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Article

Assessment of Co-sublimation for the Formation of Multicomponent Crystals

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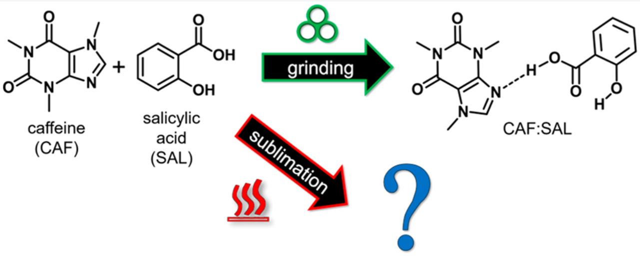

ABSTRACT: The merits of co-sublimation and mechanochemistry as screening techniques for multicomponent crystal formation are compared. Several multicomponent crystals that can be formed both mechanochemically and by sublimation are investigated, allowing for a comparison between the relatively unknown technique of co-sublimation and a well-known, robust solid-state screening methodology. This work aims to determine the general utility and versatility of co-sublimation in the preparation of multicomponent crystals. Co-crystals and salts, as well as their polymorphs, have been investigated, and problems that can arise due to sublimation temperature differences, isomerization, and degradation are discussed. Co-sublimation is shown to be a valuable co-crystallization technique for the discovery and identification of new multicomponent materials.

INTRODUCTION

A multicomponent crystal forms when two or more different molecules or ions solidify together as a crystalline single-phase material. When such a material contains only neutral components in a stoichiometric ratio, it is called a co-crystal.[1] When the components are charged, such as when a hydrogen atom shifts from an acid to a base, a salt is formed. Such an ion pair may also crystallize alongside the neutral conjugate form of either the acid or the base, in which case, the material can be called a co-crystal salt.[2] Multicomponent crystals are of significant interest due to the potential improvement of physical properties they may offer over the single-component material.[3] A multicomponent material can have different mechanical properties,[4] optical properties,[5] thermal stability,[6] or reactivity[7] when compared to its constituent species. The discovery of new multicomponent forms is therefore an important step in the development of new materials.

In order to identify new multicomponent forms, a molecule of interest will often be co-crystallized with a large number of other organic molecules, called coformers. Such systematic multicomponent screening tests need to be simple, fast, and efficient. Solution crystallization is perhaps the most widely used co-crystallization methodology; however, mechanochemical grinding has been shown to require less time and effort[8] and be more effective when it comes to screening for multicomponent crystals.[9,10] To carry out mechanochemical screening, the two components are either ground together by hand in a mortar and pestle, or milled mechanically. A small amount of solvent can be added to speed up the reaction (liquid-assisted grinding; LAG) and the transformation usually does not take longer than 30 min.

A number of other crystallization[11−13] and computational[14,15] techniques have been employed for the screening of potential multicomponent crystals; however, due to the large number of variables, one can never be sure whether all solid forms have been identified. It is possible that multicomponent crystal forms exist that are not detected due to biases imposed by the techniques themselves. For instance, two coformers may not be soluble in the same solvents, which would inhibit their interaction and co-crystallization when solution-based techniques are used. It has also been shown that the solvent used can favor, or disfavor, specific types of intermolecular interactions.[16,17] Therefore, if all multicomponent forms are to be discovered, it is important that a variety of crystallization techniques are used.[10] This led us to study crystallization by sublimation as an alternative to the standard solution-based crystallization techniques.

Co-sublimation of neutral components to yield multicomponent crystals has not been studied in great depth, and when used, it is often simply reported as an inconsequential detail—the general versatility and practicality of this technique has not been discussed. During co-sublimation, neutral components are simultaneously sublimed so that they may interact in the gas phase and crystallize as the multicomponent form. A limited number of co-crystals have been formed by co-

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Scheme 1. Summary of the Coformers Used for the Multicomponent Crystallizations, as Well as Their Predicted Vaporization Enthalpies at 101.325 kPa[23]

