equimolar reaction with $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$, different products are obtained from solution and solid-state reactions, respectively. The preparation of single crystals of $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}] \cdot 5\text{H}_2\text{O}$ was obviously indispensable for the determination of the exact nature of the co-grinding product. In order to do so, the powder diffraction pattern computed on the basis of the single-crystal structure was compared with the one measured on the product of the solid-state preparation. Figure 10 shows that the structure of $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$ is based on a one-dimensional coordination network comprising alternating $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ and ZnCl_2 units, joined by Zn-N bonds. As mentioned above, upon co-grinding of the solid reactants, a new zinc compound of unknown stoichiometry was obtained as a powder material. Even though attempts to obtain single crystals of this latter compound have failed, there is a relationship between the compound obtained initially by co-grinding and the one obtained from solution. In fact, the co-grind phase can be partially transformed

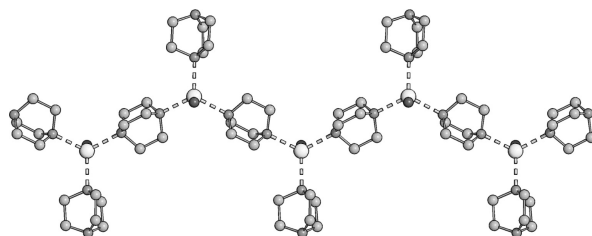


Figure 9. The coordination network in $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}]\cdot 5\text{H}_2\text{O}$. Note the chain of $\text{Ag}\cdots[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\cdots\text{Ag}\cdots[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\cdots\text{Ag}$ with each silver atom carrying an extra pendant $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ ligand and a coordinated water molecule in tetrahedral coordination geometry.

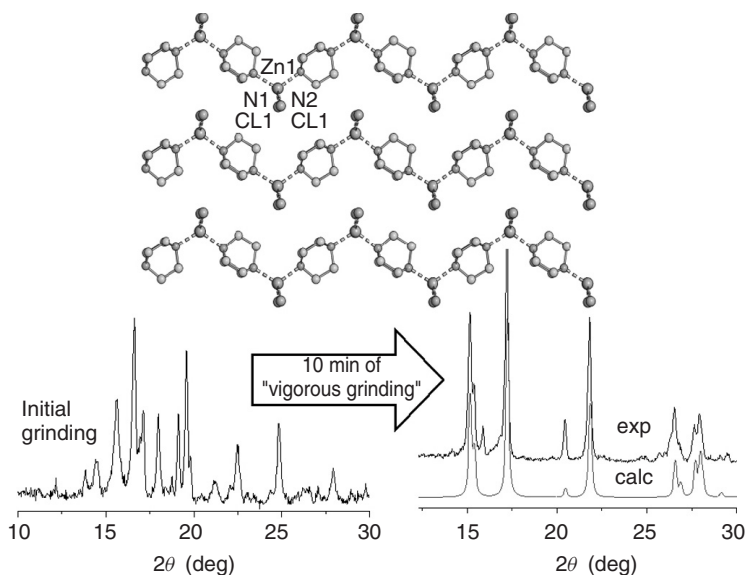


Figure 10. The one-dimensional coordination network present in crystals of $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$ and a comparison of the powder diffraction pattern measured on the product of initial co-grinding and that obtained after prolonged grinding. Note how the latter coincides with the diffractogram computed on the basis of the single-crystal structure depicted on top.

by prolonged grinding into the known anhydrous phase $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$, shown in Figure 10.

Steed and Raston *et al.* have explored the use of mechanochemistry in the synthesis of extended supramolecular arrays [42]. Grinding of $\text{Ni}(\text{NO}_3)_2$ with 1,10-phenanthroline (phen) resulted in the facile preparation of $[\text{Ni}(\text{phen})_3]^{2+}$ accompanied by a dramatic and rapid color change. Addition of the solid sodium salt of tetrasulfonatocalix[4]arene (tsc) gives two porous π -stacked supramolecular arrays $[\text{Ni}(\text{phen})_3]_2[\text{tsc}^{4-}]\cdot n\text{H}_2\text{O}$ and the related $[\text{Na}(\text{H}_2\text{O})_4(\text{phen})][\text{Ni}(\text{phen})_3]_4[\text{tsc}^{4-}][\text{tsc}^{5-}]\cdot n\text{H}_2\text{O}$ 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 color change from blue to blue-green over approximately 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, $[\{\text{Cu}(\text{OAc})_2\}_2(\mu\text{-dpp})]_n$, could be obtained from solution containing methanol, acetic acid or ethylene glycol guest species [43].

4. THE SOLVENT-FREE CHEMISTRY OF THE ZWITTERION $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$

In this section we summarize the solvent-free chemistry of the zwitterionic sandwich complex $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ [44]. Thanks to its amphoteric behavior, the complex undergoes reversible gas–solid reactions with the hydrated vapors of a variety of acids (e.g. HCl, CF_3COOH , CCl_3COOH , CHF_2COOH , HBF_4 and HCOOH [45–48], and bases (e.g. NH_3 , NMe_3 and NH_2Me [45]) as well as solid–solid reactions with crystalline salts MX ($\text{M} = \text{K}^+$, Rb^+ , Cs^+ and NH_4^+ ; $\text{X} = \text{Cl}^-$, Br^- , I^- and PF_6^- , though not in all permutations of cations and anions). The reactions with crystalline alkali salts carried out by manual co-grinding of the powdered materials yields crystalline solids of formula $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2 \cdot \text{M}^+ \text{X}^-$ [49]. The gas–solid and solid–solid reactivity of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ is summarized in Table 1.

The zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ can be quantitatively prepared from the corresponding dicarboxylic cationic acid $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]^+$. The amphoteric behavior of the zwitterion depends on the presence of one $-\text{COOH}$ group, which can react with bases, and one $-\text{COO}^{(-)}$ group, which can react with acids. Incidentally, the organometallic zwitterion of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ is easy to handle and it is thermally stable up to a temperature of 506 K. $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ undergoes fully reversible heterogeneous reactions with the hydrated vapors of a variety of acids (e.g. HCl, CF_3COOH , CCl_3COOH , CHF_2COOH , HBF_4 and HCOOH) and bases (e.g. NH_3 , NMe_3 and NH_2Me), with formation of the corresponding salts.

Table 1. Summary of the gas–solid (top) and solid–solid (bottom) reactions of the zwitterionic sandwich complex $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$

Solid–gas reactivity of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$	
Acid vapor	Product
HCl	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl} \cdot \text{H}_2\text{O}$
CF_3COOH	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CF}_3\text{COO}]$
CH_2ClCOOH	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CH}_2\text{ClCOO}] \cdot \text{H}_2\text{O}$
CHF_2COOH	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CHF}_2\text{COO}]$
HBF_4	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{BF}_4]$
HCOOH	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$
Base vapor	Product
NH_3	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{NH}_4] \cdot 3\text{H}_2\text{O}$
$(\text{CH}_3)\text{NH}_2$, $(\text{CH}_3)_3\text{N}$	Novel, unidentified products
Solid–solid reactivity of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$	
Solid salt of formula MX	Product
LiCl, LiBr, LiI, NaBr	Novel, unidentified products
NaCl, KCl, RbCl, CsCl, KI, RbI	No reaction
KBr, RbBr, CsBr, NaI, CsI	$[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2 \cdot \text{M}^+ \text{X}^-$

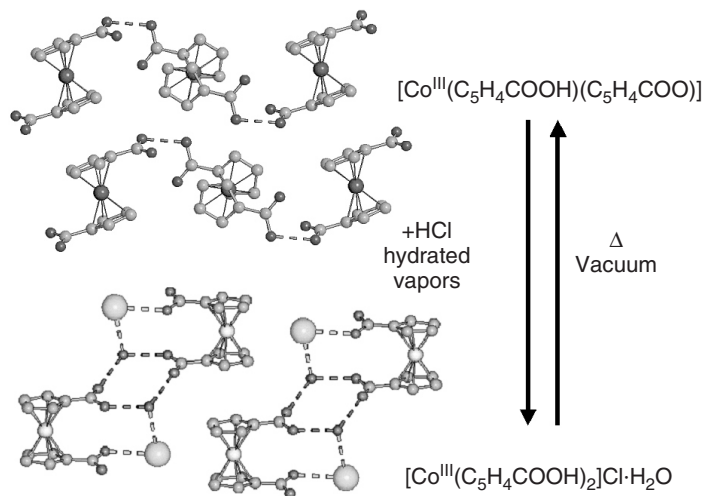


Figure 11. The reversible reaction between anhydrous $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ and HCl leading to formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ (bottom). The solid-state structure of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ has been obtained from single-crystal x-ray diffraction experiment on crystals obtained from solution.

For instance, complete conversion of the neutral crystalline zwitterion into the corresponding crystalline chloride salt $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ is attained in 5 min of exposure to vapors of aqueous HCl 36% (Figure 11). Formation of the salt in the heterogeneous reaction is easily assessed by comparing the observed x-ray powder diffraction pattern with that calculated on the basis of the single-crystal structure. Crystals can be grown to adequate size by seeding the water solution of the salt obtained from the heterogeneous reactions.

Crystalline $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ (Figure 11), can be converted back to neutral $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ by heating the sample for 1 h at 440 K under low pressure (10^{-2} mbar). A thermogravimetric analysis demonstrates that the solid product releases, stepwise, one water molecule and one HCl molecule per molecular unit at 394 and 498 K, respectively. The powder diffractogram of the product after thermal treatment corresponds precisely to that of anhydrous $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$. The formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ from the zwitterions implies a substantial rearrangement of the hydrogen-bonding interactions: O–H---O bonds between zwitterionic molecules are broken and new links of the types O–H---Cl[−] and O–H---O(water) are established.

The behavior of the zwitterion toward NH_3 is similar to that toward HCl but, obviously, opposite in terms of proton exchange. Single crystals of the ammonium salt for x-ray structure determination can be obtained if the reaction of the zwitterion with ammonia is carried out in aqueous solution. Experiments showed that 1–10 mg of the neutral system quantitatively transforms into the hydrated ammonium salt $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$ upon 5 min exposure to vapors of aqueous ammonia 30% (Figure 12). The salt is characterized by the presence of charge-assisted $(^+)\text{N}-\text{H}\cdots\text{O}^{(-)}$ interactions between the ammonium cations and the deprotonated $-\text{COO}^{(-)}$ groups on the organometallic anion.

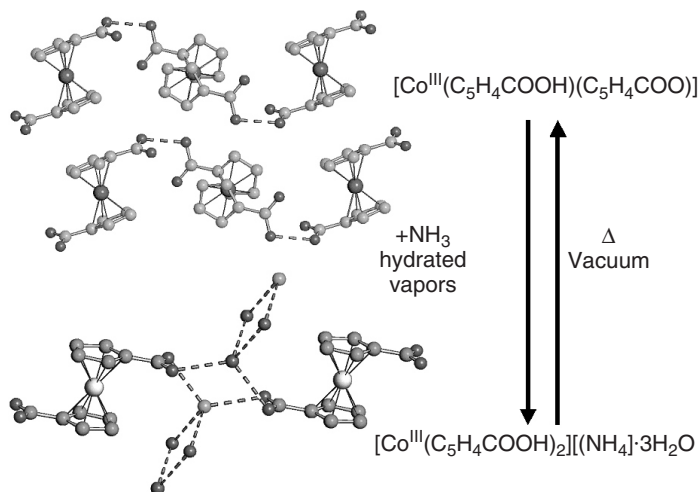


Figure 12. The reversible reaction between anhydrous $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ and NH_3 leading to formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$ as obtained from single-crystal x-ray diffraction experiments.

