A gallic acid–succinimide co-crystal landscape: polymorphism, pseudopolymorphism, variable stoichiometry co-crystals and concomitant growth of non-solvated and solvated co-crystals†

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The structural landscape of the binary gallic acid–succinimide combination has been explored. A recently reported dimorphic 1 : 2 co-crystal was shown to exhibit a third polymorph at a high temperature by differential scanning calorimetry (DSC). Further, seven solvated co-crystals have been obtained, including three different hydrates (gallic acid : succinimide : water in 1 : 1 : 1, 2 : 2 : 1 & 2 : 4 : 1 ratios) and solvates with 1,4-dioxane (1 : 1 : 1), tetrahydrofuran (2 : 2 : 1), acetone (2 : 2 : 1) and ethyl acetate (3 : 3 : 1). A rare phenomenon of concomitant solvation, besides concomitant polymorphism, in the 1 : 2 co-crystal is recognized, which posed difficulties in obtaining phase-pure crystal forms in bulk quantity. Based on structural insights, methods to obtain pure co-crystals and design of several solvates are suggested. Additionally, a 1 : 1 co-crystal, which had been elusive under ambient conditions, is found to show polymorphic behavior for the materials obtained under nitrogen atmosphere and by high temperature desolvation of several solvates as analyzed by powder X-ray diffraction (PXRD) and DSC.

Introduction

The study of structural landscapes has major implications in comprehending the crystal form diversity of molecular solids and is therefore of importance in terms of both fundamental and application facets.¹ It facilitates the understanding of crystallization processes and can assist in the design of a desired solid form. The landscape of an organic system encompasses polymorphs, its multi-component adducts such as solvates, co-crystals, and even its homologues and analogues.¹⁻³ In the context of co-crystals being more amenable to design and having immense potential for tailored solutions in areas like pharmaceuticals,² organic synthesis and separation,³ optoelectronics⁴ etc., studies on the landscape of these systems are deemed important. Gallic acid (abbreviated as GA, Fig. 1) is a dietary polyphenolic acid and possesses anti-oxidant, anti-microbial and anti-cancer properties, apart from its usage for various applications in the drug industry.⁵ The potential to form varied and multiple hydrogen bonding motifs with its carboxylic acid and three hydroxyl groups allows its polymorphism, pseudopolymorphism, solvatomorphism and co-crystal polymorphism.⁶ Braun et al.⁶ studied the crystal energy landscape of gallic acid and its monohydrate and successfully obtained polymorphs of gallic acid which were elusive for over seventy years since their discovery. Driven by this background and our own studies⁴⁻⁶ on the diversity and applications of gallic acid crystal forms, further studies on gallic acid co-crystals have been undertaken to investigate the factors responsible for the rich structural diversity exhibited by this system. Herein, we report the polymorphism, pseudopolymorphism and variable stoichiometry co-crystals of a gallic acid–succinimide (GA–SM) combination.

In a co-crystallization experiment, the combination of internal (presence of various/multiple hydrogen bonding groups, mismatch of donor–acceptor ratio, awkward shape and conformational freedom of a molecule) and external factors (crystallization conditions such as solvent, temperature, supersaturation, solution kinetics) gives rise to multifarious possibilities of supramolecular association such that the outcome of co-crystallization becomes less predictable; the product can altogether be a new polymorph/pseudopolymorph/solvate/co-crystal/co-crystal solvate or a concomitant mixture of any of these.¹,⁶,⁷ Hence, the formation of polymorphs, hydrates/solvates, variable stoichiometry co-crystals, multiple Z' structures, salt co-crystals and solvates of co-crystals/salts can be considered a nemesis⁷ to crystal engineering
because of the unpredictability and lesser design control associated with it. Although each of these materials has its own importance, what is paramount from a practical outlook is to zero-in on a particular material and its landscape and gain control over its formation. In the present study, gallic acid can invoke various supramolecular motifs with its three hydroxyl groups to give rise to various kinds of adducts, since the influence of a hydroxyl group is three-fold: (i) its strength and structure directing effect, (ii) its bent nature presenting both donor and acceptor sites for hydrogen bonding and (iii) its conformational flexibility.4 Herein, a rare phenomenon of concomitant manifestation of solvates,9 including hydrates, along with the polymorphs of a 1 : 2 GA–SM (represented as 2 : 1 SM–345THBA in our previous study6) co-crystal is observed. Polymorphic and hydrate impurities are of major concern for pharmaceuticals, from production to consumption, because of physical property and intellectual property issues involved.7f,g,m,10 This warrants the development of a methodology to generate a desired solid form devoid of impurity. In this study, we describe the efforts undertaken to obtain materials in a phase-pure state. Furthermore, the polymorphic behavior of a 1 : 1 GA–SM co-crystal obtained under non-ambient conditions is also discussed.

