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A disruption index for quantifying the solid state disorder induced by additives or impurities. II. Evaluation from heat of solution

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Summary

In a previous report a dimensionless disruption index (d.i.) was proposed for quantifying the disruptive influence of an additive or impurity (the guest substance) when present in solid solution in the crystal lattice of a host substance at mole fractions, x_2, less than 0.05. The d.i. value was defined as the rate of change of the difference between the entropy of the solid, S_{solid}, and that of the liquid, S_{liquid}, with respect to the ideal entropy of mixing of the components of the solid, ΔS^m_{ideal}, i.e. d.i. $= -\delta(S_{liquid} - S_{solid})/\delta(\Delta S^m_{ideal})$. The determination of $(S_{liquid} - S_{solid})$ from the heat of fusion and the melting point using differential scanning calorimetry (DSC) or differential thermal analysis (DTA) could itself change the entropy and the concentration of point defects and dislocations by an annealing process. To overcome these problems $\delta(S_{solution} - S_{solid}) = \delta(\Delta S^s)$, which is shown to approximate closely to $\delta(S_{liquid} - S_{solid})$, is determined isothermally (e.g. at 25 or 37°C) using solution calorimetry and measurements of J, the dissolution rate per unit surface area. ΔS^s is derived from the heat of solution, ΔH^s, and from the Gibbs free energy of solution which is changed by $RT \cdot \delta(\ln J)$ on doping, where R is the gas constant and T is the absolute temperature. The possibilities that ΔS^s can be calculated from ΔH^s directly assuming enthalpy–entropy compensation, or simply by ignoring the term containing $\delta(\ln J)$, are also considered. The above possibilities are examined using the limited data available for adipic acid doped with hexanoic, octanoic, undecanoic or oleic acid. The d.i. values from solution calorimetry are of the order 10^3, indicating an enormous potential for lattice disruption, while d.i. values from DSC are generally smaller and decrease with decreasing chain-length of the guest molecule. This suggests that heating in DSC promotes rearrangement of the guest molecules and annihilation of crystal defects. Ignoring $\delta(\ln J)$ changes d.i. by up to 15%. Much larger influences of $\delta(\ln J)$ are given by oleic acid as the guest which tends to concentrate on the surface. In general, the pseudo-disruption index, p.d.i., calculated as $-\delta(\Delta H^s/T)/\delta(\Delta S^m_{ideal})$, may approximate sufficiently closely to d.i. to be useful. Thus, the p.d.i. value for cephaloridine monohydrate doped with cephaloridine anhydrate, corresponding to slight moisture loss from the lattice of the former, is of the order 1, which suggests very little lattice disruption.

Introduction

In a previous report (York and Grant, 1985) a dimensionless quantity, termed the 'disruption index' (d.i.) was proposed for quantifying the disruptive influence of an additive or impurity (the guest substance), when present in solid solution in the crystal lattice of a host substance at mole fractions, x_2, less than 0.05. The d.i. $(= b - c)$ is defined as the rate of change of the difference between the entropy of the solid, S_{solid}, and the entropy of the liquid, S_{liquid}, with respect to the ideal entropy of mixing of the components of the

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solid, ΔS^m_{ideal}. A small change, δ, in ΔS^m_{ideal} brought about by the incorporation of the additive or impurity into the crystal lattice results in corresponding small changes, δ, in S_{solid} and S_{liquid}, thus:

$$\delta(S_{solid}) = b \cdot \delta(\Delta S^m_{ideal}) \quad (1)$$

$$\delta(S_{liquid}) = c \cdot \delta(\Delta S^m_{ideal}) \quad (2)$$

Subtracting Eqn. 2 from Eqn. 1 affords:

$$\delta(S_{solid}) - \delta(S_{liquid}) = (b - c) \cdot \delta(\Delta S^m_{ideal}) \quad (3)$$

where b and c are positive, dimensionless proportionality constants which represent the sensitivity of the disorder of the host solid and liquid respectively to simple mixing or dilution with a guest substance, for which mixing is represented by ΔS^m_{ideal}. By definition, d.i. = b − c, which represents the difference between the sensitivity of the entropy of the solid to contamination and that of the liquid. Since

$$\delta(S_{solid}) - \delta(S_{liquid}) = \delta(S_{solid} - S_{liquid}) \quad (4)$$

Eqn. 3 may be written in the form

$$\delta(S_{liquid} - S_{solid}) = -(b - c) \cdot \delta(\Delta S^m_{ideal}) \quad (5)$$

