Calorimetry as a Tool to Investigate Polymorphism in Organic Compounds

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Polymorphism is a common phenomenon in organic compounds, which consists in the ability of a molecule to crystalize in different packing arrangements. The structural differences between polymorphs are often accompanied by significant changes in physical and chemical properties (e.g. solubility, dissolution rate, fusion and decomposition temperature, etc.). The control of polymorphism is, therefore, a key aspect in the production of materials, such as active pharmaceutical ingredients (APIs), that need to be obtained with highly reproducible properties. A critical aspect within this scope is the assessment of the relative stability of the various polymorphic forms that may coexist under a given set of ambient conditions. A good indicator of that stability hierarchy is the standard molar enthalpy of transition between forms, $\Delta_{tn}H^{o}_{m}$, which reflects their difference in lattice energy, and can be experimentally determined from enthalpy of solution measurements.[1] Quite often, however, the amount of each polymorph available during development stages is insufficient for the application of common solution calorimetry techniques that typically require samples of more than 100 mg per experiment.[1]

The present work describes a novel electrically calibrated solution calorimetry cell (Fig. 1a), that requires samples of only 1-10 mg, and was specifically designed for a Thermal Activity Monitor (TAM) calorimeter (Fig. 1b). The accuracy and precision of the system was tested, based on the measurement of the standard molar enthalpy of solution of KCl in water. The apparatus was then used to determine the standard molar enthalpy of transition between the two known polymorphs of 4'-hydroxyacetophenone (HAP), at 298.15 K, from measurements of their standard molar enthalpies of solution in DMSO. The obtained result was in excellent agreement with a previously reported value measured in ethanol using ~7 times larger amounts of sample and solvent. The fact that the two HAP polymorphs are easily prepared and such good agreement was observed between results from two considerably different calorimetric techniques and solvents, suggests that HAP can be proposed as benchmark system for the validation of solution calorimetry measurements or force field predictions on the relative enthalpic stability of organic polymorphs.

(a) (b)

Fig. 1 (a) Calorimetric cell developed in this work. (b) Thermal Activity Monitor (TAM) instrument used in the experiments.

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