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Non-linear van't Hoff solubility–temperature plots and their pharmaceutical interpretation

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Summary

The aqueous solubilities of acetaminophen, adipic acid and the parabens (methyl, ethyl, propyl and butyl *p*-hydroxybenzoate) have been measured over a temperature span of at least 50°C. Both the van't Hoff plots of ln x_2^{sat} against $1/T$ and the Hildebrand plots of ln x_2^{sat} against ln T are non-linear, where x_2^{sat} is the mole fraction solubility at an absolute temperature, T. The pharmaceutical significance and the physicochemical origin of such non-linear behaviour are discussed, since the pharmaceutical literature indicates it is by no means uncommon and may give rise to errors and misconceptions. When more than 5 data points covering a relatively wide range of temperatures are available, it is recommended that the data be treated by multiple regression analysis according to the equation: $\ln(\text{solubility}) = (-a/R)(1/T) + (b/R) \ln T + c$, where a, b and c are constant for the solute–solvent system and R is the gas constant. From a, b and c, the *apparent* thermodynamic parameters for the solution process may be calculated, e.g. $\Delta H = a + bT$, and $\Delta C_p = b$. This treatment has been applied to the parabens series in particular which is shown not to be as homologous as formerly supposed. The van't Hoff plot ($b = 0$) and the Hildebrand plot ($a = 0$, $b = \Delta S$) are special cases of the recommended equation applicable only over a relatively narrow temperature span. The addition of further adjustable constants into the recommended equation is considered to be unnecessary at the present time.

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Introduction

General

For many pharmaceutical purposes, especially in preformulation studies, it is necessary to measure the solubility of a drug in a given solvent at various temperatures and to express the data as a solubility–temperature curve. Linear solubility–temperature plots are often considered desirable, because: (a) they can be interpolated and extrapolated quite accurately; (b) they can be treated by the usual statistics of linear regression; and (c) they can provide thermodynamic data for the solution process.

Two solubility–temperature functions have emerged as providing good linear plots in most cases. The original van't Hoff (1886) plot of log (solubility) against $1/T$, where T is the absolute temperature, has undoubtedly found most favour. Hildebrand (1952), Hildebrand and Scott (1962) and Hildebrand et al. (1970) have, however, shown theoretically that plots of ln (solubility) against ln T may provide better straight lines. Nevertheless, Yalkowsky (1981) has demonstrated experimentally that the van't Hoff plot is more appropriate for expressing the temperature dependence of solubility for nearly ideal solid–liquid systems.

The main purpose of the present report is to examine and discuss solubility–temperature data which give pronounced deviations from linearity in both the van't Hoff and Hildebrand plots. These deviations are generally of similar order for the two plots when water is the solvent and are attributed to the abnormal properties of water as expressed in hydrophobic interactions. This solubility behaviour is particularly relevant to pharmaceutical materials in aqueous solution over the temperature range of approximately 0–50°C and is important in preformulation studies of drugs. A second objective of this communication is to alert pharmaceutical scientists to the danger of erroneously attributing the non-linear behaviour to a slope discontinuity and interpreting this as a phase change in the solid state, such as polymorphism or solvate formation. As well as considering the pharmaceutical implications of the non-linearity, the present communication proposes a useful m hod for analyzing solubility–temperature data for the aqueous solubility of drugs.

Theoretical

The van't Hoff isochore may be expressed in the following exact form at constant pressure

$$\frac{d \ln a_2^{sat}}{dT} = \frac{\Delta H_2}{RT^2} \tag{1}$$

where a_2^{sat} is the activity of the solute at saturation with respect to a suitable standard state, T is the absolute temperature, R is the gas constant (8.3143 $J \cdot K^{-1} \cdot mol^{-1}$) and ΔH_2 is the partial molar enthalpy of solution of the solute. In general

$$a_2^{solid} = a_2^{sat} = \gamma_2^{sat} s_2 \tag{2}$$

where a_2^{solid} is the activity of the pure solid solute that is in equilibrium with the

saturated solution in which s_2 is the solubility of the solute in terms of a suitable concentration scale and γ_2^{sat} is the activity coefficient of the solute. Eqn. 1 is usually applied in the approximate form

$$\frac{d \ln s_2}{dT} = \frac{\Delta H_2^*}{RT^2} \tag{3}$$

where ΔH_2^* is the apparent partial molar enthalpy of solution which is generally not equal to ΔH_2 in Eqn. 1, since in the following equation

$$\Delta H_2^* = \Delta H_2 (\partial \ln s_2 / \partial \ln \alpha_2)_T \tag{4}$$

the partial differential is equal to unity only for ideal solutions (Hollenbeck, 1980).

