“Total Synthesis” Supramolecular Style: Design and Hydrogen-Bond-Directed Assembly of Ternary Supermolecules**

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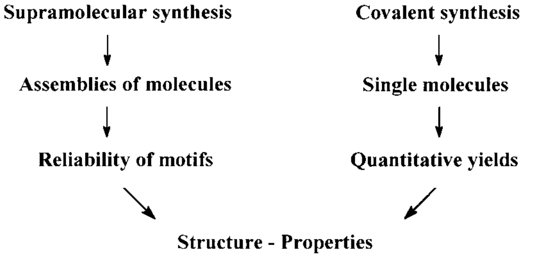
> “Molecular chemistry, thus, has established its power over the covalent bond. The time has come to do the same for non-covalent intermolecular forces.”[1]

Chemical synthesis, the making and breaking of covalent bonds, is a fundamental scientific discipline with consequences for all aspects of human existence. A vast number of reactions have been devised, discovered, and refined allowing more and more complicated molecules to be made using extraordinary multistep synthetic processes.[2] In contrast, crystal engineering, a new but rapidly expanding area of science concerned with the construction and properties of assemblies and extended networks of molecules, has yet to reach anywhere near the same level of sophistication.[3] Nevertheless, covalent *and* supramolecular (noncovalent) synthesis can be seen as having considerable overlap in terms of both methods and focus (Scheme 1).

> “The consequences of directed and selective hydrogen-bond interactions on sets of molecules… are to a solid-state chemist what a new synthesis is to a solution chemist.”[4]



Scheme 1. Comparison between covalent and supramolecular synthesis.

In recent years many systematic and elegant studies have been witnessed that demonstrate how molecular assemblies of increasing complexity and dimensionality can be put together with complementary intermolecular interactions, for example, hydrogen bonds and $\pi-\pi$ interactions. Typically, these are homomeric architectures: “most crystals are built from identical (or enantiomeric) copies of the same molecule”.[5] However, in order to bring crystal engineering to a higher level of refinement and versatility it is necessary to identify reliable supramolecular reactions and synthetic strategies that will allow us to build multicomponent heteromeric structures, such as binary and ternary supermolecules.[6]

Much of the important ground work regarding the preparation and utility of cocrystals was carried out by Etter and Frankenbach:[7] binary cocrystals were synthetic goals, but these cocrystallization reactions were also used as probes of the competition between different hydrogen-bonding interactions. An important rule of thumb resulted from this work: in a system with a multitude of hydrogen-bonding functionalities “the best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another”.[8] From this it also follows that the second-best donor will form a hydrogen bond to the second-best acceptor, etc. It is still important to remember, however, that solid-state assembly is an enormously complex process governed by a subtle balance between relatively weak and often ill-defined intermolecular forces (in addition to possible complications posed by competition between kinetic and thermodynamic factors). This certainly helps to explain the fact that multistep intermolecular synthesis is not commonplace. In fact, to the best of our knowledge,[9–11] there is not a single example in the Cambridge Crystallographic Database[12] (amongst over 224000 entries) of a 1:1:1 ternary cocrystal containing supermolecules with well-defined and predictable connectivity that was synthesized using a deliberate supramolecular design strategy.[13]

Our approach to the design of ternary structures is based upon two simple principles: 1) Hydrogen bonds often form in a hierarchical fashion (best donor to best acceptor, second-best donor to second-best acceptor, etc.)[8] and 2) a small number of specific intermolecular interactions can provide a large part of the stabilization energy of molecular crystals.[14]

The centerpiece in our supramolecular systems is isonicotinamide. This molecule readily reacts with aromatic carboxylic acids to form 1:1 binary cocrystals that contain a robust and reproducible hydrogen-bonded motif (shown in Figure 1 for benzoic acid as the carboxylic acid (**1**)).[15]

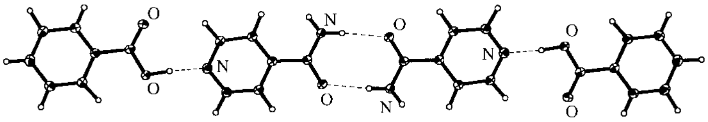


Figure 1. The supermolecule in the 1:1 cocrystal **1** of isonicotinamide and benzoic acid held together by acid ··· pyridine and amide ··· amide hydrogen-bonding interactions.

