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Crystal Engineering |*Hot Paper*|

Survival of the Fittest: Competitive Co-crystal Reactions in the Ball Mill

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Abstract: The driving forces triggering the formation of co-crystals under milling conditions were investigated by using a set of multicomponent competitive milling reactions. In these reactions, different active pharmaceutical ingredients were ground together with a further compound acting as coformer. The study was based on new co-crystals including the coformer anthranilic acid. The results of the competitive milling reactions indicate that the formation of co-crystals driven by intermolecular recognition are influenced and inhibited by kinetic aspects including the formation of intermediates and the stability of the reactants.

Introduction

In recent years, the interest in the synthesis of co-crystals has increased tremendously because the co-crystallisation of an active pharmaceutical ingredient (API) with an appropriate coformer can improve the physicochemical properties of the API.[1] Typically, co-crystals are defined as homogeneous, crystalline phases consisting of stoichiometric amounts of two or more neutral molecular species, which are solid under ambient conditions.[2] On the basis of noncovalent interactions between these molecules,[3] a new crystal lattice is formed leading to a change of the crucial properties of the respective API - like water solubility, dissolution behavior, melting point, photoemission, electronic behavior, and stability against physical or chemical stress.[1d,4]

Until now, various methods for co-crystal syntheses have been applied, ranging from spray drying, freeze drying and slow evaporation to the formation from melt.[5] Compared with these typically employed co-crystallization methods, mechanochemistry represents an effective and environmentally sustainable alternative. The term "mechanochemistry" covers solid-state reactions induced by mechanical energy, for example, by grinding in a ball mill.[6] Mechanochemical reactions bear many advantages. Typically, no solvent or only a small amount of solvent is needed and the reactions are quantitative. Furthermore, several co-crystals are only accessible mechanochemically and cannot be synthesized under common synthesis conditions.[6a,7] Besides the tremendous interest in mechanochemical syntheses and the success of the method for the formation of co-crystals,[8] a fundamental understanding of the formation pathways and driving forces during the milling syntheses is still lacking.[9]

Although considerable work concentrates on the theoretical calculation of possible crystal structures,[10] up to now, it is impossible to predict the products of co-crystal syntheses reliably.

The first real-time and in situ measurements using synchrotron X-ray powder diffraction (PXRD) and Raman spectroscopy provided direct insights in the formation pathway of milling reactions.[11] These experiments can offer an understanding of formation pathways, but information about the driving forces of mechanochemical syntheses is scarce. Usually, the hierarchy of supramolecular synthons derived from CSD database entries is a first reference point. Co-crystal structures containing coformer with two or more different moieties in the same molecule are investigated.[12]

Here, we analyze the initial interactions in the milling process based on the molecular recognition of the reactants. To elucidate the key factors of these interactions, a set of multicomponent milling reactions was chosen based on four new co-crystals including the coformer anthranilic acid (ana) and the APIs carbamazepine (cbz), salicylic acid (sa), theobromine (tb) and theophylline (tp). Our results indicate that the co-crystal-milling product is not only related to preferred intermolecular interaction but also the kinetic aspects have to be considered.

Results and Discussion

Syntheses and characterization of model compounds

We focus our investigation on co-crystals of the coformer ana, which is known for its excellent ability to form co-crystals.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500925: A detailed description of the co-crystal syntheses, the XRD and synchrotron measurements, the Raman and ssNMR spectroscopy and the DTA-TG analysis.

Grinding experiments with the APIs cbz, sa, tb, and tp were conducted. All APIs co-crystalize with ana in stoichiometric ratios of 1:1, 2:1, or 2:3. Additionally, a mechanochemically synthesized theobromine:salicylic acid (tb:sa) co-crystal could be identified. All pure co-crystals were synthesized by neat or liquid-assisted grinding. The corresponding PXRD patterns shown in Figure 1 indicate the completeness of the reaction.