Instead of the usual assumption that the apparent partial molar enthalpy of solution of the solute, ΔH_2^*, is independent of temperature, we assume that it is a linear function of temperature, as follows

$$\Delta H_2^* = a + bT \tag{5}$$

where T is the absolute temperature and where a and b are constants. Now a may be considered to be the *hypothetical* value of ΔH_2^* at the absolute zero of temperature and b is the change in the apparent partial molar heat capacity of the solute at constant pressure, ΔC_{p2}^*, which is itself assumed to be independent of temperature. There is evidence that the introduction of terms containing higher powers of T, e.g. cT^2, dT^3, etc., is unnecessary (Gill et al., 1976).

From Eqns. 3 and 5 at constant temperature, we obtain

$$\frac{d \ln s_2}{dt} = \frac{a}{RT^2} + \frac{b}{RT} \tag{6}$$

which, on integration, affords

$$\ln s_2 = -\frac{a}{R} \cdot \frac{1}{T} + \frac{b}{R} \cdot \ln T + c \tag{7}$$

where c is constant of integration.

The proposed method of quantifying the variation of solubility, s_2, with absolute temperature, T, involves multiple linear regression analysis between $\ln s_2$, on the one hand, and $1/T$ and $\ln T$, on the other hand. The analysis gives the value of 3 unknowns, a, b and c, and therefore an absolute minimum of 3 pairs of experimental (s_2, T) values are required for the analysis.

If b in Eqn. 5 is assumed to be negligible, meaning that ΔH_2^* is independent of temperature, Eqn. 6 becomes the practical differential form of the van't Hoff (1886) isochore equation thus:

$$\frac{d \ln s_2}{dT} = \frac{a}{RT^2} \tag{8}$$

which on integration affords

$$\ln s_2 = -\frac{a}{R} \cdot \frac{1}{T} + c \tag{9}$$

where $a = \Delta H_2^*$ and c is a constant. This is the equation which is most commonly used to express the variation of s_2 with T.

If a in Eqn. 5 is assumed to be negligible, meaning that $\Delta H_2^* = T\Delta C_{p2}^*$, then Eqn. 6 becomes the practical differential form of the Hildebrand (1952) equation, thus:

$$\frac{d \ln s_2}{dT} = \frac{b}{RT} \tag{10}$$

$$\text{or } \frac{d \ln s_2}{d \ln T} = \frac{b}{R} \tag{11}$$

which on integration affords

$$\ln s_2 = \frac{b}{R} \cdot \ln T + c \tag{12}$$

where b represents ΔC_{p2}^*, the change in the apparent partial molar heat capacity of the solute, and c is a constant of integration. Hildebrand and Scott (1962) and Hildebrand et al. (1970) have demonstrated that $\Delta C_{p2} \simeq \Delta S_2$, and so b represents ΔS_2^*, the apparent partial molar entropy of solution of the solute. They showed that Eqn. 12 may often give a better linear correlation for the variation of solubility with temperature than the van't Hoff isochore Eqn. 9.

Materials and Methods

Materials

The parabens, methyl *p*-hydroxybenzoate (MP), ethyl *p*-hydroxybenzoate (EP), propyl *p*-hydroxybenzoate (PP) and butyl *p*-hydroxybenzoate (BP) were supplied by B.D.H. Chemicals, Toronto, and were recrystallized from toluene to constant melting points. Adipic acid was kindly provided by I.C.I. Nylon Works at Wilton, U.K., as a highly pure grade (> 99.8% by titration) containing less than 20 μg/g of specified impurities which were mainly other aliphatic carboxylic acids. Acetaminophen (NF grade) was kindly supplied by McNeil Laboratories, Toronto. The water used was double-distilled in an all-glass apparatus.

