

Guest-Directed Assembly of Caffeine and Succinic Acid into Topologically Different Heteromolecular Host Networks upon Grinding

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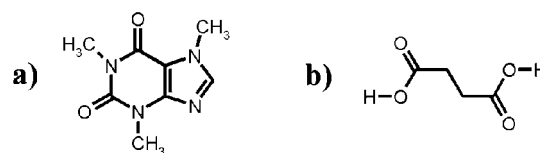
ABSTRACT: Two alternative inclusion host lattices are formed upon cocrystallization of caffeine and succinic acid in the presence of an appropriate guest. The host lattices differ in topology as well as in the stoichiometric ratio of caffeine and succinic acid. Both host frameworks are based on the assembly of a common, dumbbell-shaped heteromolecular building block involving molecules of caffeine and succinic acid. A grinding-based screening procedure revealed that host formation is independent of the state of aggregation, allowing the inclusion of compounds that are either solids, liquids, or gases under ambient conditions. The selectivity to form a particular host is directed by the molecular recognition properties of the guest. The ability of the guest to form C–H···O and halogen bonds appears to be the key factor in controlling the topology of the inclusion matrix, allowing the stoichiometric ratio of caffeine and succinic acid to be varied by appropriate choice of the guest.

Introduction

Cocrystals have emerged as an important tool in the design and construction of solid-state materials with tailor-made properties.¹ The reported uses of cocrystals include pharmaceutical materials,² electronic and optical materials,³ as well as media for conducting controlled solid-state organic syntheses.⁴ This interest in cocrystals has provided an impetus to improve cocrystallization methodologies and reagents.⁵ In the context of cocrystallization methodology, it has been demonstrated by several groups,⁶ including ours,⁷ that solid-state grinding (neat grinding) is a more efficient method for screening for cocrystal formation than the traditional cocrystallization from a solution. Furthermore, a small amount of liquid added during grinding further enhances the yield and crystallinity of the final product.^{8,9} Indeed, the efficiency of such liquid-assisted grinding has led to its use in exploring novel reactions in the solid state—for example, reactions between enantiomeric cocrystals.¹⁰

The ability to construct cocrystals by using reliable hydrogen-bonding motifs,¹¹ that is, supramolecular synthons,¹² suggests that host lattices could also be constructed via noncovalent assembly of two or more molecular species. Presumably, the modularity of this approach would enable the metric design of host structures. Indeed, this has already been demonstrated in the case of guanidinium sulfonate frameworks held together via charged-assisted hydrogen bonds between cationic and anionic components.¹³ However, this approach has hitherto, received significant attention only in the context of metal–organic frameworks (MOFs) held together via metal–ligand coordination bonds.¹⁴ Nevertheless, the benefits realized in the area of molecular inclusion within MOFs,¹⁵ as well as their covalent counterparts zeolites¹⁶ and covalent organic frameworks,¹⁷ encourage us to begin exploring multicomponent host frameworks held together by hydrogen bonds. In principle, the modular nature of such heteromolecular host frameworks provides an opportunity to design and construct solids for

Scheme 1. Molecular Diagrams of (a) Caffeine and (b) Succinic Acid



molecular inclusion with tailored materials properties. This opportunity is particularly attractive in the context of molecular (particularly gas) storage within molecular solids,¹⁸ as well as the construction of molecular sensors.¹⁹ Several hydrogen-bonded heteromolecular lattice hosts are known today,²⁰ and most are based on a synthetic strategy, introduced by MacGillivray and Atwood, that relies upon the use of bowl-shaped molecules as building blocks.²¹ Whereas most known heteromolecular host frameworks are binary, Nangia and co-workers have recently reported the serendipitous synthesis of a three-component host lattice consisting of 1,3,5-cyclohexanetricarboxylic acid, 1,2-bis(4-pyridyl)ethane, and 1,4-bis(4-pyridyl)butane.²² With our interest in pharmaceutical solids, we have reported a series of model pharmaceutical cocrystals involving caffeine (**caf**) as a model active pharmaceutical ingredient and carboxylic acids as cocrystal formers (Scheme 1).²³ In contrast to all the other carboxylic acids investigated, a binary cocrystal of **caf** and succinic acid (**sa**) could not be obtained. Instead, liquid-assisted grinding of **caf** and **sa** in the presence of a suitable guest provided a three-component system based on **caf** and **sa** in a 1:1 stoichiometric ratio to give the host matrix **1** (Figure 1) along with guest molecules.^{9,24} Compounds that are either liquids or solids under ambient conditions were readily incorporated as guests within **1**. We now describe how further screening of potential guests for **1** via liquid-assisted grinding has revealed the incorporation of a gaseous guest within the host lattice **1**, as well as the formation of an alternative two-component host matrix (**2**), also based on **caf** and **sa**.²⁴ The results of the screening procedure, in combination with X-ray crystallographic data, indicate that this alternative framework is stabilized only by such guests that can form both C–H···O

