Molecular Networks

Bearbeitet von
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ISBN 978 3 642 01366 9
Format (B x L): 15,5 x 23,5 cm
Gewicht: 427 g

Weitere Fachgebiete > Chemie, Biowissenschaften, Agrarwissenschaften > Biochemie > Supramolekularchemie
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Crystal Polymorphism and Multiple Crystal Forms

Dario Braga, Fabrizia Grepioni, Lucia Maini, and Marco Polito

Abstract This chapter discusses the phenomenon of polymorphism in organic and organometallic compounds. Polymorphism is first introduced and then, to give the work some context, background information is given concerning properties and techniques for characterizing the solid phases. In particular, desolvation and interconversion are examined, and the gas–solid reactions are presented as a successful route to obtaining new crystalline phases. Co-crystal definition is then described and the problem in distinguishing co-crystals and salts is evaluated.

Keywords: Co-crystal · Hydrogen bond · Organic salt · Polymorphism · Solid-gas reaction · Solid-state NMR · Solvate · X-ray diffraction

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1 Introduction

The isolation, identification and characterization of different crystal forms (polymorphs, solvates, salts and co-crystals) of the same molecule or of aggregates of the same molecule with other molecules represents one of the most active areas of modern solid state chemistry. The investigation of crystal forms impacts on fundamental science as well as on utilitarian objectives because different crystal forms may display a range of different physico-chemical properties, which may affect application and utilization of the solid materials.

Polymorphism [1] is one of the most fascinating phenomena of solid state chemistry and indeed is a “difficult” phenomenon, studied for many decades mainly, and separately, in the fields of organic and inorganic chemistry. In spite of the huge efforts of many researchers our knowledge of the phenomenon is still embryonic, and the relationship between growth of a crystalline phase and nucleation of the first crystallites is often mysterious. It is a fact that, despite the ambitions of the scientist, crystal construction is not yet strictly under human control. Many examples exist of appearing and disappearing polymorphs, some of which have had great practical consequences. The reader is addressed to the review by Dunitz and Bernstein for a number of intriguing examples [2].

2 Definition of Crystal Forms

Although the existence of three different crystal forms of calcium carbonate (calcite, vaterite and aragonite) was identified by Klaproth in 1788 [3], formal recognition of the phenomenon of crystal polymorphism is attributed to the work of Mitscherlich in 1823 [4]. In more general terms, the solid phase of a material, whether formed of organic molecules, inorganic ions or extended covalent networks, can exhibit different structures which, although possessing the same chemical composition, may manifest different properties. In addition to these polymorphic modifications the material may also lack long-range order and appear as an amorphous solid, which can be considered as another polymorph.

A number of authors have suggested that polymorphism is ubiquitous in crystal chemistry. McCrone stated long ago that: “…every compound has different polymorphic forms” and that, “…in general, the number of forms known for a given compound is proportional to the time and energy spent in research on that compound” [5]. In 1951 Findlay noted in his book that polymorphism: “…is now recognized as a very frequent occurrence indeed” [6]. Buerger and Bloom stated: “…polymorphism is an inherent property of the solid state and it fails to appear only under special conditions” [7]. Similarly, Sirota wrote in 1982: “Polymorphism is now believed to be characteristic of all substances, its actual non-occurrence arising from the fact that a polymorphic transition lies above the melting point of the substance or in the area of as yet unattainable values of external equilibrium factor or other conditions providing for the transition” [8].
In 1965 Kuhnert-Brandstätter investigated by hot stage microscopy three common classes of drug: 70% of barbiturates, 60% of sulphonamides and 23% of steroids exist in various polymorphic or solvate forms [9, 10]. A number of statistical estimates of the extent of polymorphism have also been carried out. A search of the Cambridge Structural Database on the keywords “polymorph”, “form”, “modification” and “phase” indicated that about 3.5% of the ∼350,000 entries fall into this category. Approximately 25% of the entries are either solvates or hydrates. Other studies based on different selection criteria reveal a much larger occurrence [11–13]. For instance, Grierser and Burger have collected information on about 600 polymorphic forms and solvates (including hydrates) of pharmaceutical compounds that are solid at 25°C [14].

