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Solid-solid phase transitions between crystalline polymorphs of organic materials

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Abstract

In this review, the analysis of solid-solid phase transitions between crystalline polymorphs of organic molecules is discussed. Although active pharmaceutical ingredients (APIs) are the scope of the review, whether an organic molecule has a biological activity or not, does not particularly define its interactions in the crystalline state. Therefore, other small organic molecules have been included in this analysis and in certain cases polymers have been discussed too. The focus of the review is on experimental analysis; however, a section on computational and theoretical methods has been added, because these methods are becoming important and are obviously helpful in understanding for example transition mechanisms because the results can be easily visualized. The following aspects of solid-solid phase transitions between crystalline structures are discussed. The thermodynamics of phase transitions between polymorphs involving thermodynamic equilibrium and the variables temperature and pressure closely linked to the Gibbs free energy are discussed. The two main transition mechanisms in the organic crystalline solid, displacive and concerted, are discussed. Experimental methods that are used to understand the mechanisms and thermodynamic equilibrium between different polymorphs of an API are reviewed. The switching of polymorph properties is discussed, and heat storage and release is reviewed as it is one of the main applications of solid-state phase transitions. Of interest for the control of drug products, constraining phase transitions has been reviewed, as it may help in increasing the bioavailability of an API by using metastable phases. Finally, second order phase transitions of organic materials, which appear to be rare, are discussed. It can be concluded that although the general theory of polymorphism and phase transitions is well understood, how it works out for a specific molecule remains difficult to predict.

Keywords

Pharmaceutical ingredient, crystalline materials, crystal, phase behavior, phase diagram, transition mechanism.

1 Introduction

For the development of drugs, the solid state of active pharmaceutical ingredients (API) is important as it has an impact on the solubility and the stability of APIs and they are directly linked to the bioavailability and the shelf life of a drug formulation.[1,2] The solid state of an API is not only its crystal structure that was found at crystallization after the initial synthesis; it is in fact extensive information about the different crystal forms or polymorphs that the API can crystallize in, the thermodynamic stability hierarchy of these different crystal forms and often the transition dynamics of a less stable polymorph into a more stable polymorph. This implies that while drugs are tested on efficacy and toxicity, simultaneously, the solid state needs to be thoroughly screened [3-7] and decisions need to be made on the drug formulation [8,9]. These decisions depend on the solubility behavior of a given drug molecule and the different crystal structures that a drug crystallizes in. The more thermodynamically stable a certain crystal structure, the less soluble will this structure be and therefore its bioavailability may be limited. This may lead to the development of a less stable form or even the amorphous state; however, in those cases, it will need to be demonstrated that the drug formulation will remain within specifications for the required shelf life. In other words, next to a clear mapping of the thermodynamic stability ranking of the different polymorphs, the dynamics of the transitions of one form into another need to be studied. If necessary, measures need to be taken to slow down or inhibit the dynamics to avoid a decrease in solubility of the formulated drug.

Although many new developments are taking place in medicine, the preferred drug formulation remains a solid due to easy administration and storage [10]. Thus solid-state knowledge is essential during development. Most drugs delivered in the solid form are organic molecules with a molecular weight ranging from about 100 to 1000 g mol^{-1}. From the point of view of thermodynamic behavior and polymorphism, there is little importance whether an organic molecule is an API, and solid-state behavior has its implications in other fields too such as agrochemicals, pigments, or explosives.

Organic molecules often possess many different potential crystal structures that can be determined with crystal structure prediction[9]. However, experimentally, often only a few structures are found and thus for some reason or another, most of the structures are not suitable for a given molecule or simply not easily accessible in an experimental setting. It was Kitaigorodsky, who proposed that observed crystal structures presented the denser packings [11]; however, this is not always true, in particular if strong hydrogen bonds can be formed in the crystal structure and therefore the densest structures are not always the most stable ones [12].

Thermodynamically, the system, which may be an API with or without excipients, tends to proceed towards the state of lowest Gibbs energy (G). This is a balance between the enthalpy (H), which can be considered the total interaction energy for the API within a crystal packing, and, at a given temperature (T), the entropy (S) of the system (in the present case crystalline organic material). In the process of one state changing into another as for example a solid-solid transition between two crystalline structures, the total change in the Gibbs free energy can be written as:

$$\Delta G = \Delta H - \Delta TS \qquad (1).$$

However, for stability purposes, it is more convenient to investigate the tendency and direction of the change of the Gibbs energy (in terms of the infinitesimal change dG) as a function of its characteristic variables temperature (T) and pressure (p):

$$dG = -S\,dT + v\,dp \quad (2),$$

with v the volume of the system.
The lowest Gibbs energy of all states available to the system (organic molecule or API) as a function of temperature and pressure is favored. This is the basis of phase theory and phase diagrams [13-15]. Although the theoretical basis of crystalline polymorphism is therefore well understood, prediction of the crystalline behavior of a specific molecule, in particular if the molecule is large flexible, is still a serious challenge.
And even if polymorphs and Gibbs energies are known, a phase transition from a metastable form towards a more stable form may not occur. This depends on the transition dynamics. The current review will focus on solid-solid transitions between crystal structures of organic molecules. It will on the one hand review stability studies, which are the basis of whether a transition is spontaneous and therefore is allowed to occur or not and on the other hand on mechanistic studies, which contain information on whether a transition is capable of occurring, whether there is a possible mechanism for the solid-solid transition. It may become clear that the mechanisms of solid-solid transitions are often not well understood and that even when thermodynamically the stability ranking is known, a transition may remain unpredictable.
The ***solid state or solid-solid phase transitions*** discussed in this paper ***will be limited to transitions between different crystalline phases***. This excludes recrystallisation of amorphous materials and melting, both of which deserve a review of their own. Although the focus in this paper is on the phase behavior of APIs, studies involving other organic molecules are relevant for our understanding and they have been incorporated in this review, even if this review does not pretend to be complete. Metal systems and or inorganic materials have been left out of this review because the interactions within the crystal structures are often very different from those of molecules. The paper is divided in thermodynamic studies, mechanistic studies, experimental techniques that are specifically used to study transitions and references to computer-oriented studies and theory, property changes due to the solid-solid transitions and transitions used for heat storage. The review is concluded with some discussion on the inhibition of polymorphic transitions and a limited treatment of the occurrence of second order solid-solid phase transitions in organic materials.

2 Recent Advances

2.1 Thermodynamic studies

Thermodynamics is important because it informs us about the spontaneity of the solid-solid transition and thus whether the transition is thermodynamically allowed under a certain set of conditions. This understanding is necessary because it allows us to design a drug in such a way that it is in its most stable state and therefore not prone to change. Although the variable pressure may not immediately be considered relevant for APIs, studies under pressure help understanding the observations we do under normal conditions and in tableting or grinding pressures may (locally) become high enough to trigger polymorphic transitions.
Thermodynamics is mostly studied through the Gibbs free energy and a system is in equilibrium when its Gibbs free energy is at its lowest possible state. The characteristic variables of the Gibbs free energy are temperature and pressure. They work on the specific volume and the entropy of the system under study, implying that if the pressure increases, the system will search for a denser form and if the temperature increases, the system will

search for a form that contains more entropy. Because entropy is difficult to measure experimentally, it is often replaced by the quantity $\Delta H/T$, i.e., the transition enthalpy divided by the equilibrium temperature, which is equal to the change in entropy at equilibrium; however, if the system is out of equilibrium, this equality does not hold anymore and $\Delta H/T$ becomes at most an estimate of the entropy change ΔS.

A paper on the polymorphic phase transition in 4'-hydroxyactophenone is an excellent example in which thermodynamics and transition dynamics are studied with a considerable number of techniques consisting of powder X-ray diffraction (PXRD), diffuse reflectance infrared, Raman spectroscopy, temperature-stage microscopy, temperature-resolved second harmonic generation, differential scanning calorimetry (DSC), adiabatic calorimetry and solubility measurements [16]. The system contains a form II, orthorhombic $P2_12_12_1$, Z' = 2, which enantiotropically transforms into form I, monoclinic $P2_1/c$, Z' = 1 with an equilibrium temperature at 300 K and an enthalpy change of 0.49 kJ·mol^{-1}. The mechanism of the transformation is not clear, but the activation energy appears to be higher than the lattice energy of form II, the low temperature form. Therefore, a hysteresis in transition temperature is observed depending on the heating rate of the sample up to 70 degrees at a heating rate of 80 K min^{-1}. It is understood that form I nucleates slowly and then grows within form II, once the equilibrium shifts to form I. This paper is a good example of the difficulty of interpreting transition data in terms of thermodynamic equilibrium, when the system is highly influenced by the transition dynamics [16].