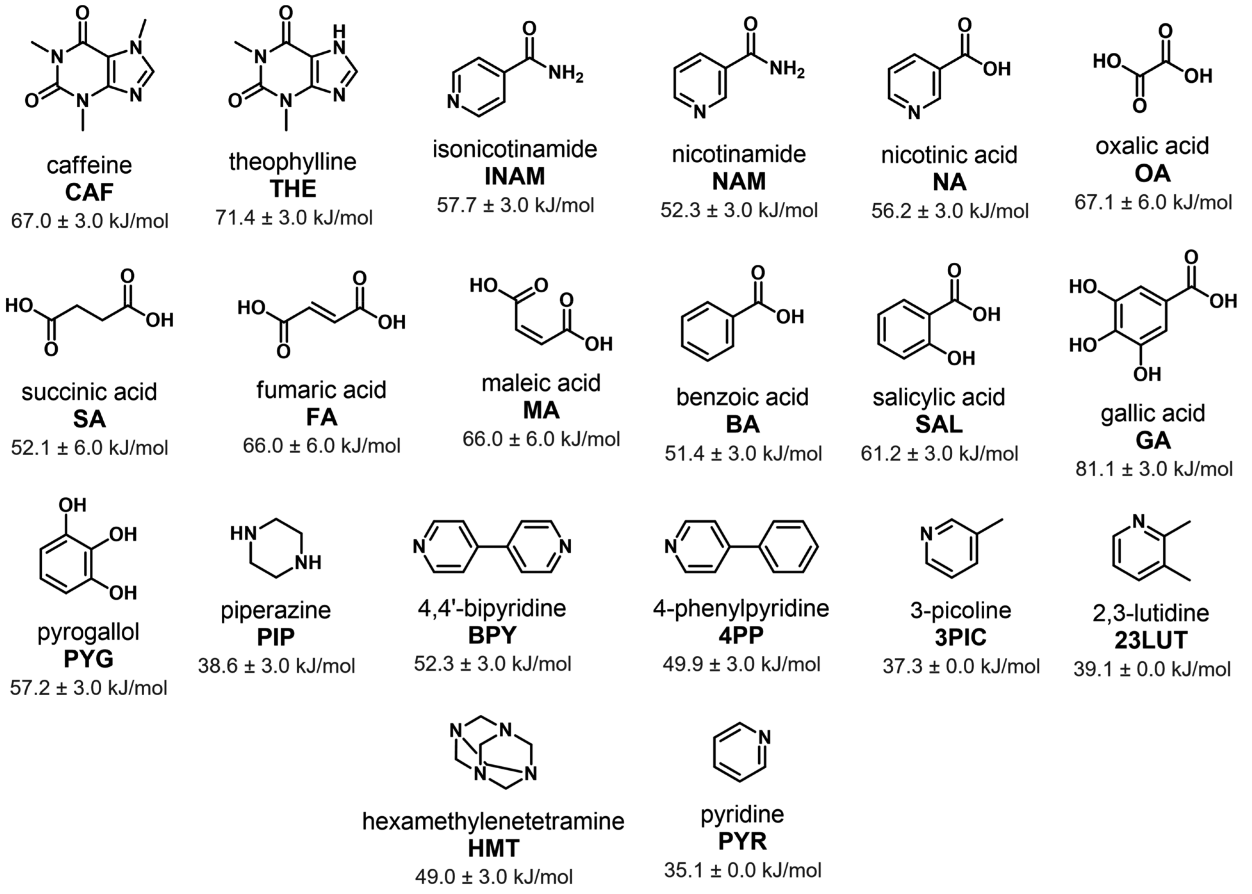

Table 1. Summary of the Multicomponent Crystals Investigated, Which Includes the Sample Code Used in This Report, the Coformers, Stoichiometry, Classification in Terms of Ionization, and the Temperature Used for Crystallization by Co-sublimation (T_{subl})

code	coformers		classification	T_{subl} (°C)	code	coformers		classification	T_{subl} (°C)
1	CAF	SAL	1:1 co-crystal	140	**9a**	SA	PIP	2:1 salt	NA
2	CAF	OA	2:1 co-crystal	120	**9b**	SA	PIP	1:1 salt	140
3	THE	SAL	1:1 co-crystal	140	**10**[a]	MA	PYR	1:1 salt	120
4	THE	OA	2:1 co-crystal	160	**11a**	FA	PYR	1:2 co-crystal	120
5	THE	INAM	1:1 co-crystal	120	**11b**[a]	FA	PYR	1:1 co-crystal salt	170
6a	FA	23LUT	1:2 co-crystal	140	**12a**	FA	3PIC	1:2 co-crystal	NA
6b I	FA	23LUT	2:1 co-crystal salt	140	**12b**[a]	FA	3PIC	1:1 co-crystal salt	130
6b II[a]	FA	23LUT	2:1 co-crystal salt	140	**13**	NA	OA	1:1 salt	120
7 I	NAM	BA	1:1 co-crystal	100	**14**	PYG	HMT	1:1 co-crystal	110
7 II	NAM	BA	1:1 co-crystal	100	**15**	GA	4PP	1:1 salt	NA
8	MA	BPY	2:1 salt	100	**16**[a]	PYG	4PP	1:1 co-crystal	190

[a]These crystal structures are presented here for the first time.

sublimation,[18−22] and we have recently shown that molecular salts and co-crystal salts can easily be formed by sublimation as well.[19] We generally employ a very simple sublimation strategy: an evacuated Schlenk tube containing a mixture of starting materials is heated using an oil bath. The use of more sophisticated apparatus may improve the outcome of co-sublimation experiments and produce higher yields. However, our goal in this work was not to perfect the formation of a particular co-crystal, but rather to study a wide variety of systems so that some general observations can be made regarding the technique of co-sublimation itself.

In this study, we report on the co-crystallization of 16 combinations of common organic molecules (Scheme 1, Table 1) by mechanochemistry (neat- and liquid-assisted grinding) and co-sublimation in order to determine how these techniques compare. Can sublimation compete with a robust screening technique such as mechanochemistry? Does crystallization by sublimation offer any advantage over other methods? Common problems that can be encountered during co-sublimation will be discussed, as well as how they can potentially be overcome.

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■ EXPERIMENTAL SECTION

Compounds were purchased from Sigma-Aldrich and used without further purification (Scheme 1).

Mechanochemistry. A FTS1000 Shaker Mill from Form-tech Scientific was used for mechanochemical experiments, which were performed using two 15 mL stainless steel grinding jars each with two 6 mm steel balls as the milling medium. Milling was carried out either without any solvent (neat) or with the addition of a small amount of solvent (η = 0.25 μL mg^{-1}), added with a micropipette. Unless otherwise stated, samples were milled at room temperature for 20 min at 20 Hz.

Co-sublimation. Co-sublimation was carried out by simultaneously subliming the starting materials in a Schlenk tube, with a physical mixture of the starting materials placed together at the bottom of the tube. The sublimation tube was evacuated (0.6 mbar line pressure) and the end containing the coformers heated in an oil bath. In most cases, a thin Schlenk tube (14 mm diameter, 220 mm length) was used so that a temperature gradient formed along the sides of the tube, along which crystals could deposit depending on their vapor pressure (usually within a few hours). This temperature gradient resulted in products crystallizing in separate bands, allowing for easy removal of pure materials. In some cases, sublimation was carried out using a larger Schlenk tube equipped with a water-cooled cold finger on which crystals could grow.

Re-sublimation. The term re-sublimation is used to describe the recrystallization by sublimation of pre-formed multicomponent material. This is distinct from co-sublimation, where unreacted coformers are sublimed. Experimentally, re-sublimation was carried out in a similar manner to co-sublimation. Instead of unreacted neutral starting materials, the pre-formed multicomponent materials (formed by grinding) were added to the tube and sublimed to form crystals of the multicomponent materials.

Powder X-ray Diffraction. Powder X-ray diffraction (PXRD) was carried out at room temperature using a Bruker D2 Phaser benchtop diffractometer equipped with a copper radiation source (λ = 1.54183 Å) and operating at 30 kV and 10 mA. Powdered samples were loaded onto a zero-background holder and data collected in the range of 2θ = 4−40° at a speed of 0.5 s per scan (0.016° step size). Data analysis was carried out using X'Pert HighScore Plus.[24]

Single-Crystal X-ray Diffraction. Single-crystal X-ray diffraction (SCXRD) was carried out using a Bruker Duo diffractometer equipped with a CCD area detector and an Incoatec IμS microsource coupled with a multilayer mirror optics monochromator. Data were collected at room temperature or 100 K, with the temperature being controlled by an Oxford Cryosystems Cryostat (700 Series Cryostream Plus). Single crystals were irradiated (MoKα, λ = 0.71073 Å) and data collected and reduced using the Bruker software package SAINT,[25] operated through the Apex3 software. Data were subsequently corrected for absorption and other systematic errors using SADABS.[26,27] Crystal structures were solved using direct methods (SHELXT-18)[28] within the graphical user interface XSeed,[29,30] and then refined using SHELXL-18.[31] All atoms (except hydrogen atoms) were refined anisotropically. Hydrogen atoms bonded to carbon atoms were placed in calculated positions using riding models, while O-H and N-H hydrogen atoms were located using electron density maps and their positions allowed to refine. Images were created using POV-ray,[32] as visualized within XSeed.[29,30]

IR Spectroscopy. Fourier Transform Infrared spectroscopy (FTIR) was carried out using a Bruker Alpha P spectrometer with a Platinum ATR attachment.