On the basis of the powder patterns, the solution and refinement of the crystal structure of the co-crystals carbamazepine:anthranilic acid (2:1) (cbz:ana), salicylic acid:anthranilic acid (sa:ana), and theophylline:anthranilic acid (2:3) (tp:ana) was possible (Figures S1–S4 in the Supporting Information). The structure of the tb:sa was solved based on the single-crystal data. The crystal structures and intermolecular interactions of the new co-crystals are presented in Figure 2. As expected, all crystal structures are dominated by the formation of intermolecular hydrogen bonds leading to the formation of layers (sa:ana), chains (tb:ana), or isolated entities (cbz:ana, tp:ana, tb:sa).

The products were characterized by using differential thermal analysis and thermogravimetric analysis (DTA-TG), Raman spectroscopy and solid-state NMR (ssNMR) spectroscopy. On the basis of the Raman and ssNMR data, we can identify the formation of salts. With the exception of both sa co-crystals, all co-crystals consist of neutral molecules and a salt formation can be excluded. The Raman spectrum of the sa:ana co-crystal shows that the protons of the molecules are bridged strongly, since the stretching band of the carboxylate group of ana at $\tilde{\nu}=1373\ cm^{-1}$ does not vanish. The results of the corresponding ssNMR investigations back this assumption, since the acidic proton of ana leads to a signal at $\delta=16.3$ ppm. The tb:sa co-crystal shows also a high-shifted proton signal at $\delta=15.6$ ppm. The shift of the corresponding Raman absorption bands of the reactants is not sufficient to indicate a complete salt formation. The Raman band of sa at $\tilde{\nu}=1635\ cm^{-1}$ (C=O stretching, carbonyl group) and of tb at $\tilde{\nu}=3116\ cm^{-1}$ (N–H stretching, secondary amine) shifted by approximately $\tilde{\nu}=15\ cm^{-1}$ in the co-crystal.[13] Because we did not observe the additional Raman band of an ammonium ion, we could not assume that a complete salt formation had occurred. The investigations using DTA-TG reveal the thermal stability of the co-crystals, whereas the co-crystal of cbz and ana has the lowest melting point. The results of these investigations and the lattice constants of the co-crystals are summarized in Table 1.