Results and discussion

Co-crystallization experiments of GA–SM combination were performed by mechanochemical grinding (both neat and liquid-assisted grinding)11 and using evaporative crystallization2e,7f methods (as detailed in the Experimental section). Table 1 lists the polymorphs and solvates of the combination. It is noteworthy that a concomitant mixture of polymorph I of a 1 : 2 co-crystal and a solvated co-crystal (Table 1) was always obtained and attempts to obtain a 1 : 1 GA–SM co-crystal were unsuccessful. It appears that the conditions tried were not right for the crystallization of a 1 : 1 co-crystal. On the other hand, polymorph II of a 1 : 2 co-crystal, despite being more stable than polymorph I based on energy calculations (Table 2), did not crystallize in significant amounts. Neat/liquid-assisted (NG/LAG) grinding of 1 : 1 GA–SM–water was performed at 75 °C. Independent water-, DMF- and DMSO-assisted grinding of 1 : 2 GA–SM–water, 1 : 1 : 1 GA–SM–dioxane and 3 : 3 : 1 GA–SM–ethyl acetate were desolvated at 140 °C and 70 °C, respectively.

Table 1 Co-crystallization results of GA–SM combination

<table>
<thead>
<tr>
<th>Stoichiometry</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 1</td>
<td>Solution crystallization</td>
<td>1 : 2 GA–SM co-crystal polymorph I + 1 : 1 : 1, 2 : 2 : 1 and 2 : 4 : 1 GA–SM hydrates</td>
</tr>
<tr>
<td></td>
<td>Methanol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,4-Dioxane</td>
<td>1 : 2 GA–SM co-crystal polymorph I + 1 : 1 : 1 GA–SM–14D solvate</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>1 : 2 GA–SM co-crystal polymorph I + 1 : 2 : 1 GA–SM–THF solvate</td>
</tr>
<tr>
<td></td>
<td>Acetone</td>
<td>1 : 2 GA–SM co-crystal polymorph I + 2 : 2 : 1 GA–SM–Act solvate</td>
</tr>
<tr>
<td></td>
<td>Ethyl acetate</td>
<td>1 : 2 GA–SM co-crystal polymorph I + 3 : 3 : 1 GA–SM–EtOAc solvate</td>
</tr>
<tr>
<td></td>
<td>DMF and DMSO</td>
<td>1 : 2 GA–SM co-crystal polymorphs I and II</td>
</tr>
<tr>
<td></td>
<td>Neat grinding</td>
<td>1 : 1 : 1 GA–SM hydrate</td>
</tr>
<tr>
<td></td>
<td>Water-assisted grinding</td>
<td>1 : 1 : 1 GA–SM hydrate</td>
</tr>
<tr>
<td>1 : 2</td>
<td>Neat grinding</td>
<td>1 : 2 GA–SM co-crystal polymorph I</td>
</tr>
<tr>
<td></td>
<td>Independent water-, DMF- and DMSO-assisted grinding</td>
<td>1 : 2 GA–SM co-crystal polymorph I</td>
</tr>
<tr>
<td>Solvate</td>
<td>Desolvation temperature</td>
<td>Result</td>
</tr>
<tr>
<td>1 : 1 : 1 GA–SM–water</td>
<td>75 °C</td>
<td>1 : 1 GA–SM co-crystal</td>
</tr>
<tr>
<td>1 : 1 : 1 GA–SM–dioxane</td>
<td>140 °C</td>
<td></td>
</tr>
<tr>
<td>3 : 3 : 1 GA–SM–ethyl acetate</td>
<td>70 °C</td>
<td></td>
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</table>
SM under ambient conditions resulted in the formation of a 1:1:1 hydrate as confirmed by PXRD (Fig. 2) and TGA (Fig. 3). NG/LAG of GA–SM with a 1:2 stoichiometry exclusively resulted in metastable polymorph I of the 1:2 co-crystal (Fig. 4). All in all, a phase-pure 1:1 co-crystal and stable polymorph II of a 1:2 co-crystal could not be obtained from routine crystallization experiments. In principle, it should be possible to obtain a 1:1 co-crystal by desolvation, as the majority of solvated co-crystals have GA and SM in equal stoichiometries (Table 1). Indeed, we were successful in obtaining a 1:1 co-crystal upon careful desolvation of several solvates (1:1:1 GA–SM–water, 1:1:1 GA–SM–dioxane and 3:3:1 GA–SM–ethyl acetate) at elevated temperatures (Table 1), apart from neat grinding of the combination in nitrogen atmosphere. The structural reasons for the concomitant solvation of GA–SM co-crystals are discussed first, followed by X-ray crystal structures of solvates and then characterization of the 1:1 GA–SM co-crystal and polymorph III of the 1:2 GA–SM co-crystal in the subsequent sections.