A paper on the trimorphism of N-methylurea discusses the thermodynamic relationships between the three phases and the transition behavior [17]. The techniques used in the study were temperature-resolved PXRD and DSC. Form I, orthorhombic $P2_12_12_1$ appears to be the stable form, whereas form II, monoclinic $P2_1/c$, and form III, monoclinic $P2_1/c$, are enantiotropically related to each other with ΔH = 7.6 J·g^{-1} and they are both metastable towards form I. Hysteresis in the transformation between form II, the high-temperature form, and form III, the low-temperature form, is observed between -118 and -143°C, however, the transition is reversible and observed on every run. The transformation from form II into form I is much more haphazard and can take several days. It also depends on the presence of humidity. Spontaneous transformation from form II into form I has been observed, however. The melting enthalpies indicate the following stability ranking: $\Delta_{fus}H_I > \Delta_{fus}H_{III} > \Delta_{fus}H_{II}$. Forms II and III were discovered by crystallization from the melt.

An example in which the solid-solid transition is easily overlooked is the benfluorex hydrochloride system with form I, monoclinic $P2_1/n$, and form II, orthorhombic $Pbca$ [18,19]. The system was studied with DSC, temperature-resolved (TR) PXRD, and high-pressure differential thermal analysis (HP-DTA). It was shown that depending on the heating rate of the DSC, the solid-solid transition occurred simultaneously with the fusion of the low temperature form II. At 10 K·min^{-1}, barely any trace of the fusion of the higher melting form was present, so the solid-solid transition seemed completely absent. By running the DSC at heating rates below 1 K·min^{-1}, a clear heating rate dependent solid-solid transition was visible with a constant melting transition of the higher melting form I and with an enthalpy of 10.4 J·g^{-1}. A pressure-temperature phase diagram was established demonstrating that form I was only stable above 395 K at low pressure, whereas above 150 MPa the system becomes monotropic with form II the only stable form.

Forms II and III of benzocaine exhibit a clearly reversible solid-solid transition that barely demonstrates any hysteresis [20]. Form II is orthorhombic $P2_12_12_1$ and form III is monoclinic, $P2_1$. Form II is the high-temperature form with the transition found at 265 K and an enthalpy

of 3 $J \cdot g^{-1}$. The system was studied by DSC, PXRD, and HP-DTA. It was shown that although form II is the more stable form at room temperature, with increasing pressure, form III becomes the only stable form above 463 MPa. Form I was not obtained during these experiments and the phase relationship between form I and the other two forms is not clear yet; therefore, form I may still prove to be the most stable of the three polymorphs.

Butamben belongs to the same family of drug molecules as benzocaine, and its phase behavior appears to be similar. Two forms have been observed, form II, a low temperature form, and form I, the high temperature form, which both crystallize in a $P2_1/c$ space group. The transition temperature is found at 280 K with a tiny transition enthalpy of 375 $J \cdot mol^{-1}$. The polymorphs form an overall enantiotropic system. DSC, HP-DTA, PXRD and densitometry of the liquid phase have been used to establish the phase relationships between the two solids [21].

A study on camphor is one of the rare investigations in which the solid-solid transitions of both the enantiomer and the racemic crystal have been studied as a function of pressure [22,23]. For the enantiomers three solid phases are observed, the low temperature form III, which is orthorhombic $P2_12_12_1$, the intermediate temperature form II, which is hexagonal, and the high temperature form I, which is cubic. Very similar solid phases are observed for DL-camphor, the racemic mixture with the orthorhombic form III *C*mcm. Forms I and II are plastic crystals and any scalemic mixture is a solid solution, with the racemic mixture exhibiting disorder in the position of the D- and L-molecules: due to the plasticity of the crystals, caused by the freedom of rotation for the spherical molecules, the D- and L-molecules cannot be differentiated within the crystal structure. The low temperature form III of the racemic crystal contains considerable disorder that may be part of the system [24]. The transition temperatures and enthalpies differ between the pure enantiomer and the racemic system, in particular those of the III→II transition (T_d = 242.7 K compared to T_{dl} = 206.7 K and $\Delta_d H$ = 11.2 $kJ \cdot mol^{-1}$ compared to $\Delta_{dl} H$ = 1.3 $kJ \cdot mol^{-1}$) and a typical eutectic shape of the transition behavior between forms III and II is observed (the plastic crystals having fluidlike characteristics; Figure 1). The low temperature transition between III and II exhibits a certain level of hysteresis with a link to the disorder. The system was studied by DSC, PXRD, volumetric measurements as a function of temperature, and HP-DTA. Direct measurements by HP-DTA and topological calculations of the temperature-pressure phase diagram indicate that none of the three forms becomes metastable under pressure and that all maintain a stable temperature range irrespective of the pressure. It appears however, that under pressure the excess Gibbs energy of the racemic crystal becomes larger with respect to the ideal mixture. A special mention should be made of a very meticulous measurement on the transition temperature and the disorder of the racemic form III by adiabatic calorimetry, although even this measurement could not find a fully ordered racemic form III, suggesting that the disorder is inherent to the phase [24].

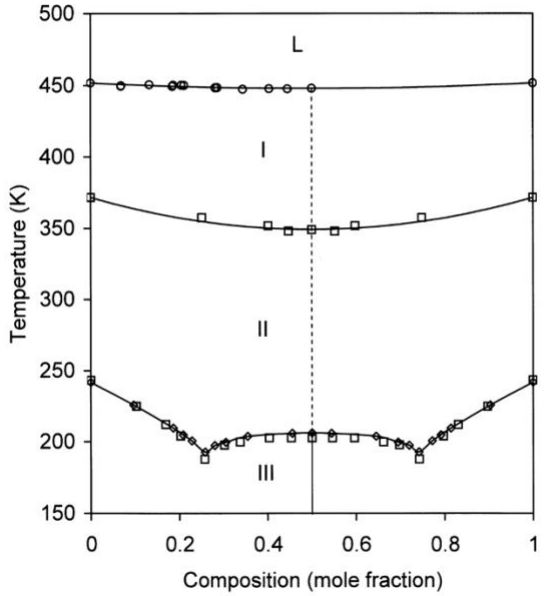

Figure 1. The binary phase diagram of D- and L-camphor with the racemate in the center. The II to III phase transition exhibits the familiar shape of a eutectic, because of the liquidlike characteristics of the plastic crystals of form II. Reproduced with permission from [22].

Piracetam possesses three polymorphs: form I monoclinic, $P2_1/n$, form II triclinic, P-1, and form III monoclinic, $P2_1/n$. Its pressure-temperature phase diagram has been elucidated using DSC, TR-PXRD, specific volume measurements, sublimation under temperature gradient, piezo-thermal analysis (PTA) and HP-DTA [25]. The solid-solid transitions are difficult to link with their thermodynamic stability. Both forms II and III transform into form I at temperatures depending on the heating rate of the DSC. Transitions between form II and III are not observed at all. It appears in fact that form III is the low-temperature and high-pressure form, form II is found under intermediate conditions and form I is a low-pressure, high-temperature form that has a stable melting point. Only under pressure, was it possible to really solve this system and the PTA and HP-DTA methods were indispensable. Through the high-pressure measurements, the different melting equilibria could be traced as a function of pressure and temperature, after which using thermodynamics in combination with the triple points in the system, the other phase equilibria could be placed in the system (Figure 2). The II-III equilibrium under ordinary pressure is located around room temperature, the I-II equilibrium at about 375 K and the I-III equilibrium at about 365 K (Figure 2) [25]. The II-III equilibrium is stable, even if it is not observed experimentally.

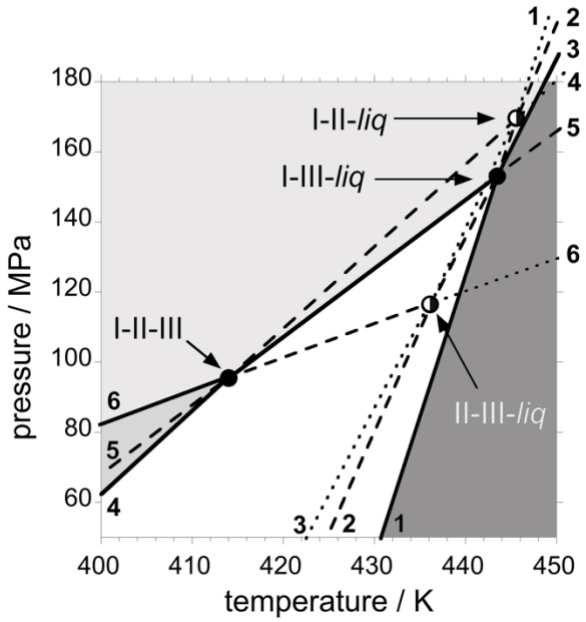

Figure 2. The pressure-temperature phase diagram of piracetam. Form III (light grey area) is stable under pressure and at low temperature, form II (darker grey area)) is stable under intermediate conditions and form I (white area) is stable at high temperature and low pressure up to the melt (very dark grey area). Reproduced with permission from [25].

The dimorphism of rimonabant was found to be monotropic with form II, $P2_1/c$, the only stable form in the entire pressure-temperature domain [26]. Interestingly, no transition of form I, *P*-1, into form II has ever been observed and the less stable form, I, contains hydrogen bonds, whereas the stable form, II, does not. The phase diagram has been determined using single crystal (SC) XRD, optical microscopy, DSC, sublimation under a temperature gradient, volume measurements as a function of temperature and HP-DTA.