■ RESULTS AND DISCUSSION

A number of multicomponent materials formed from small organic molecules were investigated (Table 1). Results are discussed below grouped according to either the type of multicomponent material or the type of molecules used. In all cases, co-crystallization was attempted by mechanochemical grinding using a ball mill, and by vacuum sublimation. Products were analyzed by PXRD and, where possible, SCXRD. The majority of the crystal structures have been reported previously; however, five new multicomponent materials were identified (Table 1), and their crystal structures determined. Full experimental details and information regarding these crystal structures are given in the Supporting Information.

Simple Co-crystals. A series of known co-crystals containing the xanthines caffeine (CAF) and theophylline (THE) were investigated (Figure 1). These co-crystals were straightforward to synthesize by both mechanochemistry and co-sublimation. The starting materials do not degrade, and their sublimation temperatures are comparable, such that there exists a temperature at which both sublime at a similar rate, ensuring the coformers are in the gas phase simultaneously. The co-crystallization of caffeine and salicylic acid is described here as a representative example. Co-crystals **2**−**5** can be formed in a similar manner; details are reported in the Supporting Information.

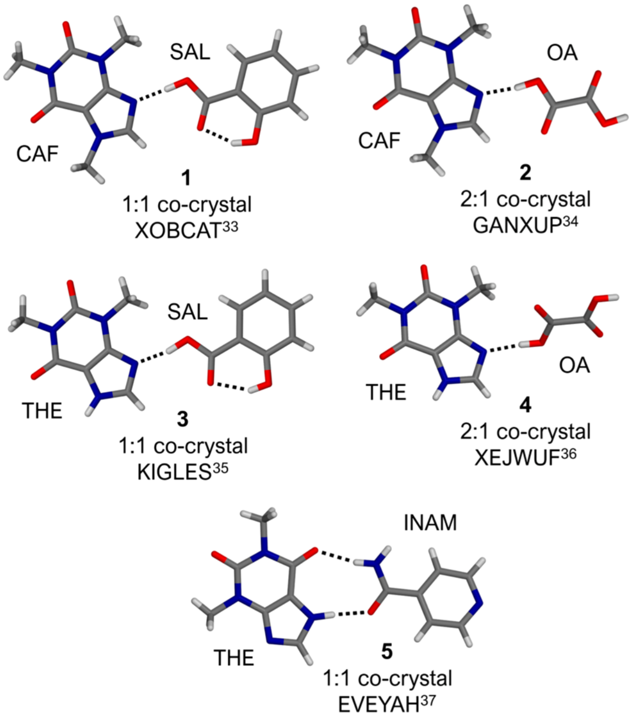

Figure 1. Hydrogen bonding between coformers in the crystal structures of co-crystals **1**−**5** formed by caffeine and theophylline. Images were generated from crystal structures deposited in the Cambridge Structural Database; refcodes are indicated with references to the literature.[33−37]

CAF and SAL. The combination of CAF and SAL produced a 1:1 co-crystal (**1**) in all experiments. Grinding a 1:1 molar ratio of caffeine and salicylic acid without the addition of solvent led to the formation of **1** in quantitative yield. Co-sublimation of the two starting materials (1:1 molar ratio) *in vacuo* in a Schlenk tube at 140 °C (a temperature at which both compounds sublime rapidly) yielded a powder of the co-crystal in between bands of CAF and SAL crystals (Figure 2). While the amount of **1** that formed was relatively small, the three crystallization zones did not overlap, and pure co-crystal powder could be collected for identification via PXRD (Figure 3).

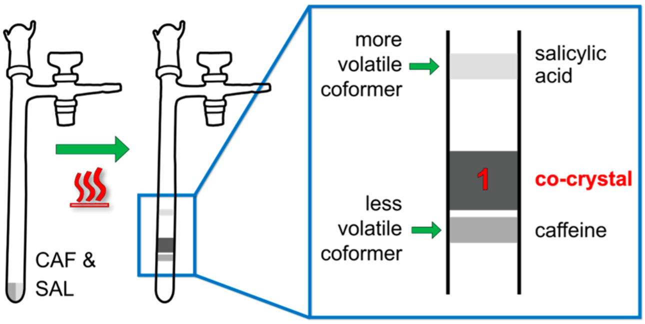

Figure 2. Schematic representation of the co-sublimation of CAF and SAL in a Schlenk tube, which yielded a powder of the co-crystal in between bands of CAF and SAL crystals.

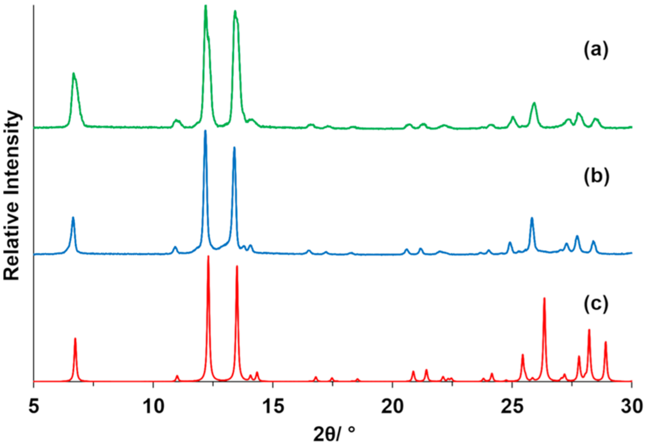

Figure 3. Experimental powder patterns of **1** obtained from (a) co-sublimation and (b) neat grinding, compared to (c) the pattern simulated from single-crystal data obtained from the CSD (refcode: XOBCAT).[33]

Co-crystals **2**−**5** could be prepared by co-sublimation in a similar fashion. From these simple co-crystallizations, we observe a general trend. When two starting materials are combined using co-sublimation the more volatile component crystallizes high up in the sublimation tube, in the coolest region. The least volatile component crystallizes lower down in the tube where it is warmer, and the co-crystal crystallizes between these two limits. The three crystallization zones do not usually overlap, allowing the collection of pure co-crystal from these experiments.