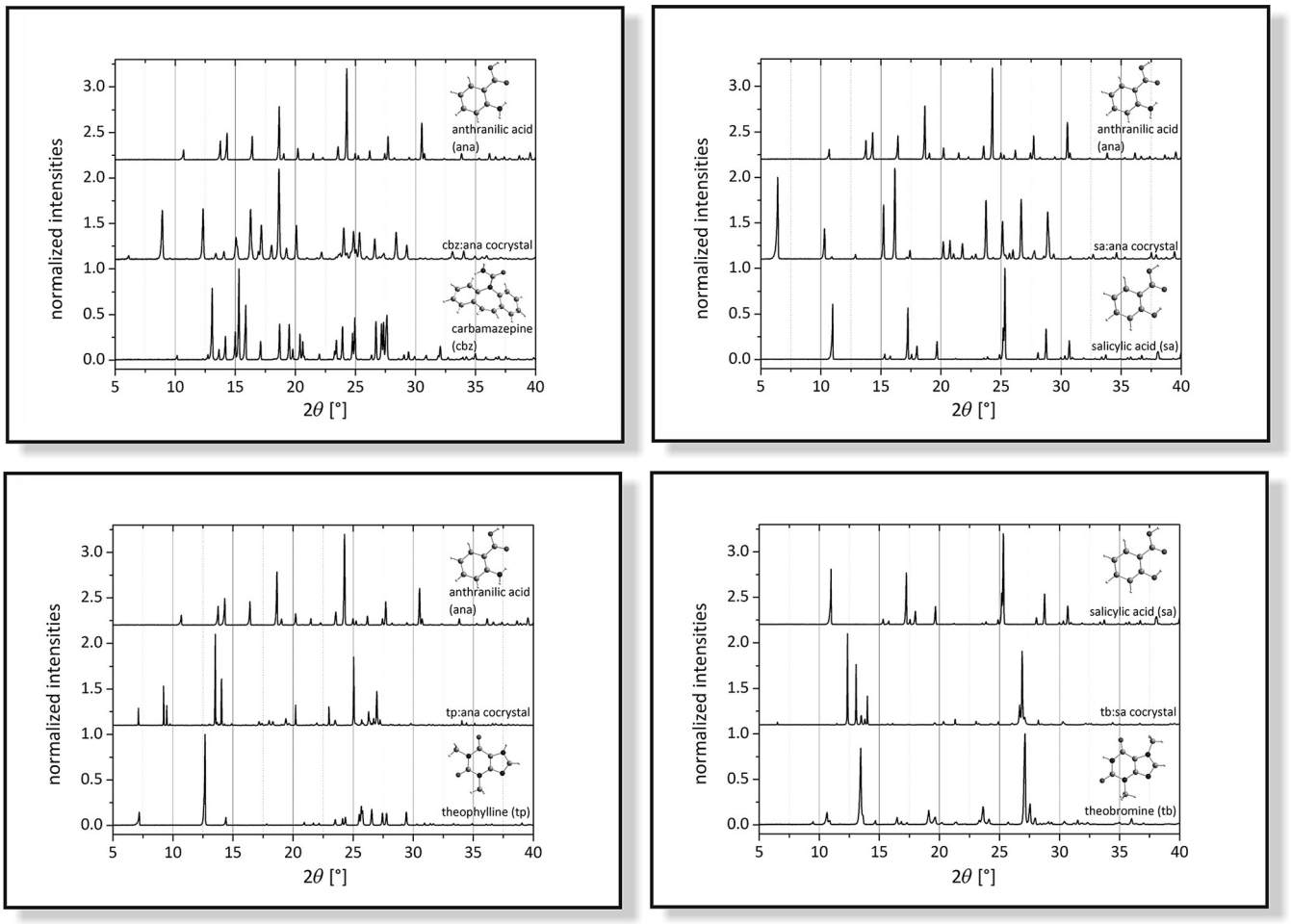

Figure 1. Powder XRD patterns of the new co-crystals carbamazepine:anthranilic acid 2:1 (cbz:ana) (top left), salicylic acid:anthranilic acid (sa:ana) (top right), theophylline:anthranilic acid 2:3 (tp:ana) (bottom left), and theobromine:salicylic acid (tb:sa) (bottom right) and their corresponding reactants.

Table 1. General and crystallographic data of the tb:ana, cbz:ana, sa:ana, tp:ana, and tb:sa co-crystal.

			Co-crystal		
	tb:ana	cbz:ana	sa:ana	tp:ana	tb:sa
formula	$(C_7H_8N_4O_2)$:$(C_7H_7NO_2)$	$(C_{15}H_{12}N_2O)_2$:$(C_7H_7NO_2)$	$(C_7H_6O_3)$:$(C_7H_7NO_2)$	$(C_7H_8N_4O_2)_2$:$(C_7H_7NO_2)_3$	$(C_7H_8N_4O_2)$:$(C_7H_6O_3)$
M_w [g mol^{-1}]	317.3	609.68	275.26	771.45	318.28
crystal system	monoclinic	triclinic	monoclinic	triclinic	triclinic
space group	$P2_1/c$	$P\bar{1}$	$P2_1$	$P\bar{1}$	$P\bar{1}$
a [Å]	6.56078(27)	14.74569(67)	4.38114(13)	20.1369(11)	6.7950(8)
b [Å]	21.84702(89)	11.08411(52)	10.91555(42)	13.29925(68)	7.9364(10)
c [Å]	11.01679(44)	10.86061(58)	14.47135(59)	7.16109(30)	14.0600(18)
α [°]	90	113.9659(27)	90	96.8582(38)	94.047(4)
β [°]	112.9011(19)	93.7022(31)	109.1491(20)	94.8506(37)	103.658(4)
γ [°]	90	101.1102(25)	90	72.0511(39)	103.467(3)
V [Å^3]	1454.61	1571.33	657.76	1809.07	710.17
Z	4	2	2	2	2
method	PXRD	PXRD	PXRD	PXRD	single crystal
T [K]	293	293	293	293	100
salt formation	no	no	yes	no	no
T_m [°C]	[a]	128	137	144	[a]

[a] Stepwise thermal decomposition.