Solubility measurements

Solubilities of acetaminophen and the parabens from 0°C to 25°C were determined as follows. A small amount of the solid solute, in excess of the solubility limit, was placed with 10 cm^3 of water in a borosilicate glass test tube, 1.5 × 8 cm, which was equilibrated in a thermostatic water bath at ±0.05°C. The contents of each tube

were agitated by means of glass rod stirrers. To obtain temperatures below room temperature, the water bath was kept in a cold room at 4°C. Saturation was achieved within 72 h at 15–25°C and within 120 h at 0–10°C. Solubilities of acetaminophen and the parabens above 25°C were determined by agitating the materials stated above in 25 cm^3 conical flasks placed in a thermostatic shaking incubator. Saturation was then achieved within 24 h.

For analysis each sample of solution of acetaminophen or a paraben was quickly withdrawn through a warm Pasteur pipette containing a glass wool plug to act as a filter. At different time intervals triplicate samples were removed, weighed and analyzed and the mean composition was determined at saturation. For this purpose the concentration of each solute in each solution, after dilution if necessary, was determined by means of a Zeiss UV-visible PMQ 11 spectrophotometer with 1 cm quartz cells at $\lambda_{max} = 242$ nm for acetaminophen and at 257 nm for each paraben.

Using a Cary 118 instrument, UV spectrophotometry of nearly saturated solutions of acetaminophen and each paraben at the highest temperatures used (Table 1) showed a constant UV spectrum over the time span of the solubility experiments, indicating that hydrolysis was negligible under the conditions employed. This accords with reasonable estimates from literature data (Koshy and Lach, 1961; Raval and Parrott, 1967; Kamada et al., 1973; Blaug and Grant, 1974).

Saturation of the adipic acid solutions was achieved by vibration of an excess of the solid with water for 4 h using a Vibro-Mixer EI (Chemap AC, Mannedorf, Switzerland). Temperature control, ±0.05°C, was achieved in a thermostatic water bath. After equilibration excess of the solid was allowed to settle for 1 h and then samples of the clear supernatant were titrated with 0.1 mol · dm^{-3} sodium hydroxide solution using phenolphthalein as the indicator. All solubilities were expressed as mole fraction of solute at saturation, x_2^{sat}.

Hot-stage microscopy (HSM)

A fraction of a mg of sample was placed between a microscope slide and cover slip and heated at a rate of 1–5°C/min under a Kofler hot-stage microscope (Reichert, Austria).

Differential scanning calorimetry (DSC)

DSC curves and enthalpies of fusion, ΔH^f, of the solids were determined using a Perkin-Elmer DCS-2C differential scanning calorimeter. From these data the activities, α_2, of the solid solutes were calculated as described by Grant and Abougela (1982), the standard state being the pure supercooled liquid at 298.15K (Hildebrand and Scott, 1950, 1962; Hildebrand et al., 1970).

X-Ray diffraction

X-Ray diffractometer traces on powdered samples were determined by means of a Philips PW 1130/90 generator using copper K_α radiation and a Philips PW 1050/25 goniometer.

Results and Discussion

When attempts are made to linearize the solubility–temperature data using either the van't Hoff plot (Fig. 1, left) according to Eqn. 9 or the Hildebrand plot (Fig. 1, right) according to Eqn. 12, distinct non-linear behaviour is apparent. In the absence of prior knowledge, each of these plots might be interpreted as two straight lines intersecting at a certain temperature which might be regarded as a transition temperature (e.g. at about 37°C for acetaminophen or at 25–29°C for PP). The slopes of the two linear regions and the temperature at which they intersect, however, are highly dependent on the number of points and their temperature spread. Further, samples of the equilibrated crystals harvested from the mother liquor near the extremes of the temperature ranges (e.g. at 10°C and at 50°C) were found to give identical behaviour under HSM and DSC (i.e. melting points and enthalpies of fusion) and identical X-ray powder diffraction patterns as the original crystals. No polymorphic changes or other solid transitions were observed. This shows that the internal crystalline structure of each drug is not changed in the solubility experiments. However, in the case of BP, we observed that the excess solute, when in contact with water, undergoes a solid to liquid phase change between 35 and 37°C which, as far as we are aware, has not previously been reported. At and