ΔS^m_{ideal} is determined by chemical analysis of the respective mole fractions, x_j, of the host substance, x_1, and of each guest substance, x_2, x_3, etc., as described previously (Chow et al., 1985a; York and Grant, 1985), thus:

$$\Delta S^m_{ideal} = -R \sum x_j \ln x_j \quad (6)$$

Since the entropy of fusion, ΔS^f, is defined by the equation

$$\Delta S^f = S_{liquid} - S_{solid} \quad (7)$$

Eqn. 5 can be written thus:

$$\delta(\Delta S^f) = -(b - c) \cdot \delta(\Delta S^m_{ideal}) \quad (8)$$

As described and discussed by York and Grant (1985), d.i. (= b − c) may be determined as the negative slope of the plot of ΔS^f against ΔS^m_{ideal} for $x_2 < 0.05$, i.e.

$$\Delta S^f = \Delta S^f_0 - (b - c) \cdot \Delta S^m_{ideal} \quad (9)$$

where the intercept, ΔS^f_0, represents the entropy of fusion of the pure crystals of the host substance. ΔS^f is given by the enthalpy of fusion, ΔH^f, divided by the absolute melting point, T_m. Two disadvantages of this procedure have been pointed out by York and Grant (1985). Firstly, differential thermal analysis (DTA) and differential scanning calorimetry (DSC), which are the most common methods of determining ΔS^f, may themselves change the degree of disorder of the crystal lattice, S_{solid}. During the heating procedure these thermal analytical techniques will increase the thermal motion and/or change the concentration and nature of the crystal imperfections, i.e. point defects and dislocations, in a process known as 'annealing' in metallurgy and materials science. These effects may be reduced by the use of a rapid heating mode. Secondly, the measurement of ΔS^f itself, for thermo-labile materials or for substances which decompose near the melting point, will be liable to appreciable errors reducing the reliability of d.i. values.

In order to overcome the above problems inherent in the thermal analytical techniques, it may be possible to employ an isothermal procedure for assessing changes in $(S_{liquid} - S_{solid})$ in Eqn. 5. Solution calorimetry will normally provide accurate measurements of the enthalpy of solution, ΔH^s, of the crystals in a suitable solvent at a more suitable defined temperature, such at 25 or 37°C. From ΔH^s it may be possible to arrive at values of the entropy of solution, ΔS^s, of the crystals. ΔS^s may then be employed in place of ΔS^f in Eqns. 7–9. The present report explores and appraises this alternative procedure for determining d.i.

Theoretical Background

The thermodynamic quantities for the solution process are defined as follows:

$$\Delta H^s = H_{solution} - H_{solid} \quad (10)$$

$$\Delta S^s = S_{solution} - S_{solid} \quad (11)$$

$$\Delta G^s = G_{solution} - G_{solid} \quad (12)$$

$$= -RT \cdot \ln \gamma_s C_s \quad (13)$$

$$\simeq -RT \cdot \ln C_s \quad (14)$$

ΔG^s is the free energy of transfer (or solution) of one mole of the major solute component (the host) from the solid to the solution standard state. The latter corresponds to unit concentration of the host, while the solubility, C_s, must be sufficiently low that the laws of dilute solution apply. Under these conditions the activity coefficient of the dissolved solute, $\gamma_s \simeq 1$, and the solubility of the doped crystals reflects the free energy of the solid according to Eqn. 14.

The presence of small mole fractions of additives or impurities in solid solution will produce small changes, δ, in each of the quantities in Eqns. 10–12 thus:

$$\delta(\Delta Y^s) = \delta(Y_{solution}) - \delta(Y_{solid}) \quad (15)$$

where Y may stand for any thermodynamic state function, e.g. H, S or G. The presence of small mole fractions (< 0.05) of additives or impurities probably exerts a much smaller influence on $Y_{solution}$ than on Y_{solid}. However, it is probably less accurate to ignore this influence than to assume that it is the same as the corresponding influence on Y of the liquid host, Y_{liquid}, thus:

$$\delta(Y_{liquid}) \simeq \delta(Y_{solution}) \neq 0 \quad (16)$$

Eqn. 15 may then be written in the form

$$\delta(\Delta Y^s) \simeq \delta(Y_{liquid}) - \delta(Y_{solid}) \quad (17)$$

$$\simeq \delta(\Delta Y^f) \quad (18)$$

where the superscript f indicates the fusion process (cf. Eqns. 4 and 7). In other words, a change in the enthalpy (or entropy) of solution due to doping is equal to the corresponding change in the enthalpy (or entropy) of fusion at any given convenient temperature, which could well be ambient. Eqns. 16–18 are most accurate if the environment of the impurity molecules in the solution are the same as that in the host liquid. However, Eqn. 16 will be reasonably reliable when the mole fractions of the additives are small (< 0.05) and when the solvent used for dissolving the crystals provides intermolecular interactions that are similar in strength and nature to those in the supercooled liquid host. Eqn. 18 indicates that Eqns. 8 and 9 can be expressed in terms of the entropy of solution, thus:

$$\delta(\Delta S^s) = -(b - c) \cdot \delta(\Delta S^m_{ideal}) \quad (19)$$

$$\Delta S^s = \Delta S^s_0 - (b - c) \cdot \Delta S^m_{ideal} \quad (20)$$

Thus, for small values of x_2 (< 0.05) a plot of ΔS^s against ΔS^m_{ideal} should be linear with a slope of $-(b - c)$, where d.i. is given by $(b - c)$. The intercept ΔS^s_0 represents the entropy of solution of a pure crystal of the host substance for which $\Delta S^m_{ideal} = 0$, because no doping of the crystal lattice has taken place.

However, ΔS^s is more difficult to derive from ΔH^s than is ΔS^f from ΔH^f, because ΔS^s is a function of both ΔH^s and ΔG^s according to the following thermodynamic identity:

$$\Delta S = (\Delta H - \Delta G)/T \quad (21)$$

whereas $\Delta S^f = \Delta H^f/T_m$ at the melting point. Applying the standard states appropriate for Eqn. 14, Eqn. 21 leads to

$$\Delta S^{s\theta} = \Delta H^s/T + R \cdot \ln C_s \quad (22)$$

The second term on the right of this equation reflects the deduction from Eqns. 12–14 that any change in G_{solid} as a result of doping of the crystal is equivalent to an equal change in $RT \cdot \ln C_s$. This influence may be stated as follows:

$$\delta G_{solid} = RT \cdot \delta(\ln C_s) \quad (23)$$

where δ is an operator denoting a small change as a result of doping of the host crystal lattice.

ΔS^s may, in principle, be calculated from experimental values of ΔH^s and solubility using Eqn. 22. In practice, however, the intrinsic solubility of imperfect or doped crystals is difficult to determine directly by equilibrium measurements

because processes of recrystallization, which accompany dissolution at equilibrium, will lead to reductions in ΔG^{s}, G_{solid}, a_{solid} and C_s towards those of the pure crystals. Two approaches to this problem are proposed.

The first suggestion is to measure the dissolution rate per unit surface area of the crystals (intrinsic dissolution rate, J). This is related to the intrinsic solubility, C_s, according to the equation of Noyes and Whitney (1897) in the form:

$$J = \frac{dm}{dt} \cdot \frac{1}{A} = k(C_s - C) \tag{24}$$

where m is the mass dissolved in time t, (dm/dt) is the practical dissolution rate, A is the surface area of the crystals, C is the concentration dissolved and k is the rate constant for dissolution. Under sink conditions $C \ll C_s$, so that J is simply proportional to C_s, thus:

$$J = kC_s \tag{25}$$

$$\ln C_s = \ln J - \ln k \tag{26}$$

It is often difficult to evaluate k. For the purpose of estimating d.i. ($= b - c$) in Eqn. 19, it is necessary to ascertain the small changes, δ, in ΔS^{s} and ΔS^{m}_{ideal} as a result of doping. The corresponding small changes to the variables in Eqns. 25 and 22 are respectively:

$$\delta \ln C_s = \delta \ln J \tag{27}$$

$$\delta(\Delta S^{s}) = \delta(\Delta H^{s})/T + R \cdot \delta(\ln C_s) \tag{28}$$

$$\delta(\Delta S^{s}) = \delta(\Delta H^{s})/T + R \cdot \delta(\ln J) \tag{29}$$

since $\delta(\Delta S^{s\theta}) = \delta(\Delta S^{s})$. Eqns. 29 and 19 may be combined as follows:

$$\delta(\Delta H^{s})/T + R \cdot \delta(\ln J) = -(b - c) \cdot \delta(\Delta S^{m}_{ideal}) \tag{30}$$

Thus, at any convenient temperature, T, the d.i. as a result of doping of a given crystalline solid by a given additive or impurity may be evaluated from measurements of ΔH^{s} and J at various dopant levels whose analytical concentration in the crystals affords ΔS^{m}_{ideal} according to Eqn. 6.