### A. GA–SM co-crystal solvates and non-formation of a 1:1 co-crystal and polymorph II of the 1:2 co-crystal

The supramolecular basis for the formation of all solvates can be understood based on the design schematics for 1:1 acid–imide co-crystals in our recent study. Among various supramolecular motifs, a tetrameric unit, named as Thomo-II unit, composed of carboxylic acid (GA) and carboximide (SM) homodimers (Fig. 5), connected by hydroxyl (GA)−⋅imide (SM) interactions appears to be energetically favorable. These Thomo-II units can generate a staircase supramolecular assembly containing voids (Fig. 5) to allow for the accommodation of solvent molecules. Indeed, crystal structure analysis of the obtained GA–SM solvated co-crystals shows that all manifest the same void-containing staircase network (Fig. 5) with a void volume of ~40 Å³. Thus, the tendency of 1:1 combination to form void-containing supramolecular assembly appears to be the reason for non-formation of non-solvated 1:1 GA–SM co-crystal. On the other hand, although polymorph II of the 1:2 GA–SM co-crystal features Thomo-II units akin to solvated co-crystals (Fig. 5), it did not crystallize in significant amounts. In this context, the occurrence of a rare phenomenon of concomitant crystallization of 1:2 GA–SM co-crystal polymorph I and a solvated co-crystal (Table 1) is of particular interest. This can be explained based on ‘Ostwald’s rule of stages’.

![Fig. 2](image-url)  
**Fig. 2** The PXRD pattern of the 1:1 GA–SM neat ground (NG) material (black) is distinct from that of the parent materials, GA (magenta) & SM (green), and shows a good match with the simulated X-ray diffraction pattern of the 1:1:1 GA–SM hydrate (red). The 1:1 GA–SM water ground material (blue) also shows a complete match with the 1:1:1 GA–SM hydrate. Peaks of the simulated (110 K) and experimental (298 K) patterns at higher angles are offset to each other due to the temperature difference.

### Table 2 Lattice energy calculations of 1:2 GA–SM polymorphs

<table>
<thead>
<tr>
<th>E value</th>
<th>Polymorph I (kJ mol⁻¹)</th>
<th>Polymorph II (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSSE (Hartrees)</td>
<td>0.0126</td>
<td>0.0139</td>
</tr>
<tr>
<td>ΔE(coval) (Hartrees)</td>
<td>-0.1607</td>
<td>-0.1666</td>
</tr>
<tr>
<td>ΔE(cohesive energy) (Hartrees)</td>
<td>-0.1480</td>
<td>-0.1527</td>
</tr>
</tbody>
</table>

a (see the Experimental section).

