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Mechanochemical Synthesis of Multicomponent Crystals: One Liquid for One Polymorph? A Myth to Dispel

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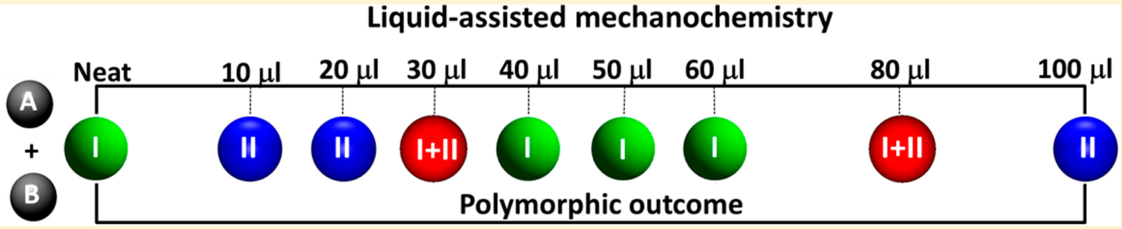
Supporting Information



ABSTRACT: Identifying as many polymorphs as possible for a molecular compound is important in the design of materials with desired properties. In this paper we demonstrate, using a simple experimental procedure, how the amount of liquid present during liquid-assisted mechanochemical reactions can be used to rapidly explore polymorph diversity. Through detailed experimental evidence it is concluded that for the specific (multicomponent) crystal system investigated (caffeine−anthranilic acid) the commonly accepted rule "one liquid for one specific polymorph" is not correct. Additionally we demonstrate that through modification of the amount of added liquid it is possible to form a polymorph previously obtained only by a desolvation reaction. We believe that while the results raise many mechanistic questions the approach is advantageous as a means of rapidly screening for polymorph diversity as well as being a simple screening methodology. While we focus here on a cocrystal system, we believe a similar approach will be advantageous for single component systems.

■ INTRODUCTION

Polymorphism is one of the most relevant characteristics of solid materials, with practical consequences in many branches of solid state chemistry and industry.[1−7] The formation of a specific polymorph is determined by an interplay of thermodynamics and kinetics.[8−11] When thermodynamics dominates a process, the lowest free energy product will be obtained. Kinetics, however, often dominates and alternative crystalline solids with higher free energies and therefore significantly different properties can be obtained.

A control of the thermodynamic and kinetic factors would increase the likelihood of a rational synthesis of a desired polymorph. Such control, however, is frequently absent. One approach which appears to vary the kinetic/thermodynamic balance is liquid-assisted grinding (LAG) where the addition of a small amount of a specific liquid added during mechanochemical treatment has been demonstrated to vary the polymorphic outcome.[12−23] It is normally accepted that the chemical nature of the liquid in LAG experiments is the most significant variable having a pronounced effect on the polymorphic outcome, every liquid being selective for a specific polymorph form.[20−22]

To date experimental conditions such as grinding time, number of added grinding media, total amount of powder, volume of liquid, and grinding intensity/frequency have often been set by trial-and-error. In this paper we were particularly interested in the relationship between the amount of the liquid during LAG and the polymorphic outcome. We were motivated by the study of a one-liquid screen of carbamazepine reported by Getsoian and co-workers[24] in which it was reported that by targeting multiple crystallization temperatures and supersaturation levels, three of the four polymorphs of carbamazepine could be obtained from a single solvent—isopropyl benzene. We were also encouraged by the report of Friscic et al.,[25] who attempted to identify general and qualitative guidelines for the design of mechanochemical cocrystallization experiments which are mediated by a minimal amount of added liquid. In that paper, the authors defined a η value, the volume of the liquid (in μL) divided by the sample weight (in mg), as an empirical parameter for the specific required amount of reactants and liquid to achieve favorable conditions for cocrystal formation. The η value can have a significant influence on the rate of cocrystallization, and a range from 0.05 to 1 is suitable in LAG cocrystallization reactions for complete reactant conversion.[25]

We selected the caffeine-anthranilic acid (CAF-ANA, Figure 1) as a model cocrystal since it has been previously explored using LAG for the production of different polymorphic forms.[26] Similar to the study reported by Friscic et al.[25] we decided to perform LAG screening by keeping fixed the amount of solid