As in the case of the chloride salt, formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$ in the heterogeneous reaction is assessed *via* comparison of the observed and calculated x-ray powder patterns. Absorption of ammonia is also fully reversible: upon thermal treatment (1 h at 373 K, ambient pressure) the salts converts quantitatively into the starting material.

It is worth stressing that the two crystalline powders $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ and $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$ can be cycled through several absorption and release processes of HCl or ammonia without decomposition or detectable formation of amorphous material.

Similar behavior is shown toward other volatile acids. Exposure of the zwitterion to vapors of CF_3COOH and HBF_4 , for instance, quantitatively produces the corresponding salts of the cation $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]^+$, namely, $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CF}_3\text{COO}]$ (Figure 13), and $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{BF}_4]$ (Figure 14). As in the previous cases, all heterogeneous reactions are fully reversible and the acids can be removed by thermal treatment, which quantitatively regenerates the starting material. In terms of crystal structure organization, formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CF}_3\text{COO}]$ and of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{BF}_4]$, besides leading from a formally neutral system to molecular salts, implies profound molecular rearrangements and breaking and forming of non-covalent interactions. From the analogy between gas–solid and solution reactions, one may be brought to suppose that the gas–solid reactions occur via a process of dissolution and recrystallization as the vapors are adsorbed by the crystalline powder. The reverse process, that is, reconstruction of the zwitterionic 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 unlikely. Probably, removal of HCl or ammonia causes phase reconstruction as the gas leaves the crystals.

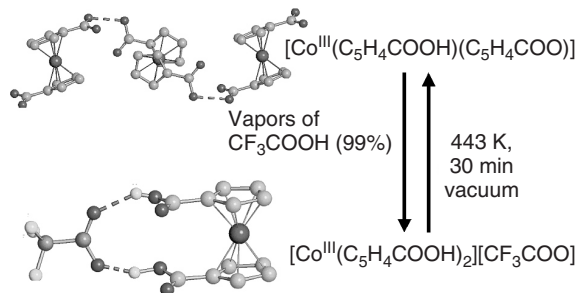


Figure 13. The structure of $[(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2\text{Co}^{\text{III}}][\text{CF}_3\text{COO}]$ as determined from single-crystal x-ray diffraction experiments. The same compound is prepared by gas uptake. Formation of the salt is assessed by comparison of the observed and calculated x-ray powder patterns.

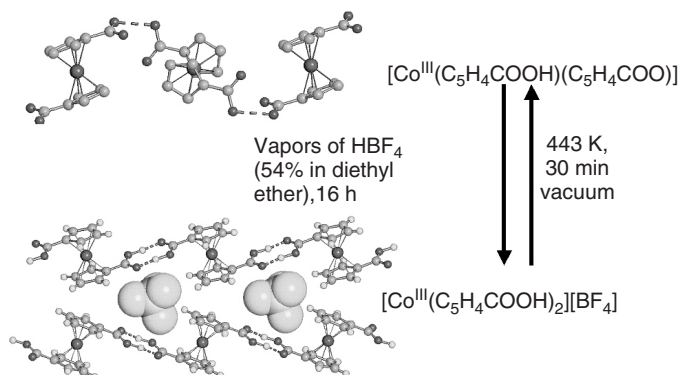


Figure 14. The structure of $[(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2\text{Co}^{\text{III}}][\text{BF}_4]$ as determined from single-crystal x-ray diffraction experiments. The same compound is prepared by gas uptake. Formation of the salt is assessed by comparison of the observed and calculated x-ray powder patterns.

Exposure of the solid zwitterion to vapors of CHF_2COOH quantitatively produces the corresponding salt of the cation, $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CHF}_2\text{COO}]$ (Figure 15). The solid–gas reaction implies a profound rearrangement of the hydrogen-bonding patterns with formation of ionic pairs between organometallic and organic moieties. The reaction with hydrated vapors of CH_2ClCOOH produces the hydrated salt $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CH}_2\text{ClCOO}]\cdot\text{H}_2\text{O}$.

Finally, we should report that the zwitterion also reversibly absorbs formic acid from humid vapors forming selectively a 1:1 co-crystal, $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$, from which the starting material can be fully recovered by mild thermal treatment (Figure 16). Contrary to the other compounds of this class, no proton transfer from the adsorbed acid to the organometallic moiety is observed. Hence, the reaction between $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})](\text{solid})$ and $\text{HCOOH}(\text{vapor})$ would be more appropriately described as a special kind of solvation rather than as a heterogeneous acid–base reaction.

As shown in Figure 16, crystalline $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$ comprises pairs of zwitterion molecules linked by $\text{O}\text{---}\text{H}\cdots\text{O}$ bonds between the protonated

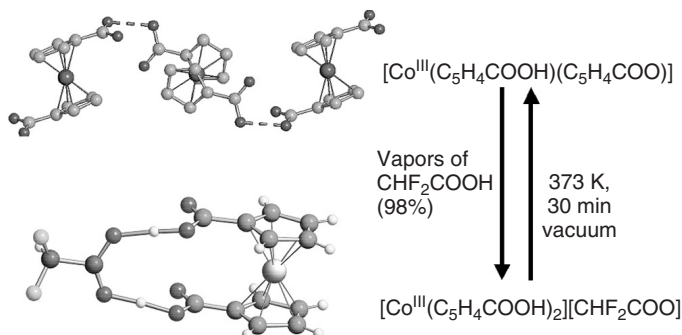


Figure 15. The packing in $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2][\text{CHF}_2\text{COO}]$ as determined from single-crystal x-ray diffraction experiments. The same compound is prepared by gas uptake. Formation of the salt is assessed by comparison of the observed and calculated x-ray powder patterns.

