Sublimation crystallisation and polymorph stability

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In the case that an organic compound exhibits crystalline polymorphism, it is often necessary to know, which of the polymorphs is the most stable one, in particular for pharmaceuticals. Polymorph stability can be obtained through computational methods, but often experimental proof is required as well. Whereas computational methods may suffer from approximated interaction potentials, experimental values have their own shortcomings and depend on the purity of the sample -unknown impurities are well-known triggers for polymorphism-, its propensity to decompose during measurement or a sheer impossibility to experimentally obtain a certain polymorph that has been found in silico. Presently the most used method by far in the literature to determine polymorph stability is a few differential scanning calorimetry runs. Although, the speed of DSC measurements can definitely be considered as an advantage, the precision and accuracy of the results have suffered with respect to adiabatic calorimetry.

Using examples from pyrazinamide and benfluorex[1], it will be shown that solid-solid phase equilibrium temperatures can be hard to observe by DSC. Although the absence of solid-solid transitions can be due to activation barriers that are too high to overcome in the solid state, it is often the case that DSC measurements are just too fast for the experimental question at hand. Another approach to obtain polymorph stabilities as a function of temperature is sublimation crystallisation under a temperature gradient, although whether or not it is possible to observe transition temperatures depends to a large extent on the vapor pressure of the molecular compound. As an example, the formation of two polymorphic crystals of carbamazepine under a gradient has been shown in Figure 1.

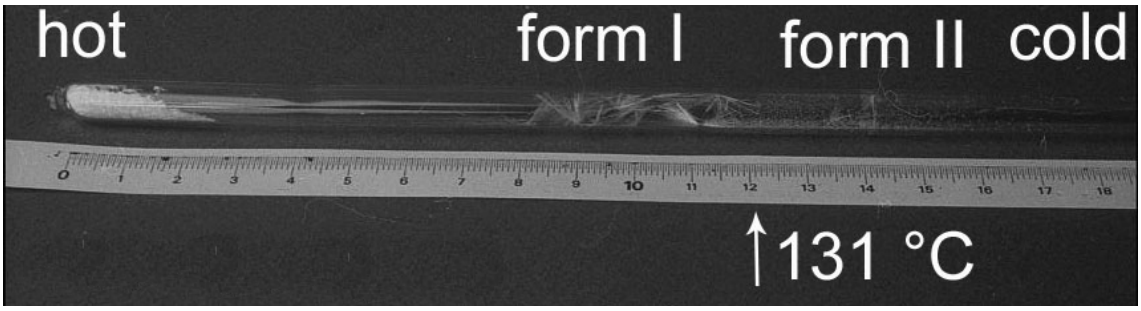

Figure 1 Sublimation under a temperature gradient of carbamazepine

Although the sharp boundary in Figure 1 for carbamazepine is the preferred outcome, sublimation experiments are not often this clear-cut.[2] In the case of pyrazinamide polymorphs alpha and gamma were found both in a range of temperatures. Therefore, sublimation measurements at specific temperatures were carried out and the preferential growth of single crystals of one of the polymorphs was used to determine the equilibrium temperature between them. This temperature can then be used with enthalpy data from the DSC and specific volumes of the two polymorphs from X-ray diffraction to draw up a pressure-temperature phase diagram of the system. It will be shown that redundancy in such pressure-temperature phase diagrams and thermodynamic requirements can be used to confirm and improve data analysis.

References

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