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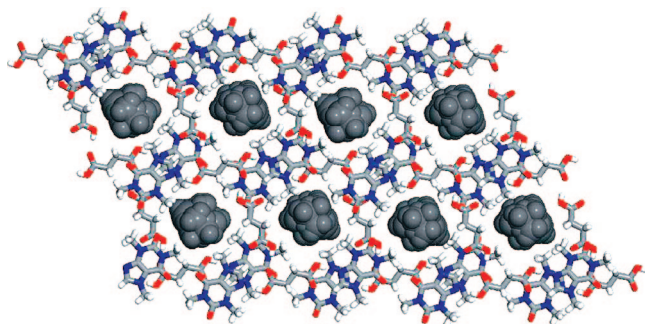


Figure 1. Fragment of the two-component host framework **1** along with disordered guest molecules (thioxane in this particular case). Components of the host and guest are shown using wireframe and space-filling models, respectively.

hydrogen and $X \cdots N$ (where $X = \text{Cl}, \text{Br}$) halogen bonds.²⁵ The comparison of the structures of the two hosts suggests a possible explanation why **caf** and **sa** only form host lattices, rather than a simple binary cocrystal.⁹

Experimental Section

All chemicals and reagents were commercially available from Sigma-Aldrich Chemical Co. and were used without purification.

Grinding screening experiments were performed by placing 200 mg of a manually ground mixture of **caf** and **sa** in a 1:1 stoichiometric ratio into a 10 mL stainless-steel grinding jar, accompanied by three drops of a potential liquid guest. In the cases where the guest was not a liquid, 50 μL of acetonitrile was added to the grinding mixture. Grinding in the presence of the CFCl_3 guest was done by adding 50 μL of a solution of CFCl_3 in acetonitrile (prepared by mixing equal volumes of cold liquid CFCl_3 and acetonitrile) to the grinding mixture. Grinding was performed in every case on a Retsch MM200 grinding mill over a period of 20 min, at a grinding frequency of 30 Hz, using two stainless-steel grinding balls with a 7 mm diameter. The products of grinding were analyzed immediately using X-ray powder diffraction (XRPD).

X-ray diffraction quality single crystals of $2 \cdot (\text{CHBr}_3)_2$ were obtained by the slow evaporation of a solution of 200 mg of a 4:1 mixture of **caf** and **sa** in 2 mL of 1:1 (v/v) mixture of methanol and bromoform.

Results and Discussion

The results of the XRPD analysis indicate that the neat grinding of equimolar quantities of **caf** and **sa** in the presence of chloroform produces a solid with an XRPD pattern that is different from that of the reactants or the structure **1** (Figure 2). After this solid had been left to stand in air, the XRPD pattern changed and corresponded to the starting materials, suggesting that the initial product could be a chloroform solvate of a new host structure different than **1**. In order to characterize this chloroform-containing material by means of single-crystal X-ray diffraction, we have attempted numerous cocrystallizations of **caf** and **sa** from solvent mixtures containing chloroform. Whereas almost all of such cocrystallization experiments failed, providing only mixtures of crystalline **caf** and **sa** powders, in a single case, small, well-developed crystals were obtained from a mixture of methanol and chloroform. The structure solution revealed the formation of a three-component inclusion compound in which a different type of host topology could be identified. Within this new host (**2**), chloroform molecules could clearly be identified as guests.