In the case of **1**−**5**, the co-crystals obtained by co-sublimation are equivalent to those formed mechanochemically. They were quick to form, and in each case, co-sublimation was successful on the first attempt, provided a suitable sublimation temperature, at which both components can sublime, was chosen.

Polymorphic Systems. Molecules can often arrange in more than one way when they solidify, and thereby form polymorphs. Even though such polymorphs contain the same components, they can differ with regard to their physical properties.[38] Unfortunately, regulating which form is obtained is not always easy. It is possible to selectively isolate a particular polymorph of a pure- or multicomponent material when carrying out crystallizations in solution or mechanochemically, by altering variables such as the temperature and the solvent used.[39−41] It is also possible to selectively obtain polymorphs of molecular materials when using sublimation, particularly by using additives[42] and controlling the temperature of the area where de-sublimation occurs.[43,44] To our knowledge, the use of sublimation to selectively prepare a specific multicomponent crystal polymorph has not been reported. Two sets of multicomponent polymorphs will be presented here to compare their formation using solid-state and gas-phase techniques.

FA and 23LUT. The combination of fumaric acid and 2,3-lutidine is known to form a 1:2 co-crystal (**6a**) and a 2:1 co-crystal salt (**6b I**) (CSD refcodes: RESFOL and RESFIF).[45] Using co-sublimation, we discovered that a second polymorph of the co-crystal salt, **6b II**, could also be produced. Due to the similarities between these materials, the crystal structures of **6a** and **6b I** were re-determined along with that of **6b II**.

The crystal structure of **6a** comprises hydrogen-bonded base-acid-base trimers, while the co-crystal salts (**6b I** and **6b II**) are made up of infinite hydrogen-bonded nets of FA and FA$^-$ with pendant cations (Figure 4). In both **6b I** and **6b II**, each hydrogen fumarate ion forms an additional charge-assisted hydrogen bond with a lutidinium cation which is positioned inside each of the apertures in the nets (Figure 4). Two of these nets pair up to form a bilayer such that the apertures align. Each of these holes in the bilayers is then filled with two cations, one bonded to each net. The layers exist in both polymorphs, and they are identical in this regard. However, the way in which the layers stack is slightly shifted in each form (Figure 4).

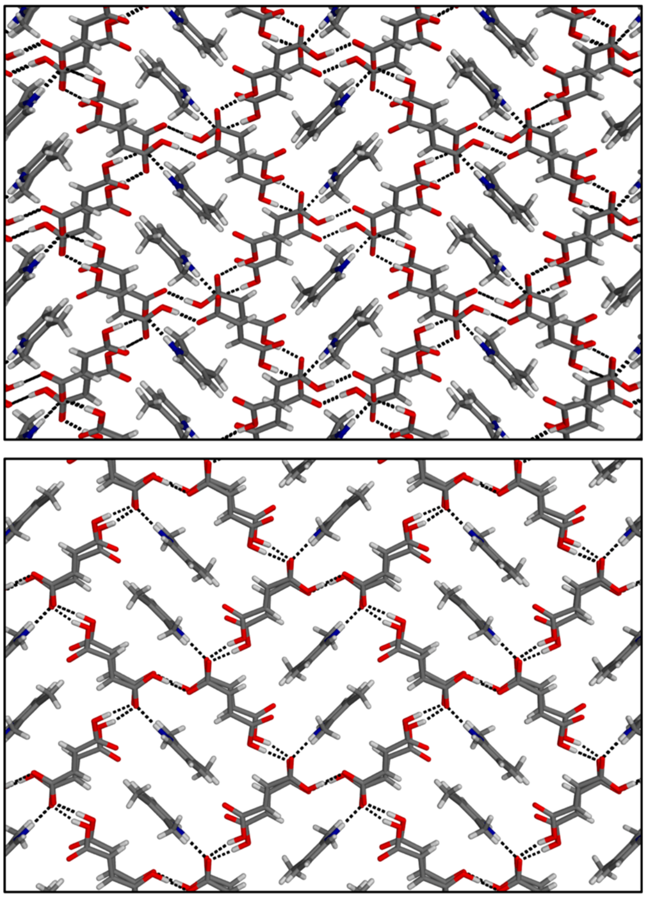

Figure 4. Packing diagram for **6b I** (top) and **6b II** (bottom), both viewed along [100]. Each polymorph is made up of identical layers that differ in how they stack.

All three crystal forms were produced mechanochemically, but not as pure materials. Co-crystal **6a** was obtained by milling a 1:2 ratio of FA and 23LUT; however, using a 2:1 ratio led to formation of both polymorphs **6b I** and **6b II** simultaneously (with the peaks for **6b II** in the powder pattern being much less prominent) (Figure S7). Additionally, when ground, **6b II** partially converted to **6b I**—even during preparation of a powdered material for PXRD. This makes sense considering the polymorphs only differ by a slight shift of the layers within their structures. However, the transformation did not proceed to completion; some **6b II** remained even after 3 h of milling.

Heating FA and 23LUT together under vacuum produced all three forms by sublimation. Different ratios of starting materials were used, but this did not appear to have an effect on the product obtained, and co-sublimation of these molecules most often produced a mixture of **6b I** and **6b II**, as single crystals, irrespective of the ratios used. On occasion, these crystals were accompanied by a powder of **6a** (Figure 5).

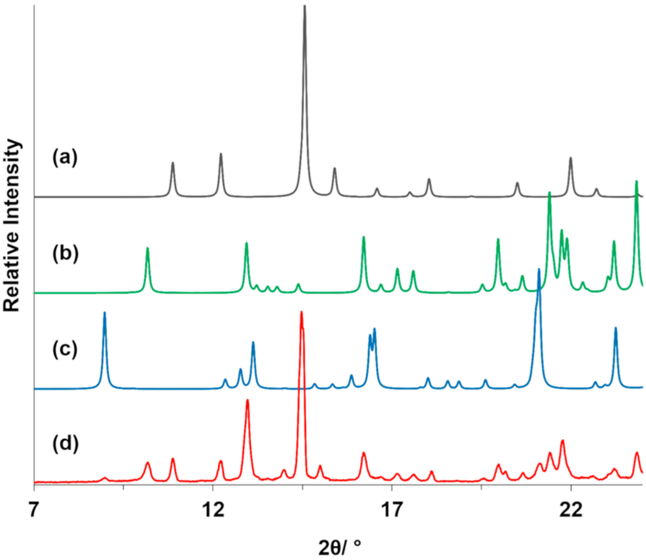

Figure 5. Simulated powder diffraction patterns for (a) **6a**, (b) **6b I**, and (c) **6b II**. A mixture of these three forms can be obtained by co-sublimation (d).