The second approach is to derive $\delta(\Delta S^{s})$ from an extrathermodynamic relationship between ΔS^{s} and ΔH^{s} known as enthalpy–entropy compensation (Tomlinson, 1983). This principle states that

$$\delta(\Delta H) = \beta \cdot \delta(\Delta S) \tag{31}$$

where δ denotes the difference between a variable and defined system, such as the introduction of a molecular additive into a crystal lattice or liquid, which is undergoing a process involving a change in enthalpy and entropy, and β is a proportionality constant possessing the dimensions of absolute temperature and known as the isoequilibrium (or isokinetic) temperature or compensation temperature. Some examples of enthalpy–entropy compensation include the linear free energy relationships (LFER) of physical organic chemistry (e.g. the Brønsted, Hammett and Taft relationships), and the quantitative structure–activity relationship (QSAR) of medicinal chemistry (e.g. Hansch analysis). A survey of the variety of chemical, physical and biological systems to which enthalpy–entropy compensation has been found to apply (Tomlinson, 1983) suggests that there may be at least equal justification in applying this extrathermodynamic relationship to the present system in which the independent variable is the concentration of a given guest substance in solid solution in a host crystal lattice and in liquid solution in the host liquid.

If enthalpy–entropy compensation occurs, Eqn. 31 may be applied to Eqn. 19, thus:

$$\delta(\Delta H^{s}) = -(b - c) \cdot \beta \cdot \delta(\Delta S^{m}_{ideal}) \tag{32}$$

which predicts a linear relationship between ΔH^{s} and ΔS^{m}_{ideal}. In practice, β is usually an unknown temperature. In the absence of prior information, it may be helpful to define a pseudo-disruption index (p.d.i.) $= (b' - c')$ as follows:

$$T(b' - c') = \beta \cdot (b - c) \tag{33}$$

where T is the temperature of the calorimetric

TABLE 1

THERMODYNAMIC PROPERTIES OF CRYSTALS OF ADIPIC ACID (MOLE FRACTION, x_1) DOPED WITH A FATTY ACID (MOLE FRACTION, x_2) AND WATER (MOLE FRACTION, $x_3 = 0.04726$); DATA FROM CHOW ET AL., (1984, 1985b)

x_2 ($\times 10^5$)	ΔH^s [a] ($kJ \cdot mol^{-1}$)	$\delta(\Delta H^s)/T$ ($J \cdot K^{-1} \cdot mol^{-1}$)	J [b] ($mg \cdot min^{-1} \cdot m^{-2}$)	$R \cdot \delta(\ln J)$ ($J \cdot K^{-1} \cdot mol^{-1}$)	$\delta(\Delta S^s)$ [c] ($J \cdot K^{-1} \cdot mol^{-1}$)	$\frac{\beta}{298.15\ K}$ [d]	ΔH^f [e] ($kJ \cdot mol^{-1}$)	T_m [f] (K)	ΔS^f [g] ($J \cdot K^{-1} \cdot mol^{-1}$)	$\delta(\Delta S^f)$ ($J \cdot K^{-1} \cdot mol^{-1}$)	$\delta(\Delta S^m_{ideal})$ [h] ($mJ \cdot K^{-1} \cdot mol^{-1}$)
Additive = hexanoic acid											
0	33.193	0	75.18	0	0	–	33.91	420.9	80.56	0	0
82.6	24.295	−29.844	94.72	+1.921	−27.923	1.069	31.92	415.4	76.84	−3.71	55.28
516	(increasing)						30.28	413.7	73.21	−7.35	266.85
Additive = octanoic acid											
0	33.193	0	75.18	0	0	–	33.91	420.9	80.56	0	0
23.8	28.683	−15.127	56.82	−2.328	−17.454	0.867	32.85	421.3	77.98	−2.57	18.38
66.9	(increasing)						32.02	416.1	76.95	−3.60	45.97
Additive = undecanoic acid											
0	33.193	0	75.18	0	0	–	33.91	420.9	80.56	0	0
21.9	29.207	−13.369	90.31	+1.524	−11.845	1.129	26.87	405.3	66.30	−14.3	17.10
Additive = oleic acid		Unwashed crystals									
0	33.193	0	75.18	0	0	–	33.91	420.9	80.56	0	0
3.86	31.509	−5.647	73.23	−0.218	−5.865	0.963	32.11	417.2	76.95	−3.60	3.57
6.98	28.752	−14.897	21.62	−10.361	−25.257	0.590	31.28	414.4	75.49	−5.07	6.11
Additive = oleic acid		Chloroform-washed crystals									
0	33.193	0	75.18	0	0	–	–	–	–	–	0
3.86	31.509	−5.647	128.35	+4.447	−1.200	4.706	–	–	–	–	3.57
6.96	28.752	−14.897	150.15	+5.751	−9.145	1.629	–	–	–	–	6.11