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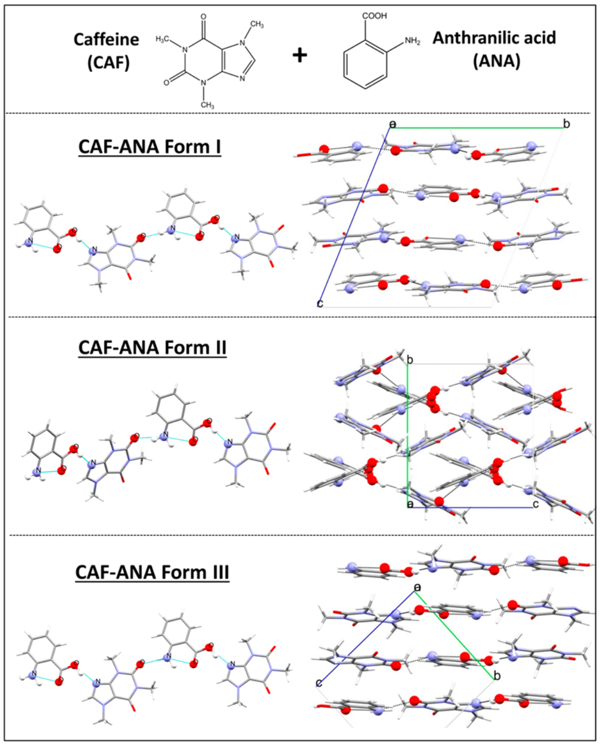

Figure 1. Crystal packing of (top) CAF-ANA Form I,[26] (middle) Form II,[26] and Form III.[27] Form I and Form III crystallize in a triclinic system, (space group $P\bar{1}$) with two molecules of each reactant in the asymmetric unit: Form II forms an orthorhombic crystal system in space group $Pna2_1$. The hydrogen bonding patterns are identical in all three polymorphic forms: ANA and CAF molecules interact through O—H(carboxyl)···N(imidazole) and N H(amine)···O═C(carbonyl) hydrogen bonds. In Forms I and III all the molecules of a chain are in plane forming a layered planar structure, while in the polymorphic Form II the zigzag chains are slightly twisted and V-shape cross sections are observed.

reactant mixture at 200 mg and modifying the η value by changing the liquid volumes. The liquid volumes were selected between 10 and 100 μL (η value between 0.05 and 0.5) that comply with the η range suggested in the previous study.

The 1:1 CAF-ANA cocrystal system consists of three known polymorphic forms (Forms I–III, Figure 1). CAF-ANA cocrystal Form I was initially obtained by grinding 200 mg of an equimolar mixture either neat or by LAG using 50 μL of nitromethane, diethyl ether, tetrahydrofuran, and ethanol. Form II could be obtained only by LAG using of 50 μL of acetonitrile (η value = 0.25). Form III was obtained only by desolvation of a particular group of solvates, i.e., toluene hemisolvate and monosolvate, chlorobenzene hemisolvate, and *p*-xylene monosolvate.[27]

In an attempt to understand the influence of the liquid on the formation of a particular CAF-ANA polymorph by LAG, Fischer et al.[28] extended the library to 19 different liquids. The grinding experiments were performed in a MM400 Retsch ball mill maintaining the same η value of 0.25 as in the study reported by Madusanka et al.[26] Indeed, 1 g of reactant mixture was treated mechanochemically in the presence of 250 μL of a liquid at 30 Hz for 25 min. The screening study increased the number of liquids promoting the mechanochemical formation of Form II to 3 (namely, acetonitrile, acetone, and dimethylformamide), while the remainder (16 out 19 liquids) resulted in Form I. The authors concluded that the polymorphic outcome was strongly dependent on the identity of the liquid such that liquids with low dipole moments produced Form I, while Form II required a liquid with a high dipole moment. Importantly, none of their experiments resulted in Form III.[28]

EXPERIMENTAL SECTION

Materials. Anhydrous CAF, ANA, and all liquids for LAG experiments were purchased from Sigma-Aldrich Company, Ltd. (Gillingham, UK), and used without further purification.