L-Tyrosine ethyl ester forms a trimorphic system; form I is orthorhombic $P2_12_12_1$ as are forms II and III. This system has been studied with DSC, TR-PXRD, HP-DTA, synchrotron XRD and Raman spectroscopy. The solid-solid transition between form II, the room temperature form, and form I, the high-temperature form, depends on the scanning rate of the DSC; however, the *equilibrium* temperature between the two forms is located at 306 K [27]. Once form II has transformed into form I, the solid-solid transition does not revert back, and form II can only be obtained through melting and recrystallisation. Form III is obtained by subjecting form I to pressure and releasing the pressure will immediately result in the formation of form I again [28,29]. Form II under pressure will not convert into form III, thus the system needs to be in the right state for a transition to occur and specific transition mechanisms must exist that have not been specifically investigated.

Pyrazinamide is a flat molecule, capable of forming several hydrogen bonds. It possesses four known polymorphs: form α, $P2_1/n$, form β, $P2_1/c$, form γ, *P*c, and form δ, *P*-1. Several papers have studied its phase transitions and the thermodynamic stability, which was difficult because most polymorphs transformed into more stable forms at much higher temperatures than the actual equilibrium temperatures [30,31]. This reluctance to transform is in this case clearly linked to the flat molecule in combination with the hydrogen bonding, which makes reorientation of the molecule difficult and the activation energy of the transformation large. Methods used in the elucidation of the phase behavior involved DSC, vibrational spectroscopy, sublimation crystallization under a temperature gradient as well as at constant temperature,

TR-PXRD, Synchrotron PXRD, HP-DTA, vapor pressure measurements and solubility measurements. In this particular case, because most polymorphs transformed only after considerable hysteresis, it was possible to obtain vapor pressures of the different forms over large temperature intervals, which is a direct reflection of the Gibbs free energy of the polymorphs. This allowed establishing the stability hierarchy between the polymorphs and subsequently the pressure-temperature phase diagram. It was in particular interesting to see that even form β possesses a stable temperature domain under ordinary pressure conditions at low temperature, leading with increasing temperature to stability domains from $\beta \rightarrow \delta \rightarrow \alpha \rightarrow \gamma$ [32]. HP-DTA and sublimation clearly defined the equilibrium temperature between forms α and γ at 392 K with a transition enthalpy of 13.2 $J \cdot g^{-1}$ [33].

Trimorphic cysteamine hydrochloride possesses a monoclinic form I, $P2_1/c$, a triclinic form II, *P*-1, and a monoclinic form III, *I*2/a. The system has been studied with DSC, TR-PXRD, HP-DTA, thermogravimetric analysis (TGA), and differential vapor sorption (DVS). The latter two methods were used, because cysteamine hydrochloride is sensitive to water and forms a saturated solution even under low levels of humidity. The transition from form I to form III was found to have an equilibrium temperature at 310 K and an enthalpy change of 9.9 $J \cdot g^{-1}$. Below 200 K, form II was found to be more stable than form III, but no clear equilibrium temperature could be established, therefore the stability ranking between form I and form II remains unclear too. A hysteresis was observed between I and III, but only of about 10 degrees [34].

Spironolactone demonstrates that not observing a solid-solid transition can be dependent on the origin of the sample even if the system is monotropic [35]. Topological pressure-temperature phase diagrams have been established for TNT [36], for which it is difficult to establish the equilibrium temperature of the solid-solid transition due to hysteresis, for FK664 a cardiotonic agent, which is overall monotropic [37], although no solid-solid transformations have been observed at all, and for finasteride [38], which has an enantiotropic phase relationship, but the solid-solid phase transition is slow and shows considerable hysteresis.

A special mention should be made of systems like metacetamol. It has two polymorphs, but under ordinary pressure, the system is monotropic with form I the only stable form. Form I is also the densest form, but due to the entropy and the density relationships between the two polymorphs, a stable domain for the lesser dense form II exists at high pressure and high temperature (Figure 3) [39]. Paracetamol shares the fact that the two main polymorphs exhibit a monotropic relationship, but in the case of paracetamol, the high-pressure form II is also the denser form and the understanding that form II becomes stable under pressure is more straightforward [40,41]. Similar to the system of paracetamol, is benzophenone for which form II, metastable at ordinary pressure, is denser than form I and has a stable domain under increased pressure [42]. No solid-solid transition has been observed between the two forms.

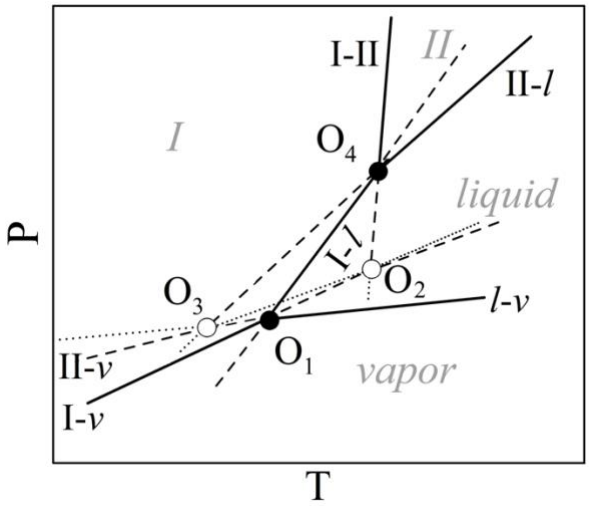

Figure 3. Pressure-temperature phase diagram of metacetamol with a stable domain for a less dense form (form II) at high pressure and high temperature. Reproduced with permission from [39].

Fluoxetine nitrate is a system like metacetamol (Figure 3) in which a less dense polymorph becomes stable under pressure at high temperature. Here again, it is important to consider both the density and the entropic contribution to the stability of the polymorph [43]. The same behavior is observed for ritonavir, for which in first instance the low-density, high-pressure form was obtained and marketed. Only later was the more stable, denser form found, which caused quite a stir for this already marketed API [44-46].
In the case of 1,4-diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-bromophenyl ester fumarate, a selective alpha-7 nicotinic receptor partial agonist the solid-solid transition is not observed between the two known polymorphs. The stability ranking has been determined through vapor pressure measurements, which has led to the thermodynamic equilibrium temperature between the two polymorphs [47].
In relation to the thermodynamic behavior of solid-solid transitions under pressure, the slope, d*P*/d*T*, can be calculated with the Clapeyron equation:

$$\frac{dP}{dT} = \frac{\Delta S}{\Delta v} = \frac{\Delta H}{T\Delta v} \qquad (3).$$

Of all the observed solid-solid transitions under pressure, the equilibrium lines (Figures 2 and 3) remain straight over the observed temperature and pressure range [20,21,23,25,34]. It means that the ratio between the change in entropy Δ*S* and in specific volume Δ*v* remains constant, as this ratio defines the slope. It is thus likely that Δ*v* and therefore also Δ*S* remain more or less constant under pressure (or slowly change in a similar fashion). Thus, knowing the slope of a solid-solid transition at one point in a pressure-temperature phase diagram makes it possible to extrapolate this equilibrium towards higher pressures as a straight line. This approach can also be used for solid-liquid transitions (fusion); however, in the latter case, the equilibrium lines are more curved, due to the higher compressibility of the liquid phase under pressure in comparison with the solid.
A paper by Boldyreva clearly points out that as is the case with temperature, also with pressure the transformation dynamics play an important role and it remains therefore very difficult to distinguish thermodynamic phase behavior from delayed phase transitions due to

hindered transition mechanisms [48]. However, it should be borne in mind that if one observes a transformation of one form into another under set pressure and temperature conditions that under these conditions the appearing form must be more stable than the disappearing form. It does not provide us necessarily with an equilibrium pressure and temperature, but it does provide us with a stability ranking point within the thermodynamic pressure and temperature space. Nonetheless, if solvents or other substances are present, they may displace the phase equilibria and conclusions about stability rankings between two polymorphs in a binary system may not be directly applicable in the related unary system (i.e., a system in which only a single chemical substance is present and in which interactions only occur between the same chemical species).

The behavior of crystal structures subjected to the thermodynamic variables pressure and temperature may give rise to applications, as inversely the steam engine resulted in thermodynamics. Although this is often the realm of inorganic materials, heat exchange due to pressure through solid-solid transitions may be used as an alternative to a heat pomp with a gas as has been shown by the large baro-caloric effects observed for plastic crystals of 1-Cl-adamantane and 1-Br-adamantane [49]. More about applications involving heat storage will be discussed in a later section.

