Crystal Engineering

Screening for Inclusion Compounds and Systematic Construction of Three-Component Solids by Liquid-Assisted Grinding**

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The rational construction of cocrystals (crystalline solids made up of more than one molecular component) has recently attracted the attention of solid-state scientists and materials chemists.[1] The interest, founded on the growing number of applications of multicomponent solids, includes the discovery of new cocrystals, as well as the development of efficient methods for cocrystal synthesis and screening.[2,3] Whereas reliable strategies have been developed to design and construct two-component (binary) cocrystals by using hydrogen bonds,[4] halogen bonds,[5] $\pi\cdots\pi$[6] or van der Waals forces,[7] the construction of ternary and higher-order cocrystals still presents a challenge.[8,9]

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One possible strategy towards three-component solids is a host–guest design, wherein the host is a crystalline lattice assembled using two molecular species.[10] Traditionally, inclusion compounds have been synthesized by crystallizing the host and guest compounds from a solution.[11] Whereas the choice of components available for the construction of such systems is limited by the solubilities of the host and the guest, the limitations become more severe in multicomponent systems that require balancing the solubilities of several molecular species.

A possible way to circumvent such solubility issues is through the use of mechanochemical methods.[12] Notably, our group, and others, have reported that binary cocrystals can readily be constructed by grinding together individual components, either neat or in the presence of a small amount of a liquid phase (liquid-assisted grinding).[13,14] That the amounts of liquid involved in liquid-assisted grinding experiments are typically very small suggests that the solubilities of individual components are not decisive for cocrystal formation by grinding. Consequently, neat and liquid-assisted grinding methods are expected to be more efficient than solution crystallization in recognizing guests available to a particular host. Indeed, such a possibility has already been hinted at by Toda and co-workers in the case of the inclusion compound of 1,1-di(*o*-hydroxyphenyl)cyclohexane and naphthoquinone.[15]

With our interest in three-component systems, we have decided to explore neat and liquid-assisted grinding as screening and synthetic methods that would identify guest molecules compatible with a particular two-component host and, correspondingly, facilitate the systematic construction of three-component solids.[9] We were encouraged in our efforts by the recent report of Braga and co-workers on the mechanochemical synthesis of metal–organic intercalation compounds.[16] We now communicate the use of grinding methods for the efficient screening of guests in inclusion compounds, as well as for the deliberate construction of ternary solids independent of the state of aggregation of the guest (that is, liquid or solid).

We have focused our attention on the novel two-component host **1**, which is assembled from caffeine (caf) and succinic acid (sa) in a 1:1 stoichiometric ratio (Scheme 1). Host **1** can be obtained as an inclusion compound with 1,4-dioxane by cocrystallizing caf and sa from the solvent. Whereas the attempted cocrystallization of caf and sa from common organic solvents results in the precipitation of the individual components, mechanical agitation in 1,4-dioxane affords the recrystallization of the initially precipitated caf into cocrystals composed of caf, sa, and 1,4-dioxane. The stoichiometric ratio of the components in the cocrystal is 1:1:0.66 caf/sa/1,4-dioxane, as established by ^{1}H NMR spectroscopy and thermal analysis.
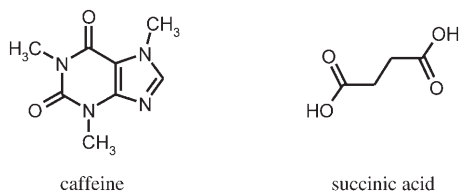
As determined by single-crystal X-ray diffraction, caf and sa molecules form layers held together by O−H···O, O−H···N, and pairs of C−H···O hydrogen bonds. Stacking of the layers produces the framework **1**. The framework contains channels, which are occupied by columns of disordered 1,4-dioxane molecules so as to give a solid of composition **1**·0.66 $C_4H_8O_2$ (Figure 1). The synthesis of **1**·0.66 $C_4H_8O_2$ was also achieved
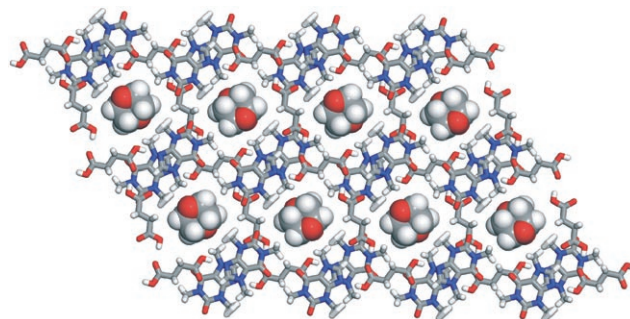

