

How high-resolution X-ray powder diffraction should help the construction of topological p-T diagrams leading to the stability hierarchy of polymorphs

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High-resolution X-ray powder diffraction (XRPD) allowed a rapid breakthrough in crystal structure determination without single crystals. Regarding polymorphism of pharmaceuticals, this answered the first request of industrial drug-discoverers. Unfortunately, the second one, « can you predict how many forms may occur », remains a matter for some unpowdered crystal ball. Gibbs thermostatics should help answer the last request : « given a set of forms, please let us know about the stability ranking ». However, regarding phase transitions (or 2-phase equilibria), thermostatics reduces to heat measurements (*i.e.* calorimetry) when « work » is ignored because ΔV is neglected. $\Delta G = \Delta H - T.\Delta S = \Delta U + P.\Delta V - T.\Delta S$ becomes $\Delta G = \Delta U - T.\Delta S$, that entails $\Delta U = Q_p$ instead of $\Delta U = Q_v$.

p-T phase diagrams for one-component systems involving polymorphism can be topologically constructed using the Clapeyron equation $dp/dT = \Delta S/\Delta V$ or $\Delta H/T.\Delta V$, incorporating ΔH and T from DSC runs and ΔV FROM HIGH-RESOLUTION XRPD as a function of T combined with liquid density measurements. This construction is achieved through simple (or obvious) assumptions, and is particularly useful for understanding and describing cases when polymorphs do not transform into each other experimentally.

The main assumption is that condensed phases are in equilibrium with their vapour phase when examined in « open » conditions. Since p , the vapour pressure, is positive for any $T > 0$ Kelvin, high-resolution XRPD provides ones with specific volumes for phases in equilibrium with their vapour, and DSC runs with ΔH values for phase changes at triple points involving this vapour. Thus, the dp/dT slopes for 2-phase equilibrium curves can be obtained without (vapour) pressure measurements. Since the origin of such curves are triple points involving the vapour phase, any p-T diagram can be constructed using simple inferences from basic classical thermodynamics (and without using empirical rules).

The stability hierarchy of polymorphs is then inferred from the relative positions of the sublimation curves at any temperature, following the Ostwald rule (the lower the pressure, the stabler the phase), which provides ones with inequalities in the vapour pressures of polymorphs without measurements of usually very small, thus questionable, vapour pressures.