A popular method to study the stability of different polymorphs is liquid assisted grinding (a slurry) as the following published examples demonstrate: caffeine-citric acid cocrystal polymorphism [50], entacapone, a drug to treat Parkinson's disease [51], theophylline, a bronchodilator to treat asthma [52], the muscle relaxant metaxalone [53], the antibiotic trimethoprim [54], and co-crystals of furosemide-nicotinamide [55]. Although, obviously phase transitions may occur in the slurry and therefore the process is mentioned here, the interpretation of the results is not straightforward. Firstly, the transitions are mediated by the presence of a liquid and thus no real solid-solid transition may take place and a dissolution-recrystallization process is more likely to occur. Secondly, the presence of a solvent may change the conditions of the equilibrium between the crystalline polymorphs, so that stabilities obtained in the presence of a liquid do not necessarily need to be the stabilities of the pure molecule (the Gibbs-Duhem principle). This is an important issue in the interpretation of the phase behavior of APIs and other organic molecules of interest to industry and society.

Thus, to conclude this subsection with recent thermodynamic studies of solid-solid phase transitions, the overview demonstrates that the heat exchanges during a transition are relatively small. Moreover, systems are mostly studied with XRD and DSC, although other methods are used such as for example vapor pressure measurements and adiabatic calorimetry. The interpretation of the phase behavior remains difficult for each new case due to the interplay of thermodynamics and the transition dynamics. The dynamics may be accelerated by adding solvent in a slurry, however, this may complicate the interpretation of the phase behavior of the unary system.

2.2 Mechanistic studies

It is clear from the previous section that the understanding of transition mechanisms is important as it allows us to interpret observed phase behavior in terms of thermodynamics and dynamics. Moreover, understanding the mechanistic background of a solid-solid phase transition may allow the design of systems in which a metastable polymorph can be used in a drug formulation by inhibiting the transformation to the more stable form.

The best known approach to describe the kinetics of solid-solid phase transitions is the classical Kolmogorov-Johnson-Mehl-Avrami (KJMA) equation [56]:

$$X = 1 - e^{(-K(t-t_0)^n)} \quad (4).$$

In this equation, X is the transformed fraction of the new solid phase at a given time t, K is the prefactor of frequency factor, also expressed as k^n, t_0 is the induction time, and n is the Avrami exponent. To obtain the Avrami exponent from experimental data, ln(-ln(1-X)) is plotted as a function of ln(t-t_0) for which the slope equals the exponent. Eq. 4 is valid under the assumption that the nucleation of the new phase is random and that the shape of the growing phase is convex; thus, it assumes that a wavefront of the new phase moves through the entire crystal. Nonetheless, eq. 4 only describes the kinetics of the phase transition and does not rule out any specific transition mechanism *a priori*.

Mechanistic studies are difficult to carry out because the nucleation, which happens randomly is often hard to detect and growth, especially within a crystal, remains difficult to interpret from a mechanistic point of view, because most analysis methods are indirect or based on the appearance of the crystals after the transition. Molecular modelling would be a logical approach to study mechanisms; however, as can be seen in section 2.4, relatively little is being done in the realm of organic molecules or APIs.

In terms of mechanisms in solid-solid transitions, the close packing of molecules in a solid in combination with directional bonds such as hydrogen and halogen bonding does not provide much opportunity for molecules to move, once one form becomes metastable and another crystalline form becomes more stable due to a change in temperature, for example. Therefore, many solid-solid transitions are delayed or don't even occur, resulting in the metastable form melting at its equilibrium temperature of fusion instead (see for example spironolactone [35] or benfluorex hydrochloride [18]).

In the case of spironolactone, the melting of the metastable form leads to a recrystallisation into the stable crystalline form, which could be interpreted as a solid-solid transition [35]. It should be very clear that in the latter case, two transitions from two separate thermodynamic equilibria are involved, which therefore cannot be classed as a solid-solid transition. If a metastable form melts, it turns into a metastable liquid, which depending on the dynamics and its proximity to the melting point of the stable form, subsequently converts into the stable solid phase. Within a DSC experiment, this can result in a confusing peak or even a peak that looks like a single transition, even if it isn't [35]. Therefore, phase transitions always should be studied with several complementing experimental methods.

Another mechanism that should not be classed as a solid-solid transition is one aided by the vapor phase. This will obviously only occur if the vapor pressure of the API is high enough as in pyrazinamide [33,57]. In pyrazinamide, molecules are flat and closely packed, which provides little space for the molecules to change position to adjust to another more stable crystalline phase. Thus, with a high enough vapor pressure and with enough time, the appearance of the more stable phase can be observed due to sublimation and recrystallisation by deposition [57,58].

As discussed in the previous section, solution or solvent mediated phase transitions (i.e., in a slurry) do most likely not result in a direct solid-solid transition either but are much more like vapor pressure mediated transitions [59,60]. Although mechanisms that occur in suspensions may be multiple, there is a large probability, in particular with sufficient solubility, that a metastable form dissolves and recrystallizes into the more stable form. This obviously may be

the intention of the exercise and it definitely will indicate the stable polymorph under the given conditions (i.e., in the presence of the solvent); however, it will not be a solid-solid transition in the sense that one crystalline solid converts into another crystalline solid without the presence of a third phase in the form of a liquid or a vapor.

Thermodynamically, two solids in equilibrium in a unary system is categorically different from the mechanisms described above. In the case of a metastable form melting and recrystallizing in the stable form, a cascade of metastable forms into the stable form occurs, whereas in solvent mediated phase transformations, the system is not unary, which will have an effect on the equilibrium conditions in accordance with the Gibbs-Duhem principle. Obviously, solvent mediated phase transitions and the related equilibria may be the method of choice if one seeks to know what happens in the presence of a specific solvent, but this falls outside of the scope of this review.

For the mechanisms of solid-solid phase transitions that occur at equilibrium between two solid phases, basically two mechanisms exist: diffusive/reconstructive and non-diffusive/displacive [61]. Thus, either the molecules find a way to move concertedly into the new crystalline phase (non-diffusive/displacive), or within the transition, the molecules are obliged to break up the metastable structure, while searching for the structure of the more stable phase (diffusive/reconstructive). The diffusive mechanism would clearly result in a wavefront moving through the crystal as assumed in the KJMA equation (eq. 4). This wavefront would consist of diffusing molecules, which therefore represents a transitory amorphous zone. As different nucleation points can arise, a single crystal undergoing such a transformation will generally end up with different crystalline domains or even fall apart (see figure 4a). In case of the concerted movement, this may be concerted over the entire crystal, resulting in a sudden crystalline change (as shown in figure 4b); however, if the molecular movement is relatively slow due to available free volume or molecular flexibility, a wavefront will also occur as well as multiple nucleation points. Thus, these two mechanisms may in principle be fitted with the KJMA equation. Recent studies involving these two mechanisms will be discussed below.

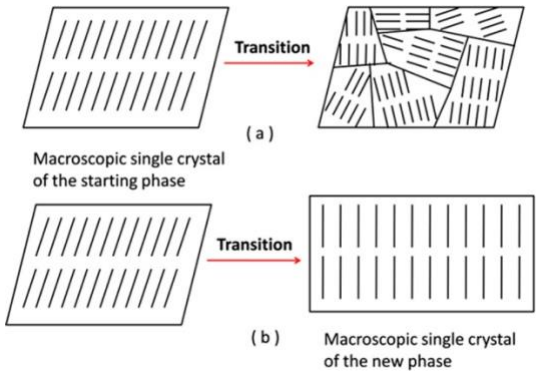

Figure 4. (a) The diffusive/reconstructive mechanism resulting in a crystal with several domains and **(b)** the non-diffusive/displacive mechanism, which may result in a different single crystal if the transition is rapid and fully concerted. Reprinted with permission from [61]. Copyright 2018 American Chemical Society.

Monoalkoxynaphthalene-naphthalimide has been used to prepare orange crystals that turn yellow on heating. Because of the change in color, it is possible to follow the wave front of the solid-solid transition. The transition starts at the rim of the crystal or at a crack; thus, the transition clearly nucleates and then proceeds through the crystal. The mechanism is a sliding

movement of the molecule to exchange a head-to-head configuration in the orange crystal to a head-to-tail configuration in the yellow crystal [62], which is a movement that is not restricted by the crystal packing as it only requires small shifts of the individual molecules.

A reversible phase transition with very little hysteresis occurs in the dapsone system between two $P2_12_12_1$ structures, forms III and II. The enthalpy change linked to the transition is only 2 $kJ \cdot mol^{-1}$. DSC, XRD and thermal stage polarization microscopy (TSPM) were used for the analysis. The fact that both forms easily convert into one another is because the crystal structures are very similar. There is a slight change in molecular configuration and packing on transition, which allows for a slightly denser system for the high temperature form II.[63] For this system, once the stable form nucleates the phase change rapidly occurs and spreads throughout the entire crystal.

DL-Methionine has two known polymorphs, the high-temperature form α, space group $P2_1/c$, and the low-temperature form β, space group $C2/c$. It was studied by SC-XRD, DSC, TSPM, and solid-state NMR (SS-NMR). The equilibrium temperature between the two forms is located between 305 and 317 K; however, it could not be determined more precisely due to hysteresis. Of interest is that single crystals exhibited a more clear-cut transition than powders, which indicates that the transition is related to a nucleation followed by cooperative or concerted movement of the molecules ("crystal growth"); thus, nucleation events seem relatively rare and growth of the new phase is relatively rapid [64].