The best donor (carboxylic acid) and the best acceptor (pyridine nitrogen atom) form a short intermolecular N ··· O hydrogen bond, and the supermolecule is completed through a self-complementary amide ··· amide interaction. Isonicotinamide is a good example of a suitable building block for ternary cocrystals: it has two distinctly different, yet relatively strong, hydrogen-bonding moieties, and it shows good “structural flexibility” (it can form well-defined crystals with different components).[16] The primary hydrogen bond in this

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[**] We are grateful for financial support from the NSF (CHE-0078996) and Kansas State University.

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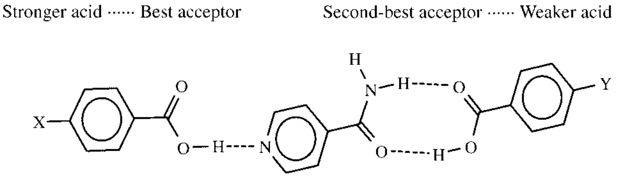
system is the acid ··· pyridine interaction and, since hydrogen bonds have large electrostatic components, the strength of this interaction is governed by the acidity of the carboxylic acid donor. Of course, if the acid is too strong, the proton will be transferred to the nitrogen atom; this will result in an ionic compound and not in a cocrystal.[17]

The "weaker" link in the tetrameric motif in **1** is the amide ··· amide interaction. Since many reported structures contain heteromeric amide ··· acid hydrogen bonds (in preference to the corresponding homomeric options),[12, 18] our plan was to replace the amide ··· amide interaction with a more favorable heteromeric acid ··· amide interaction, thereby allowing the introduction of a third component in a specific manner. By offering two different carboxylic acids to the isonicotinamide molecule, we expected the stronger acid to interact preferentially with the best acceptor (the pyridine nitrogen atom) and the weaker acid to form a heteromeric motif with the remaining amide moiety (Scheme 2).



Scheme 2. Proposed scheme for the construction of a three-component supermolecule.

This supramolecular design strategy was put to the test by allowing equimolar amounts of a weaker acid, a stronger acid, and isonicotinamide to react in an aqueous solution. Herein we present the crystal structures of three different cocrystals obtained using this approach.[15, 19]

Compound **2** is a 1:1:1 ternary cocrystal of 3,5-dinitrobenzoic acid, isonicotinamide, and 3-methylbenzoic acid that contains the desired three-component supermolecule with the expected connectivity. The stronger acid ($\mathrm{p}K_a = 2.8$)[20] interacts with the pyridine nitrogen atom, and the weaker acid ($\mathrm{p}K_a = 4.3$)[20] competes successfully for the amide moiety and forms a heteromeric hydrogen-bonded motif (Figure 2). Compound **3** is a ternary cocrystal of 3,5-dinitrobenzoic acid, isonicotinamide, and 4-(dimethylamino)benzoic acid with the intended three-component supermolecule. Again, the strong acid ··· pyridine nitrogen atom interaction persists, and the weaker acid ($\mathrm{p}K_a = 6.5$)[20] generates a heteromeric motif with the amide moiety (Figure 2). Finally, compound **4** is a 1:1:1 ternary cocrystal of 3,5-dinitrobenzoic acid, isonicotinamide, and 4-hydroxy-3-methoxycinnamic acid with the same primary supramolecular connectivity as in **2** and **3** (Figure 2). It is important to note that the desired trimer persists even in the presence of the potentially disrupting OH moiety on the weaker acid ($\mathrm{p}K_a = 4.4$).[21]

Two important intermolecular synthons,[22] carboxylic acid ··· pyridine and carboxylic acid ··· carboxamide, have been utilized in the assembly of a family of 1:1:1 ternary cocrystals. All three structures contain a heteromeric, three-component supermolecule synthesized through the use of hierarchical (best donor/best acceptor, second-best donor/second-best acceptor) hydrogen-bonding interactions. None of the crystals incorporate solvent molecules in the lattice. There is no ambiguity about the classification of these compounds: they are molecular cocrystals, not ionic compounds. All the hydrogen atoms were located from difference density maps, and the C−O distances on each carboxylic acid moiety are distinctly different, and indicate the presence of one C−O and one C=O bond. In addition, the C-N-C angles on the isonicotinamide molecules are in the range of 117.7–118.5°, which is consistent with those exhibited by other nonprotonated pyridine derivatives.[23] All three structures (**2**–**4**) are also stabilized by additional π(weak acid)–π^*(strong acid) charge-transfer interactions (see Figure 3).