Grinding Procedure. CAF-ANA cocrystals were prepared mechanochemically following the experimental conditions previously reported:[26] 200 mg of equimolar material (117 mg of CAF and 83 mg of ANA) were added to a 15 mL steel jar containing two grinding balls of 7 mm diameter. Snap-closed grinding jars were used to minimize liquid evaporation. While the amount of solid reactants was kept fixed for each mechanochemical cocrystallization reaction, the amount of the liquid added was different and volumes ranged 10–100 μL (in terms of η value the range was 0.05–0.5[25]). The mixture was then ground for 60 min in a Retsch MM200 grinding mill at a frequency of 25 Hz. In the case of the interconversion studies of pure cocrystals approximately 180 mg of Form I, II, or III was separately treated under similar conditions (with 50 μL of liquid added to the grinding jar). X-ray pure cocrystal Forms I–III were prepared by LAG with 50 μL of nitromethane, 50 μL of acetonitrile and 10 μL of ethyl acetate, respectively. The purity of each polymorphic form was verified by comparing the measured PXRD pattern with the respective calculated one.

Determination of Approximate Solubility. The approximate solubility of CAF and ANA in six different liquids, namely, methanol, ethanol, ethyl acetate 2-butanone, acetonitrile, and nitromethane was determined at 25 °C using a rapid high-throughput method previously described.[25] Specifically, 10 mg of either CAF or ANA was added to a 1.1 mL well plate. A multichannel pipet was used to add liquids in 10 μL aliquots. After each liquid addition the well was mixed using 1 s pulses of ultrasound. The approximate solubility of CAF and ANA in the selected liquids is reported in Table 1.

Table 1. Approximate Solubility Values for CAF and ANA in Different Liquids

	CAF (mg/mL)	ANA (mg/mL)
methanol	20	80
ethanol	10	>100
ethyl acetate	10	>100
2-butanone	10	>100
acetonitrile	20	80
nitromethane	40	10

Preparation of Presaturated Solutions. A large excess of either CAF or ANA was added to 1 mL of a liquid in a glass vial. The vial was kept overnight with stirring at room temperature. The slurry was subsequently filtered using a 0.22 μm Millex-GP syringe filter unit (Merck Millipore) and the solution used for LAG experiments.

PXRD Analysis. Products were characterized by powder X-ray diffraction (PXRD) performed at room temperature using a Panalytical X'Pert Pro Diffractometer with Ni-filtered Cu Kα radiation (wavelength 1.5418 Å) equipped with an RTMS X'celerator detector. A small amount of powder (20–30 mg) was gently pressed on a glass slide to give a flat surface and subsequently analyzed. The data were collected in the 2θ range 3–40° using a step size of 0.0334° and a scan speed of 0.142°/s. For each analysis the total number of steps was 1107 and the total time was 5 min.

RESULTS

An experimental data set was first obtained with a series of alcohols to observe if a combination of variable volumes of

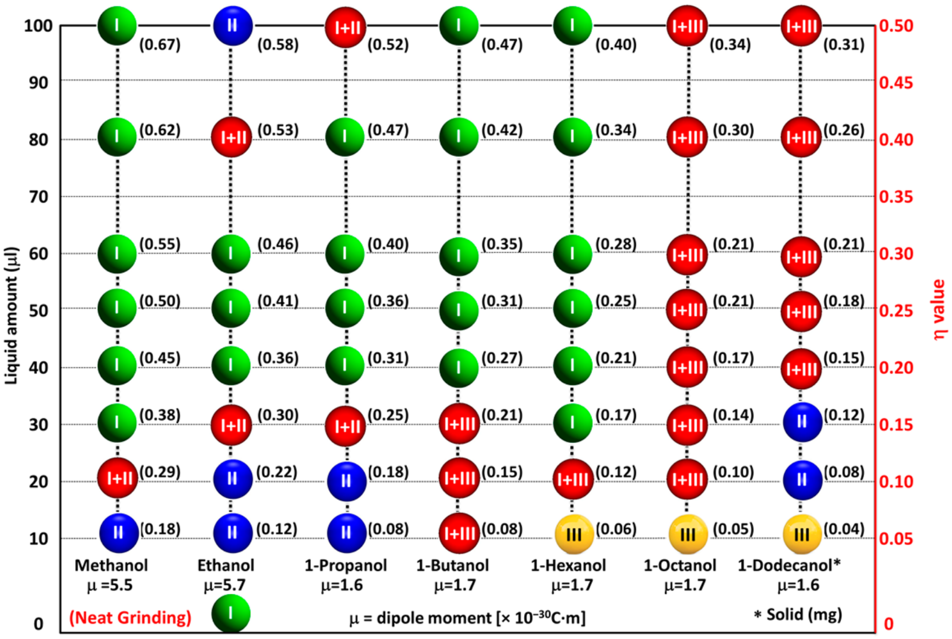

Figure 2. Summary of LAG experiments performed with different amounts of alcohols having different molecular weight. In parentheses the liquid mole fraction over the total amount of the starting materials is reported. Green, blue, and yellow balls represent solid products containing X-ray pure Form I, Form II, and Form III, respectively, while red balls indicate a solid product containing a mixture of either polymorphic Form I and II or Form I and III.

liquids having the same functional group but different molecular weights affected the polymorphic outcome. The results are summarized in Figure 2, while the experimental PXRD patterns are reported in the SI Figures 1−5.