[a] ΔH^s = Enthalpy of solution in water at 298.15 K.
[b] J = Intrinsic dissolution rate at 277.15 K (Eqn. 24).
[c] ΔS^s = Entropy of solution in water at 298.15 K.
[d] $\beta = \delta(\Delta H^s)/\delta(\Delta S^s)$ = Compensation temperature.
[e] ΔH^f = Enthalpy of fusion at the melting point.
[f] T_m = Melting point.
[g] ΔS^f = Entropy of fusion ($= \Delta H^f/T_m$).
[h] ΔS^m_{ideal} = Ideal entropy of mixing (Eqn. 6).

TABLE 2

VALUES OF THE ENTHALPY OF SOLUTION, ΔH^s, AT TEMPERATURE, T = 298.15 K, OF CRYSTALS OF δ-CEPHALORIDINE MONOHYDRATE (MOLE FRACTION, x_1) DOPED WITH δ-CEPHALORIDINE ANHYDRATE (MOLE FRACTION, x_2) AND THE IDEAL MOLAR ENTROPY OF MIXING, ΔS^m_{ideal}, OF THE COMPONENTS IN THE CRYSTALS; DATA FROM PIKAL ET AL. (1978) — FIG. 5

Mole Fractions		ΔH^s	$\Delta H^s/T$	$\delta(\Delta H^s/T)$	ΔS^m_{ideal}
x_1	x_2	($kJ \cdot mol^{-1}$)	($J \cdot K^{-1} \cdot mol^{-1}$)	($J \cdot K^{-1} \cdot mol^{-1}$)	($J \cdot K^{-1} \cdot mol^{-1}$)
1.000	0	15.1	50.5	0	0
0.929	0.071	14.4	48.4	−2.1	2.130
0.905	0.095	13.8	46.3	−4.2	2.610
0.844	0.156	13.0	43.5	−7.0	3.600
0.784	0.216	12.1	40.7	−9.8	4.338

measurement of ΔH^s. Eqn. 32 then becomes:

$$\delta(\Delta H^s) = -(b' - c')T \cdot \delta(\Delta S^m_{ideal}) \qquad (34)$$

Comparison of Eqns. 30 and 34 indicates that (b′ − c′) approximates to (b − c), i.e. p.d.i. ≈ d.i., when $RT \cdot \delta(\ln J) \ll \delta(\Delta H^s)$.

Analysis of the Available Data

Table 1 shows values of ΔH^s (determined calorimetrically), J (initial dissolution rate divided by specific surface area, Eqn. 24), and ΔS^m_{ideal} (calculated from the analytical data using Eqn. 6) for adipic acid doped with fatty acids by crystallization from aqueous solution (Chow et al., 1984,

TABLE 3

COMPARISON OF THE LINEAR REGRESSIONS OF THE FOLLOWING FUNCTIONS OF CRYSTAL DOPING AGAINST $\delta(\Delta S^m_{ideal})$ FROM EQN. 6: $\delta(\Delta S^s)$ FROM EQN. 29, $\delta(\Delta H^s)$ FROM SOLUTION CALORIMETRY, $\delta(\Delta S^f)$ FROM $\Delta H^f/T_m$ USING DSC; DATA FROM TABLES 1 AND 2

Host Lattice	Guest(s)	$\delta(\Delta S^s)$ according to Eqn. 19					
		No. of data (n)	Corr. coeff. ($-r$)	Resid. [d] S.D./ mean y	− Slope = (b − c) = d.i.	Slope S.D.	Intercept $\delta(\Delta S^s)_0$ ($J \cdot K^{-1} \cdot mol^{-1}$)
Adipic acid	Hexanoic acid + Water (constant)	2 [a]	–	–	505	–	0
Adipic acid	Octanoic acid + Water (constant)	2 [a]	–	–	950	–	0
Adipic acid	Undecanoic acid + Water (constant)	2 [a]	–	–	693	–	0
Adipic acid (unwashed)	Oleic acid + Water (constant)	3 [a]	0.922	0.696	3 972	1 664	2.44
Adipic acid (chloroform-washed)	Oleic acid + Water (constant)	3 [a]	0.878	0.976	1 422	775	1.14
Cephaloridine monohydrate	Cephaloridine anhydrate	–	–	–	–	–	–
		–	–	–	–	–	–

[a] These data points were taken from Table 1 (originally from Chow et al., 1984, 1985b).