The host **2** consists of **caf** and **sa** in a 4:1 stoichiometric ratio and, in a manner similar to that seen in **1**, contains channels that are occupied by disordered guest molecules (Figure 3). Owing to the fast rate of decomposition of the single crystals,

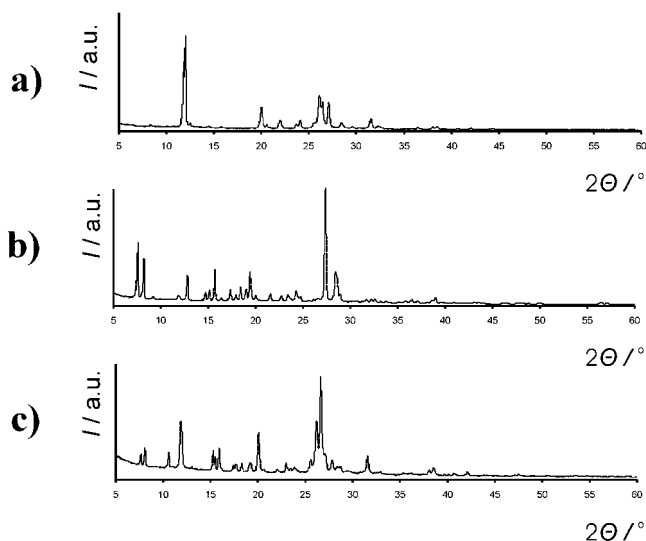


Figure 2. XRPD patterns for (a) a physical 1:1 mixture of **caf** and **sa**, (b) the inclusion compound of **1** prepared by grinding **caf** and **sa** with dioxane, and (c) the product of grinding **caf** and **sa** in the presence of chloroform.

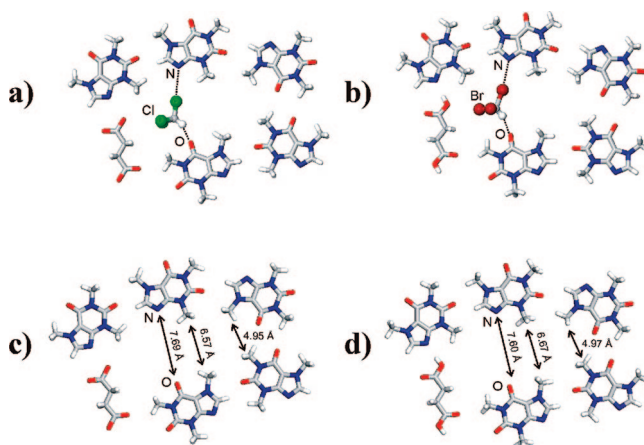


Figure 3. Fragments of the host framework **2** illustrating the guest positioning in (a) $2 \cdot (\text{CHCl}_3)_2$ and (b) $2 \cdot (\text{CHBr}_3)_2$ and the differences between channel sizes of (c) $2 \cdot (\text{CHCl}_3)_2$ and (d) $2 \cdot (\text{CHBr}_3)_2$.

it was not possible to determine the relative stoichiometric amount of chloroform in the cocrystal. In order to increase the relative stability of the three-component crystals, we then investigated the possible inclusion of the higher molecular weight (higher boiling point) guest bromoform. In particular, we speculated that a molecule with a shape and size similar to that of chloroform would provide an identical cocrystal inclusion lattice. Indeed, preliminary grinding experiments involving **caf**, **sa**, and bromoform provided a solid with an XRPD pattern similar to that obtained by grinding with chloroform, suggesting the formation of an inclusion compound based on **2** with bromoform as the guest. Cocrystallization of **caf** and **sa** in a 4:1 molar ratio from a 1:1 mixture of bromoform and methanol yielded crystals that were sufficiently stable to be handled in air without apparent degradation. Single-crystal X-ray diffraction revealed that the solid indeed consisted of the host framework **2**. The enhanced stability of the bromoform cocrystal enabled the relative stoichiometric amounts of **sa**, **caf**, and CHBr_3 to be determined via thermogravimetric analysis. The results indicated a composition of $(\text{sa}) \cdot (\text{caf})_4 \cdot (\text{CHBr}_3)_2$ (i.e., $2 \cdot (\text{CHBr}_3)_2$).²⁴ The crystallographic parameters (Table 1) of the chloroform and