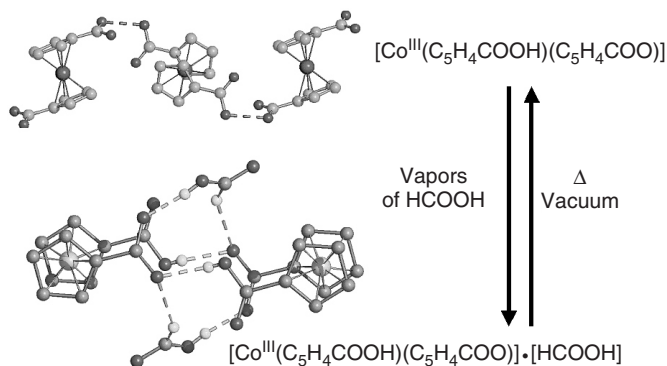


Figure 16. The structure of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$ (bottom) as determined from single-crystal x-ray diffraction experiments.

$-\text{COOH}$ and the deprotonated $-\text{COO}^-$ groups [O---O separation 2.526(4) Å]. On the other hand, the C–O distances within the HCOOH moiety [1.305(5) and 1.199(5) Å] indicate that the formic acid molecule retains its acidic hydrogen atom. This is also confirmed by ^{13}C CPMAS NMR spectrometry. Conversion to the starting material is attained by leaving the sample at room temperature in the air for a few days or by mild heating.

We have also exploited the great versatility of the organometallic zwitterion in the preparation of hybrid organometallic-inorganic salts by reacting $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ with a number of MX salts ($\text{M} = \text{K}^+, \text{Rb}^+, \text{Cs}^+$ and NH_4^+ ; $\text{X} = \text{Cl}^-, \text{Br}^-, \text{I}^-$ and PF_6^- though not in all permutations of cations and anions) obtaining compounds of general formula $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{M}^+\text{X}^-$. As in the cases discussed above, exact information about the solid-state structures of the reaction products were obtained by single-crystal x-ray diffraction experiments carried out on crystals obtained from the reaction powders. Information on the hydrogen-bonding nature and on the relationship between structures in solution and those obtained in the solid state by mechanical grinding were obtained by a combination of solution and solid-state NMR methods. In some cases ($\text{M} = \text{Rb}^+, \text{Cs}^+$, $\text{X} = \text{Cl}^-, \text{Br}^-$ and I^-), it was necessary

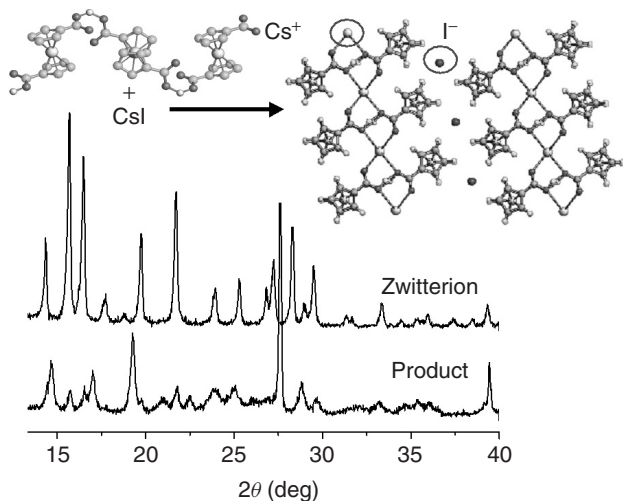


Figure 17. A pictorial representation of the process leading from $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{-COO})]$ and CsI to $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{Cs}^+\text{I}^-$ and a comparison of calculated and observed powder diffractograms.

to resort to *kneading* by adding a few drops of water to the solid mixture in order to obtain the desired product.

Since all compounds of formula $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{M}^+\text{X}^-$, ($\text{M} = \text{K}^+, \text{Rb}^+, \text{Cs}^+$ and $[\text{NH}_4]^+$, $\text{X} = \text{Br}^-, \text{I}^-$ and PF_6^-) are isostructural, compound $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{Cs}^+\text{I}^-$ can be used as an example to describe structure and supramolecular architecture. This class of compounds is characterized by the presence of a supramolecular cage formed by four zwitterionic molecules encapsulating the alkali or ammonium cations. The cage is sustained by $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds between carboxylic $-\text{COOH}$ and carboxylate $-\text{COO}^{(-)}$ groups, and by $\text{C}-\text{H}\cdots\text{O}$ bonds between $-\text{CH}_{\text{Cp}}$ and $-\text{CO}$ groups, while the anions are layered in between the cationic complexes, as shown in Figure 17. The process leading to formation of the cage can be seen as a sophisticated solvation operated by the organometallic complex. The zwitterion is capable of “extracting” via $\text{O}\cdots\text{X}^-$ interactions the alkali cations from their lattice, while the anions are “extruded” and left to interact with the peripheral $\text{C}-\text{H}$ groups via numerous $\text{C}-\text{H}\cdots\text{X}$ interactions. The solid–solid process can thus be seen as the dissolution of one solid (e.g. the alkali salt) into a *solid solvent*.