![Fig. 3](image-url)  
**Fig. 3** TGA plot of the 1:1 GA–SM neat ground (red) and water ground (blue) materials. The weight proportion of one water molecule in the 1:1:1 GA–SM hydrate is 6.2% and the former shows a weight loss of 5%, indicating partial water absorption and partial formation of a hydrate. The latter, with a 6% weight loss, shows complete hydrate formation.

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Three different stoichiometry hydrates (1:1:1, 2:2:1 and 2:4:1) of the GA-SM co-crystals were obtained concomitantly with polymorph I of the 1:2 co-crystal upon crystallization of 1:1 GA-SM from methanol (see Table 1). Remarkably, all the three hydrates possess the same staircase supramolecular network with voids occupied by water molecules (Fig. 5 and 6).

Among other GA-SM co-crystal solvates, at first, 1,4-dioxane and acetone solvates were obtained. Based on the structural similarity between 1,4-dioxane and tetrahydrofuran on one hand and acetone and ethyl acetate on the other, respective solvates were anticipated and indeed obtained. They have different stoichiometries (GA-SM-THF in 2:2:1 and GA-SM-EtOAc in 3:3:1 ratios) as compared to the GA-SM-14D (1:1:1) and GA-SM–Act (2:2:1) solvates (Tables 1 and 3; Fig. 5). Interestingly, all these solvates always crystalize concomitantly with polymorph I of the 1:2 GA-SM co-crystal and also exhibit the same supramolecular network. 2:2:1 GA-SM–THF and 1:1:1 GA-SM–14D are nearly isomorphous (see Table 3). 2:2:1 GA-SM–Act shows doubling of the a-axis and corresponding doubling of the unit cell volume with respect to 1:1:1 GA-SM–14D. 3:3:1 GA-SM–EtOAc shows doubling of the a-axis and a 1.5 fold increase in the b-axis resulting in a corresponding tripling of the unit cell volume with respect to 1:1:1 GA-SM–14D. Further, 3:3:1 GA-SM–EtOAc shows an almost 1.5 fold increase in the b-axis and a corresponding 1.5 fold increase in the unit cell volume with respect to 2:2:1 GA-SM–Act (Table 3). It is noteworthy that the structures of the 2:2:1 and 3:3:1 solvated co-crystals show that the excess GA-SM stoichiometries which correspond to unique molecules have no effect on the overall crystal packing as compared to the 1:1:1 GA-SM co-crystal (Fig. 5). Independent liquid-assisted grinding experiments of 1:1 GA-SM using 1,4-dioxane, ethyl acetate, tetrahydrofuran and acetone reproduced the respective solvated co-crystals as established by PXRD (Fig. 7). The GA–SM–THF and GA–SM–Act solvates were formed only when dry solvents were used and especially under nitrogen atmosphere, otherwise the 1:1:1 GA-SM hydrate was always obtained. It should be noted that such conditions are not the case with the dioxane and ethyl acetate solvates which could be easily obtained. The affinity of THF and acetone, apart from the 1:1 GA-SM combination, with water should be the reason for the formation of hydrates under ambient conditions for those cases.

To see whether the common supramolecular motifs found in the solvates are modular and translate into their ability for solvent exchange, we have performed solvent exchange experiments on the 1:1:1 GA-SM hydrate, 1:1:1 GA-SM–14D and 3:3:1 GA-SM–EtOAc, independently. Since isolating single crystals of solvates has been cumbersome because of concomitant crystallization, bulk powders were used for the experiments. Each of the solvate powder materials was subjected to independent vapor diffusion (as detailed in the Experimental section) and LAG experiments with other solvents (1:1:1 GA-SM hydrate with water and ethyl acetate; 3:3:1 GA-SM–EtOAc with water and 1,4-dioxane) and analyzed by PXRD. The transformation of a given solvate to another solvate was found to be facile and reversible. This confirms the robustness of T_homo-II units in the GA-SM combination to generate void-containing supramolecular assemblies for solvent incorporation, as well as solvent exchange. The final observation from these experiments is that the GA-SM combination displays an extensive hydration tendency along with ability to form several solvates.

