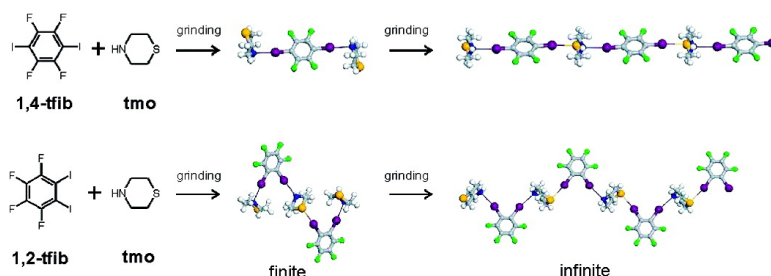


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A Stepwise Mechanism for the Mechanochemical Synthesis of Halogen-Bonded Cocrystal Architectures

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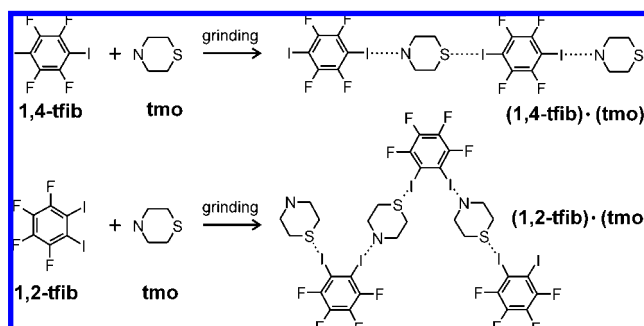
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The synthesis of multicomponent crystals (cocrystals) has been recognized as a versatile approach to construct functional organic solids for pharmaceutical, optical, and electronic applications, as well as for organic synthesis.¹ This interest has resulted in exploration of novel methods of cocrystal synthesis. Our group² and others³ have demonstrated that mechanochemical methods (i.e., grinding) are frequently more effective for the synthesis of cocrystals than traditional solution methods. At the moment, however, while an understanding of the mechanism of mechanochemical cocrystallization is increasingly important, few mechanistic studies of cocrystallization via grinding have been reported. These studies have mostly focused on bulk phenomena such as the formation of eutectic or amorphous phases.⁴ With an objective of understanding grinding from the perspective of underlying molecular recognition processes,⁵ rather than bulk phase transformations, we now present a mechanism of mechanochemical cocrystallization that considers the competition between supramolecular interactions.⁶

As model systems, we selected cocrystals of thiomorpholine (**tmo**) with tetrafluoro-1,4-diiodobenzene (**1,4-tfib**) or tetrafluoro-1,2-diiodobenzene (**1,2-tfib**). The cocrystals were anticipated to consist of linear and zigzag halogen-bonded⁷ chains (Scheme 1).⁸ We previously reported that grinding a 1:1 mixture of **1,4-tfib** and **tmo** for 30 min provided linear halogen-bonded chains of (**1,4-tfib**)·(**tmo**) in quantitative yield (Figure 1a).⁸ As a first entry to studying the mechanism of this mechanochemical synthesis, we now investigate the reaction course at shorter grinding times. After 4 min of grinding, the X-ray powder diffraction (XRPD) pattern of the solid mixture revealed the formation of (**1,4-tfib**)·(**tmo**), along with an unknown crystalline compound (Figure 1b). To obtain this possible intermediate in the form of crystals suitable for single-crystal measurements, we systematically explored the cocrystallization of **1,4-tfib** and **tmo** from solution. Crystallization of **1,4-tfib** from liquid **tmo** provided single crystals identical in structure to the grinding intermediate.⁹ Single-crystal structure determination revealed the intermediate consisted of finite (**1,4-tfib**)·(**tmo**)₂ assemblies (Figure 1c).

