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

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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[1,2]. Understanding how molecules in solution aggregate, and how these aggregates evolve into different crystal forms (polymorphs), constitutes a fundamental scientific problem. Its elucidation would establish a critical step for polymorphism control, preventing polymorphism industrial incidents, such as those involving the Norvir, Tegretol and Avalide drugs[3].

Although surprisingly scarce, studies of families of compounds are relevant to obtain insights on how systematic variations in molecular structure influence solute-solvent and solute-solute interactions, and how they mediate molecular aggregation throughout a crystallization pathway. Nicotinic acid and its hydroxy derivatives are excellent models in this regard, as they include different functional groups, which can form highly directional interactions through H-bonding (either as acceptor or donor), and are prone to polymorphism. This family has 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[4].

In this work, results concerning the crystallization of nicotinic and hydroxynicotinic acids 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}H-NMR study of nicotinic acid aggregation during cooling crystallization in DMSO-d_6 (Figure 1).

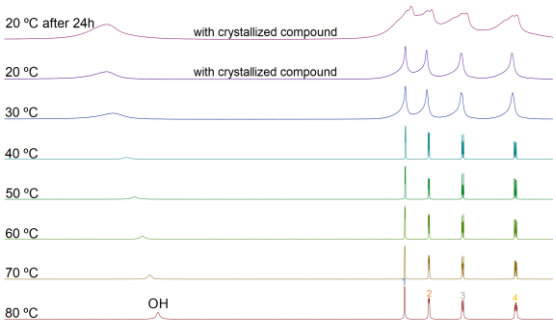

Figure 4. 1H-NMR spectra for the cooling crystallization of nicotinic acid in DMSO-d_6

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References

[1] R. J. Davey, J. Garside, From Molecules to Crystallizers – An Introduction to Crystallization, Oxford University Press, New York, 2000.
[2] J. W. Mullin, Crystallization, fourth ed., Butterworth-Heinemann, Oxford, 2001.
[3] A. Y. Lee, D. Erdemir, A. S. Myerson, Ann. Rev. Chem. Biomol. 2 (2011) 259.
[4] B. Elvers, S. Hawkins, Vitamins, fifth ed., VCH Weinheim, A27 (1986) 5814.