It should be noted that single crystals of all three forms were also obtained from solution, also as mixtures that mostly contained only **6b I** and **6b II** (crystals of **6a** were obtained only once). The same was observed during re-sublimation of pre-formed **6a**, **6b I**, and **6b II**, i.e., crystals of the two polymorphs formed, occasionally accompanied by the co-crystal.

NAM and BA. The combination of nicotinamide and benzoic acid is known to form two 1:1 co-crystal polymorphs (**7 I** and **7 II**) (CSD refcodes: GAZCES and GAZCES01).[46] Lukin *et al.* reported two further polymorphs that could be obtained mechanochemically; however, their structures have not been determined.[46] In both polymorphs, **7 I** and **7 II**, the carboxylic acid functional group of BA forms a hydrogen bond to the pyridine nitrogen atom of NAM. However, in **7 I**, the amide groups also hydrogen bond to form NAM dimers, while in **7 II**, the N−H and O of each amide interact with two different NAM molecules (Figure 6).

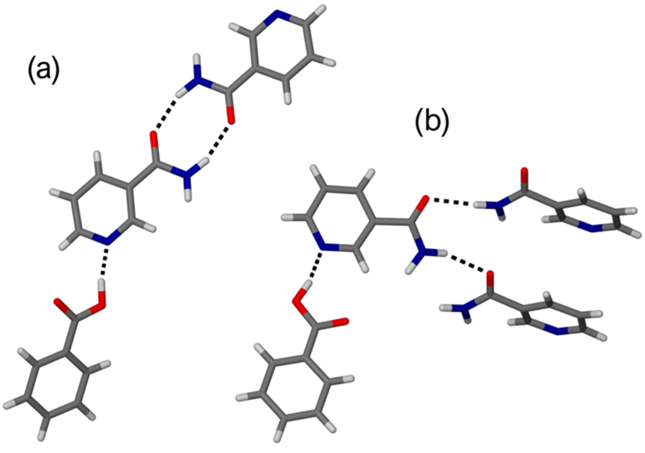

Figure 6. Hydrogen bonding in (a) **7 I** and (b) **7 II**. Images generated from published crystal structures.[46]

Co-subliming NAM and BA in a 1:1 molar ratio at 100 °C led to formation of polycrystalline **7 I** and **7 II**, as a mixture. BA and NAM crystallized above and below the multicomponent crystals, respectively. Conversely, depending on the solvent used, grinding a 1:1 molar ratio of these starting materials produced either **7 II** or a material with a PXRD pattern corresponding to a previously reported material for which the crystal structure has not been determined.[46] In the published study, more variables were explored (such as different solvent additives and milling duration) and the authors found that it was possible to form both **7 I** and **7 II** mechanochemically, and determined the crystal structures from powder diffraction data.

In general, we have observed that co-sublimation can be used for the formation of polymorphic multicomponent crystals, but not in a selective manner—mixtures of polymorphs are obtained. Sublimation apparatus which allows for more precise control over temperature may be useful in this regard. However, polymorphs that are not easily identified in an initial series of LAG screening experiments can be identified using co-sublimation. These may form as powders, but, as we see in the case of **6b I** and **6b II**, can also sublime as single crystals. Co-sublimation could therefore be useful both for the identification of polymorphs and for the determination of their crystal structures.

Co-crystallization When Molecules Have Different Sublimation Temperatures. For multicomponent crystals to form by co-sublimation, the coformers need to encounter one another in the gas phase. However, the components to be co-sublimed need not have the same sublimation temperature for there to be enough of each present in the gas phase. Often, as in the previous examples, each coformer crystallizes separately from sublimation, with the multicomponent material crystallizing in between them. However, if one coformer has a much lower sublimation temperature than the other, it may sublime and crystallize as the molecular material completely separately from the other component.

Fortunately, it is possible to modify the amount of each component present in the gas phase to some extent. The simplest way to go about this is by changing the relative amounts of the starting materials used as this will influence the relative amounts of each coformer in the gas phase during the initial stages of co-sublimation. Technically, the amount of each component in the gas phase at equilibrium is only dependent on the vapor pressures of the solids, and not on the quantities used. However, because co-crystallization starts as soon as a sublimation experiment begins (as soon as heat is applied), the compound with the lower volatility may not reach equilibrium before co-crystallization occurs. Adding excess of the less volatile solid allows more of that coformer to enter the gas phase initially. Another possibility is to heat the coformers at two different temperatures, so that they sublime almost simultaneously; i.e., the vapor pressures of the two components are equalized. Such an example has been published recently where this technique was shown to be very effective.[22] It is also possible to control relative amounts of coformers in the gas phase by pre-forming the multicomponent material, with the desired stoichiometry, as a powder before sublimation is carried out. When this multicomponent material is re-sublimed under vacuum conditions, both coformers can potentially enter the gas phase simultaneously, in the correct ratio. In this case, sublimation has to be coupled with another technique, such as grinding, but it has the potential to form diffraction-quality single crystals. Three cases are reported here to demonstrate each of these approaches.

MA and BPY. The combination of maleic acid and 4,4′-bipyridine is known to form a 2:1 salt (**8**) from solution, the structure of which has been previously determined (CSD refcode: GIPQAX01).[47] This adduct was crystallized from solution; however, we observed that isomerization frequently occurred in solution so that a fumaric acid co-crystal formed instead. In our hands, salt **8** could be made mechanochemically by grinding a 2:1 ratio of MA and BPY, but when recrystallized from solution, the FA co-crystal formed instead. The simplest way of obtaining single crystals of **8** turned out to be co-sublimation, even though the starting materials differ greatly with regard to sublimation temperature (BPY sublimation starts at 50 °C and MA at 100 °C). When a 2:1 ratio of starting materials was used, the salt did not form, as BPY is too volatile compared to MA, and the starting materials sublimed separately. However, when a 4:1 molar ratio of MA:BPY was used, co-sublimation at 100 °C was successful and single crystals of the salt formed within 4 h. It is therefore possible for the gas-phase coformer concentration during co-sublimation to be altered by changing stoichiometry and using an excess of the least volatile starting material.