[b] These data points at $x_2 = 0$ and 0.071 were taken from Table 2 (originally from Pikal et al., 1978).

1985b). The data presented in Table 1 are more accurate than those previously quoted and include the changes in the above quantities brought about by doping, including $\delta(\Delta S^s)$ calculated from Eqn. 29. The corresponding values of ΔH^f, T_m and ΔS^f are also shown to facilitate comparison with the fusion method of determining d.i. (York and Grant, 1985). The possibility of enthalpy–entropy compensation is examined by inclusion of values of the compensation temperature, β, calculated by means of Eqn. 31. For each guest substance only those values are presented which correspond to increases in lattice strain and crystal energy (i.e. decreasing ΔH^s and ΔH^f), since it is probable that higher levels of doping (i.e. higher x_2) cause a release of lattice strain (Chow et al., 1984) and even a limit of solid solubility (Chow et al., 1985a).

Consideration has been given to the appropriate conditions for determining J using Eqn. 24 (Chow et al., 1984, 1985b). The wetted surface area, A, is assumed to be proportional to the specific surface area determined by nitrogen adsorption. The initial dissolution rate, dm/dt, was determined from the profile of the dissolved concentration versus time. The dissolution medium should be the same as the medium used for the enthalpy of solution. Ideally, both media should approximate to the liquid solute to ensure that Eqns. 16–18 are very good approximations, but this may give an impracticably high dissolution rate, except for solids of high T_m. For adipic acid, a pure fatty acid would represent an ideal but impracticable choice of solvent. In fact, acidified water containing a trace of a surfactant was preferred as the dissolution medium. This polar, hydrogen-bonded solvent system must approximate quite closely to supercooled liquid adipic acid, while the dissolution rate is slow enough to be measurable. To reduce the dissolution rate sufficiently to provide accurate initial rates, the temperature was reduced from 25°C to 4°C. In Table 1 it is assumed that the logarithm of the ratio of doped to undoped dissolution rates, i.e. $\delta(\ln J)$, is independent of this temperature difference. Whereas the choice of the conditions employed for the determination of J may introduce errors, the magnitude of these errors is probably within experimental variability.

Oleic acid is believed not to be uniformly distributed throughout the adipic acid during crystal growth (Chow et al., 1985b). Unwashed adipic acid crystals exhibit a decreasing dissolution rate on increased doping with oleic acid. Washing of the crystals with chloroform to remove the adsorbed hydrophobic oleic acid before carrying out

$\delta(\Delta H^s)$ according to Eqn. 34						$\delta(\Delta S^f)$ according to Eqn. 8					
No. of data (n)	Corr. coeff. ($-r$)	Resid. [d] S.D./ mean y	$-$ Slope/T = (b′ − c′) = p.d.i.	Slope S.D.	Intercept $\delta(\Delta H^s)_0$ (kJ · mol^{-1})	No. of data (n)	Corr. coeff. ($-r$)	Resid. [d] S.D./ mean y	$-$ Slope = (b − c) = d.i.	Slope S.D.	Intercept $\delta(\Delta S^f)_0$ (J · K^{-1} · mol^{-1})
2 [a]	–	–	540	–	0	3 [a]	0.945	0.460	24.7	8.5	−1.04
2 [a]	–	–	823	–	0	3 [a]	0.937	0.446	75.2	28.0	−0.447
2 [a]	–	–	782	–	0	2 [a]	–	–	834	–	0
3 [a]	0.972	0.362	2383	572	0.250	3 [a]	0.990	0.180	841	120	−0.176
–	–	–	–	–	–	–	–	–	–	–	–
2 [b]	–	–	0.991	–	0	–	–	–	–	–	–
4 [c]	0.997	0.095	3.379	0.176	4.92	–	–	–	–	–	–

[c] These data points at $x_2 = 0.071$ to 0.216 were taken from Table 2 (originally from Pikal et al., 1978).
[d] Residual standard deviation/mean value of the dependent variable, $\delta(\Delta S^s)$, $\delta(\Delta H^s)$ or $\delta(\Delta S^f)$.

the dissolution experiment increases the dissolution rate relative to similarly washed, undoped crystals. Therefore, the more appropriate choice of J values, whether for unwashed crystals or for washed crystals, becomes problematic. Consequently, both sets of J values are presented in Table 1.