C. Characterization of the 1:1 GA-SM co-crystal

The preferential formation of the supramolecular motifs based on the T_homo-II units as seen above seem to hinder the formation of the 1:1 GA-SM co-crystal under ambient conditions (even in solvent-less conditions of neat grinding; see

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**Fig. 4** The PXRD patterns of the 1:2 GA-SM neat ground and water/methanol/DMSO ground materials exhibit a complete match with the simulated X-ray diffraction pattern of 1:2 GA-SM co-crystal polymorph I.
Fig. 5  A tetrameric \(T_{\text{homo-II}}\) unit, composed of acid and imide homodimers, serves as a building block for a staircase network containing voids in 1:1 carboxylic acid–carboximide combinations. Water molecules are held in voids through O–H⋯O interactions and other solvents through C–H⋯O interactions in their respective solvates. Symmetry independent molecules are shown in different colors.
Fig. 2). The fact that nitrogen atmosphere facilitated the formation of the THF and acetone solvated co-crystals, which are otherwise inaccessible due to the hydration tendency of the GA-SM combination, led us to attempt neat grinding of the combination under nitrogen atmosphere to access the elusive 1:1 co-crystal. Our efforts have successfully resulted in the formation of a 1:1 co-crystal as evaluated by PXRD (Fig. 8), DSC & TGA (Fig. 9) analyses of the ground material. On the other hand, the higher stoichiometry solvated co-crystals viz. 2:2:1 GA-SM–THF/Act/H2O and 3:3:1 GA-SM–EtoOAc, which are in principle solvates of the 1:1 co-crystal, besides 1:1:1 GA-SM–H2O/14D, can lose their solvents and consequently generate a solvent-free 1:1 GA-SM co-crystal. DSC and TGA experiments were performed on the 1:1:1 GA-SM–H2O/14D and 3:3:1 GA-SM–EtoOAc solvates to know the possibility of generating a pure 1:1 GA-SM co-crystal at elevated temperatures. TGA plots of these solvates showed two-step weight loss events (one before 130 °C and another between 150–200 °C, Fig. 10) and DSC corroborated the events by showing two endothermic phase transitions followed by a common melting endotherm around 200 °C (Fig. 10). The first weight loss corresponds to loss of the respective solvent apparently leaving behind GA-SM in a 1:1 stoichiometry between 130–150 °C, after which, there was a weight loss that resulted in a non 1:1 stoichiometry. Controlled desolvation of the solvates was carried out in an oven at 130 °C for an hour and the resultant materials were analyzed by PXRD. Powder diffractograms of all the three heated materials were different from those of the starting materials (both solvates and pure components) and that of the 1:1 co-crystal obtained under nitrogen atmosphere (Fig. 8) but exhibited a complete match with each other (Fig. 11), illustrating that the desolvated solvates manifest a distinct phase. NMR purity check of the desolvated materials established their integrity as a 1:1 co-crystal. To further validate the formation of the 1:1 co-crystal, we grounded the material with an extra mole of SM and obtained 1:2 co-crystal polymorph I (Fig. 12) and...
Fig. 7 The PXRD patterns of the GA–SM solvate materials obtained upon grinding (blue traces) from respective solvents show a good match with the simulated X-ray diffraction patterns (red traces) of the corresponding solvated co-crystals. Peaks of simulated (110 K) and experimental (298 K) patterns at higher angles are offset to each other due to the temperature difference.