FA and 23LUT. The formation of co-crystal **6a** and the co-crystal salt polymorphs **6b I** and **6b II** were described earlier in this paper; however, it is pertinent to mention them again at this stage as the two coformers have vastly different volatilities. The vaporization enthalpy of FA is roughly 66.0 kJ mol^{-1}, compared to that of 23LUT, which is 39.1 kJ mol^{-1} (Scheme 1). Apparatus has been designed in our group that can be used to heat two compounds at two different temperatures under vacuum (Figure S13).[18] The apparatus consists of a U-shaped tube with a removable bulb at each end in which compounds are placed. The tube can be placed under vacuum and the bulbs suspended in adjacent oil baths or heating pockets so that each compound may be sublimed at the desired temperature. In this way, FA was sublimed at 200 °C, while 23LUT was vaporized at 40 °C, so that both compounds entered the gas phase simultaneously. The crystals that formed in the connecting tube could be identified by PXRD and unit cell determinations as **6b I** and **6b II** (Figure S14). Heating coformers at different temperatures is therefore another useful method of obtaining multicomponent crystals when vapor pressures differ.

SA and PIP. The combination of succinic acid and piperazine is known to form a 2:1 salt (**9a**) (CSD refcode: IMEZIL[48]) and a 1:1 salt (**9b**) (CSD refcode: BURWEQ[49]). Note that **9a** is classified as a co-crystal in the literature, but our structure determination indicates clearly that it is a salt: C−O bond lengths and FTIR indicate the presence of carboxylate groups. The crystal structures of **9a** and **9b** were re-determined for confirmation (Figure 7; details are given in the Supporting Information).

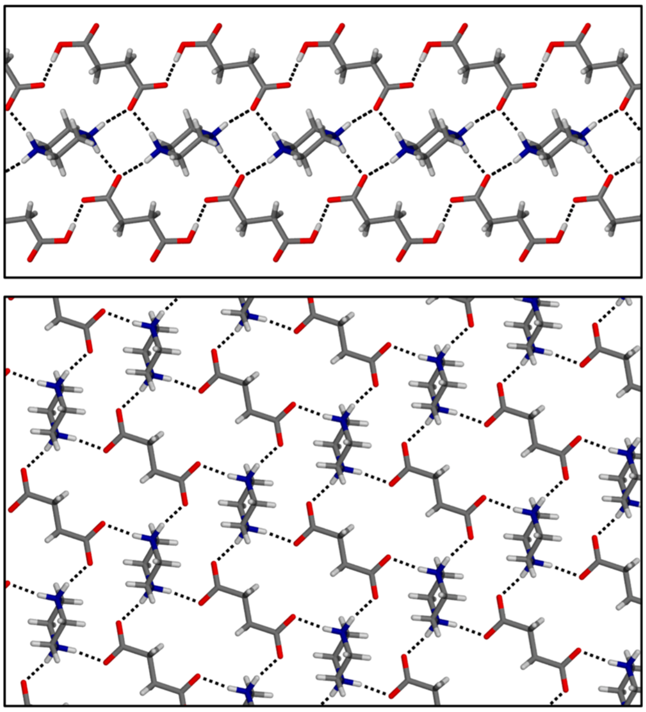

Figure 7. Top: Hydrogen-bonded ribbons in salt **9a** that run along the *a* axis. Bottom: Hydrogen-bonded layer in salt **9b**, viewed along [101].

Grinding SA and PIP in a 2:1 molar ratio (neat- or liquid-assisted), led to complete conversion to the salt **9a**, while the use of a 1:1 ratio led to the formation of **9b**. However, subliming a number of different molar ratios of SA and PIP at 120 and 140 °C (1:1, 2:1, and 4:1) led to the formation of single crystals of **9b** only. This may be a result of the differences in vapor pressure of the two coformers. PIP is very volatile and will even slowly sublime at room temperature. On the other hand, SA only sublimes at 110−120 °C, which is why co-sublimation was carried out at a higher temperature. At 120 and 140 °C, both compounds can sublime; however, PIP will always start to sublime faster than SA, with co-crystallization initiated before SA sublimation reaches equilibrium. This means that, as soon as SA sublimes, it immediately crystallizes with the PIP already present in the gas phase to form the 1:1 product (**9b**) instead of staying in the gas phase until SA is concentrated enough to form the 2:1 product. In other words, it is easier for the 1:1 salt to form than for the 2:1 salt that requires two SA molecules in the gas phase for every one molecule of PIP. Unfortunately, using an excess of succinic acid did not rectify the problem.

Fortunately, both **9a** and **9b** were able to re-sublime if pre-formed by grinding (**9a** at 160 °C and **9b** at 140 °C). When re-sublimed, **9a** recrystallized as **9a**, and **9b** recrystallized as **9b**, with some starting materials crystallizing separately. During re-sublimation of a multicomponent crystal, the components can vaporize individually. However, it is also possible that both coformers sublime simultaneously in either a 1:1 or a 2:1 ratio (in the case of **9a** and **9b**), so that either salt could in theory deposit again from the gas phase. In this case, the gas-phase stoichiometry is defined by the starting salts, and the volatility differences experienced during co-sublimation are no longer a limiting factor. Our previous work has indicated that some molecules or ions remain hydrogen bonded when they enter the gas phase.[19] If pairs or clusters of molecules specific to a particular material are retained in the gas phase, it would further drive crystallization of that material. This is possibly what is happening here too: we are not seeing interconversion between **9a** and **9b** in the gas phase; **9b** only re-sublimes as **9b**. Re-sublimation is therefore a viable alternative to co-sublimation if single crystals are desired.

Clearly, compound volatility and the compatibility of sublimation temperatures are important factors when growing multicomponent crystals by sublimation. Coformers need to be present in the gas phase in the correct stoichiometry for multicomponent crystals to form. Gas-phase concentrations can be manipulated to some extent by changing the ratio of starting material used, heating coformers at different temperatures, or by pre-forming multicomponent materials before sublimation so that the stoichiometry is pre-determined.