5. CONCLUDING REMARKS

One of the core paradigms of crystal engineering is that of being able to assemble molecular or ionic components into a target functional structure by controlling the periodical distribution of supramolecular interactions responsible for molecular recognition, aggregation, nucleation and growth of the crystalline material [1–6]. In other words, crystal engineering amounts to the deliberate construction of a molecular solid (whether a molecular complex, an adduct or a co-crystal [50]) that can perform desired functions. Hence,

it is conceptually related to the construction of a supermolecule [51]. In both molecular crystals and supermolecules, the *collective properties* depend on the aggregation *via* intermolecular bonds of two or more component units. These supramolecular interactions can be coordination bonds between ligands and metal centers and non-covalent bonds between neutral molecules or ions or, of course, any of their combinations. The process that leads, via breaking and forming of such non-covalent bonds, from reactants to products is, therefore, a supramolecular reaction.

In this chapter, we have shown that non-covalent bonds can be broken and formed in a controlled way by reactions that do not imply the use of solvent but that can be carried out directly between two crystalline solids or between a crystalline solid and a vapor. Reactions of this type have been the subject of investigation for decades in the fields of organic and inorganic chemistry. Although solid–gas and solid–solid reactions are the basis for a number of industrial processes that range from preparation of pharmaceutical compounds [52] to inorganic alloying [53], they still enjoy little popularity in the field of organometallic and coordination chemistry [54]. This is probably due, on the one hand, to the fact that crystals are depicted (even at the level of crystallography courses) as rigid, stiff, fragile materials that are good for little else beside structural analysis, and, on the other hand, to the belief that molecular crystals, being held together by non-covalent interactions, cannot compete with covalent or ionic inorganic solids in terms of cohesion and stability and are not the best materials for gas uptake and/or mechanical treatment.

Our experience is that adequately chosen organometallic crystalline materials can withstand reversible gas–solid reactions with vapors of both acidic and basic substances as well as mechanically activated reactions with other molecular crystals and inorganic salts.

In this Chapter, we have confined ourselves to essentially four classes of reactions involving organometallic molecular crystals as reactants: (i) reactions between a hydrogen-bonded molecular crystal and a vapor with formation of hydrogen-bonded supramolecular adducts, (ii) reactions leading to formation of covalent bonds for the preparation of crystal engineering building blocks, (iii) reactions between hydrogen-bonded molecular crystals to produce new molecular crystals based on hydrogen bonds, and (iv) reactions between molecular and ionic crystals via “solid-state solvation”. All these reactions involve molecular crystals and lead from a solid reactant (or a mixture of solid reactants) to a molecular crystal product. In such processes, hydrogen bonds, π -stacking, van der Waals, ion pairing interactions, and so on, are broken and formed through the reaction process leading to formation of supramolecular compounds or hybrid molecular crystals. Clearly, all these reactions (perhaps with the exception of those of type (ii)) are diffusion controlled and are not necessarily reactions in the solid state as mechanical stress may cause local melting; co-grinding may form an intermediate eutectic phase, and *kneading* probably generates locally *hypersaturated* solutions wherefrom crystals of the new phase nucleate. In all these cases, the crystal lattice is destroyed and reformed through recrystallization. It should also be stressed, that in terms of chemistry, gas–solid and solid–solid processes of the types discussed herein, are not conceptually different. In both reactions, the starting material is a molecular crystal and both reactions occur in the absence of solvent. Since the reaction products are new molecular crystals, these reactions are solvent-free means to prepare new crystalline materials. This is a useful notion for crystal engineers.

6. ACKNOWLEDGMENTS

We thank MIUR (COFIN and FIRB), the Universities of Bologna and Sassari for financial support.