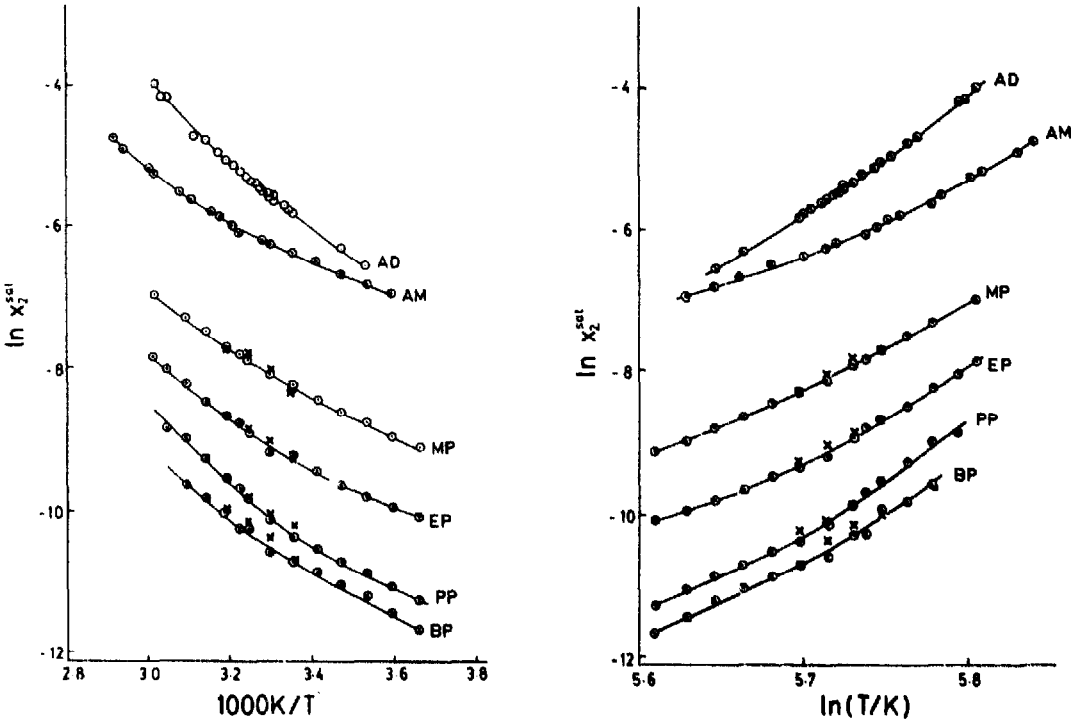

Fig. 1. van't Hoff plots (left) according to Eqn. 9 and Hildebrand plots (right) according to Eqn. 12, representing the influence of absolute temperature, T, on the aqueous mole fraction solubility, x_2^{sat}, of adipic acid (AD), acetaminophen (AM), methyl *p*-hydroxybenzoate (MP), ethyl *p*-hydroxybenzoate (EP), propyl *p*-hydroxybenzoate, (PP) and butyl *p*-hydroxybenzoate (BP): ⊙, the present data; ×, data of Alexander et al. (1978).

below 35°C, excess of BP exists as crystals identical with the original material. At and above 37°C excess of BP exists as a liquid which presumably is saturated with water and which is in equilibrium with an aqueous solution saturated with BP. Consequently, with this single exception, the two approximately linear regions in each of the solubility plots in Fig. 1 cannot be ascribed to different physical forms of the solid drug, such as polymorphs or solvates, as in the case of the β-polymorph and the monohydrate of sulphanilamide for which the transition temperature is 35.8°C (Sekiguchi et al., 1975). Unlike the sulphonamides, barbiturates and steroids, which give many polymorphic forms and solvates (reviewed by Haleblian, 1975), adipic acid and the parabens have not yet been prepared in different polymorphic forms or solvates. Acetaminophen has, however, been obtained in a second crystalline modification (form II) which melts at 154–156°C and undergoes an endothermic transition to the familiar pharmaceutical material (form I) at about 87°C (Burger and Ramberger, 1979). Since the transition temperature is well above the range of temperatures used in the present work, it is extremely unlikely that acetaminophen is undergoing a polymorphic change in the solubility determinations.