Fig. 8 The PXRD pattern of the 1:1 GA–SM ground material under nitrogen atmosphere (red) and of dehydrated 1:1:1 GA–SM–water (blue) are different from each other and are also distinct from that of GA (black), SM (brown) and the 1:1:1 GA–SM hydrate (green).
water-assisted grinding of the material resulted in 1:1:1 GA–SM–water. Altogether, it is interesting to note that even the 1:1 co-crystal, which had been elusive under ambient conditions, shows polymorphic behavior as per the PXRD and thermal analyses of the materials obtained under nitrogen atmosphere and by desolvation.

D. Third polymorph of the 1:2 GA–SM co-crystal

Interestingly, attempts to establish the stability relationship between the dimorphs of the co-crystal led to the discovery of a third polymorph. Polymorph I was harvested as the major product from various crystallization experiments and polymorph II was obtained in small quantities from DMF and DMSO mediated crystallization (Table 1). This observation, apart from lattice energy calculations (see Table 2), supports the kinetic nature of polymorph I as well as the stable nature of polymorph II based on the generality that high boiling point solvents tend to facilitate the formation of stable polymorphs. Carboxylic acid dimers and multiple O–H⋯O interactions involving imide carbonyl acceptors in polymorph II as compared to single-point interactions in polymorph I.
seem to lower the energy of the former, which is $\sim 3$ kcal mol$^{-1}$ more stable than that of the latter (Table 2). DSC, which is known to deduce the thermal stability order among polymorphs,$^{15}$ was carried out on both polymorphs. Polymorph I showed an endothermic transition around 144 °C just before melting (158 °C), whereas polymorph II showed clean melting (Fig. 13a). However, the TGA plot of polymorph I showed no weight loss (Fig. 13a) thus indicating possible polymorphic transformation and no solvent loss or sublimation. When the polymorph was subjected to a high heating rate, which minimizes polymorphic transformations, its pure melting event was observed (black trace in Fig. 13a). It was found to have a lower heat of fusion ($\sim 8$ kJ mol$^{-1}$ or 2 kcal mol$^{-1}$) compared to polymorph II ($\Delta H_{\text{fus}} = 47.4$ vs. 55.5 kJ mol$^{-1}$; Table 4), thus establishing polymorph II as the stable form. A heat–cool cycle DSC experiment on polymorph I showed reversible phase transition with an exothermic peak (cooling run) in the same temperature regime as that of the endothermic peak (heating run, Fig. 13b). This suggests the formation of a high temperature phase, a third polymorph of the 1 : 2 GA–SM co-crystal. This new polymorph, designated as polymorph III, is thus formed from polymorph I and only exists at a high temperature. The melting peak observed in the DSC plot of polymorph I (red trace in Fig. 13a) therefore corresponds to melting of polymorph III. Establishing enantiotropy/monotropy among the polymorphs has several cautions in the literature$^{10f,15,16}$ and will be unambiguous only when the DSC measurements are performed under uniform and rigorous conditions for all the polymorphs considered. Herein, since different heating rates were applied for different polymorphs and polymorph II could not be reproduced for more experimentation, we refrain from establishing an enantiotropic/monotropic relationship as the interpretation with limited data is prone to erratic conclusions. Based on the heat of fusion values obtained (Table 4), the stability order of the polymorphs at 0 K can be inferred as II (most stable) $> I >$ III (least stable).

Conclusions

Crystal form diversity in terms of polymorphs and pseudopolymorphs of the GA–SM co-crystal along with its variable stoichiometry co-crystals has been extensively studied. A rare phenomenon of concomitant solvation for the 1 : 2 GA–SM co-crystal, apart from its concomitant polymorphism, was encountered. Further, the hydration/solvation tendency of the 1 : 1 co-crystal makes it elusive to be obtained in a pure state from routine crystallization experiments. Starting with the supramolecular building blocks for the GA–SM combination, the structural reasons for the concomitant solvation and polymorphism of the 1 : 2 co-crystal and hydration/solvation of the 1 : 1 co-crystal were uncovered. Furthermore, several
Experimental section

Materials

Commercially available compounds (Sigma-Aldrich, Bengaluru, India) were used without further purification. Solvents were of analytical or chromatographic grade and purchased from local suppliers. Water purified from a Siemens Ultra Clear water purification system was used for experiments.