Even though crystal forms have been and are the subject of intense investigations, polymorphism as a phenomenon still represents a substantial scientific challenge. Indeed it is hard to predict whether a given molecule will crystallize in one or several crystal forms, whether it will form solvates with different stoichiometries or will ever be “happy” to link up with other molecules and form stable co-crystals. Such variability and unpredictability have been taken by some scientists as an intrinsic drawback of being able to construct desired crystal structures (and obtain relevant properties) from a purposeful choice of the molecular components, which is the paradigm of molecular crystal engineering [15–19].

In recent times the concept of crystal polymorphism has expanded beyond its original boundaries to encompass crystal forms of the same molecule with different molecular partners. These may be solvent molecules in solvates [20], or counterions if the molecule can be made non-neutral (by say proton or electron transfer [21]), or other molecules in co-crystals [22]. It is worth noting that the formation of solvate and hydrated forms is commonly observed during polymorph screening, therefore the use of the term “pseudopolymorphism” to describe solvate forms of a given molecular crystal ought to be discouraged, at least because solvates may, in turn, be polymorphic [23–25].

In this paper we shall discuss all four different types of crystal forms of the same molecule: polymorphs of the mere molecule, solvates and hydrates, molecular salts and co-crystals (when the same molecule can be co-crystallized with different co-crystal formers). All these crystal forms are summarized in Fig. 1.

3 Properties of Crystal Forms

From thermodynamic principles, under specified conditions only one polymorph is the stable form (except at a transition point) [26]. In practice, however, due to kinetic considerations, metastable forms can exist or coexist in the presence of more stable forms. The relative stability of the various crystal forms and the possibility of interconversion between crystal forms, between crystals with different degree of solvation, and between an amorphous phase and a crystalline phase can have very
serious consequences on the life and effectiveness of a polymorphic product and the persistence over time of the desired properties. The variety of phenomena related to polymorphism requires a thorough mapping of the “crystal space” of a substance that is ultimately intended for some specific applications (e.g. drugs, pigments, agro-chemicals and food additives, explosives, etc.).

The industrial production and marketing lines need to know not only the exact nature of the material in the process, but also its stability with time, the variability of its chemical and physical properties as a function of the crystal form, etc. The search for and characterization of crystal forms is therefore a crucial step in the development of a new chemicals with relevant consequences on intellectual property issues [1, 27–29].

Different crystal forms are often recognized by differences in the colour and shape of crystals. A striking example of these two properties is provided by the differences in colour and form of the crystal forms of ROY (ROY = red, orange, yellow polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophene carbonitrile) [30, 31]. Colour and shape are only some of the possible differences and Table 1 summarizes some major possible differences in chemical and physical properties between crystal forms and solvates of the same substance. In addition, one has to consider that new and different properties may derive from a change in the nature and chemical composition of the same molecule as a consequence of salt formation or co-crystallization. For each new crystal form obtained, a full characterization

![Schematic representation of the structural relationship between “true” polymorphs, solvates, co-crystals, salts and the amorphous phase](image-url)
should be done since the new form can have different properties, such as higher solubility or higher melting point (Fig. 2).

4 Characterization of Multiple Crystal Forms

The exploration of the “crystal form space” of a substance is the search of polymorphs and solvates in order to identify the most stable form and the existence of unstable forms that interconvert (enantiotropism) or do not (monotropism) as a function of the temperature. This also applies to amorphous and solvate forms. The relationships between the various phases and commonly used industrial and research laboratory processes are schematically illustrated in Fig. 3.

It is worth stressing that polymorph assessment in industrial research and development as well as during processing is part of the system of quality control. Therefore it is necessary to make sure that the scale-up from laboratory preparation to industrial production does not introduce variations in crystal form. Polymorph assessment also guarantees that the product conforms to the guidelines of the appropriate regulatory agencies and does not infringe the intellectual property protection that may cover other crystal forms [32].
Fig. 3 Some general relationships between polymorphs, solvates and amorphous phases and the type of research laboratory or industrial or process for preparation and interconversion: 1 crystallization; 2 desolvation; 3 exposure to solvent/vapour uptake; 4 freeze drying; 5 heating; 6 melting; 7 precipitation; 8 quench cooling; 9 milling; 10 spray drying; 11 kneading; 12 wet granulation. Analogous relationships apply to polymorphic modifications of solvate forms. Note that the figure represents general trends rather than every possible transformation; the presence or absence of an arrow or number does not represent the exclusive existence or absence of a transformation.