Figure 1. Fragment of the **1**·0.66 $C_4H_8O_2$ structure. The host framework is shown in a wire-frame representation, and the guest molecules in a space-filling representation. C gray, H white, N blue, O red.

by the neat grinding of caf and sa with 1,4-dioxane. That the products obtained by the two methods both correspond to **1**·0.66 $C_4H_8O_2$ was established by comparing the measured powder X-ray diffraction (PXRD) patterns to that calculated on the basis of the crystal structure (Figure 2), as well as by solid-state cross-polarization (CP) magic-angle-spinning (MAS) ^{13}C NMR spectroscopy.
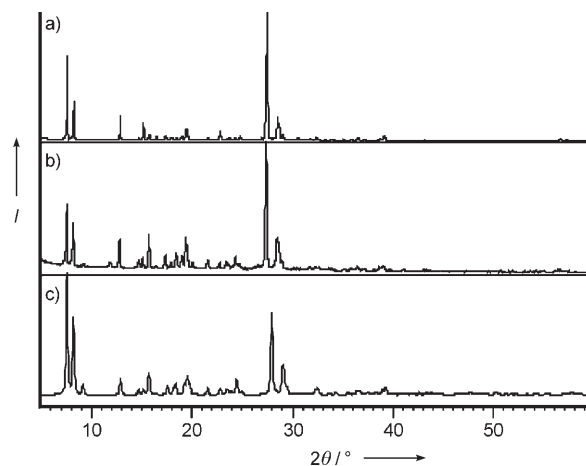

Figure 2. PXRD patterns of a) solution-grown **1**·0.66 $C_4H_8O_2$ and b) the product of the neat grinding of caf, sa, and 1,4-dioxane. c) Simulated PXRD pattern of **1**·0.66 $C_4H_8O_2$.

To compare the efficiencies of neat grinding, liquid-assisted grinding, and crystallization from solution in identifying guests for **1**, 20 liquid compounds were selected as potential guests (Table 1, entries 1–20).[17] The ability of a molecule to act as a guest was recognized by the formation of a solid isomorphous to **1**·0.66 $C_4H_8O_2$, as determined by PXRD.[18] The observation that inclusion compounds were

caffeine   succinic acid

Scheme 1.

Table 1: Formation of **1**·guest by different synthetic methods

Entry	Guest	State of aggregation[a,b]	From solution	Neat grinding[d]	Liquid-assisted grinding[e]
1	(1,4-dioxane, O···O six-membered ring)	L	Yes	Yes	Yes
2	(O···S six-membered ring)	L	Yes	Yes	Yes
3	(O six-membered ring)	L	Yes[c]	Yes	Yes
4	(S six-membered ring)	L	No	Yes	Yes
5	(O six-membered ring, unsaturated)	L	Yes[c]	Yes	Yes
6	(cyclohexane)	L	No	No	Yes
7	(cyclohexene)	L	No	Yes	Yes
8	(cyclohexadiene)	L	No	Yes	Yes
9	F—(benzene)—F	L	No	Yes	Yes
10	(bicyclic structure)	L	No	Yes	Yes
11	(five-membered ring with O)	L	No	Yes	Yes
12	(five-membered ring with O)	L	No	Yes	Yes
13	(five-membered ring with S)	L	No	Yes	Yes
14	CCl$_4$	L	No	Yes	Yes
15	CH$_3$NO$_2$	L	No	Yes	Yes
16	Hexane	L	No	No	No
17	(O···O chain, dimethoxyethane)	L	No	No	No
18	CH$_3$CN	L	No	No	No
19	CH$_3$OH	L	No	No	No
20	Acetone	L	No	No	No
21	(S···S six-membered ring, 1,4-dithiane)	S	No	No	Yes
22	(norbornane)	S	No	No	Yes
23	(norbornylene)	S	No	Yes	Yes
24	Ferrocene	S	No	No	No
25	CHI$_3$	S	No	No	No