The results indicate that it is entirely possible to perform a LAG polymorph screen simply by varying the amount of the same liquid. It is noteworthy that the addition of only 10 μL ($\eta = 0.05$) of a liquid has a clear influence on the polymorphic outcome—in terms of molarity 10 μL of methanol corresponds to 18% of total amount of starting materials, while for 1-octanol the moles contained in 10 μL would only correspond to 4% of the total amount of starting materials (Figure 2). Neat grinding produced cocrystal Form I while LAG with 10 μL of methanol or ethanol or 1-propanol gave X-ray pure Form II.[29] LAG with 10 μL of an alcohol with a larger molecular volume (such as 1-hexanol, 1-octanol, and 1-dodecanol) produced Form III. In the case of 1-butanol, experiments with low volumes of liquid resulted in mixtures of Forms I and III (Figure 2).

Also noteworthy is the alternation of the product outcome between Forms I and II in the case of LAG experiments with different volumes of ethanol and 1-propanol. Indeed, a pure Form II could be prepared in the presence of low amounts of ethanol and 1-propanol (10 and 20 μL, Figure 2), while for 30 μL a mixture of Form I and Form II was obtained and for 40 to 60 μL (η value from 0.2 to 0.3) of ethanol or 40 to 80 μL (η value from 0.2 to 0.4) of 1-propanol pure Form I resulted. Interestingly, a further increase in volume of the liquid produced again a mixture of Form I and Form II (80 μL of ethanol and 100 μL of 1-propanol) and pure Form II during LAG with 100 μL of ethanol (Figure 3).

In the case of grinding experiments with higher molecular weight (1-dodecanol) the polymorphic outcome was different—10 mg (1-dodecanol is a solid at room temperature) produced Form III, while 20 and 30 mg gave Form II. Higher amounts of 1-dodecanol produced a mixture between Form I and Form III (Figure 4).

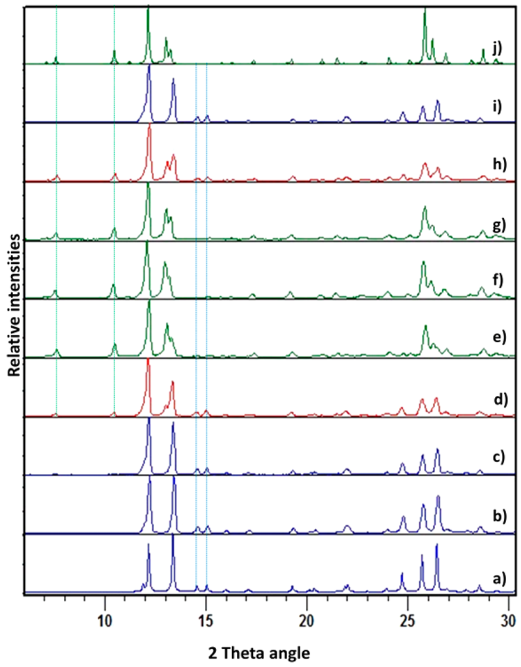

Figure 3. PXRD pattern of (a) calculated CAF-ANA Form II[26] (b), (c), (d), (e), (f), (g), (h), and (i) LAG experiments using 10, 20, 30, 40, 50, 60, 80, and 100 μL of ethanol, respectively; (j) calculated CAF-ANA Form I.[26] Green and blue patterns represent solid products containing X-ray pure Form I and Form II, respectively, while red patterns indicate a solid product containing a mixture of polymorphic Form I and Form II. The presence of Form I can be noticed particularly from the diffraction peaks at 7.5° and 10.5° of 2θ angle, while the doublet at 14.6° and 15° is the characteristic peaks of the CAF-ANA Form II.