Since neither the van't Hoff plot (Eqn. 9, Fig. 1, left) nor the Hildebrand plot (Eqn. 12, Fig. 1, right) of the data correspond to the true linear relationships, the data were subjected to multiple regression analysis according to Eqn. 7. For this purpose a Hewlett-Packard HP-85 programmable calculator was employed with the General Statistics Pac for the multiple regression programme for fitting the data to an equation of the form:

$$y = b_0 + b_1 x_1 + b_2 x_2 \tag{13}$$

where $y = \ln x_2^{sat}$, $x_1 = 1/T$, $x_2 = \ln T$, $b_0 = c$, $b_1 = -a/R$ and $b_2 = b/R$. An analogous programme can readily be written in a form suitable for the Apple II Plus computer. Table 1 presents the multiple regression parameters calculated from the experimental solubility data and ΔH_2^* at 298.15 K calculated from a an b using Eqn. 5.

The parabens form a series whose aqueous solution thermodynamics has been studied based on solubility measurements at 25, 30, 35 and 40°C (Alexander et al., 1978) which are also plotted in Fig. 1. Although these data, with the exception of BP, agree quite well with those of the present work, the ΔH_2^* values at 298.15 K calculated by Alexander et al. (1978) using the van't Hoff plot (Eqn. 9) are about 0.08, 4.4 and 5.1% higher than ours for MP, EP and PP, respectively. The method recommended here is capable of yielding more accurate enthalpy data because it is calculated from two parameters, a and b, which are influenced by all the points. Since this method uses one additional adjustable parameter, it gives better fits than do the van't Hoff or Hildebrand treatments which incorrectly predict linear behaviour. A scarcity of data points may not allow a statistically significant multiple regression analysis to be carried out according to Eqns. 7 and 13. This is illustrated by the solubility data of Alexander et al. (1978) for MP, EP, PP and BP at 25–40°C and by the present data for BP in the liquid solute range, 37–50°C, and in the solid solute range, 0–35°C (Table 1). Under these circumstances it is recommended that

TABLE 1

MULTIPLE REGRESSION ANALYSIS OF THE INFLUENCE OF THE ABSOLUTE TEMPERATURE, T, ON THE MOLE FRACTION SOLUBILITY, x_2^{sat}, OF VARIOUS CRYSTALLINE SOLUTES IN WATER, ANALYSED ACCORDING TO THE FOLLOWING EQUATION [a]:

$$\ln x_2^{sat} = -\frac{a}{R} \cdot \frac{1}{T} + \frac{b}{R} \cdot \ln T + c$$

Solute	Temp. range (°C)	n [b]	Regression coefficients (with statistics) [c,d]							Correlation coefficient			ΔH_2^* kJ mol^{-1} at 298.15 K
			−a/R			b/R			c	$\ln x_2^{sat}$ vs 1/T	$\ln x_2^{sat}$ vs/ ln T	Multiple	
			K^{-1}	s [c]	t [d]		s [c]	t [d]		r	r	r^2	
Acetaminophen	5.0–70.0	17	12200	1184	10.3	49.69	3.82	13.0	−330.4	−0.988	0.992	0.998	21.7_5
Adipic acid	10.3–58.3	31	6721	1777	3.82	38.20	5.78	6.6	−246.0	−0.995	0.997	0.998	38.8_1
Methyl *p*-hydroxybenzoate	0.0–58.5	13	6520	752	9.0	32.86	2.42	13.6	−217.3	−0.996	0.998	1.000	27.2_4
Ethyl *p*-hydroxybenzoate	0.0–58.5	14	13977	1832	7.6	58.04	6.09	9.5	−386.9	−0.990	0.993	0.998	27.6_8
Propyl *p*-hydroxybenzoate	0.0–55.0	13	16194	4501	3.6	67.81	15.05	4.5	−450.9	−0.988	0.991	0.992	33.4_5
Butyl *p*-hydroxybenzoate'	0.0–35.0 solid	8	7813	7399	1.1	37.15	25.52	1.5	−248.5	−0.993	0.994	0.991	27.1_2
	37.0–50.0 liquid [e]	4	–	–	–	–	–	–	–	−0.973	0.972	0.979	36.9_7 [f]

[a] a, b and c are constants for each solute and R is the gas constant.