Shi et al. demonstrate in the case of DL-methionine that the presence of defects is important for nucleation [65]. Defects clearly provide some space for the molecules to change position from the metastable crystal structure to the more stable one, they are therefore a logical starting or nucleation point for a phase transition. If many defects are present in the crystal structure, this will lead to more nucleation sites.

DL-Methionine is in fact part of a group of amino acids with unbranched hydrophobic side chains that crystallize in monoclinic space groups and often exhibit solid-solid phase transitions between polymorphs involving concerted movement due to the flexibility of the side chains [66]. It is surprising that a quasi-racemate L-2-aminobutyric acid-D-methionine (1/1) crystallizing in a polymorph with a monoclinic $C2$ space group with Z'=1 transforms below 229 K into a polymorph with a triclinic space group $P1$ with Z'=4 in a similar fashion [66]. The high temperature form ($C2$) exhibits considerable disorder at room temperature, which results into the Z' = 4 structure at low temperature, where all chains have a different configuration. Once again, concerted movement of bilayers, as in the other amino acids, allows the solid-solid phase transition to occur [66]. It has to be realized that the disorder observed in these crystals is probably inherent to the crystalline structure. Thus, overall, the structure is crystalline, but at certain points there is enough space for a flexible chain to adopt several different configurations. This can be inherent to the crystal because it lowers the Gibbs free energy through an increase in the entropy of the crystal [67].

In 1-F-adamantane, the solid-solid transition causes the crystal to fall apart on lowering the temperature triggering the transition from form I, $Fm\text{-}3m$, to form II, $P\text{-}42_1c$. Both forms contain disorder caused by hindered rotation of the adamantane molecule [68]. The rotational degree of freedom is larger for the high temperature cubic form than for the low temperature tetragonal polymorph. Despite the disorder, both solid forms remain crystalline.

Ciclopirox is an interesting molecule from the point of view of solid-solid transitions. On the one hand the molecule can be considered to possess four polymorphs; on the other hand, the two intermediate crystal forms can be considered as transient. The high-temperature form, $C2/c$, exhibits dynamic disorder, which becomes concerted at about -20° C on going down in

temperature. At about -40° C the dynamic disorder becomes static with loss of crystal symmetry. At -87°C, the system clearly changes crystal form with space group $P2_1/c$. This system contains a large number of molecules in the asymmetric unit to accommodate the different molecular configurations inherited from the disorder in the high-temperature form. The study has been carried out with DSC, TR-PXRD, SC-XRD, Raman and IR spectroscopy, SS-NMR, and TSPM [69]. The phase transitions are a step by step progression of one form into another, in which it is not clear whether the intermediate forms can be considered proper thermodynamic polymorphs or transition intermediates. In any case the transitions are reversible and very reproducible [69]. Due to the large role of the dynamic disorder played in these transitions, they can occur through concerted movement of the molecules and with the observed reproducibility.

4'-hydroxyactophenone has already been mentioned in the previous section. It possesses at least two polymorphs, low temperature form II and high temperature form I [16]. Form II converts consistently at 357 K into form I in the DSC at a scanning rate of 1 $K \cdot min^{-1}$. Using solubility, the equilibrium temperature between the two forms was found to be 300 K, however, it should be kept in mind that solubility measurements depend on a binary system (i.e., a system in which two components (chemical species) are present and where interactions between these two components and between the same component may occur), which may alter the Gibbs free energies of the different forms present in accordance with the Gibbs-Duhem principle. Nucleation of form I possesses a large activation energy and must be relatively difficult, but once nucleation has taken place, a transition front can be observed in single crystals and it was suggested that some sort of concerted motion mechanism for the phase transition must occur that does not break the crystal during conversion [16].

m-Hydroxybenzoic acid is a monotropic system with a metastable polymorph under ambient conditions with a space group $Pna2_1$ and the stable form has a space group of $P2_1/n$. The phase behavior was investigated with temperature-resolved second harmonic generation (TR-SHG), SC-XRD, DSC, TSPM, and multiphoton microscopy (which maps the SHG signal). The activation energy of the transition was determined to be about 140 $kJ \cdot mol^{-1}$ and the enthalpy difference between the two forms is in the order of 0.6 $kJ \cdot mol^{-1}$. From the observed data, it is concluded that the transition follows a destructive/reconstructive mechanism; however, single crystals used for the observations did remain intact and a wavefront of the phase transition could be observed after nucleation of the stable phase [70].

N-Methylurea was discussed in the previous section. Suffice to mention here that the two forms II and III have the same space groups and similar packings. Changes in temperature create limitations on molecular mobility, which initiates a concerted motion of the molecules into the other polymorph. This is valid with increasing and decreasing temperature, while the observed hysteresis between the observed transition temperatures indicates the existence of an activation energy [17].

Another system already mentioned in the previous section is the phase relationship between form I and form III of L-tyrosine ethyl ester. Under pressure, form I is compressed, which brings a hydrogen donor and acceptor pair close enough to click into place. Thus, the mechanism of this transition is a small change in configuration in the molecule resulting in the formation of a hydrogen bond. For the rest the two structures are rather similar as expected under pressure and the mechanism can therefore be considered as concerted movement [28].

An interesting system is the boc-L-methionyl glycine methyl ester, which crystalizes in a Z' = 8 structure with space group $P1$ at low temperature and around -113°C, on increasing the

temperature the space group remains *P*1, but the structure becomes dynamically disordered with Z'=4. This change can be clearly observed by XRD, but no signal is present in DSC. TR-SHG does show a different decrease in signal intensity between the two polymorphs [71]. Although the transition can be classified as and order-disorder transition, it is not clear whether it is a first or second order transition in terms of the Ehrenfest classification [72,73]. A change in volume is observed on transition, but no clear DSC signal. Nonetheless, the transition appears to be reversible and abrupt at a precisely given temperature. This would not be expected for second order transitions, which tend to be continuous in nature.

An order-disorder phase transition in the van der Waals based solvate of C_{60} and $CClBrH_2$ demonstrates a clearly first order transition at 322 K between a phase with a monoclinic space group *C*2/*m* and a high temperature hexagonal phase (*P*6/*mmm*).[74] The solvent molecules are placed in the interstices formed by the buckyballs and the disorder is caused by the position of the Cl and Br groups on the solvent molecules and by the orientational freedom of the buckyball itself in the high temperature form. The enthalpy change on transition is 4.85 $J \cdot g^{-1}$.

In the case of polymers, similar solid state transitions can be observed as for example for forms I and II of isotactic polybutene [75]. Form I has a hexagonal structure with a proposed space group *P*-3 and form II, a low temperature form, has as proposed space group the tetragonal *P*-4b2. The transition from form II into form I is not observed to revert back on lowering the temperature. The mechanism appears to be linked to a change in conformation of the chains and simultaneously in a displacement of the chains in two opposite directions resulting in the hexagonal unit cell. This happens without destruction of the crystal.

Poly(L-lactic acid) is a polymer of which the solid-state phase transitions have been thoroughly investigated [76,77]. Form α is a relatively ordered phase with the polymer chains in ordered helices that are directed alternatingly upward and downward. Transformation into form δ occurs by putting α under strain at temperatures between 70 and 160°C. δ has a similar packing to α, but the configuration of the chains is somewhat different, the structure consists of multiple domains, instead of one single domain as is found for α. The phase transition occurs through displacement of domains in the crystal structure combined with the change in chain configuration and an introduction of disorder. Form β can subsequently be obtained from form δ, by stretching the polymer crystal at high temperature (160°C). The tension creates an additional concerted shift in the positions of the polymer chains and a further change in the polymer chain configuration, while the domains remain present in the crystal.[77] Thus, also in polymer solid-state phase transitions the concerted movement of molecules is an important transition mechanism.

Solid-state phase transitions in the ferroelectric copolymer PVDF-TrFE demonstrates the presence of different mechanisms within the same system [78]. PVDF possesses several polymorphs, among others, the paraelectric α, the ferroelectric β and a form γ, which is also polar, but less so than form β. The transition from form β to form α, which occurs on increasing the temperature to about 320 K, takes place slowly and passes through form γ. It appears that most heat exchange is involved in the phase change from β to γ, in which nucleation and crystal growth occurs, so the mechanism appears to be destructive/constructive, due to a considerable change in the polymer configuration and resulting in a reduction of the ferroelectricity of the crystal. The transfer from form γ to α appears to be much easier and happens by an additional configurational change through concerted motion, while the unit cells between these two forms are relatively similar. The sequence appears to be following the Ostwald rule of stages, but with a clear mechanistic cause [78].