Table 1. General and Crystallographic Parameters for $2 \cdot (\text{CHCl}_3)_2$ and $2 \cdot (\text{CHBr}_3)_2$

	compound	
	$2 \cdot (\text{CHCl}_3)_2$	$2 \cdot (\text{CHBr}_3)_2$
crystal system	orthorhombic	monoclinic
space group	$Cmca$	$P2_1/c$
unit cell parameters	$a = 6.6439(1) \text{ \AA}$ $b = 23.2514(4) \text{ \AA}$ $c = 33.5615(7) \text{ \AA}$	$a = 6.549(2) \text{ \AA}$ $b = 33.4489(8) \text{ \AA}$ $c = 12.0064(4) \text{ \AA}$
	$V = 5184.58(2) \text{ \AA}^3$	$V = 2541.05(7) \text{ \AA}^3$
Z	4	4
$D_{\text{calc}}/\text{g} \cdot \text{cm}^{-3}$	1.48	
number of reflections: measured/unique/ $I \geq 2\sigma(I)$	14049/3152/2077	8914/5299/4439
R_1	0.089	0.122 ^a
wR_2	0.284	0.320
S	1.032	1.101
$\Delta\rho_{\text{min, max}} (\text{e} \text{ \AA}^{-3})$	0.71, -0.73	2.09, -1.22

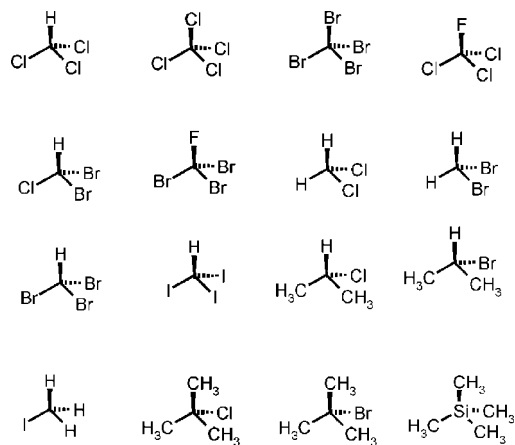
^a The disorder of the guest is complex and difficult to completely resolve, see refs 26 and 27.

bromoform inclusion compounds differ significantly: the CHBr_3 inclusion compound crystallizes in a space group of a lower symmetry, and one of the unit cell parameters (c) is approximately half the length of the corresponding parameter (b) in the chloroform compound. Nevertheless, the topology of the host framework **2** is almost identical in both inclusion compounds, suggesting that the chloroform inclusion compound should be assigned the composition $2 \cdot (\text{CHCl}_3)_2$.

In both CHCl_3 and CHBr_3 cocrystals, the molecules of **caf** and **sa** combine to form layers held together via $\text{O}-\text{H} \cdots \text{N}$ and $\text{C}-\text{H} \cdots \text{O}$ hydrogen bonds. In each layer, there are cavities formed by five molecules of **caf** and a single molecule of **sa**. Upon antiparallel stacking of the layers, the cavities give rise to channels. In both structures, the guest molecules are disordered within the channels but remain anchored to the channel wall through a $\text{C}-\text{H} \cdots \text{O}$ hydrogen bond (shortest $\text{C} \cdots \text{O}$ distances: 3.01 and 3.11 \AA for CHCl_3 and CHBr_3 , respectively), as well as through a weak halogen bond involving a halogen atom of the guest and a **caf** nitrogen atom decorating the channel wall²⁵ (Figure 3a,b).

The halogen bond separation $\text{Br} \cdots \text{N}$ (3.19 \AA) in the bromoform compound is shorter than the corresponding $\text{Cl} \cdots \text{N}$ (3.51 \AA) distance in the chloroform compound, indicating a stronger halogen bond.²⁵ The greater strength of the halogen bond can explain the difference in the population of disordered sites between the two inclusion compounds. In $2 \cdot (\text{CHCl}_3)_2$, the CHCl_3 molecule is disordered over three positions surrounding the host oxygen atom participating in the host-guest $\text{C}-\text{H} \cdots \text{O}$ bond, with the relative occupational parameters 0.25:0.50:0.25. On the other hand, the crystal structure refinement reveals that the guest molecule in $2 \cdot (\text{CHBr}_3)_2$ occupies one principal site with the relative occupational parameter 0.95.²⁶ The molecule in that site participates in both $\text{C}-\text{H} \cdots \text{O}$ and $\text{Br} \cdots \text{N}$ bonding, suggesting that the additional halogen bond effectively locks each CHBr_3 molecule on a particular site within the channel.²⁷