[b] Number of mean data points.

[c] Standard deviation of the regression coefficient.

[d] Student's *t*-value; all significant at the 5% level, except butyl *p*-hydroxybenzoate.

[e] At 37°C and higher temperatures, two saturated liquid layers are in equilibrium, the lower one being water in butyl *p*-hydroxybenzoate and the upper layer being butyl *p*-hydroxybenzoate in water.

[f] Owing to the scarcity of data points, ΔH_2^*(298.15 K) was calculated using Eqn. 9.

either the van't Hoff plot (Eqn. 9) or the Hildebrand plot (Eqn. 12) be used. Since the number of data points limits the accuracy of the thermodynamic data, it probably does not matter which plot is used. The Hildebrand plot (ln x_2^{sat} vs ln T) often gives slightly higher correlation coefficients than the van't Hoff plot (ln x_2^{sat} vs 1/T) as seen in Table 1, but the van't Hoff plot is more commonly used.

The solubility data for BP were analyzed over two temperature ranges, thus: (a) 0–35°C, corresponding to the solid solute; ΔH_2^*(298.15K) is 26% less than that for Alexander et al. (1978); and (b) 37–50°C, corresponding to liquid solute; ΔH_2^*(298.15 K) is 0.66% less than that for Alexander et al. (1978). The discrepancies in ΔH_2^* may be attributed partly to the phase change of BP, when in contact with water between 35 and 37°C, and partly to differences in the measured solubilities at 30° and 35°C (Fig. 1).

Fig. 1 and Table 1 show that the parabens series is not as homologous as originally believed. For example, the ln x_2^{sat} data are not equally separated at high and low temperatures corresponding to irregular increases in $-a/R$, b/R and ΔH_2^*(298.15K) as one proceeds from one member to the next; furthermore BP undergoes a phase change when in contact with water between 35 and 37°C. The much smaller separation between the ln x_2^{sat} data of BP and PP than between other neighbouring members of the series may be explained by the much weaker crystal lattice of BP than of the other parabens. This explanation is supported by the much higher thermodynamic activity of BP than of the other parabens (Table 2) and by the fact that BP liquefies in contact with water at 37°C and at higher temperatures. The standard state in Table 2 is the pure supercooled liquid state at 298.15K, so that the thermodynamic activity corresponds to the ideal mole fraction solubility at 25°C. The major contributing factor to the higher thermodynamic activity of BP is its lower melting point, the lower enthalpy of fusion being a minor factor. It is interesting to note that the experimental entropies of fusion in Table 2 are significantly higher than 56.5 $J \cdot K^{-1} \cdot mol^{-1}$ and 46.0 $J \cdot K^{-1} \cdot mol^{-1}$ deduced by Restaino and Martin (1964) and by Alexander et al. (1978), respectively, assuming Walden's rule. This discrepancy may be attributed to the relative flexibilities of the molecules of the parabens (Yalkowsky, 1979). The present discontinuity between BP and the other parabens parallels the discontinuity between certain of their amino analogues, the alkyl *p*-aminobenzoates (Yalkowsky et al., 1972, 1976).

Eqn. 7, and variations of it, in which the solubility of the solute is expressed in other units, have been applied to common gases, including various hydrocarbons in water from about 12 to 72°C (Morrison, 1952), to propane and butane in water and deuterium oxide from 1 to 56°C (Kreshek et al., 1965), to liquid aliphatic and aromatic hydrocarbons in water from 4 to 50°C (Gill et al., 1976), and to metolazone in *n*-butanol from 15 to 50°C (Burger, 1975). These systems are of very low solubility and the solvents, especially water, undergo considerable self-association. The published solubility–temperature data for metolazone in water, although less precise than that in *n*-butanol (Burger, 1975), may actually accord with Eqn. 7 rather better than with Eqn. 9.