Competitive and stability experiments

To understand the driving forces of mechanochemical syntheses, three types of competitive milling reactions were performed: A) Grinding a stoichiometric physical mixture of ana, tb and a further API (API2); B) Grinding the tb:ana co-crystal with a stoichiometric amount of API2; C) Grinding the ana co-crystal of API2 with tb. All grinding experiments were conducted in a MM400 mixing mill at a frequency of 30 Hz within 25 min to ensure a thorough, uniform interparticular mixture during the grinding process. To get more information about the co-crystal stabilities, slurry experiments with a mixture of a co-crystal and an API were conducted.

A) Competitive milling experiments

A physical mixture of tb, ana, and an additive API2 was milled (Figure 3) either by neat grinding or liquid-assisted grinding (LAG) using ethanol or acetonitrile. The results are schematically summarized in Figure 3 A. Three different reaction pathways were observed: 1) Formation of the co-crystal theobromine:anthranilic acid (tb:ana), while the added API remains unreacted; 2) All three possible two-component co-crystals are formed; and 3) A co-crystal of the additive API2 and ana is formed. Tb is still present in its initial crystal structure.

B) Stability milling tests of tb:ana

A set of mechanochemical experiments was conducted to evaluate the stability of a distinct co-crystal. In these experiments powders of the tb:ana co-crystal were ground together with either cbz, sa, or tp (Figure 3 B). Two types of reaction product were observed depending on the added API. Either the tb:ana co-crystal remains intact (Figure 3 B, pathway 4) or all three possible co-crystals are formed next to each other (Figure 3 B, pathway 5).

C) Stability milling tests of other ana co-crystals

Furthermore, these stability tests were performed vice versa by milling tb with powders of the ana co-crystals of cbz, sa, or tp (Figure 3 C). In this case, three different reactions were observed: An exchange of the API in the final product and the release of API2 (Figure 3 C, pathway 6). In the other cases, the co-crystal remains stable and no reaction is observed (Figure 3 C, pathway 8). For some combinations, the formation of a mixture of co-crystals was observed (Figure 3 C, pathway 7).

Results of milling and slurry experiments

To obtain further insights in the stability of the co-crystals, slurry experiments were performed. The tb:ana co-crystal was slurried with a competitive API. The co-crystals of ana with cbz, sa, or tp were stirred with tb.

In reactions with cbz, tb, and ana, the cbz:ana co-crystal is formed preferably. The milling product is formed regardless of neat or liquid-assisted grinding conditions (Figure 4). This co-crystal also remains stable during grinding with tb. The formation of the cbz:ana co-crystal can be explained by analyzing the eutectic melting points. Because cbz and ana form a eutectic phase with a melting point at 100.3 °C, which is lower than the eutectic melting point of tb with ana at 136.2 °C (the Supporting Information, Table S1), we can assume that the formation of the cbz:ana co-crystal is favored.

Abourahma et al. conducted grinding reactions of co-crystals to investigate the formation of theophylline:*p*-hydroxybenzoic acid co-crystals. The results were discussed based on Etter's rules. The rule that the best hydrogen bond donor interacts with the best hydrogen bond acceptor was considered.[14] We could show that Etter's rules are important, but a prediction of favored co-crystals is not possible based on these rules only. As described in the following, kinetic aspects influence the milling product and have to be considered also.