The screening of crystal forms is best achieved by the combined use of several solid-state techniques, such as hot stage microscopy, differential scanning calorimetry, thermogravimetric analysis and X-ray diffraction. Powerful complementary tools are also provided by solid-state spectroscopic techniques such as solid state nuclear magnetic resonance spectroscopy [33] and Raman spectroscopy [1]. Of great relevance is the possibility of determining the molecular and crystal structure of a crystal form by means of single crystal X-ray diffraction. This technique, although much more demanding than powder diffraction in terms of experiment duration and data processing, has the great advantage of providing detailed structural information on the molecular geometry. Furthermore, it affords insight into the factors controlling the packing of the molecules in the crystal and the nature and structural role of solvent molecules. Knowledge of the single-crystal structure allows a direct comparison between the X-ray powder diffraction pattern, calculated on the basis of the structure, with the one measured on the polycrystalline sample as it will be diffusely used in the following description of specific cases.

Importantly, the calculated diffraction pattern is not affected by the typical sources of errors of experimental powder diffraction (preferential orientation, mixtures, presence of amorphous phase) that often complicate or render uncertain the interpretation of measured powder diffractograms; hence the calculated powder pattern is often referred to as the “gold standard” pattern for a crystal form.

The search for various crystal forms requires that the behaviour of a solid phase is investigated as a function of the variables that can influence or determine the outcome of the crystallization process, e.g. temperature, choice of solvents,
crystallization conditions, rate of precipitation, interconversion between solid forms (from solvate to unsolvate and vice versa), pressure and mechanical treatment, absorption and release of vapour, etc. [24]. Techniques such as hot stage microscopy, DSC and micro-DSC can be used to obtain a semiempirical energy–temperature diagram [34, 35] that can be helpful in designing protocols for screening for crystal forms.

Another powerful tool for the investigation of the structural relationship between crystal forms is variable temperature X-ray diffraction that provides information on phase transitions and or on adsorption/desorption of solvent molecules (and chemical reactivity, of course, but this is of less concern in this context).

Beside the traditional thermal and solution methods for obtaining new crystal forms, many other methods are being used or developed in the quest for multiple crystal forms. Some of these methods are based on the knowledge of crystal structures in the literature [16], the application of crystal engineering principles (based on hydrogen-bonding patterns) to the preparation of new multicomponent solids [36, 37], the induction of crystal forms by using polymeric substrates [38], the development of high-throughput crystallization technology [39], the utilization of solid–solid and solid–gas reactions [40], solvent-free synthesis [41, 42], the desolvation of solvated crystals [43] and crystallization from a supercritical solvent [44, 45]. These methods, combined with the development of new technology [39], the attempts to design and control crystal structure [46], combined with some spectacular encounters with new (and undesired) crystal forms [47] (see Sect. 5) and some high profile pharmaceutical patent litigations [1], have led to many new techniques for exploring the crystal form space of any particular substance.

5 Examples of Crystal Form Identification and Characterization

There is no protocol of polymorph screening that can guarantee the identification of all crystal forms of a given molecule. As pointed out in the previous section, the understanding of a system exhibiting multiple crystal forms is best achieved by studying the system with a wide variety of analytical tools. We have chosen to illustrate this aspect by means of two recent examples coming from our own work.

The first example is that of cinchomeronic acid, which has been known for almost a century [48]. The cinchomeronic acid 3,4-dicarboxylic acid is one of the six isomers of the acid pyridinedicarboxyl; all isomers are widely utilized in the construction of coordination networks [49–51]. The presence of two of cinchomeronic forms is reported in the PDF-2 [52], while the crystal structure has been determined only for one form [53]. We have investigated the structural relationship between these two crystal forms by a combined use of single-crystal X-ray diffraction, IR and Raman spectroscopy, and solid state NMR spectroscopy [54]. Form I crystallizes in an acentric orthorhombic group, while form II crystallizes in a centric monoclinic group (Fig. 4), due to a static disorder for the nitrogen position (Fig. 5). The zwitterionic nature of the acid in both forms has been confirmed by $^1$H MAS,
Fig. 4 Concomitant polymorphs obtained from an ethanol/water solution: rods form I, blocks form II. a Comparison between the experimental and calculated powder diffractograms of form I and form II b.