Other examples for which the van't Hoff plot using Eqn. 9 is clearly inappropriate include the solubility–temperature data of many drugs and other hydrophobic

substances in water and in other self-associated solvents. These examples include fluprednisolone in water or *n*-octanol from 1[illegible] to 60°C (Haleblian et al., 1971), thiamine hydrochloride in water from 5 to 60°C (Watanabe et al., 1979) and hydrophobic ion-pair coacervates in water from 5 to about 60°C (Mukhayer and Davis, 1976, 1977a and b). The hydrophobic ion-pair coacervates just mentioned include those formed between substituted benzyltriphenylphosphonium cations and various alkyl sulphate anions.

The possibility of marked temperature dependence of ΔH_2^*, corresponding to non-linearity of the van't Hoff (and Hildebrand) plots, calls into question any data obtained by linear graphical extrapolation of log(solubility) to temperatures beyond the range of measurement. Such extrapolation has been carried out to locate the transition temperature of polymorphs, e.g. sulphamethoxydiazine forms II and III (Moustafa et al., 1971), and sulphathiazole forms α and β (Kanke and Sekiguchi, 1973). Many other examples are scattered throughout the literature. The temperature at which the linear solubility plots intersect is ascribed to the transition temperature. The present analysis indicates that such extrapolation may not be justified for water and other highly associated solvents, particularly when the extrapolation extends from about 50°C to over 100°C. We suggest that it is preferable and normally adequate to assume that ΔH_2^* is a linear function of temperature according to Eqn. 5 and to fit the solubility data to Eqn. 7 using multiple regression analysis. The transition temperature may be located by simultaneously solving the two solubility equations, one for each physical form of the solid drug, assuming equal solubilities at that temperature. For this purpose, the solubility data must be very accurate or

TABLE 2

MELTING POINT (m.p.), ENTHALPY OF FUSION (ΔH^f), ENTROPY OF FUSION (ΔS^f), AND THERMODYNAMIC ACTIVITY [a] (α_2), OF THE SOLID SOLUTES AT 298.15K

Solid solute	m.p. (°C)	ΔH^f (kJ·mol^{-1})	ΔS^f (J·K^{-1}·mol^{-1})	α_2
Acetaminophen	170	30.2 [b]	68.2	0.0185
Adipic acid	153	47.5 [b,d]	111.4	0.00317
Methyl *p*-hydroxybenzoate	131	25.7 [c]	63.7	0.0726
Ethyl *p*-hydroxybenzoate	116	26.5 [c]	68.0	0.0817
Propyl *p*-hydroxybenzoate	96.5	28.0 [c]	75.7	0.1155
Butyl *p*-hydroxybenzoate	68.5	24.1 [c]	70.4	0.3105

[a] The standard state of unit activity is taken to be the pure supercooled liquid solute at 298.15K (Hildebrand and Scott, 1950, 1962; Hildebrand et al., 1970).

[b] ΔH^f is the value at the melting point, the heat capacity correction at 298.15K being unknown.

[c] ΔH^f is the value at the melting point, the heat capacity correction at 298.15K being negligible.

[d] From the enthalpies of sublimation and vaporization near the melting point (Weast and Astle, 1982).

cover a wide range of temperatures, preferably both, in order to obtain reliable values of a and b in Eqn. 7.

That hydrophobic species give non-linear van't Hoff (and Hildebrand) plots for aqueous solubility over moderate but not unduly wide temperature ranges (e.g. 0–60°C) can readily be attributed to relatively large changes in partial molar heat capacity, ΔC_{p2}, of the solute, which are represented by b in Eqn. 9, thus:

$$b = \Delta C_{p2} = C_{p2}(\text{solution}) - C_{p2}(\text{pure solute}) \tag{14}$$

The large values of ΔC_{p2} can be attributed to the large C_{p2}(solution), i.e. the large apparent partial molar heat capacity of the solute in the associated solvent (Tanford, 1980). This is a direct result of the change in structuring of the associated solvent molecules brought about by the presence of the dissolved drug molecules. The effect is most pronounced when the solvent is water; the drug molecules are then said to be hydrophobic and the effect is commonly referred to as the hydrophobic interaction. The great increase in ordering of the associated solvent molecules around the dissolved solute molecules, together with the restricted motion of the solute molecules, account for the accompanying large apparent partial molar entropy of the solute, thus:

$$-\left(\frac{\partial(-Rt \ln x_2^{sat})}{\partial T}\right)_p = \Delta S_2 = S_2(\text{solution}) - S_2(\text{pure solute}) \tag{15}$$