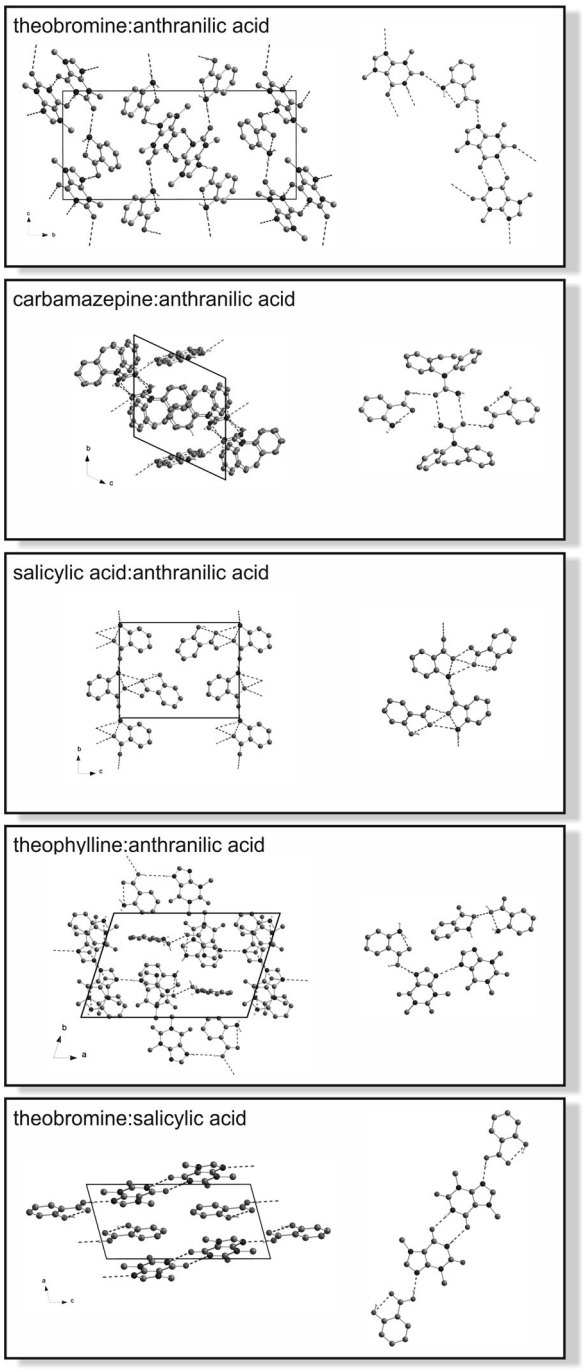

Figure 2. Crystal structure and bonding arrangement of the co-crystals theobromine:anthranilic acid (tb:ana), carbamazepine:anthranilic acid (2:1) (cbz:ana), salicylic acid:anthranilic acid (sa:ana), theophylline:anthranilic acid (2:3) (tp:ana), and theobromine:salicylic acid (tb:sa). Dashed lines indicate hydrogen bonds. All hydrogen atoms not involved in hydrogen bonds were omitted for clarity.

It was not possible to convert the tb:ana co-crystal into the cbz:ana co-crystal and tb by milling or slurrying with cbz. Because ana is a strong acid and cbz a stronger base than tb, the results of the previous competitive milling reaction can also be explained by Etter's rules, which indicate that the strongest acid interacts with the strongest base.[14b]

Consequently, the formation of cbz:ana co-crystal would be expected in the stability milling tests (Figure 3 B) if only Etter's rules were important for the product formation. However, the tb:ana co-crystal remains stable in the milling experiment with pure cbz. Obviously, kinetic factors also influence the mechanochemical reactions. As compared with the pure compounds, the tb:ana co-crystal seems to be energetically favored. This leads to a higher activation energy for the decomposition of the crystalline structure in relation to the corresponding reactants. The experiments using three pure reactants (cbz, ana, tb) suggest that the activation energy for the formation of the cbz:ana crystal is lowered because of the decomposition of the crystalline structure of ana. From the stable tb:ana co-crystal present in the reaction mixture, ana is not released and hence not present for the formation of cbz:ana.

The second model system contains tp as competitive API2 (Figure 5). In contrast to the other systems, the product of the competition milling reaction with tp depends on the synthesis parameters (Figure 3 A). During neat grinding the tb:ana co-crystal is preferred, whereas the tp:ana co-crystal is favored during liquid-assisted grinding. Therefore, it can be supposed that the kinetic barrier for the formation of the tp:ana is higher than for the tb:ana co-crystal. The tp:ana co-crystal is also not formed under neat grinding conditions. During the application of liquid-assisted grinding the activation energy is lowered because of the formation of an intermediate liquid phase, which is based on the higher solubility of tp compared with that of tb (the Supporting Information, Table S2). Neither grinding nor slurrying enables the conversion of the tb:ana into the tp:ana co-crystal. Neat grinding of the tp:ana co-crystal with tb leads to the formation of the tb:ana and pure tp. No conversion is observed when using liquid-assisted grinding. These results show that the intermediates of the formation pathway are also crucial for the course of the mechanochemical reactions.