Glycine, the simplest amino acid, possesses three polymorphs under ordinary pressure. Form α and β are monoclinic, space groups $P2_1/n$ and $P2_1$ respectively, and form γ is trigonal, space group $P3_1$. The β form undergoes a displacive phase transition into form δ ($P2_1/n$) under pressure, which is fully reversible. γ under pressure turns into form ε (*Pn*); this is a slow destructive/reconstructive transition, which should be considered rare under pressure, as there is little space for molecular mobility. Release of the pressure on form ε leads to form ζ, of which the structure was solved in space group *I*1.[79] The latter phase transition follows a concerted movement of molecular layers in form ε in combination with small molecular rotations. The transformation from form ζ into γ follows a destructive/constructive transition as the layers break up to form γ. ζ is also observed to transform into β for which most likely only a displacive motion is necessary, but the precise conditions for this transition are not clear [79].

Diglycine methanesulfonate is shown to undergo an order-disorder transition between the low-temperature form and the room-temperature form with an entropy change of 3.2 $J{\cdot}mol^{-1}{\cdot}K^{-1}$. The paper also indicates that it is very easy to misinterpret experimental data, when deducing the transition mechanism in a solid-state transition [80].

A clear example of a destructive/reconstructive mechanism, mentioned too in section 2.4, has been observed by molecular dynamics [81], whereas an example of concerted motion has been observed in thin films with molecular modelling [82].

From this section it can be concluded that the two observed mechanisms for organic crystals are indeed destructive/reconstructive and concerted motion as mentioned in the introduction of this section. It can also be seen that these mechanisms depend strictly on the structures between which the transitions occur and not on the molecules, as for the same molecule both mechanisms can be observed. In fact, it may be that in particular phase transformations, where the system passes through an intermediate form, both mechanisms occur.

2.3 Observation of phase transitions with specific experimental techniques

As must have become clear form the foregoing, the dynamic and thermodynamic aspects of polymorphic transitions make it necessary to use several different methods to study such transitions. DSC measurements are often too fast to properly determine equilibrium temperatures and measurements generally need to be carried out at different scanning rates to see whether transition temperatures depend on the scanning rate. While XRD is an excellent tool to recognize the phase that a system is in, it is often harder to properly determine the temperature at which the XRD measurement is carried out exactly, because the equipment for temperature control is often somewhat removed from the sample to avoid interfering with the diffraction signal. Many other techniques can be used to study specific aspects of solid-solid transitions, which will be discussed below.

Acetonitrile possesses a high-temperature β form, $P2_1/c$, and a low-temperature α form, $Cmc2_1$, which transform into each other at approximately 211 K [83]. Once the crystal structures are known, Raman and also infrared spectroscopy can contribute to quantifying the strength of the interactions in the different polymorphs and be used to study the transition dynamics by following the lattice modes as a function of the temperature. In this particular case, the Raman study emphasized the relative liberty of the acetonitrile molecule to reorient itself in the β form due to a certain level of plasticity in this phase, which involves the orientational disorder of the CH_3 group [83].

As mentioned above the reversible phase transition of dapsone was studied with DSC, XRD and thermal stage polarization microscopy (TSPM) [63]. TSPM can be very useful and should not be underestimated as a method to directly see what happens in the system on transition (Figure 5). It could for example be conveniently visualized that once the stable form nucleates the phase change rapidly occurs and spreads throughout the entire crystal.

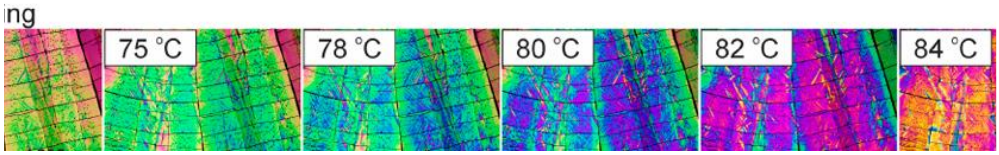

Figure 5. Dapsone observed by thermal stage polarization microscopy. Reprinted with permission from [63]. Copyright 2022 American Chemical Society.

Solid-state NMR is also a method that can be used to study the state of a phase transformation. DL-Methionine with a high-temperature form α, space group $P2_1/c$, and a low-temperature form β, space group $C2/c$ was, among others, studied by solid-state NMR (SS-NMR). It was used to determine the amount of each polymorph present in the samples, which allows the determination of the kinetics of the transformation [64]. TSPM was useful too, to follow the evolution of the phase transformation in DL-methionine.

Although the following example concerns monolayers and a solid-liquid transition, which is studied by ellipsometry, the method itself is interesting enough and may be used to study solid-solid transitions too, possibly even on crystalline surfaces; therefore this reference has been added to the review [84]. Basically, ellipsometry provides information about the density in the surface of a layer and about the layer roughness. It may be of interest to study these parameters for certain systems around the solid-solid transitions as it could provide information about transient states during a transition.

X-ray spectroscopy is mentioned here as it can be used for chemical analysis of a solid near a phase transition [85]; however, this method is mainly used to study metal systems, for which it is more interesting.

Using fluorescence, a solid-solid transition has been observed in octadecyl octadecenoate that could not be detected by DSC, although this method may only be useful for niche applications, it is of interest to see that the fluorescence depends on the environment and therefore can be used to detect changes in its environment, which in this particular case is a solid-solid transition [86,87].

Second harmonic generation or second harmonic scattering (Figure 6) has been used to monitor the transition kinetics of a solid-solid phase transition. Second harmonics only occur in space groups lacking an inversion center. In the case that one of the polymorphs is centrosymmetric and the other is non-centrosymmetric such as for m-hydroxybenzoic acid, the kinetics of the conversion can be followed with SHG as a function of time (time resolved SHG) at several different temperatures [70]. The transition was found to have a high activation energy, although the forms were monotropically related, implying that the enthalpy difference observed during the transition is negative. Because the polymorphs exhibited little structural similarity, the transition was considered to be destructive/reconstructive, which was verified by thermal stage polarization microscopy.

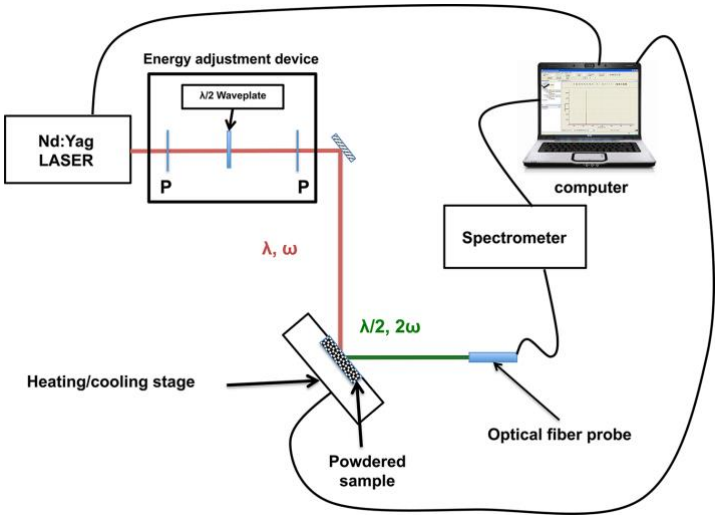

Figure 6. Experimental temperature-resolved second harmonic generation or scattering. Reprinted with permission from [70]. Copyright 2022 American Chemical Society.

A second example of the application of temperature resolved SHG (Figure 6) is for the analysis of a possible second order phase transition in 1-fluoro-adamantane [88]. In this case, on heating, the SHG signal can be seen to decrease for the low-temperature non-centrosymmetric structure with space group $P\text{-}42_1c$. The structure passes into a structure with the related $P4_2/nmc$ space group without any DSC signal and without any change in volume between the two unit cells. These three elements: lack of heat exchange, lack of change in volume and a gradual change from one form into another are strong indications that a second order phase change occurs. SHG, at least for pairs of non-centrosymmetric-centrosymmetric structures, appears to be an excellent method to observe such transitions. An overview of the applications of SHG among which the study of solid-solid phase transitions is provided in reference [89].

In situ attenuated total reflection Fourier transform infra-red, temperature controlled microscopy and time-resolved PXRD were used together to demonstrate a solid-state phase transition in the presence of a supersaturated solution [90]. The three methods give complementary information on the phases present in a mixture and can be used to study processes in situ. Due to the presence of a saturated solution, DSC data would be much harder to interpret.

X-ray diffraction under pressure and as a function of temperature using a synchrotron source can be used to obtain thermodynamic data. This has been done in the case of L-tyrosine ethyl ester and the equilibrium between polymorphs I and III [28]. Because the crystal structures were either known (form I) or obtained by the XRD experiments (form III), the unit-cell volumes were known and the change in the volume on transition could be established. In addition, the position of the I-III equilibrium could be determined in relation to the temperature and the pressure and thus the slope dP/dT. Using the Clapeyron equation (eq. 3), the entropy change of the phase change could be estimated with the slope of the phase equilibrium as was carried out in the abovementioned paper [28]. Other examples, where pressure and temperature-controlled synchrotron XRD were used, are papers on the polymorphism and solid-state transitions of pyrazinamide [32,33].

