Monitoring polymorphic transition of a cocrystal to a salt using time-resolved X-ray powder diffraction and solid-state nuclear magnetic resonance spectroscopy

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Crystal engineering has emerged as an important field of solid-state chemistry, developing tools to deliberately design functional organic solids. A particularly exciting aspect of crystal engineering is the tuneability of physicochemical properties of organic solids such as solubility, thermal stability, bioavailability etc. without altering the underlying molecular structure(s) – a concept of high relevance for pharmaceutical industry.[1] Altering physisochemical properties can be achieved by relying on different solid forms, such as polymorphs, cocrystals, and salts.[2] The latter two are multicomponent systems that, in organic solids, are essentially distinguished by the position of a proton within the crystal structure. While different chemical systems can appear in different forms, proton transfer has rarely been observed for multicomponent systems with identical stoichiometric composition.[3]

In this contribution, we present an extremely rare case of polymorphism between a metastable molecular (cocrystal) and ionic (salt) form of a two-component system based on nicotinamide and a dicarboxylic acid, induced by supramolecular tautomerism. In specific, we show the polymorphic transition from a metastable cocrystal to a salt, monitored using time-resolved powder X-ray diffraction (PXRD) and solid-state nuclear magnetic resonance spectroscopy. Both formerly unknown structures of were solved *ab initio* from PXRD data and further analyzed using spectroscopic methods, as well as density functional theory calculations.

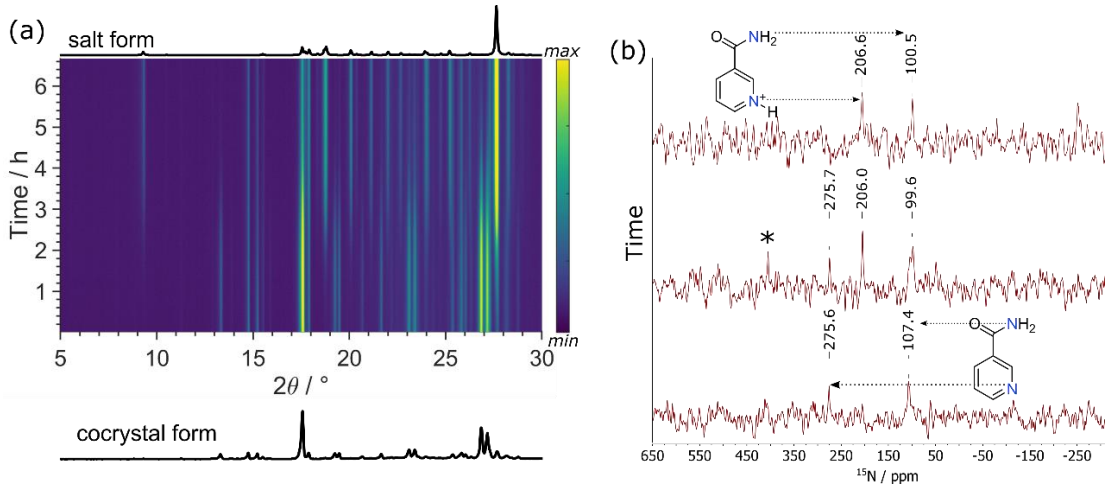

Figure 1: Monitoring the polymorphic transition from metastable cocrystal to salt using (**a**) PXRD and (**b**) ^{15}N ssNMR spectroscopy.

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