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The first steps of crystallization: aggregation of nicotinic and hydroxynicotinic acids in solution

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Abstract: Crystallization from solution is one of the oldest processes used to obtain pure products. Yet the molecular level events taking place during this process remain a major unresolved scientific question.[1] Elucidating how molecules in solution aggregate, and how these aggregates evolve into different crystal forms (polymorphs), is an essential step to prevent incidents in the pharmaceutical industry, such as those reported for Tegretol, Norvir and Avalide drugs.[2]

Nicotinic acid and its hydroxy derivatives can provide insights on how systematic variations in molecular structure affect solute-solvent and solute-solute interactions. Moreover, they might help in uncovering aggregation processes behind the formation of different crystal forms. This family of compounds also have well-known biological activity (e.g. nicotinic acid, also known as niacin or vitamin B3, is one of eight water-soluble B vitamins), and ample industrial applications, such as in the manufacture of pharmaceuticals, herbicides, and insecticides.[3] For the above stated reasons the nicotinic/hydroxynicotinic acid family is an excellent model for the studies therein. Here, preliminary results concerning the crystallization of this family of compounds from solution are presented. They include solubility determinations in water (protic solvent) and dimethyl sulfoxide (DMSO, aprotic solvent) to define the saturation conditions for crystallization and a ^{1}H-NMR study of nicotinic acid aggregation during cooling crystallization in DMSO-d_6 (Figure 1).

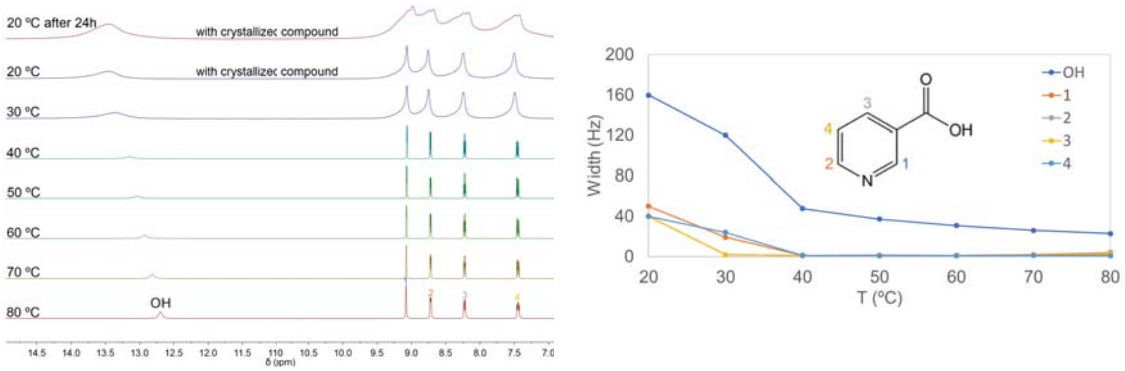

Figure 1: ^{1}H-NMR results for the cooling crystallization of nicotinic acid in DMSO-d_6 .

Keywords: Crystallization, Solubility, Crystal Nucleation, Polymorphism

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References:

1. (a) R. J. Davey, J. Garside, From Molecules to Crystallizers – An Introduction to Crystallization, Oxford University Press, New York, 2000; (b) J. W. Mullin, Crystallization, 4th ed., Butterworth-Heinemann, Oxford, 2001.

2. A. Y. Lee, D. Erdemir, A. S. Myerson, Annu. Rev. Chem. Biomol. 2 (**2011**) 259–280.

3. Vitamins, In Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., B. Elvers, S. Hawkins, Eds., VCH: Weinheim, 1986, Vol. A27, p 5814.