[a] At ambient conditions. [b] L = liquid, S = solid. [c] Very low yields.[18] [d] Approximately 2 equiv guest were used. [e] Acetonitrile was used as the liquid phase.

not formed in any experiments involving only caf, sa, and acetonitrile led to the selection of acetonitrile as the liquid phase for liquid-assisted grinding.

Screening by solution crystallization provided **1**·guest in only four cases: 1,4-dioxane, 1,4-thioxane, tetrahydropyran, and 3,4-dihydropyran (Table 1, entries 1–3 and 5).[18] Thermal analysis and ¹H NMR spectroscopy revealed the composition of the 1,4-thioxane cocrystals to be **1**·0.54 C$_4$H$_8$OS, while a crystal-structure analysis revealed that the framework **1** remained largely unchanged with respect to **1**·0.66 C$_4$H$_8$O$_2$ (see Supporting Information). However, the 1,4-thioxane guest molecules are much more disordered within the channels.

In contrast to crystallization from solution, neat and liquid-assisted grinding identified 11 additional molecules

that form complexes with **1** (Table 1, entries 4, 6–15). As evidenced from the relative intensities of signals in the PXRD patterns, a small amount of liquid can improve the yield of the ternary solid up to the quantitative level and, in some cases, enable the formation of cocrystals not obtained by neat grinding. In particular, the addition of acetonitrile enabled the formation of **1**·C$_6$H$_{12}$ (Table 1, entry 6). This observation demonstrates that liquid-assisted grinding can be more efficient than neat grinding in identifying potential guests, and indicates that the role of the liquid is more than simply providing a lubricant for the reaction. The success of grinding as a screening method encouraged us to explore compounds that are solids at ambient conditions as guests. Liquid-assisted grinding readily provided three such cocrystals, involving 1,4-dithiane, norbornane, and norbornylene (Table 1, entries 21–23).[19]

The inability to form an inclusion compound of **1** by crystallization from a liquid guest does not imply that the inclusion compound of the guest cannot be obtained from solution. For example, the complex of **1** and nitromethane forms readily by grinding, but not by crystallization from liquid nitromethane (Table 1, entry 15). However, subsequent exploration of different solvent systems provided crystals of **1**·CH$_3$NO$_2$ by the slow evaporation of a solution of caf and sa in a 1:1 CH$_3$NO$_2$/CH$_3$OH mixture (which allowed the structure of **1**·CH$_3$NO$_2$ to be determined; see Supporting Information).

Exploring the diversity of guests by neat and liquid-assisted grinding provides an opportunity to understand better the inclusion properties of **1**. Assuming that the formation of cocrystals is governed largely by the host–guest compatibility, rather than solubility, guest inclusion appears to be independent of the flexibility or electronic structure of the guest. Aromatic and fluorinated aromatic molecules, as well as saturated and unsaturated aliphatic molecules perform equally well as guests (Table 1, entries 6–10). The presence of heteroatoms does not seem to inhibit cocrystal formation (Table 1, entries 1–5, 11–13). The host also accommodates molecules that do not contain a six-membered ring (Table 1, entries 11–15). Consequently, the likelihood of a molecule to be incorporated in **1** seems to be determined largely by size. The inability to use hexane or 1,2-dimethoxyethane as guests, as opposed to cyclohexane and 1,4-dioxane, suggests that shape is also relevant for the formation of **1**·guest.