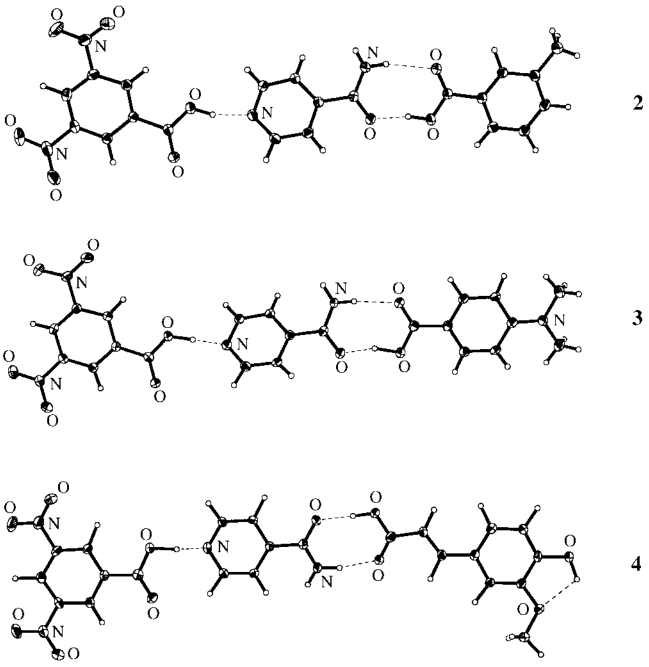


Figure 2. Structures of the ternary supermolecules in **2** (top), **3** (middle), and **4** (bottom) with the stronger acid ··· pyridine interaction being the "best" hydrogen bond and the weaker acid ··· amide interaction being the "second-best" hydrogen bond.

The ternary compounds are all colored whereas their constituent parts range from off-white to pale yellow in color. The colors of **2**–**4** reflect the changes in the resulting π–π^* separation. The weakest acid, 4-(dimethylamino)benzoic acid, has the highest energy HOMO, and therefore the smallest π–π^* separation, which results in the deep red color of **3**. Compound **4** is orange and **2** is yellow; these colors correspond to an expected increase in the energy of the π–π^* charge-transfer interaction in these compounds.[24] It is unlikely that this charge transfer takes place through the isonicotinamide molecule from the weak acid (π) to the strong acid (π^*). Instead, as the supermolecules are stacked in an antiparallel fashion (Figure 3) with considerable donor–acceptor overlap between neighboring weak and strong acids, it is reasonable to assume that the charge transfer is through space. The intrastack phenyl–phenyl separations are about 3.35 Å. Charge-transfer interactions are also known to be important for stabilizing 1:1 binary cocrystals containing weak and strong aromatic carboxylic acids.[25, 26] Of course it must be

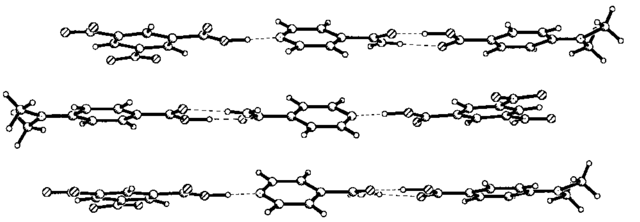


Figure 3. Side-on view of a stack of supermolecules arranged in an antiparallel fashion in **3** to illustrate the π(weak acid) – π*(strong acid) charge-transfer interactions.

noted that we have presented a strategy for the construction of ternary supermolecules: real crystals are created through the three-dimensional assembly of such building blocks. Neighboring trimeric supermolecules are linked laterally through a variety of weaker N–H ··· O and C–H ··· O interactions, which lead to lamellar architectures in all three cases.

This work has demonstrated that three-component supermolecules can be constructed through the use of known intermolecular synthetic operations. Although these forces are weaker than covalent interactions, it is clearly possible to assemble more than two different building blocks in a preconceived manner. We have every reason to believe that more complex supermolecules can be readily synthesized through an improved awareness of the balance and competition between intermolecular interactions. In addition, supramolecular reactions of this type may have important ramifications for the pharmaceutical industry (circumventing patents, modifying crystal habit, and facilitating processing), and may also lead to new strategies for chiral separation.

Received: March 19, 2001
Revised: June 18, 2001 [Z16800]

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