Pyrazinamide is also of interest because of the use of HP-DTA to trace a phase transition as a function of the pressure and the temperature [33]. HP-DTA is a thermal analysis method in which the sample and an empty reference cell are subjected to a hydrostatic pressure. Once

the pressure has been established, both sample and reference are heated from room temperature to about 200°C and the heat exchange of the sample is recorded against that of the reference. Measurements at several set pressures lead to the evolution of phase transitions as part of the pressure-temperature phase diagram.

Vapor pressure measurements should be mentioned as a means to obtain direct thermodynamic data of the relative stability of polymorphs for pyrazinamide [32,33]. In the case of pyrazinamide, it was an advantage that the compound did not transform very quickly into a more stable form and thus that vapor pressure measurements could be obtained over a reasonable temperature range. Obviously, the vapor pressure of a compound needs to be high enough to be able to obtain reliable vapor pressure data. A second example, for which the vapor pressure was important to determine the stability hierarchy between two polymorphs, was 1,4-diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-bromophenyl ester fumarate [47]. In this system, the transition temperature was not observed (while in pyrazinamide most were delayed and occurred at much higher temperatures), but this temperature could be inferred through vapor pressure measurements. In both cases the Knudsen cell technique was used, which is based on the weight loss of a sample through a set orifice size. By calculation and calibration with a standard compound, the vapor pressures can be calculated from the data.

It is already abundantly clear that solid-solid phase transitions can be difficult to study and that in a regular DSC run this type of transitions can be easily bypassed and not observed at all. Spironolactone is a good example with two known polymorphs, which exhibit a very large difference in melting temperatures. Nonetheless, the polymorphs are rarely seen to interconvert in the solid state. It pays however, to remain vigilant as certain batches of a spironolactone powder did demonstrate a solid-solid conversion, providing important information about the thermodynamics and the transition dynamics. With the help of this information a topological pressure-temperature phase diagram could be constructed leading to a more complete view of the stability relationships between the two polymorphs [35].

Triglycine sulphate has been studied with diffuse neutron and X-ray scattering [91]. This method allows the study of the local order around atoms and molecules. The actual mechanism studied here is an order-disorder transition between the disordered form, $P2_1/m$, and the ordered ferroelectric system, $P2_1$. The ferroelectric-paraelectric transition with a T_C of 322 K was found to be second order [92]. Through the diffuse scattering the step-wise change into a disordered system can be clearly followed.

Piezo-thermal analysis (PTA) was used together with HP-DTA to construct the phase diagram of trimorphic piracetam [25]. In PTA, the temperature is kept constant during a measurement, while the pressure is changed, and the heat exchange monitored. Because the temperature is constant, the enthalpy that is registered can be directly related to the entropy change of the equilibrium under study (i.e., $\Delta S = \Delta H/T$ at equilibrium).

Dielectric and conductivity measurements have been carried out on the two solid phases of ethanolamine [93]. During the irreversible transition of the metastable form II into form I, both the conductivity and the dielectric data changed. The metastable form contains static disorder, which could be observed by the dielectric loss parameters [93].

A molecular rotor, 1-propyl-3-methylimidazolium, has also been investigated by dielectric relaxation. Two phase transitions related to dynamic disorder were observed, one at 256 K and one at 359K [94].

Other methods to study transitions involving some disorder or partial glassy states, such as in the case of plastic crystals are positron annihilation lifetime spectroscopy (PALS) and electron

spin resonance (ESR), which have been used to study a solid-solid phase transition in cyclohexane [95].

To conclude this section, DSC and XRD remain the two main methods for the study of solid-solid phase transitions; however, TSPM should not be forgotten to directly visualize phase transformations in the system. Once those three methods do not provide a full picture of the phase transition under investigation, other approaches can be used, such as Raman spectroscopy, SHG, diffuse scattering, or SS-NMR, to elucidate the processes during the phase transition and the thermodynamic relationship of the involved phases.

2.4 In silico methods

At present, computer approaches have become important. Although this review mainly focusses on experimental methods, some computer approaches will be briefly mentioned here.

Phase transition mechanisms under the effect of pressure can be studied by DFT [96]. Computer programs have been developed too that list likely solid-solid phase transitions for given crystalline polymorphs [97]. Neural networks or machine learning is being used to study phase transitions [98].

The behavior of ionic liquids, their phase transitions and the mechanisms involved have been studied by molecular dynamics simulation [99]. The kinetics of consecutive phase transitions have been modelled resulting in a prediction of possible DSC curves, which may be helpful in the interpretation of DSC measurements [100].

Using molecular dynamics and Monte Carlo simulations, a phase transition has been observed for the alkane $F(CF_2)_{12}(CH_2)_{12}H$ from bilayer to monolayered structures with increasing temperature [101]. Pentaerythritol may have interesting properties for latent heat storage through a solid-solid phase transition at 459 K with a large enthalpy of transition of 277 $J \cdot mol^{-1}$. Molecular dynamics was used to study the behavior of the thermal conductivity in relation to the change in crystalline structure linked to the phase change [102].

Langevin dynamics have been used to visualize a solid-solid phase transition in a model system in which the Gibbs free energy was calculated as a function of the different conditions modelled [103].

Density functional theory can be used to calculate crystal structures from first principles, however, depending on the functional such as the often-used Perdew-Burke-Ernzerhof (PBE), calculated crystal structures correspond with a higher or lesser extent to the structures obtained by measurement. A good example of the different outcomes of various functionals compared to measured equations of state (EOS) can be found in an article on the polymorphism of 1,3,5-triamino-2,4,6-trinitrobenzene under pressure [104].

Several molecular dynamics force fields have been tested on solid-solid and solid-liquid transitions of alkanes. The transition temperatures obtained with the force fields PYS and Williams 7B manage to approach the experimental values within a few degrees [105].

Thin layers of a ceramide containing 4Z-sphingosine and palmitic acid undergo a solid-solid phase transition if the surface of the thin layer was compressed. Calculations carried out with molecular dynamics confirm the appearance of a solid-solid phase transition in this Z configuration, which is absent in the more common E configuration [106].

Atomistic molecular dynamics have been used to study a phase transition of poly(3-alkylthiophenes) between a solid and a mesophase. It was clearly shown that the transition occurs stepwise in which first the initial phase disappears and subsequently the new phase is formed; hence, a destructive-reconstructive mechanism [81].

Commensurate solid-solid phase transitions have been predicted in self-assembled monolayers of alkylthiolates as a function of the temperature by molecular dynamics. Because the sulfur atoms remain fixed on the surface and the phase change mainly involves a change in the angle of the alkyl chains, it is an example of a concerted motion mechanism [82].

The pressure behavior of hexahydro-1,3,5-trinitro-s-triazine has been studied with equilibrium molecular dynamics simulations using the Smith-Bharadwaj potential. The $\alpha \rightarrow \gamma$ phase change observed experimentally under pressure could be obtained by simulation by compressing the c-axis of the α form [107].

Models involving the kinetic parameters in solid-state phase transitions are being developed [108], and numerical simulation is being used to study phase transition mechanisms [109]. The theory of the mechanism of a photoinduced phase transitions has been studied [110]. Slowly, crystal structure prediction combined with energy calculations is starting to become capable of predicting at which temperature the stability ranking between two polymorphs changes, even if this still remains a serious challenge [111].

2.5 Property changes due to solid-solid transitions

Solid-solid phase transitions can be used for applications, although it may be difficult to harness their property changes, because of the transition temperatures that come with a system. A few examples of properties that change with the solid-state transition and that may be used for applications will be discussed.

Caged imidazolium cations exhibit an order-disorder phase transition that affects their dielectric constant, which can be switched on or off through the phase transition [112]. Using other chemical systems, switchable dielectric materials can be created that possess non-linear optical properties [113]. A similar effect can be observed in betainium chlorodifluoroacetate in which the dielectric response can be changed through a reversible phase transition [114].

Plastic crystals with ferroelectric properties have been developed that can be tuned through the polarization depending on the crystal structure [115]. Although this has not been studied in the paper, these plastic crystals may represent an example of a second order transition.

An interesting study on poled PVDF-TrFE films has investigated the mechanism of a ferroelectric to paraelectric conversion by several phase transitions. Such papers are rare as most often only the actual ferroelectric response is of interest [78]. The paper is also a good example of the Ostwald rule of stages.

Color emissions can be switched using the crystalline polymorphs of luminescent bezothiadiazole-based crystals, with the color emissions depending on the intermolecular interactions [116]. Mechano-responsive luminescence can be switched on or off via crystal-to-crystal phase transitions between chiral and non-chiral space groups [117]. The chirality of the system changes through grinding (which causes the phase transition) and the emission properties of the system change too. The switching of colors due to phase transitions is a popular subject of study as is demonstrated by a study of the solid-state phase transition mechanisms involved in the switching of the properties of monoalkoxynaphthalene-naphthalimide donor-acceptor dyads [62]. Luminescence changes in phenanthroimidazole derivatives due to crystalline polymorphism and depend on the molecule itself [118]. Although not entirely in line with the present review, but still worth mentioning is a change in solid-state luminescence due to the exchange of solvent molecules in a fluorinated aromatic tetrapyrazole [119]. In addition, a theoretical study on a phase transition that is triggered by

light in tetrathiafulvalene-p-chloranil is of interest with a description of the mechanism and the properties of the phases [110].
It should not be forgotten that also the storage of ions may involve, or can be considered as, phase transitions on charging. An example of a study in this realm is an article on the intercalation of Li^+ in dicarboxylates for lithium ion storage applications [120].
In a completely different vein, but important nonetheless, is that a solid-solid phase transition can change the reactivity of the molecules as this may depend on the polymorph. In the case of the explosive TKX-50, this is a disadvantage because phase change to a high temperature polymorph diminishes the molecular stability of the explosive, which obviously is problematic for storage [121]. The same issue plays for pharmaceutical molecules and would diminish shelf life.