Fig. 5 Chains present in form I a and form II b; the adamantoid network formed by N–H⋯O hydrogen bonds among the chains and the overall crystal structure formed by the three interpenetrating networks in form I c; interactions N–H⋯O and C–H⋯O among the chains and the 2D-network present in form II d.

$^{13}$C CPMAS and $^{15}$N CPMAS (Fig. 6). The single crystal structures give us a view of the hydrogen bonds formed by the molecule of cinchomeronic acid in the solid state; in both structures the molecules of cinchomeronic acid form infinite chains via
Fig. 6 $^{15}$N CPMAS spectra of cinchomeronic acid: form I (top) and form II (bottom) recorded at 27.2 MHz with a spinning speed of 5 kHz which confirm the zwitterionic nature of cinchomeronic acid in both crystal phases.

short O–H—O hydrogen bonds between the carboxylic and carboxylate groups (see Fig. 5). In form I the zwitterion chains are ordered and are connected via N–H—O interactions to form a threefold interpenetrating networks. In form II, on the other hand, the presence of static disorder leads to crystallographic equivalence between the –COO and –COOH groups (see Fig. 5) and the nitrogen atom is disordered over two positions, which leads to a longer and weaker N–H—O hydrogen bond consistent with the IR and Raman spectra. Both forms decompose before melting without any interconversion, which suggests the presence of a monotropic system, while the slurry experiment indicates that form I is the thermodynamically stable form. The crystal structure and spectroscopic analysis indicate that the difference in stability can be ascribed to the strength of the hydrogen bonding patterns established by the protonated N-atom and the carboxylic/carboxylate O-atoms. The possibility of optimizing the hydrogen bond interaction in form I, with respect to the somewhat looser interactions allowed by the packing in form II might be responsible for the stabilization of the crystal structure of form I.

Another example is provided by the two different crystal forms of the salt [HN(CH$_2$CH$_2$)$_3$NH] [OOC(CH$_2$)COOH]$_2$ 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.
Fig. 7 Form I (top) and II (bottom) of [HN(CH₂CH₂)₃NH][OOC(CH₂)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 (see Fig. 7). 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 [55].

6 Examples of Solvate Crystal Forms and Interconversion

An intriguing case of interconversion between unsolvate and solvate crystals is observed when [N(CH₂CH₂)₃N] is reacted with maleic acid [HOOC(HC=CH)COOH]. The initial product is the anhydrous salt [HN(CH₂CH₂)₃N][OOC(HC=CH)COOH], which contains chains of (⁺)N–H···N(⁺) bonded cations [HN(CH₂CH₂)₃N]⁺ and “isolated” [OOC(HC=CH)COOH]⁻ anions [56].

Upon exposure to humidity the anhydrous salt converts within few hours into the hydrated form [HN(CH₂CH₂)₃N][OOC(HC=CH)COOH]·0.25H₂O, which contains more conventional “charge-assisted” (⁺)N–H···O(⁻) hydrogen bonds between anion and cation (see Fig. 8). This latter form can also be obtained by co-grinding.

In a similar process, crystals of [Ru(η⁶–C₆H₆)]₂[BF₄]₂ have been crystallized from nitromethane as the solvate form [Ru(η⁶–C₆H₆)]₂[BF₄]₂·MeNO₂. These solvate crystals, if exposed to air, rapidly convert to the unsolvate form [Ru(η⁶–C₆H₆)]₂[BF₄]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(η⁶–C₆H₆)]₂[BF₄]₂·MeNO₂ [57]. The opposite process, namely solvent uptake, can often be activated by mechanical treatment of unsolvate crystals. There are several reports that even gentle grinding of a powder product may lead to the formation of a hydrated product [58–60].