The formation of a halogen bond also explains the difference in channel geometry between the two inclusion compounds. In particular, the separation between the nitrogen and oxygen atoms that anchor the guest molecule is 0.9 \AA (i.e., 11%) shorter in the CHBr_3 compound. The rest of the interatomic separations that define the channel do not change significantly (Figure 3c,d). We note that the difference in the channel sizes for $2 \cdot (\text{CHCl}_3)_2$ and $2 \cdot (\text{CHBr}_3)_2$ not only illustrates how halogen bonding can affect the structure of a hydrogen-bonded framework, but also

Scheme 2. Library of Potential Guests Applied in the Mechanochemical Screening Procedure**Table 2.** Results of Grinding Experiments Involving **caf**, **sa**, and Selected Potential Guests

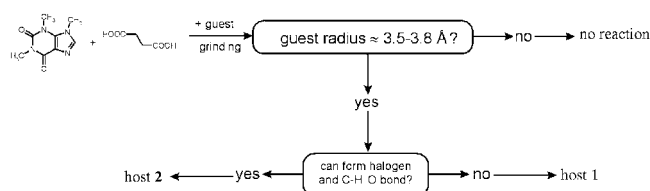
entry	potential guest	state of aggregation of the guest	product
1	CHCl_3	liquid	2
2	CCl_4 ^a	liquid	1
3	CBr_4	solid	no reaction
4	CFCl_3 ^b	gas	1
5	CHBr_3	liquid	2
6	CFBr_3	liquid	1
7	CH_2Cl_2 ^a	liquid	no reaction
8	CH_2Br_2	liquid	no reaction
9	CHClBr_2	liquid	2
10	CHI_3 ^a	solid	no reaction
11	$(\text{CH}_3)_2\text{CHCl}$	liquid	no reaction
12	$(\text{CH}_3)_2\text{CHBr}$	liquid	no reaction
13	CH_3I	liquid	no reaction
14	$(\text{CH}_3)_3\text{CCl}$	liquid	1
15	$(\text{CH}_3)_3\text{CBr}$	liquid	1
16	$(\text{CH}_3)_4\text{Si}$ ^b	gas	no reaction

^a See ref 9. ^b Guest was dissolved in acetonitrile.

demonstrates the flexibility of a two-component lattice host that is held together by noncovalent interactions.

To elucidate the factors that direct the formation of either **1** or **2** from a physical mixture of **caf** and **sa**, we decided to address the role of guest \cdots host $\text{C}-\text{H} \cdots \text{O}$ and halogen bonds. For that purpose, we constructed a library of 16 potential guests. The selected guests exhibit structural differences that influence their ability to form a $\text{C}-\text{H} \cdots \text{O}$ and/or a halogen bond (Scheme 2). Encouraged by the efficiency of the mechanochemical screening for the inclusion compounds of **1**, we decided to use grinding as the method to screen for inclusion compounds involving **caf**, **sa**, and a particular guest.

The results of grinding cocrystallization are summarized in Table 2. The general structure of a haloform molecule, that is, three halogen atoms and one hydrogen atom linked to a single carbon, appears to be essential to template the formation of **2**. Chlorine and bromine atoms appear equally suited as halogen atoms for that purpose (Table 2, entries 1 and 5). Replacement of a single bromine atom in CHBr_3 with chlorine (Table 2, entry 9) also results in the formation of **2**. The comparison of XRPD patterns indicates that the CHClBr_2 inclusion compound is structurally more similar to $2 \cdot \text{CHBr}_3$ than to $2 \cdot \text{CHCl}_3$. This suggests that the CHClBr_2 molecule in the cocrystal is most likely involved in a $\text{Br} \cdots \text{N}$ bond rather than a $\text{Cl} \cdots \text{N}$ bond, as may be expected from the relative differences of these halogen bonds. Although an $\text{I} \cdots \text{N}$ bond is supposed to be stronger than either a $\text{Cl} \cdots \text{N}$ or a $\text{Br} \cdots \text{N}$ bond,²⁵ a host framework is not