2.6 Heat storage/release

Although heat storage and release is strongly related to the material properties discussed above, it is a subject that has a proper interest of its own and it is particularly intimately related to the solid-solid transition itself, whereas in the previous section, it is often the different polymorphs, which possess the properties that are sought for and that can be switched on or off by means of a phase transition. In this section, a few studies will be mentioned in which the heat exchange on transition is investigated.
Mostly polymers are being researched for heat storage applications in relation to their solid-solid phase transitions. For example thermosetting materials composed of poly(ethylene glycol) can be mentioned [122,123]. Other options are biodegradable polyethyleneoxide/cellulose-based materials, for which the phase transition behavior in relation to the composition has been studied [124]. Composites of tetradecanol mixed with graphite are being investigated too [125]. Another example is pentaerythritol mentioned in section 2.4 on in-silico methods, which has a solid-solid transition enthalpy of 277 $J \cdot mol^{-1}$ [102].
Within this application, the baro-caloric effect discussed above in the thermodynamic section should be mentioned too, as it can be used for energy storage or cooling applications. Obviously these effects are not limited to organic materials and may also be stronger in inorganic materials [49,126,127]; however, the trade-off between stronger effects or lighter materials may make organic materials with a relatively large thermal response [49] in certain cases the better choice.
More details on thermo-physical properties related to solid phase changes and possible applications can be found in a more specific review on the subject [128].

2.7 Inhibition of polymorphic transitions

For pharmaceutical applications control over the polymorph that is developed in a particular dosage form is very important as a drug needs to be stable at least up to its use-by-date. Moreover, in other applications control over the crystal form can be of importance. The easiest way to control and maintain a polymorphic form is to choose the most stable one among the known crystal structures. Studies involved in this approach have been discussed in section 2.1. Another possibility is to mechanistically block the transition from a metastable form to the stable form. Although this is not always easy, in several molecular systems it is basically an inherent property that the polymorphs do not or only very slowly interconvert. Examples are spironolactone [35], prednisolone [129], 1,4-diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-bromophenyl ester fumarate [47], or rimonabant [26]. In these cases, it happens that a given dosage form can contain either one polymorph. More delicate systems are those in which the solid-solid transition is mainly bypassed by DSC and for which the transition is therefore observed at a higher temperature, which may cause misinterpretations in the

stability profile of the polymorphs. Examples are L-tyrosine ethyl ester [130] and benfluorex hydrochloride [18,19].

More specific investigations, where an active search for an inhibition mechanism is carried out are harder to find in the literature and most approaches will possibly happen within the pharmaceutical industry and may be found in patents, which are out of the scope of this review.

One example that has been investigated for inhibition mechanisms is pyrazinamide, a molecule against tuberculosis. It was found that certain molecules made the high-temperature form, metastable at room temperature, persist for about three years or longer [58]. This happened in particular when pyrazinamide is co-spray dried with 1,3-dimethylurea. The discovery led to other investigations in which this effect was studied using vapor deposition and grinding [57]. Moreover, the phase diagram of pyrazinamide was studied to understand to what level the high-temperature form, γ, was more stable than the other three polymorphs that are known for pyrazinamide [32,33].

There will be more examples in the literature, but it is quite likely that each inhibition mechanism will be specific for the molecule and its polymorphs at hand. This can be due to a large difference in the packing between two polymorphs, strong differences in conformational orientations and other reasons.

2.8 Second order solid-solid phase transitions in organic molecules

The order of transitions, whether they are first order or second order, was first proposed and defined by Ehrenfest [72,73]. This definition was based on thermodynamic observations and has little to do with phase transition mechanisms. First order phase transitions undergo a clear change in the structure, which from a thermodynamic point of view must therefore involve a change in the volume ($\Delta v \neq 0$), because no unit cell is exactly the same, and a change in the entropy ($\Delta S \neq 0$), because each way of packing a molecule will have a different energy signature and therefore a different entropy at a given temperature. Second order phase transitions are continuous in their structure; that is the structure changes gradually from one extreme to another. This implies that no sudden change in volume is recorded, and neither will there be a sudden change in the interaction enthalpy and entropy of the system. Nonetheless, second order phase transitions can often be detected by a change in the slope of the change of the heat and of the volume, thus in the derivatives of v and S with temperature (the heat capacity for example); therefore, the name “second order”. Second order phase transitions in the solid state are well known for inorganic materials with magnetic properties for which at a given Curie temperature a property changes often in relation with a gradual change of the crystal structure. The magnetic properties change in such a case gradually and so does the volume, while a discontinuity in the heat capacity can be observed. In organic molecules and their structures, second order phase transitions are not often reported in the literature even if it would be expected that they exist in one form or another as they exist for inorganic systems. A few examples of systems that demonstrate strong indications of undergoing second order phase transitions will be mentioned here.

The case of 1-fluoro-adamantane has already been discussed in section 2.3 with the application of SHG. This case is quite a convincing example in which disorder sets in in the crystal structure and both polymorphs have related space groups and structures that can easily and gradually interconvert [88]. Ciclopirox may also contain a second order transition, although in this case it is much less clear and the whole reason for the observation of different forms may simply be slow dynamics of the phase transitions involved due to low temperature [69].

Order-disorder transitions may involve second order behavior, but it often remains a question whether the system has simply not reached thermodynamic equilibrium (and remains thus disordered) or whether the disorder is an inherent part of the structure. An example is the low temperature crystal structure of racemic camphor, which contains disorder that diminishes on annealing, but never disappears entirely [24].
Another example of an order-disorder transition, in which the observations are more conclusive and in which the transition is also linked to a ferroelectric effect, is triglycine sulphate. This system was discussed above and most likely also exhibits a second order transition as observed by diffuse neutrons and X-ray scattering [91,92].
It can be concluded therefore that second order transitions do exist for organic molecules, but they either receive very little attention or they happen to be rare.

3 Conclusions and Outlook

This review gives an idea of the state of the art of our methods to study solid-solid transitions, even if it may not be complete. The thermodynamics of solid-solid phase transitions have been discussed and the difficulties in interpretation between thermodynamics and transition dynamics, which really may lead to erroneous conclusions about the phase behavior between different polymorphs, have been highlighted. It can also be seen in this review that the energy differences between polymorphs are often, but not necessarily, very small, which causes difficulties with the stability prediction *in silico* as the energy differences are often smaller than the error over the calculations.
Solid-solid phase transitions can either be deconstructive/reconstructive or they involve a concerted motion of molecules. The deconstructive/reconstructive mechanism often risks the breaking of crystals as the room for movement of the molecules is limited within a crystal. In the case of concerted motion, the position or the configuration of the molecules shift within the crystal structure, often but not necessarily, to a limited extent. This shift is generally relatively easy for the molecules to undergo. Understanding these mechanisms may lead to possibilities to maintain a certain (metastable) crystal structure and engineer a constraint, which may be especially "easy" if one polymorph is relatively different from the other ones for a given molecule as in the case of γ pyrazinamide.
Phase transitions are mostly studied by XRD and DSC, but a number of specific measurement methods such as SHG or diffuse scattering are interesting experimental methods that contribute to our understanding of the phase transition mechanisms. Moreover, direct observation by microscope and in silico modeling should not be forgotten!
Applications of materials are numerous, in particular for molecules with different properties that depend on their polymorphism. In this review, only a few examples have been shown and different reviews exist that deal with this subject more extensively. Heat exchange is a property specifically linked to the transformation and can be used for heat storage and cooling applications.
Inhibiting solid-solid transitions can be useful for the design of drug dosage forms with higher solubilities and therefore bioavailability for pharmaceutical ingredients, however, the mechanisms of inhibition, if they are not already present among the polymorphs of a given molecule, may be hard to control and will vary with each system.
Although second-order phase transitions are not often observed for solid-solid phase transitions in organic materials, they do exist and as was shown in several papers, they can be investigated with SHG or diffuse scattering.

As for the future of the study of solid-solid phase transitions, a lot of research will remain necessary either to make use of a switching of properties or to avoid, inhibit, unwanted phase transitions. The problem being that the temperatures and pressures at which phase transitions will occur are very hard to predict and that is often only after a lot of effort has been put into finding the experimentally accessible polymorphs of a system. Moreover, although the generalities, such as phase theory are well understood, the details of individual solid-solid phase transitions lack understanding and still need extensive study.

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