Methods

Grinding. Compounds in molar ratios combined on the 100 mg scale were subjected to both neat and liquid-assisted grinding for 15 min using a mortar-pestle. Nitrogen atmosphere for grinding experiments was created by discharging ultra high pure nitrogen through a big funnel connected to a line inside a fume hood.

Evaporative crystallization. Ground mixtures of the GA–SM combination were kept for crystallization under ambient conditions in different solvents viz. methanol, ethanol, acetone (Act), THF, 1,4-dioxane (14D), acetonitrile, EtOAc, DMF, DMSO, etc.

Table 4 Thermal data of the 1:2 GA–SM co-crystal polymorphs

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>Heating rate (°C min⁻¹)</th>
<th>Tm (°C)</th>
<th>ΔH fus (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100</td>
<td>165</td>
<td>47.4</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>161</td>
<td>55.5</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>158</td>
<td>44.4</td>
</tr>
</tbody>
</table>

Fig. 13 (a) DSC plots of the 1:2 GA–SM co-crystal polymorphs I (red: @ 5 °C min⁻¹; black: @ 100 °C min⁻¹) and II (blue: @ 5 °C min⁻¹). The small endotherm at 144 °C in polymer I (red) indicates polymorphic transformation before melting (158 °C) since there is no weight loss in the TGA plot (magenta) pertaining to endothermic transition. DSC of polymer I at a high heating rate (black) resulted in its melting at 165 °C. Polymorph II (blue) shows clean melting at 161 °C. (b) The heat–cool–reheat DSC plot of the 1:2 GA–SM co-crystal polymorph I shows endo–exo–endo peaks pertaining to reversible polymorphic transformation to a high temperature phase which actually melts at 158 °C (red trace).

In this case with regard to crystal morphology and irreproducibility.

Three: 1 GA–SM–EtOAc. A ground mixture of GA (17 mg, 0.1 mmol) and SM (10 mg, 0.1 mmol) was dissolved in 5 mL of ethylacetate. Colorless block crystals of the solvate were obtained concomitantly along with colorless needles of 1:2 GA–SM co-crystal polymorph I after a few days upon solvent evaporation.
Vapor diffusion experiments

100 mg of each of the solvate powder materials was spread in a Petri plate and exposed to vapors of other solvents (5 mL, contained in a beaker) inside standard glass desiccators (1:1:1 GA-SM hydrate independently with 1,4-dioxane and ethyl acetate; 1:1:1 GA-SM-14D with water and ethyl acetate; 3:3:1 GA-SM-EtOAc with water and 1,4-dioxane). The materials were left undisturbed until complete evaporation of the solvent and later were analyzed by PXRD for any transformation to other solvates.

Single crystal X-ray diffraction

X-ray reflections on suitable single crystals were collected on an Oxford Xcalibur (Mova) diffractometer equipped with an EOS CCD detector and a microfocus sealed tube using Mo Kα radiation (λ = 0.71073 Å). Low temperature data collection was performed using an Oxford Cobra open stream non-radiation (EOS CCD detector and a microfocus sealed tube using Mo Kα). X-ray reflections on suitable single crystals were collected on an Oxford Xcalibur (Mova) diffractometer equipped with an X-ray detector and a microfocus sealed tube using Mo Kα. Single crystal X-ray diffraction experiments were performed using CrysAlisPro (version 1.171.36.32)17 and OLEX2 (version 1.2)18 was used to solve and refine the crystal structures. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on O and N were located from difference electron density maps and all C–H atoms were fixed geometrically using HFIX command. The WinGX package19 was used for final refinement and production of CIFs and crystallographic parameter table. The 3:3:1 GA-SM-EtOAc solvate showed a positional disorder with respect to carbonyl oxygen of the solvent molecule which was resolved by refining it with an occupancy of 90:10. The oxygen atoms of the solvent molecules were kept isotropic during the refinements.

