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Determining both rate and heat of solution in an isoperibolic calorimeter

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In formulation, bioavailability issues often involve liquid-solid interactions. Measurements made in an Isoperibolic Calorimeter thus may be directly applicable. In the usual experiment, temperature change is measured as a function of time. The heat of dispersion is determined by comparing the temperature change when an ampoule containing a solid is broken (dispersing the solid in solvent) with the temperature change found using calibration heats. The dispersion of a water soluble freeze dried decapeptide into a TRIS HCl buffer (50mM, pH 7.5) at 45°C produces a large heat effect (-241.3 kJ/mol) which is a reflection of a proton linked interaction of the decapeptide (4-carboxyl groups) with the buffer whose heat of dissociation is 47.44 kJ/mol. The heat of solution of the decapeptide in water or phosphate buffer (ΔH_d = 3.3) is about +2kJ/mol. Thus using TRIS HCl amplifies the signal.

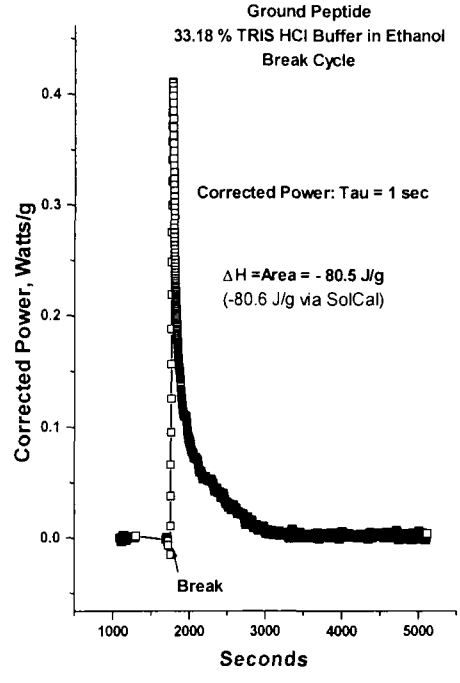
As an example of how this technique can distinguish between different forms of the same drug entity, the heat of solution of the same decapeptide ground in a mortar was measured in the same buffer. Its heat of solution was -158.5 kJ/mol. Surface area is most likely involved in the observed difference in heats of dispersion.

What has not been done by others is to use the Isoperibolic Calorimeter to measure Rates of Solution. This can be done in the SolCal instrument (Thermometric, Jarfalla, Sweden). The approach is based on using solvent mixtures that reduce solubility to the point where rates are measurable and where rates of different forms can be compared in this same solvent. Taking ground decapeptide and dispersing it into a hydroalcoholic system gives a lower heat of solution (-80.6 kJ/mol) and a protracted return to quasi equilibrium at the break compared to buffer alone (4000 vs. 300 sec).

It is possible to convert temperature vs. time into power (Watts or J/sec) vs. time. The advantage in doing this is that Power (J/sec) is directly proportional to rate of reaction (dn/dt) where the proportionality constant is simply the heat of reaction (J/mol). Heat flow (dQ/dt, J/sec) is related to temperature, T, through heat capacity (C) by

$$dQ/dt = C\,[dT/dt + 1/\tau\,(T - T_\infty)]$$

where τ is a time constant for the instrument (τ = C/k, k = heat exchange constant). Tau permits correction of heat flow for instrumental distortion. It has a value of about 1 second for systems with a heat capacity of about 350 J/K. Corrected Power vs. Time data for the dispersion of ground decapeptide into 33% Buffer/Ethanol gives for the "break" cycle:



From relationships such as these it is possible extract rate constants from fraction dispersed vs. time relationships and compare rates of solution.