REFERENCES

- (a) G. R. Desiraju, *Crystal Engineering: The Design of Organic Solids*, Elsevier, Amsterdam, 1989; (b) D. Braga, F. Grepioni and G. R. Desiraju, *Chem. Rev.*, **98**, 1375 (1998); (c) A. J. Blake, N. R. Champness, P. Hubberstey, W. S. Li, M. A. Withersby and M. Schroder, *Coord. Chem. Rev.*, **183**, 117 (1999); (d) Proceedings of the Dalton discussion on inorganic crystal engineering, the whole issue, *J. Chem. Soc., Dalton Trans.*, 3705 (2000); (e) B. Moulton and M. J. Zaworotko, *Chem. Rev.*, **101**, 1629 (2001); (f) D. Braga, G. R. Desiraju, J. Miller, A. G. Orpen and S. Price, *CrystEngComm*, **4**, 500 (2002); (g) M. D. Hollingsworth, *Science*, **295**, 2410 (2002).
- (a) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, **34**, 2311 (1995); (b) D. Braga and F. Grepioni, *Acc. Chem. Res.*, **33**, 601 (2000).
- D. Braga, F. Grepioni and A. G. Orpen (Eds.), *Crystal Engineering: From Molecules and Crystals to Materials*, Kluwer Academic Publishers, Dordrecht, 1999.
- (a) S. R. Batten, B. F. Hoskins and R. Robson, *Chem. Eur. J.*, **6**, 156 (2000); (b) S. A. Bourne, J. Lu, B. Moulton and M. J. Zaworotko, *Chem. Commun.*, 861 (2001); (c) B. Rather and M. J. Zaworotko, *Chem. Commun.*, 830 (2003); (d) B. Moulton, H. Abourahma, M. W. Bradner, J. Lu, G. J. McManus and M. J. Zaworotko, *Chem. Commun.*, 1342 (2003); (e) M. Fujita, *Chem. Soc. Rev.*, **27**, 417 (1998); (f) B. Olenyuk, A. Fechtenkötter and P. J. Stang, *J. Chem. Soc., Dalton Trans.*, 1707 (1998); (g) M. D. Ward, *Science*, **300**, 1124 (2003); (h) L. Pan, M. B. Sander, X. Huang, J. Li, M. Smith, E. Bittner, B. Bockrath and J. K. Johnson, *J. Am. Chem. Soc.*, **126**, 1309 (2004); (i) G. Férey, M. Latroche, C. Serre, F. Millange, T. Loiseau and A. Percheron-Guégan, *Chem. Commun.*, 2976 (2003); (j) F. A. Cotton, C. Lin and C. A. Murillo, *J. Chem. Soc., Dalton Trans.*, 499 (2001); (k) F. A. Cotton, C. Lin and C. A. Murillo, *Chem. Commun.*, 11 (2001); (l) W. Mori and S. Takamizawa, *J. Solid State Chem.*, **152**, 120 (2000); (m) L. Carlucci, G. Ciani, D. M. Proserpio and S. Rizzato, *CrystEngComm*, **4**, 121 (2002).
- (a) D. W. Bruce, D. O'Hare (Eds.), *Inorganic Materials*, Wiley, Chichester, 1992; (b) S. R. Marder, *Inorg. Mater.*, **115** (1992); (c) N. J. Long, *Angew. Chem., Int. Ed. Engl.*, **34**, 21 (1995); (d) T. J. Marks and M. A. Ratner, *Angew. Chem., Int. Ed. Engl.*, **34**, 155 (1995); (e) D. R. Kanis, M. A. Ratner and T. J. Marks, *Chem. Rev.*, **94**, 195 (1994); (f) O. Khan, *Molecular Magnetism*, VCH, New York, 1993; (g) D. Gatteschi, *Adv. Mater.*, **6**, 635 (1994); (h) J. S. Miller and A. J. Epstein, *Chem. Eng. News*, **73**, 30 (1995); (i) J. S. Miller, *Angew. Chem., Int. Ed. Engl.*, **42**, 27 (2003).
- D. Braga, *Chem. Commun.*, 2751 (2003).
- (a) N. L. Rosi, M. Eddaouddi, J. Kim, M. O'Keeffe and O. M. Yaghi, *Angew. Chem., Int. Ed. Engl.*, **41**, 284 (2001); (b) O. M. Yaghi, H. L. Li, C. Davis, D. Richardson and T. L. Groy, *Acc. Chem. Res.*, **31**, 474 (1998); (c) H. Li, M. Eddaouddi, M. O'Keeffe and O. M. Yaghi, *Nature*, **402**, 276 (1999); (d) M. Eddaouddi, J. Kim, N. Rosi, D. Vodak, J. Wachter, M. O'Keeffe and O. M. Yaghi, *Science*, **295**, 469 (2002). (e) N. L. Rosi, M. Eddaouddi, J. Kim, M. O'Keeffe and O. M. Yaghi, *CrystEngComm*, **4**, 401 (2002); (f) N. L. Rosi, J. Eckert, M. Eddaouddi, D. T. Vodak, J. Kim, M. O'Keeffe and O. M. Yaghi, *Science*, **300**, 1127 (2003); (g) M. E. Braun, C. D. Steffek, J. Kim, P. G. Rasmussen and O. M. Yaghi, *Chem. Commun.*, 2532 (2001).
- (a) S. R. Batten and R. Robson, *Angew. Chem., Int. Ed. Engl.*, **37**, 1461 (1998); (b) B. Moulton and M. J. Zaworotko, *Chem. Rev.*, **101**, 1629 (2001); (c) L. Carlucci,