The experimental data set was then extended to verify if the results obtained using alcohols were a general phenomenon

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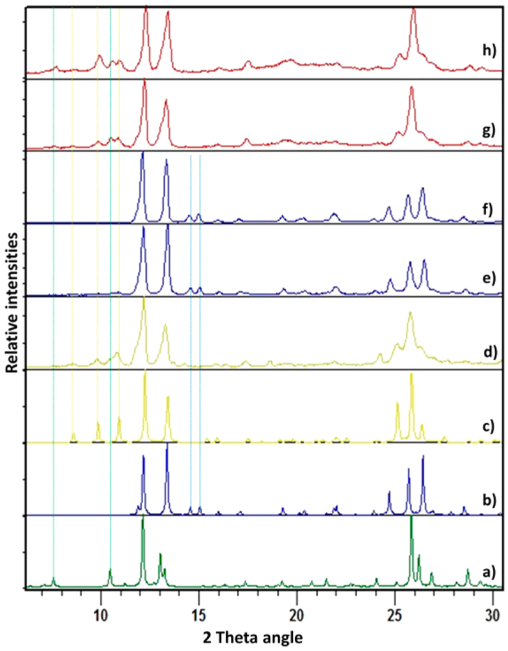

Figure 4. PXRD pattern of (a), (b), (c) calculated CAF-ANA Form I, Form II,[26] and Form III,[26] respectively; (d), (e), (f), (g), and (h) LAG experiments using 10, 20, 30, 50, and 100 mg of 1-dodecanol, respectively. Green, blue, and yellow patterns represent solid products containing X-ray pure Form I, Form II, and Form III, respectively, while red patterns indicate a solid product containing a mixture of polymorphic Form I and Form III. The presence of Form III can be noticed particularly from the diffraction peaks at 8.6°, 9.8°, and 10.9° of 2θ angle.

independent of the chemical nature of the liquid. A summary of LAG experiments performed using different volumes of nonalcoholic liquids is given in Figure 5, while the PXRD patterns of each experiment are reported in the Supporting Information Figures 6−12. The results confirmed that obtaining different polymorphs as a function of the amount of the liquid was not limited to alcohols and a similar behavior was observed with acetone, 2-butanone, ethyl acetate, and 1,4-dioxane (Figure 5). In addition with this series of liquids the observed stability regions for different polymorphic forms were simpler: volumes higher than 50 μL (η range from 0.25 to 0.5) always generated Form I, while, once again, the lower volume region (η range from 0.05 to 0.2) was more diverse and varied from liquid to liquid. Moreover, similar molecules such as acetone and 2-butanone gave comparable outcomes in terms of polymorphism. However, chemical similarity is not an absolute requirement for similar results since ethyl acetate and 1,4-dioxane, with quite different dipole moments, gave identical results (Figure 5).

In particularly sharp contrast, some liquids did not produce different polymorphic forms as a function of liquid amount: nitromethane, acetonitrile, and ethylene glycol for all volumes were highly selective to one polymorph—acetonitrile and ethylene glycol generated only Form II while nitromethane generated Form I (Figure 5). In a previous study[28] it was reported, however, that ethylene glycol produced Form I. To avoid any possible sample contamination we therefore repeated the experiments in another laboratory using new grinding jars and new reactants and liquid. However, the outcome did not change and pure Form II was obtained in each LAG experiment.[30] Additionally, similar to the LAG experiments using alcohols, we performed a series of grinding experiments with a higher molecular weight diol such as 1,6-hexandiol, a solid at room temperature. Interestingly, the polymorphic Form II was always generated (SI Figure 13).

As an initial foray into understanding the role of the amount of liquid on the polymorphic outcome in a LAG reaction, we performed a series of LAG experiments with presaturated

