MS30-O4 Supramolecular reactivity in the solid state: Step-wise assembly of ternary cocrystals through hydrogen and halogen bonding

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In the field of crystal engineering, cocrystals have been among the most pursued topics in the last two decades.[1] Devising rational strategies for systematically assembling them has been one of the greatest challenges, even more so for cocrystals consisting of more than two components. Whereas both mechanochemical assembly and disassembly of the binary cocrystals have been studied [2,3], the supramolecular reactivity of ternary cocrystals is still almost unexplored [4].

Given our interest in the orthogonality of hydrogen and halogen bonding in the context of supramolecular chemistry, we focused our interest on the combination of thioureas, phosphine oxides and various halogen bond donors. These types of molecules are known to form binary cocrystals through hydrogen (thiourea and phosphine oxide) or halogen bonds (thioureas or phosphine oxides with different halogen bond donors), and we hypothesized that the combination of all three might yield ternary cocrystals.

Our initial studies revealed successful formation of a number of ternary cocrystals, primarily sustained by N–H···O hydrogen bonds between thioureas and phosphine oxides and C–I···S halogen bonds between thioureas and halogen bond donors. Next, reactivity studies were performed in the following way: First, for a given set of three components A, B, C, each two were ground together to probe for the formation of binary cocrystals AB, BC and AC. Subsequently, each of the resulting mixtures or cocrystals was ground with the third component from the set to probe for the formation of ternary solid ABC. These experiments revealed a spectrum of possible outcomes, from component sets where all of AB, BC, AC and ABC were successfully formed, to such cases where only binary cocrystal AB was detected, with all other combinations only yielding various mixtures. Structures of the obtained binary and ternary cocrystals, as well as the results of the mechanochemical experiments, will be discussed.

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Keywords: crystal engineering, mechanochemistry, ternary co-crystals, hydrogen bonding, halogen bonding

MS30-O5 Hydrogen-bonded cocrystals of the drug metformin: From molecular interactions analysis to supramolecular synthesis and characterization of Met-bis(DCA), a pharmaceutical cocrystal with enhanced anti-leukemic activity

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N,N-dimethylbiguanide, metformin (Met) in the medical literature, is a widely used active pharmaceutical ingredient (API) of the biguanide class. Besides being the drug of first choice for oral therapy of type 2 diabetes, its anticancer activity is the subject of active research. Met can exist in three resonance-stabilized forms, *i.e.* as neutral molecule (Met), monoprotonated ($MetH^+$) or diprotonated ($MetH_2^{2+}$) cation, with dissociation constants in water typical of biguanides: pK_{a1}~12.40; pK_{a2}=2.96.

We have investigated the crystal chemistry of Met in series of pharmaceutical cocrystals (PCC) prepared using various acids as coformers (CF), with particular focus on Generally Recognized as Safe (GRAS) compounds, nutraceuticals and APIs. By cocrystallization under different conditions we obtained 33 PCCs of a quality suitable for structural determination, 27 containing $MetH^+$ and 6 $MetH_2^{2+}$. The delocalized biguanide fragment is never found to be planar and the hydrogen bond (H-bond) is the dominating molecular interaction. Crystal packing analysis reveals that Met and CF molecules are linked by extended H-bond networks with a number of conserved patterns (dimers, rings, ribbons, sheets, *etc*). The H-bond strength is increasing with decreasing ΔpK_a according to the PA/pK_a equalization principle. All complexes formed by Met with acidic compounds are salts, as predictable from the thermodynamic acid-base constants. As a consequence of the high value of pK_{a1} (12.40), neutral Met is easily protonated at the iminic nitrogen even by weak acids, giving rise to 1:1 ionic adducts consisting of monoprotonated $MetH^+$ and one anion, but since pK_{a2} is much smaller (2.96), only strong acids succeed in protonating the secondary amino nitrogen, forming 1:2 ionic adducts consisting of diprotonated $MetH_2^{2+}$ and two anions.

As successful application, we report the crystal engineering, supramolecular synthesis, crystal structure determination and in vitro biological activity testing of two new PCCs of Met with the antileukemic drug dichloroacetic acid (DCA, pK_a=0.9) in 1:1 (**1**, $MetH^+ \bullet DCA^-$) and 1:2 (**2**, $MetH_2^{2+} \bullet 2DCA^-$) ratio, respectively. The activity of **1** resembles closely the 1:1 physical mixture of NaDCA and Met.HCl, while **2** displays a significantly higher activity and induces a synergistic apoptotic cell death on primary cells of human patients. To our best knowledge, **2** is the first PCC displaying a synergistic enhancement of the anticancer activity of two APIs.

Keywords: hydrogen bond, molecular interactions, pharmaceutical cocrystals, metformin, carboxylic acids, DCA