The behavior of sa as an additive in the competitive milling reactions is different than that with tb and ana (Figure 6). Here, all possible co-crystals (tb:ana, tb:sa, and sa:ana) are formed both under neat and liquid-assisted grinding (pathway 2, Figure 3). According to Etter's rules, it is reasonable that the tb co-crystals of ana and sa are formed in the same extent, since both molecules show a comparable acidity. The remaining sa co-crystalizes with ana. The grinding experiments with the mixtures of the tb:ana co-crystal and sa or the sa:ana and tb reveal similar milling products. In both cases, again all possible co-crystals were synthesized. Among tp, cbz, and sa, only sa is able to break the hydrogen bonds of the tb:ana co-crystal during the grinding process. The sa molecules are small enough to interact with ana molecules in the corresponding tb co-crystal, leading to the same product as in the competition grinding experiments.

Slurry experiments using the tb:ana co-crystal with an equimolar amount of sa in heptane again led to a mixture of the three possible co-crystals. On the other hand, the sa:ana co-crystal stays intact during slurrying with tb. This result shows that under mechanochemical conditions the energy input per

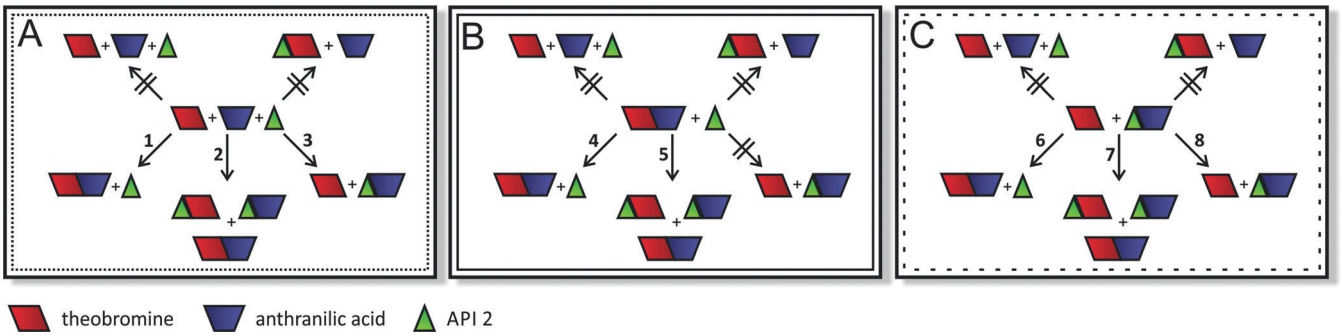

Figure 3. Schematic representation of the: A) competitive, and B, C) stability milling reactions with theobromine (red), anthranilic acid (blue), and an additional API2 (green). Different possible and observed reaction pathways are shown. The numbers indicate the different observed pathways. The other possibilities could not be observed.

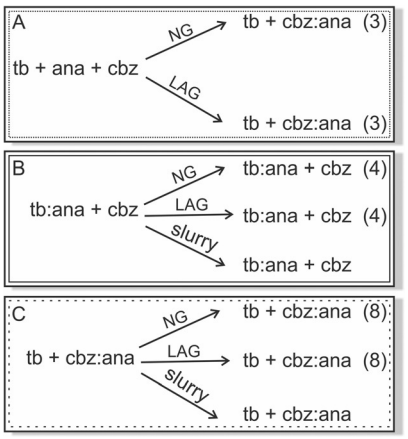

Figure 4. Results of the competition grinding reactions, the stability grinding reactions, and the slurry experiments of carbamazepine (cbz), theobromine (tb), and anthranilic acid (ana). The numbers in brackets indicate the pathways presented in Figure 3.

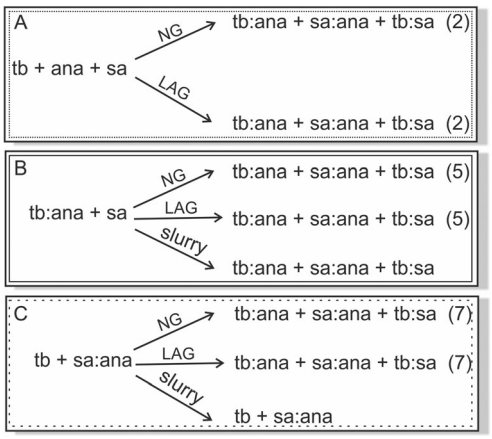

Figure 6. Results of the competitive grinding reactions, the stability grinding reactions and the slurry experiments of salicylic acid (sa), theobromine (tb), and anthranilic acid (ana). The numbers in brackets indicate the pathways presented in Figure 3.