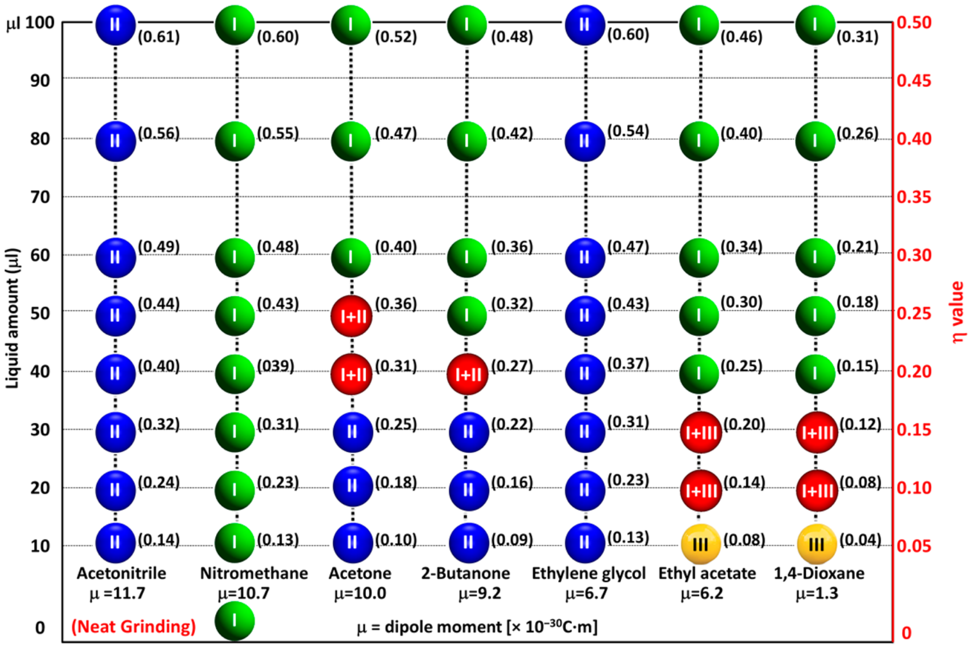

Figure 5. Summary of LAG experiments performed with different volumes of chemically different liquids. In parentheses the liquid mole fraction over the total amount of the starting materials is reported. Green, blue, and yellow balls represent solid products containing X-ray pure Form I, Form II, and Form III, respectively, while red balls indicate a solid product containing a mixture of either polymorphic Form I and Form II or Form I and III.

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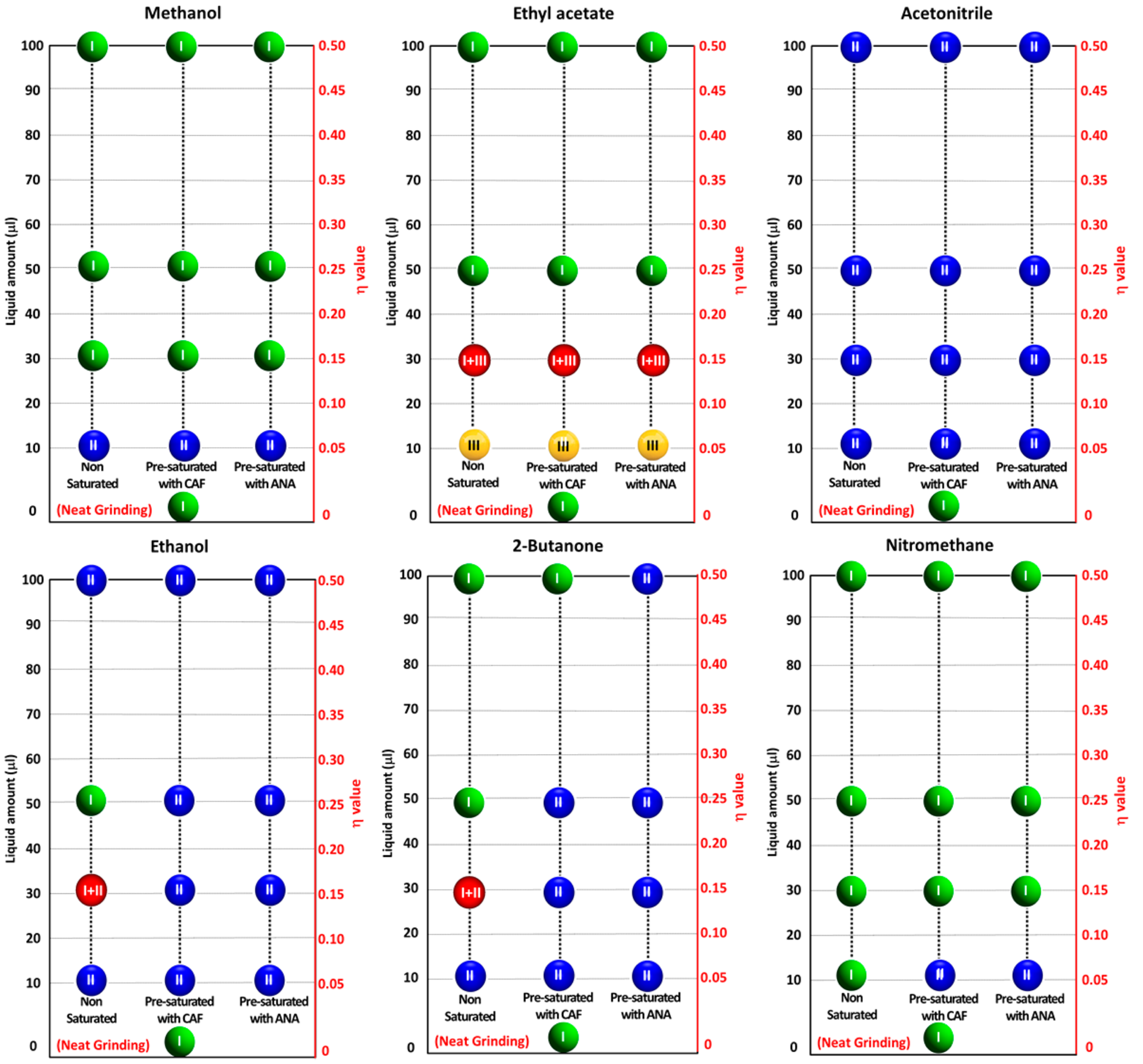