Pure (**1,4-tfib**)·(**tmo**)₂ could also be obtained by grinding together **tmo** and **1,4-tfib** in a 2:1 stoichiometric ratio. The appearance of (**1,4-tfib**)·(**tmo**)₂ as the reaction intermediate can be explained by the relative strengths of N···I and S···I bonds.^{8,10,11} We propose a stepwise mechanism for the synthesis of (**1,4-tfib**)·(**tmo**), wherein grinding of **1,4-tfib** and **tmo** is initially driven by the formation of stronger N···I bonds to provide discrete assemblies of (**1,4-tfib**)·(**tmo**)₂. Further grinding with **1,4-tfib** leads to polymerization of the assemblies via weaker S···I bonds, to form (**1,4-tfib**)·(**tmo**) chains.^{8,10} Consequently, in this mechanism, (**1,4-tfib**)·(**tmo**)₂ and (**1,4-tfib**)·(**tmo**) could be regarded as kinetic and thermodynamic products, respectively. That S···I interactions are not significant in the initial stages of the reaction is supported by the structure of **1,4-tfib** assemblies with the sulfur-free analogue of **tmo**, piperidine (**pip**). Cocrystals and assemblies of (**1,4-tfib**)·(**pip**)₂ and (**1,4-tfib**)·(**tmo**)₂ are isostructural, suggesting that thio moieties do not significantly affect the structure of such discrete assemblies (Figure 1d). Furthermore, grinding **1,4-tfib** with the nitrogen-free analogue of **tmo**, tetrahydrothiopyrane (**tht**), did not provide a cocrystal.

Scheme 1. Mechanochemical Synthesis of Linear and Bent Halogen-Bonded Chains



We believe the described mechanism arises most likely from the hierarchy of halogen bonds,¹¹ and we speculated that it might

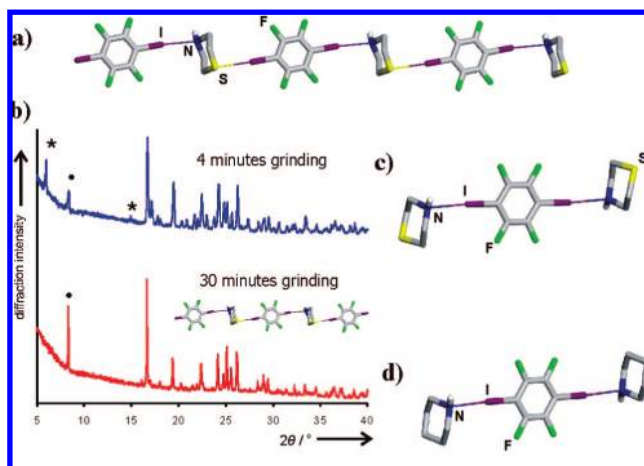


Figure 1. (a) Single (**1,4-tfib**)·(**tmo**) chain in the solid state; (b) XRPD patterns of a 1:1 mixture of **1,4-tfib** and **tmo** after 4 (blue) and 30 (red) min of grinding; (c) single solid-state assembly of (**1,4-tfib**)·(**tmo**)₂; (d) single solid-state assembly of (**1,4-tfib**)·(**pip**)₂. Diagnostic XRPD peaks for the reaction intermediate and (**1,4-tfib**)·(**tmo**) are labeled * and •, respectively.

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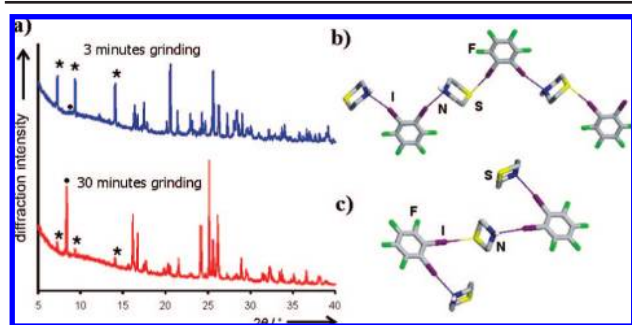


Figure 2. (a) XRPD patterns of a 1:1 mixture of **1,2-tfib** and **tmo** after 3 (blue) and 30 (red) min grinding; (b) infinite chain in $(1,2\text{-tfib})\cdot(\text{tmo})$ crystal; (c) finite five-molecule assembly in $(1,2\text{-tfib})_2\cdot(\text{tmo})_3$. Diagnostic XRPD peaks for the reaction intermediate and for $(1,2\text{-tfib})\cdot(\text{tmo})$ are labeled * and •, respectively.