- G. Ciani and D. M. Proserpio, *CrystEngComm*, **5**, 269 (2003); (d) L. Carlucci, G. Ciani and D. M. Proserpio, *Coord. Chem. Rev.*, **246**, 247 (2003); (e) S. A. Barnett and N. R. Champness, *Coord. Chem. Rev.*, **246**, 145 (2003).
9. (a) S. Takamizawa, E. Nakata, T. Saito, T. Akatsuka and K. Kojima, *CrystEngComm*, **6**, 197 (2004); (b) S. Takamizawa, E. Nakata and T. Saito, *Angew. Chem., Int. Ed. Engl.*, **43**, 1368 (2004); (c) S. Takamizawa, E. Nakata and T. Saito, *CrystEngComm*, **6**, 39 (2004); (d) S. Takamizawa, E. Nakata, H. Yokoyama, K. Mochizuki and W. Mori, *Angew. Chem., Int. Ed. Engl.*, **42**, 4331 (2003); (e) E. Le Fur, E. Demers, T. Maris and J. D. Wuest, *Chem. Commun.*, 2966 (2003); (f) D. Laliberte, T. Maris and J. D. Wuest, *J. Org. Chem.*, **69**, 1776 (2004); (g) O. Saied, T. Maris and J. D. Wuest, *J. Am. Chem. Soc.*, **125**, 14956 (2003).
10. (a) M. W. Hosseini and A. De Cian, *Chem. Commun.*, 727 (1998); (b) D. Braga and F. Grepioni, *Chem. Commun.*, 571 (1996).
11. (a) C. B. Aakeröy and K. R. Seddon, *Chem. Soc. Rev.*, 397 (1993); (b) A. M. Beatty, *CrystEngComm*, 51 (2001); (c) K. Biradha, *CrystEngComm*, **5**, 374 (2003); (d) H. W. Roesky and M. Andruh, *Coord. Chem. Rev.*, **236**, 91 (2003); (e) A. M. Beatty, *Coord. Chem. Rev.*, **246**, 131 (2003); (f) E. A. Bruton, L. Brammer, F. C. Pigge, C. B. Aakeröy and D. S. Leinen, *New J. Chem.*, **27**, 1084 (2003).
12. (a) G. R. Desiraju and T. Steiner (Eds.), *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press, Oxford, 1999; (b) D. Braga, F. Grepioni, K. Biradha, V. R. Pedireddi and G. R. Desiraju, *J. Am. Chem. Soc.*, **117**, 3156 (1995); (c) M. J. Zaworotko, *Chem. Soc. Rev.*, **23**, 283 (1994); (d) T. Steiner, *Angew. Chem., Int. Ed. Engl.*, 41 (2002); (e) M. J. Calhorda, *Chem. Commun.*, 801 (2000); (f) D. Braga, L. Maini, M. Polito and F. Grepioni, *Struct. Bonding*, **111**, 1 (2004); (g) C. Janiak, *Angew. Chem. Int. Ed. Engl.*, **36**, 1431 (1997); (h) S. George, A. Nangia, M. Bagieu-Beucher, R. Masse and J. F. Nicoud, *New J. Chem.*, **27**, 568 (2003); (i) M. Nishio, *CrystEngComm*, **6**, 130 (2004); (j) L. Brammer, M. D. Burgard, M. D. Eddleston, C. S. Rodger, N. P. Rath and H. Adam, *CrystEngComm*, 239 (2002); (k) J. Hulliger, *Chem. Eur. J.*, **8**, 4579 (2002); (l) L. Brammer, *Dalton Trans.*, **16**, 3145 (2003); (m) A. D. Burrows, *Struct. Bonding*, **108**, 55 (2004).
13. (a) L. Addadi and M. Geva, *CrystEngComm*, **5**, 140 (2003); (b) J. Aizenberg, G. Lambert, S. Weiner and L. Addadi, *J. Am. Chem. Soc.*, **124**, 32 (2002); (c) E. Beniash, J. Aizenberg, L. Addadi and S. Weiner, *Proc. R. Soc. Lond., B, Biol. Sci.*, **264**, 461 (1997); (d) L. Addadi, S. Raz and S. Weiner, *Adv. Mater.*, **15**, 959 (2003); (e) J. Johnston, H. E. Merwin and E. D. Williamson, *Am. J. Sci.*, **41**, 473 (1916); (f) S. Raz, S. Weiner and L. Addadi, *Adv. Mater.*, **12**, 38 (2000); (g) E. Loste and F. C. Meldrum, *Chem. Commun.*, 901 (2001); (h) J. Aizenberg, G. Lambert, L. Addadi and S. Weiner, *Adv. Mater.*, **8**, 222 (1996); (i) D. Braga, *Angew. Chem., Int. Ed. Engl.*, **42**, 5544 (2003).
14. (a) D. Braga and F. Grepioni, *Angew. Chem., Int. Ed. Engl.*, **43**, 2 (2004); (b) D. Braga, D. D'Addario, S. L. Giuffreda, L. Maini, M. Polito and F. Grepioni, *Topics in Current Chemistry* **254**, 71–94 (2005) (Ed. F. Toda).
15. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
16. (a) K. Tanaka and F. Toda, *Chem. Rev.*, **100**, 1025 (2000); (b) K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, 2003; (c) D. Bradley, *Chem. Br.*, 42 (2002); (d) G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2159 (2001); (e) G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, **123**, 8701 (2001); (f) F. Toda, *CrystEngComm*, **4**, 215 (2002); (g) L. R. Nassimbeni, *Acc. Chem. Res.*, **36**, 631 (2003).
17. (a) D. Braga and F. Grepioni, *Chem. Soc. Rev.*, **4**, 229 (2000); (b) D. Braga and F. Grepioni, in *Crystal Design, Structure and Function. Perspectives in Supramolecular Chemistry*, Vol. 7 (Ed. G. R. Desiraju), John Wiley, Chichester, 2003.
18. (a) D. Braga and F. Grepioni, *J. Chem. Soc., Dalton Trans.*, 1 (1999); (b) D. Braga and F. Grepioni, *Coord. Chem. Rev.*, **183**, 19 (1999); (c) D. Braga, G. Cojazzi, L. Maini, M. Polito,