Co-crystallization When Coformers Can Isomerize. The formation of certain multicomponent crystals can be hindered by unwanted isomerization of the coformers.[50] For example, in solution, maleic acid isomerizes to fumaric acid in the presence of a base. It has been reported that a co-crystal between maleic acid and pyridine could not be obtained, as pyridine catalyzes the transformation of maleic acid to fumaric acid.[50] Mohamed *et al.* reported that they could not form a co-crystal or a salt with MA and PYR as this isomerization happened within a few hours, while crystals took a week to form. Isomerization in the gas phase may proceed differently than in solution, and sublimation may thus present a new synthetic pathway for multicomponent materials containing these types of coformers. Additionally, crystal growth and nucleation generally occur much faster during co-sublimation. Crystals usually form within a few hours, and so it may be possible to form a co-crystal with maleic acid before isomerization can occur. We have already discussed a salt containing MA and BPY (**8**)—this salt was easily formed by co-sublimation, while solution crystallization was often accompanied by a fumaric acid co-crystal due to isomerization. Here, we report three new co-crystals that were discovered by co-sublimation involving maleic acid.

MA and PYR. As previously stated, no known multicomponent forms of maleic acid and pyridine have been reported. Milling different ratios of MA and PYR led to the formation of a material with a PXRD trace not matching either starting material. Single crystals of this material, a new 1:1 MA-PYR salt (**10**), were obtained by sublimation. Heating a 1:1 mixture of the two starting materials in a large Schlenk tube *in vacuo* at 120 °C yielded single crystals of **10** on the cold finger after a few hours, and its crystal structure could be determined. Unfortunately, these crystals formed concomitantly with two other types of crystals. These were a 1:2 co-crystal between fumaric acid and pyridine (**11a**, CSD refcode: GUKWOZ)[50] and a new 1:1 co-crystal salt, also containing fumaric acid and pyridine (**11b**). Re-sublimation of the MA-PYR salt obtained from grinding led to the same three multicomponent products crystallizing.

When MA and PYR were combined in solution (using a variety of common organic solvents and mild heating to aid dissolution), they reacted covalently to form a zwitterionic molecule (CSD refcode: SUCPYR).[51] However, it was eventually also possible to crystallize **10** from solution when vials were placed in the refrigerator at 4 °C. Carrying out crystallizations at low temperature allowed crystals to form quickly (within 24 h), potentially trapping maleic acid before isomerization could occur.

FA and PYR. Grinding a 1:2 molar ratio of fumaric acid and pyridine led to crystallization of the new co-crystal salt that was mentioned above, **11b**. The co-crystal **11a** was never obtained from grinding; however, another unknown product was obtained when FA and PYR were milled in a 1:1 ratio. Sublimation of a 1:1 mixture of the two starting materials at 170 °C yielded a powder of this unknown product as well as single crystals of **11b**. It is interesting that crystals of **11a** (a fumaric acid:pyridine co-crystal) could be obtained when co-subliming MA and PYR, but not when subliming FA and PYR. The reason for this may be the observed higher sublimation temperature of FA (~140 °C) compared to MA (~100 °C).

MA and 3PIC. There are no multicomponent forms of maleic acid and 3-picoline reported in the CSD. Milling different ratios of MA and 3PIC together led to the formation of a powder with an unknown PXRD trace. Crystallizing these starting materials from solution (using common organic solvents) led to the formation of another powdered material with a PXRD trace not matching either starting material, or the unknown obtained from grinding. Neither of these unknown materials has been identified, but single crystals of a third material were finally obtained by co-sublimation at 130 °C. The crystal structure was determined, which identified the crystals as a new 1:1 co-crystal salt of 3-picoline and fumaric acid (**12b**). In the CSD, there is also a 1:2 co-crystal formed by FA and 3PIC (**12a**, refcode: MOGWAI).[52] Interestingly, when FA is dissolved directly in 3PIC, crystals of **12a** are obtained after 24 h, with no **12b** forming (similar to what was observed in the literature). When the powder pattern for **12b** was simulated, it did not correspond to either of the powdered materials obtained from mechanochemistry or solution crystallization of MA and 3PIC, and neither did **12a**. Thus far, **12b** has only been obtained by sublimation.

From these examples, it is clear that co-sublimation can be very useful for obtaining new multicomponent crystals. While isomerization does occur in the gas phase and in solution, the crystallization mechanism appears to be faster, potentially leading to the formation of different materials. It is also clear that the materials formed by mechanochemistry are not always the same as those formed by sublimation.

Salts by Co-sublimation. It seems unlikely that salts would form by sublimation, as ions would not be stable in the gas phase. However, our previous work has shown that salts can indeed crystallize by co-sublimation.[19] In this paper, so far a number of salts produced by co-sublimation have been presented. Specifically, the salts **8**, **9a**, **9b**, and **10** and the co-crystal salts, **6b I**, **6b II**, **11b**, and **12b** can all be obtained from co-sublimation of neutral coformers, and generally crystallize from sublimation as diffraction-quality single crystals. One further noteworthy example will be highlighted here.

NA and OA. Co-subliming a 1:1 molar ratio of nicotinic acid and oxalic acid for 7 h at 120 °C led to crystallization of a 1:1

salt containing the two coformers (**13**, CSD refcode: HEWWAI[53]) (Figure 8). The salt formed in quantitative yield, and no starting materials sublimed separately or remained unreacted. Grinding a 1:1 molar ratio of the starting materials together similarly produced **13** in quantitative yield. According to the literature, this salt can also be formed by crystallizing the coformers from solution; however, our experiments prove that co-sublimation can definitely also be used for the efficient production of a molecular salt.

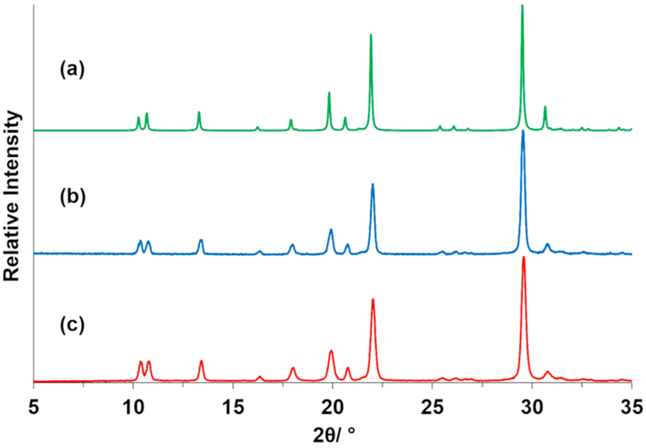

Figure 8. (a) Powder diffraction pattern for **13** simulated from single-crystal data obtained from the CSD (refcode: HEWWAI),[53] compared to experimental powder patterns of **13** obtained from (b) co-sublimation and (c) grinding.