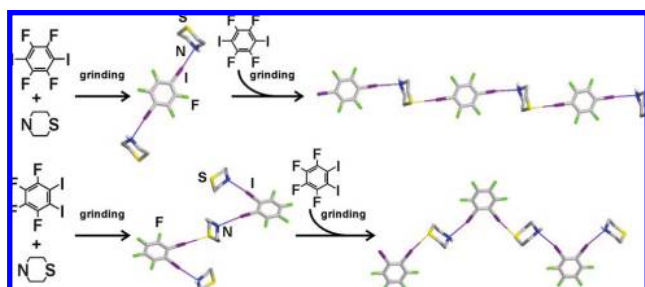


Figure 3. Stepwise mechanism for the formation of halogen-bonded chains involving strong $\text{N}\cdots\text{I}$ and weak $\text{S}\cdots\text{I}$ bonds.

be generally applicable to those cocrystals composed of different noncovalent interactions.^{6,12} To test this hypothesis, we have therefore explored the grinding synthesis of **tmo** cocrystals with **1,2-tfib** (Scheme 1, bottom).

Grinding equimolar amounts of **tmo** and **1,2-tfib** provided the cocrystal $(1,2\text{-tfib})\cdot(\text{tmo})$ as the major product. The minor product was a reaction intermediate that appeared at short grinding times and slowly disappeared by standing or by further grinding (Figure 2a). Recrystallization of the grinding product from nitromethane provided $(1,2\text{-tfib})\cdot(\text{tmo})$ as single crystals that were structurally characterized.⁹ The cocrystals consist of expected zigzag chains of **tmo** and **1,2-tfib**, held by $\text{N}\cdots\text{I}$ and $\text{S}\cdots\text{I}$ bonds (Figure 2b). The reaction intermediate could be obtained as the sole product by grinding **tmo** and **1,2-tfib** for 30 min in a 2:1 stoichiometric ratio. Single crystals of this intermediate were obtained by recrystallization from nitromethane.⁹

Structure analysis revealed that the intermediate consisted of finite five-membered assemblies $(1,2\text{-tfib})_2\cdot(\text{tmo})_3$ (Figure 2c). Each assembly is held together predominantly by $\text{N}\cdots\text{I}$ bonds and is decorated with free sulfur atoms that enable subsequent polymerization via $\text{S}\cdots\text{I}$ bonds.

To confirm the role of $(1,2\text{-tfib})_2\cdot(\text{tmo})_3$ and $(1,4\text{-tfib})\cdot(\text{tmo})_2$ in the grinding synthesis of halogen-bonded chains, each intermediate was prepared separately and ground with an equimolar amount of **1,4-tfib** or **1,2-tfib**. Grinding of the solid mixtures provided pure $(1,4\text{-tfib})\cdot(\text{tmo})$ and $(1,2\text{-tfib})\cdot(\text{tmo})$, supporting the proposed mechanism (Figure 3).⁹

Additionally, we note that the solid-state reaction of **1,4-tfib** and $(1,4\text{-tfib})\cdot(\text{tmo})_2$ to form $(1,4\text{-tfib})\cdot(\text{tmo})$ also occurs upon aging of a briefly ground solid mixture of reactants.¹³ XRPD patterns of

the mixture during aging revealed only the presence of $(1,4\text{-tfib})\cdot(\text{tmo})_2$ and/or $(1,4\text{-tfib})\cdot(\text{tmo})$, suggesting that **1,4-tfib** participates in the reaction in the amorphous form.

In summary, we describe a mechanism for the mechanochemical synthesis of halogen-bonded cocrystals. The mechanism addresses the molecular recognition between reactants and demonstrates, for the first time, the competition between supramolecular interactions in a solid-state reaction.^{6,11} The competition results in the kinetically controlled formation of reaction intermediates. The described mechanism provides a microscopic view of grinding, complementary to the one usually obtained by considering phase transformations.⁴ Whereas the latter is useful in the context of materials chemistry, the former is attractive for the synthetic chemist. In that context, the ability to isolate reaction intermediates illustrates how microscopic understanding of a grinding reaction can enable the synthesis of different cocrystals using the same components.

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Supporting Information Available: Crystallographic data for $(1,4\text{-tfib})\cdot(\text{tmo})$,⁸ $(1,4\text{-tfib})\cdot(\text{tmo})_2$, $(1,4\text{-tfib})\cdot(\text{pip})_2$, $(1,2\text{-tfib})\cdot(\text{tmo})$, and $(1,2\text{-tfib})_2\cdot(\text{tmo})_3$ in CIF format, XRPD patterns, details of grinding experiments and the synthesis of single crystals. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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