The inclusion versatility of **1** contrasts with our inability to obtain a binary cocrystal of caf and sa.[20] Removal of the guest from **1**·0.66 C$_4$H$_8$O$_2$, **1**·0.54 C$_4$H$_8$OS, or **1**·CH$_3$NO$_2$ by heating results in the separation of caf and sa. In contrast, homologues of sa readily form binary cocrystals with caf.[21] In an attempt to rationalize such behavior, we have structurally characterized the 1:1 caf/adipic acid cocrystal (**2**; see Supporting Information).

Structural comparison of **2** and **1**·guest suggests a reason for the instability of a binary solid involving caf and sa (Figure 3). Namely, **2** consists of hydrogen-bonded chains of adipic acid, which are laterally decorated with caf groups and are analogous to the sa chains observed in the complexes of **1**. In **2**, the caf molecules of neighboring chains interdigitate to
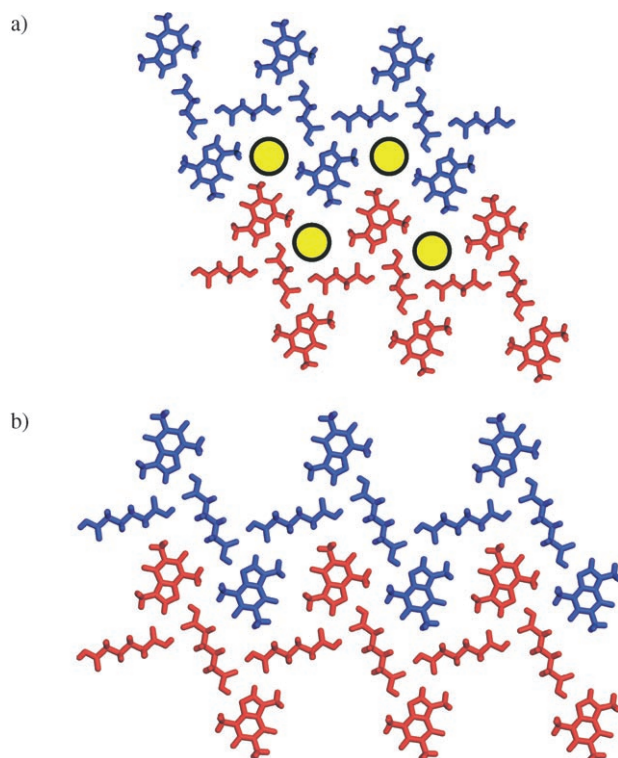
a)

b)

Figure 3. Comparison of the structures of a) **1**·guest and b) **2**. Two interdigitated hydrogen-bonded chains are shown in red and blue; the guests in **1**·guest are indicated by yellow circles.

form sheets with short (3.3 Å) contacts between methyl groups in adjacent chains. Presumably, an analogous structure with sa would lead to shorter, repulsive contacts. As a result, the caf molecules in the host **1** connect by pairs of C−H···O hydrogen bonds and interdigitate only partially, providing room for guest inclusion.

In summary, neat and liquid-assisted grinding have proven advantageous over solution crystallization as methods of screening for three-component inclusion compounds. Crystallization from solution identified 4 (22%) of the 18 inclusion guests recognized by grinding. In addition, the small amounts of liquid involved render grinding methods environmentally more acceptable.[22] From the synthetic aspect, liquid-assisted grinding circumvents the limitations imposed by the solubilities of the cocrystal components, providing a simple and efficient way to systematically construct ternary solids. In particular, liquid-assisted grinding enabled the construction of three ternary cocrystals by introducing solids as guests in a host–guest design. With the guidelines for the construction of inclusion compounds already established, grinding becomes particularly appealing as a tool to construct multicomponent solids.[23] We anticipate that grinding will open new avenues in the construction of cocrystals, in spite of the inability to characterize the products by single-crystal X-ray diffraction. With this limitation in mind, we are currently exploring the characterization of complexes of **1** by spectroscopic and computational methods,[24] as well as the determination of their structures from PXRD data.[25]

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