Figure 6. Summary of LAG experiments performed with different volumes of liquids previously saturated with either pure CAF or ANA. Green, blue, and yellow balls represent solid products containing X-ray pure Form I, Form II, and Form III, respectively, while red balls indicate a solid product containing a mixture of either polymorphic Form I and Form II or Form I and III.

liquid. Specifically, six liquids (methanol, ethanol, ethyl acetate, 2-butanol, acetonitrile, and nitromethane) were saturated overnight with either pure CAF or ANA (see Experimental Section for details), subsequently filtered and then used during LAG experiments.

The results reported in Figure 6 suggest that in some cases using a presaturated liquid does affect the polymorphic outcome. For example, LAG experiments using different amounts of ethanol, 2-butanone and nitromethane previously saturated with either CAF or ANA, produced different solid forms compared to LAG experiments with the same non-saturated liquids. However, similar experiments with acetonitrile, methanol, and ethyl acetate produced the same polymorphic forms.

■ DISCUSSION

From the results reported in Figures 2–5, some similarities can be found when chemically similar liquids are used for LAG. Indeed, different liquids in the volume range between 10 and 40 μL (η from 0.05 to 0.25) generated diverse outcomes in terms of polymorphic forms, while mechanochemical experiments using higher volumes of a liquid ($\eta > 0.25$) a general tendency toward the formation of Form I can be observed. A clear exception is that of ethanol or 1-propanol.[31]

Using presaturated liquids in the LAG experiments generated different outcomes to those of nonsaturated in 3 out of 6 cases (Figure 6 and SI Figures 14–23). Importantly, by using the presaturation strategy it was possible to transform a liquid from highly selective toward a specific polymorphic form into a nonselective liquid and vice versa. Consistent examples are nitromethane and ethanol: nitromethane showed high selectivity for the polymorphic Form I in nonsaturated conditions (Figure 5) and generated Form II at η value of 0.05 when presaturated with either CAF or ANA (Figure 6), while ethanol from an alternation of product outcome between Form I and II in nonsaturated conditions (Figure 3) was "transformed" into being highly selective toward the CAF-ANA Form II when saturated with either CAF or ANA (Figure 6). A similar behavior was also observed in the case of mechanochemical experiments with presaturated 2-butanone (Figures 5 and 6). On the other hand, presaturating methanol, ethyl acetate, and acetonitrile did not impact the product polymorphic outcome. However, the results reported in Table 1 would suggest that in the η range from 0.05 to 0.5 selected in this study and in all the six solvents it is likely that the liquids will always be saturated. Therefore, the interpretation of the results only through solubilities may be deceptive. Additionally, the results cannot be explained only on the basis of the dipole moment[28] since the same liquid, depending on the added amount and/or the saturation conditions, can produce more than one polymorphic form.

While the concept of LAG being a very efficient method for obtaining pure cocrystal products is relatively straightforward,[25] it is quite remarkable that the amount of the same liquid phase can modify the driving forces for specific polymorphic forms of the same product.

