

Crystallization of Nicotinic and Hydroxynicotinic Acids from Solution: Solubility and Aggregation

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Crystallization from solution is one of the oldest processes used to obtain pure solid materials. Yet the molecular level events behind this process remain largely unknown [1]. Understanding how molecules in solution aggregate, and how these aggregates evolve into different crystal forms (polymorphs) is a fundamental scientific problem. Its elucidation would constitute a critical step for polymorphism control, hence to prevent polymorphism related industrial incidents, such as those involving the Norvir, Tegretol and Avalide drugs [2].

Although surprisingly scarce, the study of families of compounds is of major importance to obtain insights on how systematic variations in molecular structure influence solute-solvent and solute-solute interactions that direct molecular aggregation throughout a crystallization pathway. Nicotinic acid and its hydroxy derivatives are excellent models in this regard, since they include different functional groups which can form highly directional interactions through hydrogen bonding (either as acceptor or donor) and are prone to polymorphism. They have also known biological activity (e.g. nicotinic acid, also called niacin or vitamin B3, is one of eight water-soluble B vitamins) and crystallization plays an important role in their production for a variety of industrial applications, such as in the manufacture of pharmaceuticals, herbicides, and insecticides [3].

In this work, preliminary results concerning the crystallization of the nicotinic/hydroxynicotinic acid family from solution are presented. They include (i) solubility vs. temperature determinations in water (protic solvent) and dimethyl sulfoxide (DMSO, aprotic solvent), for all hydroxynicotinic acid isomers, to define the saturation conditions for crystallization, and (ii) a $^1\text{H-NMR}$ study of nicotinic acid aggregation during cooling crystallization in $\text{DMSO-}d_6$ (Figure 1).

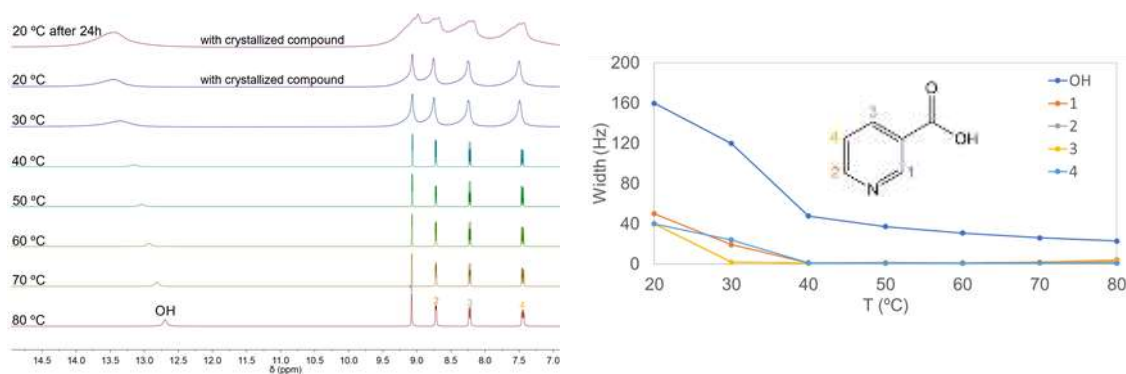


Figure 1. $^1\text{H-NMR}$ results for the cooling crystallization of nicotinic acid in $\text{DMSO-}d_6$.

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