Another example is provided by the hydrated salt [Co(η₅–C₅H₅)₂][Fe(η₅–C₅H₅COOH)(η₅–C₅H₅COO)]⁻·H₂O, which is obtained by simply grinding in air the crystalline powder of [Co(η₅–C₅H₅)₂][Fe(η₅–C₅H₅COOH)](η₅–C₅H₅COO)]⁻ that precipitates from THF or nitromethane on reacting [Co(η₅–C₅H₅)]₂ with [Fe(η₅–C₅H₅COOH)]₂ [61]. Once [Co(η₅–C₅H₅)₂]⁺[Fe
Fig. 8 Views of the packing and hydrogen bonding in the anhydrous salt \([\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{[OOC(\text{HC}=\text{CH})\text{COOH]} (left)}\) and of the hydrated salt \([\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{[OOC(\text{HC}=\text{CH})\text{COOH]}\text{H}_2\text{O}_{0.25}} (right)\)

\((\eta_5\text{–C}_5\text{H}_4\text{COOH})(\eta_5\text{–C}_5\text{H}_4\text{COO})^-\text{H}_2\text{O}\) 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.

7 Solid–Gas Reactions: A Route to New Crystal Forms

Solid–gas reactions have been known for a long time and have recently attracted a renewed interest in the strive to find environmentally friendly processes. Since the reactant is a crystalline solid, the issue of whether different crystal forms would react in the same or a different way towards a gaseous reactant is of interest to the discussion. We have tackled this question by exploiting solid–gas reactions between crystal polymorphs of the same acidic substance and vapours of volatile bases, investigating in turn the inverse process, i.e. removal of the vapours from the crystal structures by thermal treatment.

The possibility of different chemical behaviour of polymorphic modifications has been explored before only in the case of indomethacine amorphous and crystal forms reacted with ammonia by Stowell, Griesser, Byrn et al. [62]. We have investigated two rather different systems, namely the polymorphic forms of barbituric acid [63] and of ferrocene dicarboxylic acids [64], which have been reacted with
volatile bases. Solid barbituric acid is known as two polymorphic forms (forms I and II) and as a dihydrate form for which single crystal data are available allowing computation of the theoretical powder diffractograms [65–68]. Views of the packings of the three forms are shown in Fig. 9. De-hydration of the dihydrate form has also been investigated, showing that it releases water to yield exclusively crystals of form II. We have been able to show that forms I, II and the dihydrate form of barbituric acid react with ammonia leading to the same crystalline ammonium barbiturate salt NH$_4$\((C_4H_3N_2O_3)\), while the gas–solid reactions of form II with methylamine and dimethylamine yield the corresponding crystalline salts CH$_3$NH\((C_4H_3N_2O_3)\) and \((CH_3)_2NH\((C_4H_3N_2O_3)\), respectively. The processes are shown in Fig. 10.

Thermal desorption of the bases at ca. 200°C leads to formation of a new crystal form of barbituric acid, form III, as confirmed by H$^1$-NMR spectroscopy and by chemical behaviour. Unfortunately several attempts to crystallize compound III yielded only the formation of the dihydrate form (Fig. 11).

Similarly, the reactions between solid 1–3 dimethylbarbituric acid (dmb) with vapours of NH$_3$ and of the volatile amines NH$_2$(CH$_3$), and NH(CH$_3$)$_2$ have been investigated [69]. The barbiturate salts [NH$_4$]dmb, [NH$_3$(CH$_3$)]dmb and [NH$_2$(CH$_3$)$_2$]dmb have been characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry and thermogravimetric analysis. The solid–gas reactions were monitored by UV–Vis spectroscopy in the solid state. In the case of [NH$_2$(CH$_3$)$_2$]dmb, recrystallization from methanol yields the salt
Fig. 10 Schematic representation of the XRPD patterns of the polymorphic forms of barbituric acid I and II and that of the dihydrate form. The interaction with NH$_3$ leads to the formation of the same product, NH$_4$(C$_4$H$_5$N$_2$O$_3$)
Fig. 11 XRPD recorded at different temperatures from room temperature to 250°C on crystalline 
NH$_4$(C$_4$H$_3$N$_2$O$_3$) showing the presence of new reflections at 200°C

[CH$_3$(CH$_3$)$_2$][DMB]·2[DMBA], while recrystallization of [NH$_3$(CH$_3$)]dmb yields
both the dimerization product [NH$_3$(CH$_3$)][(C$_6$O$_3$N$_2$H$_6$)$_2$–OH]·2H$_2$O and the
hydrolate salt [NH$_3$(CH$_3$)$_2$][(C$_6$O$_3$N$_2$H$_6$)$_2$], i.e. the product [NH$_3$(CH$_3$)]dmb is only
accessible via. the solid–gas reaction.