In an attempt to examine the utility of ΔH^s according to Eqns. 32 and 34 for estimating p.d.i. ($= b' - c'$), the analogous data of Pikal et al. (1978) for δ-cephaloridine monohydrate doped with anhydrous cephaloridine (i.e. partially dehydrated δ-cephaloridine monohydrate) are presented in Table 2 together with the calculated values of ΔS^m_{ideal}. The plot of ΔH^s against ΔS^m_{ideal}, according to Eqn. 34, can be interpreted in terms of two regions. The first region occurs at x_2 between 0 and 0.071 and therefore corresponds quite closely to the limiting conditions (x_2 between 0 and 0.05) stipulated by York and Grant (1985) for the determination of d.i. In fact, this first region affords p.d.i. = 0.99. The second region occurs at x_2 between 0.071 and 0.216, which is well above the level recommended for the determination of d.i. The statistical parameters for the linear regression analysis of $\delta(\Delta H^s)$ against $\delta(\Delta S^m_{ideal})$, together with the apparent values of p.d.i. are shown in Table 3.

Discussion

For adipic acid crystals doped with fatty acids Table 3 also shows the statistical parameters for the linear regression analysis of: (a) $\delta(\Delta S^s)$ versus $\delta(\Delta S^m_{ideal})$ (according to Eqn. 19); (b) $\delta(\Delta H^s)$ versus $\delta(\Delta S^m_{ideal})$ (according to Eqn. 34); and (c) $\delta(\Delta S^f)$ versus $\delta(\Delta S^m_{ideal})$ (according to Eqn. 8). These variables at different levels of doping (x_2) were taken from Table 1. In those cases for which only two pairs of values are available only the order of magnitude of the regression coefficient can be regarded as significant. The regression coefficients in Table 3 afford values of d.i. (or p.d.i.).

Table 3 shows that, in general, the d.i. values derived from enthalpies of fusion at the melting point (about 420 K) using DSC and Eqn. 8 (York and Grant, 1985) are smaller than those derived from solution calorimetry at 298.15 K using Eqns. 19 or 34. This suggests that the heating procedure inherent in DSC promotes intermolecular rearrangement and reduces the concentration and nature of the point defects and dislocations by a process analogous to annealing, as suggested in the Introduction. For adipic acid crystals doped with fatty acids the d.i. values from solution calorimetry (Eqn. 19 or 34) are of the order 10^3 (500–4000) indicating that each molecule of additive gives rise to very extensive disruption of the crystal lattice. The increase in disorder (entropy) is here about 10^3 times more than that expected for an ideal solution (corresponding to simple molecular substitution or molecular dilution). The d.i. values determined by DSC using Eqn. 8 (on the right in Table 3) became smaller the shorter the chain length of the fatty acid dopant, parallelling an increased propensity for molecular rearrangement in the crystal lattice.

Comparison of the d.i. ($= b - c$) values derived from Eqns. 19 and 29 with the p.d.i. ($= b' - c'$) values derived from Eqn. 34 shows no great differences in order of magnitude indicating that $RT \cdot \delta(\ln J) < \delta(\Delta H^s)$. It is therefore probably adequate for practical purposes to use p.d.i. values which do not require knowledge of the intrinsic dissolution rate. The compensation temperature, β, shown in Table 1 is seen to vary from guest to guest and from level to level. In several instances, particularly at low levels of guest, β is within 10% of 298.15 K suggesting that the use of Eqn. 34 is satisfactory in practice.

The possible inhomogeneity of distribution of guest molecules throughout the crystal lattice and the possibility of incomplete wetting of the crystal surfaces may account for the apparently complicated dependence of intrinsic dissolution rate, J, on the nature and mole fraction, x_2, of the incorporated guest. In the case of oleic acid as the guest, whether or not these hydrophobic molecules are washed from the surface greatly influences the direction as well as the magnitude of the change in dissolution rate (Table 1). When d.i. is calculated for oleic acid using Eqns. 19 and 29, the term containing $\delta(\ln J)$ greatly influences the derived value of d.i. Comparing d.i values with the p.d.i. value for which $\delta(\ln J)$ is ignored, the inclusion of $\delta(\ln J)$ for unwashed crystals increases d.i. by 67%,

whereas the inclusion of $\delta(\ln J)$ for washed crystals reduced d.i. by 40% (Table 3). Whenever there is some uncertainty about the distribution of guest molecules or about the interpretation of the dissolution rate data, it is probably a good pragmatic decision to omit J and to calculate p.d.i. from ΔH^s using Eqn. 34.