- L. Scaccianocce and F. Grepioni, *Coord. Chem. Rev.*, **216**, 225 (2001); (d) D. Braga, L. Maini, M. Polito, E. Tagliavini and F. Grepioni, *Coord. Chem. Rev.*, **246**, 53 (2003).
19. (a) V. V. Boldyrev and K. Tkacova, *J. Mater. Synth. Process.*, **8**, 121 (2000); (b) J. F. Fernandez-Bertran, *Pure Appl. Chem.*, **71**, 581 (1999).
20. (a) G. Kaupp, in *Comprehensive Supramolecular Chemistry*, Vol. 8, (Ed. J. E. D. Davies), Elsevier, Oxford, 381 (1996); (b) G. Kaupp, *CrystEngComm*, **5**, 117 (2003).
21. (a) J. M. Cairney, S. G. Harris, L. W. Ma, P. R. Munroe and E. D. Doyle, *J. Mater. Sci.*, **39**, 3569 (2004); (b) G. Bettinetti, M. R. Caira, A. Callegari, M. Merli, M. Sorrenti and C. Tadini, *J. Pharm. Sci.*, **89**, 478 (2000); (c) Y. A. Kim, T. Hayashi, Y. Fukai, M. Endo, T. Yanagisawa and M. S. Dresselhaus, *Chem. Phys. Lett.*, **355**, 279 (2002); (d) K. Wiczorek-Ciurova, K. Gamrat and K. Fela, *Solid State Ionics*, **164**, 193 (2003).
22. N. Shan, F. Toda and W. Jones, *Chem. Commun.*, 2372 (2002).
23. S. Watano, T. Okamoto, M. Tshuri, I. Koizumi and Y. Osako, *Chem. Pharm. Bull.*, **50**, 341 (2002); S. Watano, J. Furukawa, K. Miyunami and Y. Osako, *Adv. Powder. Technol.*, **12**, 427 (2001).
24. N. Morin, A. Chilouet, J. Millet and J. C. Rouland, *J. Therm. Anal. Calorim.*, **62**, 187 (2000).
25. (a) G. Bruni, A. Marini, V. Berbenni, R. Riccardi and M. Villa, *J. Incol. Phenom. Macro. Chem.*, **35**, 517 (1999); (b) F. Taneri, T. Guneri, Z. Aigner and M. Kata, *J. Incol. Phenom. Macro. Chem.*, **44**, 257 (2002); (c) R. Saikosin, T. Limpaseni and P. Pongsawadsi, *J. Incol. Phenom. Macro. Chem.*, **44**, 191 (2002).
26. (a) T. L. Threlfall, *Analyst*, **120**, 2435 (1995); (b) N. Kubota, N. Doki, M. Yokota and D. Jagadesh, *J. Chem. Eng. Jpn.*, **35**, 1063 (2002).
27. P. Seiler and J. D. Dunitz, *Acta Crystallogr., Sect. B* **38**, 1741 (1982); D. Braga, G. Cojazzi, D. Paolucci and F. Grepioni, *CrystEngComm*, **1** (2001).
28. R. J. Davey, N. Blagden, G. D. Potts and R. Docherty, *J. Am. Chem. Soc.*, **119**, 1767 (1997).
29. H. Koshima and M. Miyauchi, *Cryst. Growth Des.*, **1**, 355 (2001).
30. J. Dunitz and J. Bernstein, *Acc. Chem. Res.*, **28**, 193 (1995).
31. (a) D. Braga, L. Maini, M. Polito, L. Mirolo and F. Grepioni, *Chem. Commun.*, **24**, 2960 (2002); (b) D. Braga, L. Maini, M. Polito, L. Mirolo and F. Grepioni, *Chem. Eur. J.*, **9**, 4362 (2003).
32. D. Braga, L. Maini, G. de Sanctis, K. Rubini, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem. Eur. J.*, **9**, 5538 (2003).
33. M. R. Caira, L. R. Nassimbeni and A. F. Wildervanck, *J. Chem. Soc., Perkin Trans.*, **2**, 2213 (1995).
34. D. Braga and L. Maini, *Chem. Commun.*, 976 (2004).
35. D. Braga, D. D'Addario, M. Polito and F. Grepioni, *Organometallics*, **23**, 2810 (2004).
36. (a) A. Suzuki and N. Miyaura, *Chem. Rev.*, **95**, 2457 (1995); (b) A. Suzuki and N. Miyaura, *J. Org. Chem.*, **63**, 4726 (1998); (c) D. Villemin and F. Caillot, *Tetrahedron Lett.*, **42**, 639 (2001); (d) G. W. Kabalka, G. R. M. Pagni and C. M. Hair, *Org. Lett.*, **1**, 1423 (1999); (e) M. Melucci, G. Barbarella and G. Sotgiu, *J. Org. Chem.*, **67**, 8877 (2002).
37. M. Braccacini, D. Braga, D. D'Addario, F. Grepioni, M. Polito, L. Sturba and E. Tagliavini, *Organometallics*, **22**, 214 (2003).
38. D. Braga, D. D'Addario, F. Grepioni, M. Polito, D. M. Proserpio, J. W. Steed and E. Tagliavini, *Organometallics*, **22**, 4532 (2003).
39. V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *Chem. Commun.*, 1606 (2002).
40. A. Orita, L. S. Jiang, T. Nakano, N. C. Ma and J. Otera, *Chem. Commun.*, 1362 (2002).
41. D. Braga, S. Giaffreda, F. Grepioni and M. Polito, *CrystEngComm*, **6**, 458 (2004).
42. P. J. Nichols, C. L. Raston and J. W. Steed, *Chem. Commun.*, 1062 (2001).
43. W. J. Belcher, C. A. Longstaff, M. R. Neckenig and J. W. Steed, *Chem. Commun.*, 1602 (2002).
44. D. Braga, L. Maini, M. Polito and F. Grepioni, *Organometallics*, **18**, 2577 (1999).

-
45. D. Braga, G. Cojazzi, D. Emiliani, L. Maini and F. Grepioni, *Chem. Commun.*, **21**, 2272 (2001).
 46. D. Braga, G. Cojazzi, D. Emiliani, L. Maini and F. Grepioni, *Organometallics*, **21**, 1315 (2002).
 47. D. Braga, L. Maini, M. Mazzotti, K. Rubini and F. Grepioni, *CrystEngComm*, **29**, 154 (2003).
 48. D. Braga, L. Maini, M. Mazzotti, K. Rubini, A. Masic, R. Gobetto and F. Grepioni, *Chem. Commun.*, **20**, 2296 (2002).
 49. D. Braga, L. Maini, S. Giaffreda, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem. Eur. J.*, **10**, 3261 (2004).
 50. G. R. Desiraju, *CrystEngComm*, **5**, 466 (2003); J. D. Dunitz, *CrystEngComm*, **5**, 506 (2003).
 51. (a) M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*. VCH: Weinheim, 1995; (b) W. Steed and J. L. Atwood, *Supramolecular Chemistry*, John Wiley & Sons, 2000.
 52. (a) A. Burger, in *Topics in Pharmaceutical Sciences*, (Eds. D. Breimer and P. Speiser), Elsevier, Amsterdam, 1983, p. 347; (b) S. R. Byrn, *Solid State Chemistry of Drugs*, Academic Press, New York, 1982, p. 79.
 53. V. V. Boldyrev and K. Tkacova, *J. Mater. Synth. Process.*, **8**, 121 (2000).
 54. (a) M. Albrecht, M. Lutz, A. L. Spek and G. van Koten, *Nature*, **406**, 970 (2000); (b) M. Albrecht, R. A. Gossage, M. Lutz, A. L. Spek and G. van Koten, *Chem. Eur. J.*, **6**, 1431 (2000).