In an analogal study, crystalline form I (monoclinic) and form II (tri-
clinic) of ferrocene dicarboxylic acid [Fe(η$^5$–C$_5$H$_4$COOH)$_2$] have been reacted
at room temperature with the gaseous bases NH$_3$, NH$_2$(CH$_3$) and NH(CH$_3$)$_2$
[64]. The two crystal forms behave in exactly the same way in the solid–
gas reaction generating the same products, identified as the anhydrous crys-
talline salts [NH$_4$]$_2$[Fe(η$^5$–C$_5$H$_4$COO)$_2$], [NH$_3$CH$_3$]$_2$[Fe(η$^5$–C$_5$H$_4$COO)$_2$], and
[NH$_2$(CH$_3$)$_2$][Fe(η$^5$–C$_5$H$_4$COO)$_2$]. Interestingly though, all these crystals revert
via vapour release exclusively to the metastable crystalline form I, as shown in
Fig. 12.

This is not surprising per se, because there is no reason why, if the reaction is
quantitative, the crystalline salt product should “remember” which crystal form it
comes from. It is instead of relevance that forms I and II of [Fe(η$^5$–C$_5$H$_4$COOH)$_2$] are not known to interconvert via a solid–solid phase transition, hence they constit-
tute a monotropic system. The ammonia absorption/release process, therefore, can
be seen as a solid state way to convert the thermodynamically stable form II into the
metastable form I. The process is schematically represented in Fig. 13.
Fig. 12 Comparison between the experimental powder diffractograms of compound 1, obtained from the solid–gas reaction with ammonia of form I (top) and form II (bottom), respectively.

Fig. 13 Reaction of crystalline forms I and II with vapours of NH$_3$ yields the same salt, which upon heating and removal of NH$_3$ generates only the monoclinic form I.

8 Co-Crystals and Salts, Co-Crystals or Salts?

In this last section we focus on co-crystals. Although co-crystals, i.e. multicomponent crystals containing chemically different molecular units in the asymmetric unit have long been known [70], they have recently become an important field of new discoveries and innovation under the strive to find new drugs and the potential of extension of IP protection on existing ones [71–73].
The definition of a co-crystal is still matter of debate [74, 75]. The definition initially put forward by Aakeroy focused on the aggregation state: “co-crystals are made from reactants that are solids at ambient conditions” [76] and has also been taken up by others [71, 77]. This definition, however, is not without ambiguity (see below). We prefer to take up Dunitz’ more liberal view of co-crystals as “encompassing molecular compounds, molecular complexes, solvates, inclusion compounds, channel compounds, clathrates, and other types of multi-component crystals.” This view has been echoed recently by Stahly [78] who wrote that: “co-crystals consist of two or more components that form a unique crystalline structure having unique properties.” At the bottom line, these multicomponent systems ought to be looked at as crystals of supermolecules whereby the component units interacting via non-covalent interactions generate collective physico–chemical properties that are different from those of the homo-molecular crystals formed by the components.

One may wonder whether solvates would fall under the same broad definition. We would argue in favour, not only because solvent molecules themselves form their own crystalline materials at appropriate temperature (ice!) but also because, as we have argued above, solvate crystals do not necessarily come from solutions since vapour or any other volatile molecule can be taken up from the ambient atmosphere and become incorporated into the crystal. Since we are dealing with crystal forms, it is useful to also remind the reader that the term pseudopolymorphism is not appropriate to refer to solvate forms of a given molecular crystal [23, 79, 80] because solvate crystals can themselves be polymorphic!

In a recent paper, Bond listed a number of interesting controversial examples of co-crystals [81]. For example, dioxane, C₄H₈O₂, forms isostructural 1:1 two-component crystals with I₂, Br₂ or Cl₂, which at room temperature and 1 bar pressure are solid, liquid, and gas, respectively [82–84]. Clearly a distinction based on the aggregation state of one component has little significance.