β-Lactam antibiotics provide examples of crystalline drugs which are decomposed by heat and for which DSC cannot therefore be used to determine d.i. These drugs are obvious candidates for the application of solution calorimetry to obtain values of d.i. The example discussed here is δ-cephaloridine whose crystal lattice can accommodate up to one mole proportion of water (Fig. 5 in Pikal et al., 1978). δ-Cephaloridine monohydrate can be continuously dehydrated to δ-cephaloridine anhydrate and vice versa without any phase changes, as indicated by X-ray diffraction data (Pikal, 1985). Thus, dehydration is considered to be equivalent to the formation of a solid solution of vacancy point defects, each resulting from the loss of a water molecule. Since each vacancy is equivalent to a single anhydrate molecule, the system under consideration is equivalent to the doping of δ-cephaloridine monohydrate with δ-cephaloridine anhydrate. For this system (Fig. 5 in Pikal et al., 1978) p.d.i. can be calculated but not d.i., because dissolution rate data are not available. The small value of p.d.i. = 0.99 for this system at x_2 between 0 and 0.071 indicates that the crystal lattice of the monohydrate can accommodate molecules of the anhydrate with relatively low levels of lattice disruption. In other words, loss of moisture from crystals of cephaloridine monohydrate produces relatively little disorder in the crystal lattice. If the host were to undergo simple substitution or dilution with the guest molecules to produce the same degree of disordering in the crystal lattice as in the liquid state, then b = c and d.i. = 0 (York and Grant, 1985). In practice, this would mean that $b' \approx c'$ and p.d.i. ≈ 0. This situation might arise when each phase approximates to an ideal or regular solution.

A second, linear region in the plot of $\delta(\Delta H^s)$ against $\delta(\Delta S^m_{ideal})$ for partially-dehydrated cephaloridine monohydrate occurs at x_2 between 0.071 and 0.216 (Tables 2 and 3) and corresponds to an apparent p.d.i. value of 3.4. This suggests an approximately 3.4-fold greater lattice disruption than at lower values of x_2. Evidently, increasing dehydration of cephaloridine monohydrate beyond x = 0.071 increases the rate of build-up of lattice strain. This contrasts sharply with the influence of increasing levels of hexanoic, octanoic, undecanoic or oleic acid in adipic acid crystals, which cause a release of lattice strain at $x_2 > 0.007$, > 0.0008, > 0.0002 or > 0.00007, respectively (Chow et al., 1984, 1985b). Nevertheless, an apparent p.d.i. value of 3.4 for partially-dehydrated cephaloridine monohydrate still indicates a relatively low potential for disruption of the crystal lattice.

A more rigorous thermodynamic treatment, based on partial molar quantities, arrives at essentially the same conclusions as those described under Theoretical Background and in our previous paper on the subject of d.i. (York and Grant, 1985). We intend to develop a more rigorous thermodynamic approach in a subsequent report. This more rigorous treatment will express d.i. in terms of excess entropy and will define more exactly the approximations inherent in the evaluation of d.i.

Conclusions

Solution calorimetry at 25°C affords larger values of d.i. for adipic acid crystals doped with fatty acids than does heat of fusion measurements at the melting point (about 150°C) from DSC or DTA. This suggests that the heating mode of DSC or DTA eliminates an appreciable proportion of the impurity-induced imperfections in the crystal lattice by processes akin to annealing. The high values of d.i. (of the order 10^3) from solution calorimetry at 25°C indicate an enormous potential for the disruption of the crystal lattice of adipic acid by traces of a fatty acid as an additive or impurity. This probably explains why doping of adipic acid crystals with a fatty acid produces such readily observable changes in physical properties, such as crystal habit (Fairbrother and Grant, 1978, 1979), density, energy, entropy, surface properties and dissolution rate (Chow et al., 1984, 1985b). The question which now remains to be answered is the extent to which the various pharmaceutically-

important physico-chemical and physico-technical properties of solids are related to the d.i. of each host and guest system. These relationships will be examined in later reports, since they may help to elucidate the origins and consequences of batch-to-batch variations among pharmaceutical solids and may show how additives in solid solution can be employed to modify the properties of solid drugs and excipients.

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