A possible explanation why different amounts of a liquid produce different polymorphic forms may be related to the particle size: polymorphs which are metastable as micrometer-sized or larger crystals can often be thermodynamically stabilized at the nanoscale.[32,33] Moreover, a recent study[34] (reporting on the polymorph interconversion and solid-state dynamic covalent chemistry) demonstrated that in all the mechanochemical experiments performed a dynamic equilibrium was reached, with changing milling conditions affecting the free energy difference between the two polymorphs. The authors concluded that this effect is again due to the surface solvation energy[32,33] combined with the high surface to volume ratio of the resulting nanocrystalline powder.[34] An alternative explanation may relate to the different growth mechanisms during cocrystallization between the polymorphic forms. Specifically, the results obtained with a series of liquids suggests that it is quite frequent to observe the presence of a mixture of either Form I and Form III or Form I and II. However, it was not possible to obtain a solid product in the form of a mixture between Form II and Form III. In this context, the possibility of interconverting by grinding the different polymorphic forms was also investigated by performing neat and LAG experiments with ethanol on preformed cocrystals Forms I–III. It was found that Form I and Form II were stable to transformation under neat and LAG conditions with different amounts of ethanol, while Form III readily converted to polymorphic Form I by both neat and LAG (SI Figure 26). These observations would suggest that although both polymorphic Forms I and II can be reproducibly generated by grinding reactants with different amounts of ethanol, the interconversion of the pure forms either neat or by LAG does not readily occur. Therefore, the alternation of the mechanochemical product between Form I and Form II under LAG with different amounts of ethanol and more specifically their concomitant presence during LAG with 30 and 80 μL of the same liquid cannot be attributed to a possible interconversion of the two polymorphic forms. These observations would also suggest that Form I depending on the experimental conditions can be formed either directly or in a stepwise process with Form III as an intermediate product. Indeed, it is likely that since Form III converts to Form I on both neat and by LAG, the presence of a mixture of polymorphic Forms I and III is a kinetic feature and further grinding likely produces a solid composed of only Form I.

■ CONCLUSIONS

In summary, we have successfully provided extensive experimental evidence that the commonly accepted concept "one liquid for one specific polymorphic form" for LAG reactions is not always true. Indeed, for the multicomponent crystal system studied here, formed by CAF and ANA in 1:1 stoichiometric ratio, only 4 out of 15 liquids, namely, acetonitrile, nitromethane, ethylene glycol, and 1,6-hexanediol, were found to be highly selective for one polymorphic form, while 11 out of 15 produced more than one cocrystal polymorphs. In the case of liquids that gave only one polymorphic form, 3 out of 4 liquids were highly selective for Form II which, based on the previous slurry studies,[26] is not the most stable polymorphic form. In the case of liquids that gave more than one polymorphic form, although each liquid behaves differently, some similarities can be found when (chemically) similar liquids are used for LAG purposes. Moreover, the screening through the modification of the amount of added liquid also allowed mechanochemical production of the pure Form III, which so far could be obtained only by desolvation.

There are many unanswered questions, the most important perhaps related to the reason a small modification of the volume of the added liquid can have such a dramatic impact on the reaction itself. Another important question would be whether the polymorphic outcome during LAG experiments with a specific liquid can be used as a predictive method during solution crystallization at least for those liquids that were highly selective toward a specific polymorphic form. Hence, the results reported here can be used as opportunities for future work, in terms of both mechanistic understanding and development of practical methods for the selection of an appropriate liquid to industrially produce (via solution crystallization) the desired polymorphic form without the risk of obtaining other (kinetic) forms and without the risk of solvate formation. In this way possibly we will be able to connect for the first time mechanochemistry and solution crystallization at the industrial scale. Finally, we believe that there is no reason these results cannot be extended for the one-liquid study of polymorphism through mechanochemistry in single component crystals.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.6b00682.

PXRD patterns of LAG experiments (PDF)

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Notes

The authors declare no competing financial interest.

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(29) The identity and phase purity of each cocrystal product was confirmed by comparing their measured PXRD patterns to the calculated PXRD patterns of each polymorph.

(30) We would like to emphasize that this is not a criticism of the veracity of the previous work but simply a reflection of the complexity of the polymorph behaviour of the system.

(31) All grinding experiments were repeated twice to check repeatability. The results suggested that LAG experiments performed with most solvents were perfectly repeatable; exceptions were mechanochemical cocrystallizations in the presence of 1-butanol and 1-octanol. Indeed, in some cases LAG experiments with 1-butanol and 1-octanol gave pure Form I instead of a mixture of polymorphs (data not shown). We believe that in such cases the lower repeatability is due to a kinetic effect since Form III converts to Form I.

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