Co-crystallization Using Heat-Sensitive Molecules. Not all coformers are well suited for co-sublimation, as some compounds can degrade or melt during heating. For example, maleic acid starts to degrade above 100 °C. Despite this, we have demonstrated its use in co-sublimation (see above). Being aware of the heat sensitivity of coformers is crucial in co-sublimation experiments, so that appropriate measures can be taken to overcome any degradation. When forming salt **8**, which contains MA, the temperature of co-sublimation had to be restricted to 100 °C. Co-crystallization was achieved by using specific ratios of starting materials to ensure sufficient amounts of each coformer in the gas phase. Of course, this will not always work—some co-crystals and salts cannot be formed by co-sublimation at all. Another potential solution to this problem is to reduce the pressure in the system, which would allow for sublimation to occur at a lower temperature. Problems involving heat-sensitive coformers can thus potentially be solved by generating a stronger vacuum, although this was not explored in this study. Further examples concerning heat-sensitive coformers are discussed below.

SA and PIP. Consider again the case of succinic acid and piperazine. It was determined that salt **9b** re-sublimed at 140 °C, while salt **9a** only re-sublimed at 160 °C. Additionally, during co-sublimation at 140 °C, salt **9b** was obtained, while **9a** did not form. It is possible that **9a** would also be able to form if co-sublimation were carried out at 160 °C. However, it was not possible to use such a high temperature because SA would melt at this temperature. If co-sublimation could be carried out at a lower pressure, using a more powerful vacuum pump, it should be possible to prevent SA from melting before it sublimes, which could allow for **9a** to form by co-sublimation.

PYG and HMT. The combination of pyrogallol and hexamethylenetetramine is known to form a 1:1 co-crystal (**14**), the structure of which has previously been solved from powder diffraction data (CSD refcode: BINDIL).[54] Grinding a 1:1 molar ratio of the starting materials together produced **14** in quantitative yield. Co-sublimation of the two starting materials at 110−120 °C for 6 h afforded crystalline material with a powder pattern matching that of **14**. However, one additional peak was observed which corresponds to a co-crystal between 1,2-dihydroxybenzene and HMT. Unit cell determination of single crystals confirmed the presence of this co-crystal in the products of the co-sublimation experiment (CSD refcode: CERXIH).[55] Pyrogallol clearly partially degrades during sublimation, but not before the majority co-crystallizes with HMT.

GA and 4PP. The combination of gallic acid and 4-phenylpyridine is known to form a 1:1 salt (**15**, CSD refcode: TICZIQ).[56] Salt **15** can easily be made by liquid-assisted grinding, but in this case, GA degradation entirely prevents formation of **15** by co-sublimation. It was possible to sublime the gallic acid monohydrate starting material on its own to form an anhydrous polymorph of gallic acid (CSD refcode: IJUMEG06), as reported in the literature.[57] However, GA also tends to decarboxylate and degrade at high temperatures. During co-sublimation with 4-phenylpyridine, the gallate salt did not form; instead, powder diffraction shows the formation of products which do not match the salt or either starting material. We suspect that these are multicomponent materials containing GA decomposition products, such as pyrogallol or dihydroxybenzenes. It was possible to identify one such product by single-crystal diffraction, namely, a pyrogallol:4-phenylpyridine co-crystal **16**, the structure of which is described in the Supporting Information.

Coformer decomposition or melting can therefore be a major hindrance during sublimation. However, it is clear that there are some ways to overcome heat sensitivity (at least partially), such as carefully controlling temperature, pressure, and reagent ratios. Additionally, new multicomponent materials containing decomposition products may be discovered inadvertently.

■ CONCLUSION

We have shown that co-sublimation is an efficient crystallization technique for the formation of co-crystals, salts, and the intermediate co-crystal salts. When two starting materials have similar sublimation rates and temperatures, co-sublimation can be a quick and easy way to determine whether a multicomponent crystal exists, and potentially to obtain single crystals of the material. In fact, even when sublimation temperatures differ, co-sublimation can still be successful. When this temperature difference is very large, the gas-phase coformer concentrations can be manipulated by changing coformer stoichiometries, pre-forming multicomponent crystals by mechanochemistry, or by heating the starting materials at two different temperatures. In this way, even multiple polymorphic forms can be obtained by co-sublimation. Our simple sublimation apparatus did not allow for sufficiently precise temperature control to selectively form particular polymorphs, but a new polymorph of a known co-crystal salt was identified from single crystals obtained by co-sublimation (**6b II**). Co-sublimation is more challenging when one of the coformers can isomerize or degrade during sublimation, but we have demonstrated how these problems can be overcome and have successfully produced multicomponent crystals containing maleic acid by co-sublimation. When coformer decomposition could not be prevented, degradation products, as well as multicomponent crystals formed with them, could easily be identified by SCXRD.

Mechanochemistry is a rapid and efficient crystallization technique convenient for screening for multicomponent materials. Unfortunately, single crystals are not produced. On the other hand, co-sublimation successfully produced multicomponent crystals in most of the examples presented here, and often formed diffraction-quality single crystals. We also observed that the products formed during co-sublimation are not always the same as those obtained from mechanochemistry (or solution crystallization), which has allowed us to discover new multicomponent crystals (**10**, **11b**, and **12b**), one of which has not been obtained using any other technique (**12b**). It would be interesting to attempt a number of failed co-grinding experiments by co-sublimation, but unfortunately, these are rarely published. Further study into the mechanisms of gas-phase crystal growth is definitely warranted.

Co-sublimation is more laborious than mechanochemical grinding and will therefore not replace it as a routine technique. However, sublimation is clearly a valuable co-crystallization technique for the discovery and identification of new multicomponent materials. We encourage the incorporation of co-sublimation into screening protocols in addition to other crystallization methodologies, especially when working on complex or problematic systems. In our opinion, a multitechnique approach is always best.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.0c01148.

> Full details of all experimental procedures and analysis of powder X-ray data and FTIR spectra. Single-crystal X-ray diffraction data for **6a**, **6b I**, **6b II**, **8**, **9a**, **9b**, **10**, **11b**, **12b**, and **16** (PDF)

Accession Codes

CCDC 2023387−2023396 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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