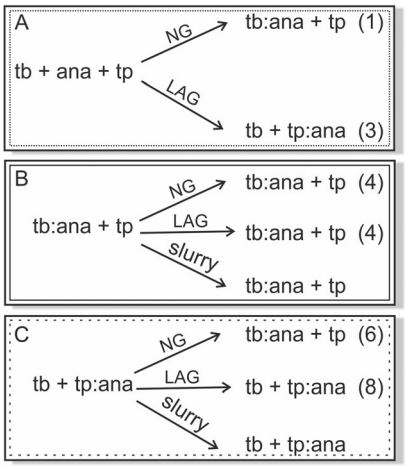

Figure 5. Results of the competitive grinding reactions, the stability grinding reactions, and the slurry experiments of theophylline (tp), theobromine (tb), and anthranilic acid (ana). The numbers in brackets indicate the pathways presented in Figure 3.

unit time per unit material is strikingly higher than that obtained in the slurry experiments.

Conclusion

The formation of co-crystals under grinding conditions was investigated to elucidate the factors that influence the formation of a distinct product. A set of competitive reactions were chosen, which allowed addressing different aspects of milling reactions. The energy input during mechanochemical reaction is sufficient to decompose the crystalline structure of pure compounds as well as co-crystals. One would suggest that the formation of the reaction products under these conditions are based on preferred intermolecular interactions. Our results show that the co-crystal-milling product is not only triggered by preferred intermolecular interactions but it is also significantly influenced by the crystalline starting phase and possible intermediates based on the synthesis condition. These results are in good accordance to previous experiments.[9a] Therefore, mechanochemical co-crystal reactions are more complex than

generally expected. For a successful synthesis, the kinetics of the reaction have to be considered.

Experimental Section

Materials: Anthranilic acid (ana), $C_7H_7NO_2$ (98+%, Acros Organics, Belgium), carbamazepine (cbz), $C_{15}H_{12}N_2O$ (99%, Acros Organics, Belgium), salicylic acid (sa), $C_7H_6O_3$ (AppliCem, pure Pb. Eur., Germany), theobromine (tb), $C_7H_8N_4O_2$ (99%, Acros Organics, Belgium), and theophylline (tp), $C_7H_8N_4O_2$ (99+%, Acros Organics, Belgium) were purchased commercially and were used without further purification.

Synthesis of the pure co-crystals: The milling syntheses were conducted by neat or liquid-assisted grinding (LAG) in a ball mill (MM400, Retsch, Germany) at 30 Hz for 25 min. A 10 mL steel vessel with two steel balls (10 mm diameter, 4 g) was used for a total load of 1 g.

Competitive milling synthesis: The competitive milling syntheses were conducted by neat grinding or LAG of stoichiometric amounts of tb, ana and an additional API (cbz, sa, tp) in a ball mill (MM400, Retsch, Germany) at 30 Hz for 25 min. A 10 mL steel vessel with two steel balls (10 mm diameter, 4 g) was used for a total load of 1 g. For the LAG experiments, 250 μL of ethanol or acetonitrile were added to the reaction mixture.

Stability milling synthesis: The stability milling syntheses were conducted by neat grinding or LAG of stoichiometric amounts of an existing co-crystal and a competitive API (API2) in a ball mill (MM400, Retsch, Germany) at 30 Hz for 25 min. A 10 mL steel vessel with two steel balls (10 mm diameter, 4 g) was used for a total load of 1 g. For the LAG experiments, 250 μL of ethanol or acetonitrile were added to the reaction mixture.

Slurry experiments: Slurry experiments were conducted by stirring a slurry of a stoichiometric mixture of an existing co-crystal and a competitive API2 in heptane for seven days under ambient conditions. The solid phase was gained by filtration and analyzed by powder X-ray diffraction (PXRD).

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Keywords: crystal engineering · kinetics · mechanochemistry · structure determination · X-ray diffraction

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