Scheme 3. Flowchart Summarizing the Inclusion Behavior of Heteromolecular Host Frameworks 1 and 2


obtained with iodoform (Table 2, entry 13), most likely because of the larger molecular radius (~ 4.1 Å), compared to that of CHBr_3 or CHCl_3 . On the other hand, the failure of CH_2Cl_2 , CH_2Br_2 , and CH_3I to form an inclusion compound with **caf** and **sa** can be explained by their smaller sizes. Consequently, the lower limit of the guest size for the formation of **2** is related to the radius of a CHCl_3 molecule (~ 3.5 Å), and the upper size roughly corresponds to a radius less than the radius of a CHI_3 molecule. That size is not the only factor in the formation of **2** is illustrated by the inability of $(\text{CH}_3)_2\text{CHCl}$ and $(\text{CH}_3)_2\text{CHBr}$ to form either **2** or **1** (Table 2, entries 11 and 12). This is explained by the reduced capability of the guest to form either a $\text{C}-\text{H}\cdots\text{O}$ or a halogen bond, since both potential guests have sizes comparable to CHCl_3 or CHBr_3 but with fewer electron-deficient halogen and hydrogen atoms. The importance of the $\text{C}-\text{H}\cdots\text{O}$ bond for the formation of **2** is apparent in the case of CFCl_3 and CFBr_3 as potential guests (Table 2, entries 4 and 6). These molecules, that lack the ability to hydrogen bond and have sizes very similar to that of CHCl_3 and CHBr_3 , template the formation of **1**, instead of **2**. This result bears additional significance, since CFCl_3 is a gas under ambient conditions (boiling point 23.7 °C). To the best of our knowledge, this is the first example of gas inclusion within a cocrystal lattice host. In addition, we note that the ability to switch between different cocrystal hosts by varying the guest offers an interesting possibility to modify the relative stoichiometric amounts of components in a cocrystal. That **1** also forms with CCl_4 , $(\text{CH}_3)_3\text{CCl}$, and $(\text{CH}_3)_3\text{CBr}$ (Table 2, entries 2, 14, and 15) suggests that a molecular radius around 3.50 Å is beneficial for the formation of **1**. That **1** does not form with molecules larger than CCl_4 , that is, CBr_4 and $(\text{CH}_3)_4\text{Si}$ (Table 2, entries 3 and 16), indicates that a radius in the range from 3.5 to 3.8 Å is optimal for the formation of **1**.

To summarize, molecules with an approximate radius of 3.50 Å that are capable of $\text{C}-\text{H}\cdots\text{O}$ bonding serve as templates to form the framework **2**. The crystal structures of $\mathbf{2}\cdot(\text{CHCl}_3)_2$ and $\mathbf{2}\cdot(\text{CHBr}_3)_2$ suggest that a halogen bond is most likely not required to form **2** but will stabilize its structure. Molecules of a similar size that cannot form a $\text{C}-\text{H}\cdots\text{O}$ bond generally template the formation of **1**.²⁸ This is illustrated in the flowchart of Scheme 3.

The exploration of different guests via grinding provides insight into the structural properties of the guests that direct the formation of either **1** or **2**. It is, however, still unclear why **caf** and **sa** form ternary cocrystal inclusion compounds rather than binary cocrystal inclusion compounds. We have previously rationalized the formation of inclusion compounds of **1** through a comparison with the 1:1 cocrystal of adipic acid and **caf**.^{9,29} The comparison of **1** and **2** now allows us to attempt a further rationalization of the inability to obtain a binary cocrystal of **caf** and **sa**. Both host frameworks are based on a common building block: a three-membered assembly of composition $(\text{caf})_2\cdot(\text{sa})$. The assembly has an identical structure in both frameworks. Neighboring $(\text{caf})_2\cdot(\text{sa})$ assemblies connect via pairs of $\text{C}-\text{H}\cdots\text{O}$ hydrogen bonds into infinite linear chains.

