Solubility Measurements: A Powerful Tool to Investigate Polymorphism in Molecular Organic Solids and Molecular Self-Assembly in Solution

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INTRODUCTION

It is common knowledge that solubility is a property of significant practical importance. The single fact that it is essential for the development of crystallization processes involved in the manufacture of a variety of solid products, provides sufficient justification.[1]

The relevance of solubility information has, however, a much wider scope. In this work, examples of how solubility measurements can be used to characterize polymorphism in molecular organic solids and, when supported by molecular dynamics (MD) simulations, to investigate the self-assembly processes behind the crystallization of organic compounds from solution, will be presented.

DESCRIPTION OF THE WORK

Solubility measurements in different solvents as a function of temperature, complemented with the characterization of the solid phase in equilibrium with the solution by powder X-ray diffraction, were used to determine the stability domains of the known polymorphic forms of 4'-hydroxybenzaldehyde and 4'-hydroxy-acetophenone.

Analogous measurements made on simvastatin, combined with MD simulations, provided insights into the interplay of solvent-solute interactions and solute self-assembly processes behind the observed solubility differences.

RESULTS AND DISCUSSION

Based on the solubilities of 4'-hydroxybenzaldehyde and 4'-hydroxyacetophenone shown in Fig. 1(a,b), the transition temperatures delimiting the stability domains of the know polymorphs of these compounds could be established as 277 K and 300 K, respectively.[2,3]

In the case of simvastatin, Fig.1(c,d), the MD simulation results suggested that the experimentally observed solubility trend essentially depends on the ability of the solvent molecules to interact with large solute aggregates present in solution, rather than individual molecules.[4]

FIGURES AND TABLES

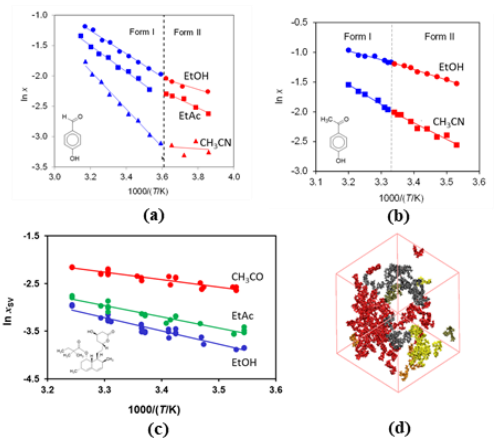

Fig. 1: Solubilities of (a) 4'-hydroxybezaldehyde, (b) 4'-hydroxyacetophenone and (c) simvastatin in different solvents. (d) Snapshot of the simulation box for a simvastatin solution in ethanol close to saturation.

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