The crystal structures of 13 co-crystals formed by n-alkylcarboxylic acids and pyrazine in 2:1 stoichiometry have been reported [85, 86]. The acids include formic acid, which is liquid at room temperature, up to the tridecanedioic acid which is solid. Pyrazine is also a solid. Clearly, the early members of this series cannot be called solvates only because the co-former is liquid, while from decanoic to tridecanedioic the acid/pyrazine systems are co-crystals. Another example is the two-component crystals formed by picric acid forms and benzene, naphthalene and anthracene (amongst others), which contain stacks of alternating molecular components that are clearly comparable in all three structures [87–89]. All of these crystals are stable at room temperature.

Not only it is difficult to distinguish between a co-crystal and a solvate (as a matter of fact all molecules are solid and form crystals at sufficiently low temperature) but it is also often difficult to distinguish between a crystal and a salt. As discussed above in the case of hydrogen-bonded systems between acids and bases the transition between a salt and a co-crystal may be a very semantic issue depending exclusively on the position of a proton along a N···O supramolecular link [90].

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 [91, 92].

Mootz and Wiechert 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 interactions are present (see Fig. 14) [93]. Examples of this kind are rare, but serve to stress how the phenomenon of polymorphism can be, at times, full of ambiguity.

In order to tackle the problem of the co-crystal or salt nature of acid–base adducts we have used the same approach illustrated above in the case of the polymorphs of barbituric and cinchomeronic acid, namely a combined use of diffraction and spectroscopic methods in the investigations. We have shown that mechanical mixing of a di-nitrogen base [N(CH₂CH₂)_3N] (dabco) and of dicarboxylic acid HOOC(CH₂)_nCOOH (n = 1–7) affords a series of hydrogen-bonded adducts of general formula [N(CH₂CH₂)_3N]–H–[OOC(CH₂)_nCOOH](n = 1–7, that is to say 1C₃, 1C₄, 1C₅, 1C₆, 1C₇, 1C₈, and 1C₉) (see Fig. 15) [21].

These compounds can be classified as co-crystals or salts depending on whether proton transfer from oxygen to nitrogen takes place or not along the O–H—N bonds [94]. In order to address this issue we have compared the results of an X-ray investigation carried out on single crystals grown from the solid-state products by seeding the corresponding methanol solutions with those obtained from the polycrystalline powder by solid-state ^1H and ^15N and ^13C spectroscopy.

For example, it has been possible to correlate the isotropic ^1H and ^15N chemical shift data with the N–O distances of the atoms involved in the hydrogen bond interaction in a series of solid adducts of formula [N(CH₂CH₂)_3N]–H–[OOC(CH₂)_nCOOH](n = 1–7) (Fig. 16). The ^1H MAS and ^15N CPMAS NMR data are in agreement with the X-ray data and allow discrimination between the proton transfers for the 1C₃ and 1C₅ adducts and the strong N···H–O interactions.

![Fig. 14 The 1:1 co-crystal of pyridine and formic acid where the proton transfer does not occur (left) and the 1:4 co-crystal of pyridine and formic acid where the formate anion is present (right)](image-url)
(without proton transfer) for the 1C4, 1C7, 1C8 and 1C9 co-crystals. 1C6 represents an intriguing case in which one of the nitrogen atoms of dabco is intermediate between the protonated and non-protonated forms. Density functional theory, applied to explore changes upon hydrogen bonding in the $^1$H and $^{15}$N shielding parameters, is in agreement with the experimental values found by solid-state NMR spectroscopy [95, 96].
Comparison of melting point data of the neutral organic acids and of the co-crystals and salts discussed herein yields another interesting observation. As shown in Fig. 17, the melting points of compounds 1C3–1C9 follow a trend very similar to that of the acids, i.e. they show an alternation of melting points as a function of the even–odd carbon chain length.
In summary, at room temperature malonic and glutaric adducts are salts; adipic is ambiguous; succinic, pimelic, suberic and azelaic adducts are co-crystals. Diffraction data and solid-state NMR data are in agreement except in the case of compound 1C6, which shows proton motion on the NMR time scale. Salt or co-crystals – does it matter? The melting points of compounds 1C3–1C9 do not correlate with the salt-like or co-crystal nature of the adducts, but rather with the even–odd carbon chain length in spite of the substantial differences in supramolecular arrangements in the crystals of the adducts with respect to those of the parent diacids.