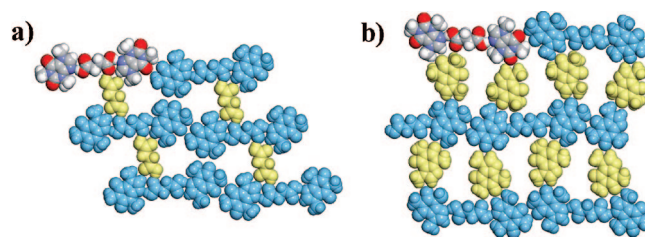


Figure 4. Comparison of the structures of the two host frameworks (a) **1** and (b) **2**. For clarity, the dumbbell-shaped building block $(\text{caf})_2\cdot(\text{sa})$ is shown in blue and the additional “pillars” of **sa** (in framework **1**) and **caf** (in framework **2**) are shown in yellow.

The linking of assemblies into chains in **1** involves different pairs of carbon and oxygen atoms than in **2**, resulting in different chain topologies for each case. Consequently, the frameworks **1** and **2** are composed of different chains of $(\text{caf})_2\cdot(\text{sa})$, separated by pillars of additional **sa** (in **1**) or **caf** (in **2**) molecules (Figure 4). For that reason, we speculate that the inability of **sa** to form a binary cocrystal with **caf** can be accounted for by the difficulty of obtaining a close-packed structure involving only dumbbell-shaped assemblies of $(\text{caf})_2\cdot(\text{sa})$. Indeed, a molecular inclusion that results from a particular molecular shape has been observed for molecules,³⁰ metal–organic complexes,³¹ and in a single case for a supramolecular species.³² We note that the guest-directed formation of different framework topologies using the same building block is reminiscent of zeolite chemistry, where the same structural units will assemble, via covalent bonds, into different topologies if provided a suitable molecular template.³³

In summary, we have described two host frameworks based on the same heteromolecular building block $(\text{caf})_2\cdot(\text{sa})$. The two frameworks have different topologies, and their formation is dependent on the nature of the guest. In contrast to a previously reported design for multicomponent host lattices that achieved molecular inclusion using bowl-shaped constituents, the $(\text{caf})_2\cdot(\text{sa})$ building block is a flat molecular assembly. We suggest that the inclusion capability of the new hosts is most likely caused by the dumbbell shape of the assembly that hinders the formation of a close-packed structure in the absence of a guest. The mechanochemical screening for potential guests provided insight into the structural parameters of the guests that direct the formation of different host topologies. In particular, the screening of a library of 16 potential guests established that the formation of **2** requires a guest with the ability to form a $\text{C}-\text{H}\cdots\text{O}$ bond and a halogen bond. Switching off the capacity to form a $\text{C}-\text{H}\cdots\text{O}$ bond (e.g., by replacing the hydrogen atom of the guest with a fluorine atom) leads to the formation of the alternative host framework **1**, whereas reducing the capacity to form a $\text{C}-\text{H}\cdots\text{O}$ bond as well as a halogen bond prevents cocrystallization in general. The ability to switch between different host frameworks allows the variation of relative ratios of components in a cocrystal. In particular, the ratio of **caf** and **sa** was changed from 1:1 (e.g., when using CCl_4 as the guest) to 4:1 (e.g., when using CHCl_3 as the guest). In addition to providing a strategy to manipulate the stoichiometric composition of a cocrystal, the heteromolecular host frameworks described herein also exhibit properties attractive for molecular storage: the versatility to absorb molecules that are solids, liquids, or gases at ambient conditions (observed for **1**) and the flexibility of the inclusion channel (observed for **2**). We are currently interested in the synthesis of further host lattices based on dumbbell-shaped heteromolecular assemblies, and we are

now investigating cocrystals of **caf** with other long-chain aliphatic dicarboxylic acids.

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Supporting Information Available: X-ray crystallographic information files (CIF) for $2 \cdot (\text{CHCl}_3)_2$ and $2 \cdot (\text{CHBr}_3)_2$. Thermogravimetric analysis curve for $2 \cdot (\text{CHBr}_3)_2$ crystals grown from solution and XRPD patterns for all relevant materials. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (27) The molecule in the major occupancy position probably adopts two different orientations, as indicated by the observed disorder of a single bromine atom (relative occupancies: 0.63:0.32). The two orientations are most likely very similar, as indicated by the inability to observe such disorder for remaining atoms in the molecule.
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