Powder X-ray diffraction

PXRD was carried out on a PANalytical X’Pert diffractometer using Cu-Kα X-radiation (λ = 1.54056 Å) at 40 kV and 30 mA. X’Pert HighScore Plus (version 1.0.d)20 was used to collect and plot the diffraction patterns. Diffraction patterns were collected over a 2θ range of 5–40° using a step size of 0.06° 2θ and time per step of 1 s.

NMR spectroscopy

Solution state 1H NMR spectroscopy was carried out on a Bruker Avance spectrometer at 400 MHz using DMSO-d₆ as solvent.

1:1 GA-SM: δ (ppm): 2.55 (4H, s), 6.90 (2H, s), 8.77 (1H, s), 9.13 (2H, s), 11.03 (1H, s), 12.17 (1H, s).

Thermal analysis

DSC was performed on a Mettler Toledo DSC 822e module and TGA was performed on a Mettler Toledo TGA/SDTA 851e module. High heating rate (100 °C min⁻¹) DSC experiments were performed on a Mettler Toledo DSC 1 module. The typical sample size is 1–3 mg for DSC and 3–5 mg for TGA. The temperature range used in both DSC and TGA is 25–350 °C, and the samples were heated at 5 °C min⁻¹. The samples were placed in crimped but vented aluminum pans for DSC and in open alumina pans for TGA and were purged by a stream of dry nitrogen flowing at 50 mL min⁻¹.

Packing diagrams

X-Seed was used to prepare the packing diagrams.21

Lattice energy calculations

The lattice energy of a molecular crystal is the energy difference between the total energy of the unit cell and the isolated single molecule in the gas phase. It corresponds to the packing energy due to the interactions among the molecules in the crystal. For comparatively rigid molecules (i.e. those having an almost similar geometry in the gas phase and in the crystal), the cohesive energy expression reduces to:

\[ E(\text{lattice energy}) = \Delta E(\text{cond}) + BSSE, \]

where,

\[ \Delta E(\text{cond}) = E(\text{bulk})/Z - E(\text{mol, bulk}), \quad BSSE = E(\text{mol, bulk}) - E(\text{mol, ghost}) \]

The terms have the following meanings:

- \( E(\text{bulk}) \) = Total energy of the unit cell and must be referred to as the value of \( Z \) (\( Z \) = the number of molecules in the unit cell).
- \( E(\text{mol, bulk}) \) = Energy associated with a single molecule having the same geometry as that in the bulk.
- \( E(\text{mol, ghost}) \) = Calculated energy of a single molecule with an augmented basis set by using ghost functions on the surrounding atoms.

These calculations were carried out on 1:2 GA-SM co-crystal polymorphs I & II using CRYSTAL09 at the DFT (B3LYP) level of theory using the 6-31G** basis set.22 The calculations were performed using the coordinates obtained from the experimental X-ray crystal structures of the polymorphs of determined at 130 K and 110 K, respectively. The X–H bonds were neutron normalized prior to calculations.

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Notes and references


16 Several cautions in establishing enantiotropy/monotropy between the polymorphs observed in the literature\textsuperscript{19,15} are: (i) routine DSC measurements, which are generally done from room temperature and using 10 K min\textsuperscript{-1} heating rate, suffer from bias since phase transition can be at a low temperature or may be unobserved because of the slow transition rate; (ii) the slope/curvature of a typical phase diagram is a schematic and can be skewed such that the ‘heat of fusion rule’\textsuperscript{15b} for establishing thermodynamic stability is not universal and exceptions are possible; (iii) melting temperatures of different polymorphs obtained from different heating rates cannot be compared and considered for establishing polymorphs as low/high melting ones. This is because different rates of heating can give different melting temperatures for the same polymorph such that interpretation from ‘heat of fusion rule’ becomes ambiguous. However, heat of fusion values integrated for different heating rate DSC measurements remain almost same and therefore can be used to establish a stability order among polymorphs.


21 L. J. Barbour, X-Seed, Graphical Interface to SHELX-97 and POV-Ray, Program for Better Quality of Crystallographic Figures, University of Missouri-Columbia, Columbus, MO, 1999.