On closing this discussion on co-crystal systems, it is useful to cite few examples (selected from the many available in a rapidly expanding literature) of the importance of co-crystals in the pharmaceutical field. Piracetam, (2-oxo-1-pyrrolidinyl) acetamide), has been co-crystallized by Zaworotko et al. with gentisic acid and p-hydroxybenzoic acid (see Fig. 18) [22].

Co-crystals of 4-hydroxybenzoic acid (4HBA) and 2,3,5,6-tetramethylpyrazine (TMP) (2:1) have been reported as a case of supramolecular synthon polymorphism in a co-crystal (see Fig. 19); in fact the two forms exhibit different hydrogen bond interactions. The co-crystal form I does not follow the hierarchy of hydrogen bonding, and converts into the stable form II, which follows the hierarchy of hydrogen bonding [97].

In yet another example, a co-crystal of caffeine and adipic acid [98] has been isolated by a co-crystallization methods based on a suspension/slurry containing both components of the co-crystal system. This approach provides an optimal environment for the putative co-crystal formation because the activity values of both

![Fig. 18 Co-crystals of piracetam, (2-oxo-1-pyrrolidinyl) acetamide with gensitic a and c, and p-hydroxybenzoic acids b and d](image-url)
components are held at one. This method was applied to 16 pharmaceutically related co-crystal systems and was found to be 100% successful [99]. In the case of the co-crystal caffeine/adipic acid, a suspension of caffeine and adipic acid (1:1 molar ratio) in acetonitrile was prepared and equilibrated overnight at ambient temperature. The powder X-ray diffraction pattern of the solid after equilibration indicated formation of a new solid phase, which was then characterized as shown in Fig. 20.
Evaporative crystallization experiments containing equimolar ratios of the API and guest has been instead used to obtain co-crystals of chlorzoxazone with carboxylic acids [100]. Two polymorphs of a chlorzoxazone:2,4-dihydroxybenzoic acid co-crystal and one form of a chlorzoxazone:4-hydroxybenzoic acid co-crystal have been characterized and the crystal structure of chlorzoxazone:2,4-dihydroxybenzoic acid (form 1) reported and analyzed, revealing an uncommon carbonyl–carbonyl interaction and a destabilizing C–H⋯Cl–C interaction (see Fig. 21).

9 Conclusions

The scope of this review has not been that of providing the reader with a comprehensive coverage of the topic of crystal forms, rather we have aimed at an introductory view of the phenomena of multiple crystals forms in general, and polymorphism in particular. For reasons of space, many problems have not been addressed (e.g. theo-
retical methods to study polymorphism), in particular the computational exploration of the possible crystalline structures of a given molecule. The interested reader will find in the necessarily limited number of references a good starting point for further reading.

The question on whether a crystalline material contains only molecules A in different arrangements (e.g. polymorphs), or molecules A and molecules B, and whether this latter association ought to be considered a co-crystal or a solvate is somewhat semantic. It is unquestionable, however, that crystals of different composition not only have different crystal structures but also may possess different physical properties, such as solubility, thermal behaviour, resistance to mechanical stress, gas-absorption/release capacity, colour, melting point etc. These differences may be relevant, and carry economical and practical implications, when considering, for instance, the bio-availability of a drug or the thermal stability of a pigment.

Reproducibility and predictability are paradigms in the exact sciences. This is why, beside all the utilitarian reasons associated with the marketing of solid state materials, we would like to learn how to make polymorphs, or, which is the same, how to effectively prevent polymorph formation. If seeds of a polymorphic modification can be obtained from non-solution methods (i.e. mechanical, thermodynamical, perhaps solid state reactions) these can be used in the seeding process, which may allow growth of less kinetically favoured crystal forms. Seeding may be valuable not only to obtain the desired crystalline form, but also to prevent crystallization of undesired forms. One could argued that polymorphism, with its high degree of serendipity, could be the nemesis of crystal engineering because polymorphism is in logical contrast with a discipline that aims to control and reproduce univocally a given crystal structure. This is not true (rather the investigation of crystal forms) of the way a molecule recognizes another molecule, whether the same or a different one, and links to form stable or metastable supramolecular arrays, it is rather a way to tune synthetic and assembly strategies to obtain the desired crystal structure, which is the paradigm of crystal engineering.

References

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