There is considerable evidence that hydrocarbon molecules interact more strongly with water molecules than with each other. For example, the liquid hydrocarbon–water interfacial free energy (50–52 $mJ \cdot m^{-2}$) exceeds the liquid hydrocarbon surface free energy (20–26 $mJ \cdot m^{-2}$) (Shinoda, 1978) and the partial molar enthalpy of solution of the lower aliphatic hydrocarbons in water is negative near room temperature (Tanford, 1980). This suggest that the term *hydrophobic* interaction is a misnomer when applied to hydrocarbons. The reason for the generally unfavourable enthalpies of solution of hydrocarbons in water is the unusually strong interactions between the water molecules themselves. These considerations must also apply to many drug molecules with hydrocarbon moieties, but in addition the strong solute–solute interactions in the crystal lattice as reflected in the relatively high melting points (100–200°C), makes a major contribution to the large positive ΔH_2^* values of drugs.

The latter point is illustrated by adipic acid whose ΔH_2^* (Table 1) is paralleled by its high ΔH^f (Table 2). The thermodynamic activity, α_2 (Table 2), is controlled by ΔH^f and the melting point which together confer low values of α_2 on both adipic acid and acetaminophen. Nevertheless, these solutes have relatively high aqueous solubilities (Fig. 1) which are attributable to the relatively strong solute–water hydrogen bonding interactions. Our recommended treatment of solubility–temperature data can accommodate these relatively hydrophilic solutes as well as the more hydrophobic ones (Table 1).

Some so-called hydrophobic solutes, such as benzene (Gill et al., 1976) and

ion-pair coacervates mentioned above (Mukhayer and Davis, 1976, 1977a and b), give minima in the aqueous solubility–temperature curves. At such minima $\Delta H_2^* = 0$, which, according to Eqn. 4, must occur when $T = -a/b$ and which can therefore easily be accommodated by our recommended treatment. The values of a and b in Table 1 show that the hypothetical minimum solubility of the solutes investigated would occur at temperatures well below the freezing point of water.

The major assumption of our recommended treatment of solubility–temperature relationships is that ΔC_{p2} is a constant independent of temperature. The calorimetric data of Gill et al. (1976) show that any discrepancies resulting from this assumption are within experimental error for hydrocarbon liquids in water from 15 to 35°C. Kresheck et al. (1965) obtained particularly accurate data on aqueous solubility over the range 4–50°C. It is interesting to note that $\Delta C_{p2} \simeq 90$ cal · k^{-1} · mol^{-1} for propane and $\Delta C_{p2} \simeq 110$ cal · K^{-1} · mol^{-1} for butane in both water and deuterium oxide, although there is some evidence of temperature dependence of ΔC_{p2} which appears to decrease with increasing temperature in water and to increase in deuterium oxide over the range 4–50°C (Kresheck et al., 1965). This study of the temperature dependence of ΔC_{p2} is justified by the accuracy of the solubility data. Since solubility data for drugs at such a high order of accuracy is seldom required or available, it is normally sufficient to assume that ΔC_{p2} is constant.

The temperature dependence of solubility may be expressed empirically as polynomials in T. Kresheck et al. (1965) proposed

$$-RT \ln x_2^{sat} = \Delta G^{\theta} = A + BT + CT^2 + DT^3 \quad (16)$$

while Mukhayer and Davis (1976, 1977a and b) proposed for ion-pair coacervates

$$\log(\text{solubility product}) = 2 \log(\text{molar solubility}) = A - BT + CT^2 - DT^3 \quad (17)$$

where, in each equation, A, B, C and D are adjustable constants giving the best fit. Such power series may be differentiated to give other thermodynamic functions, such as ΔS_2, ΔH_2, ΔC_{p2}. We suggest that it is simpler, more convenient and perhaps more meaningful, to restrict the number of adjustable parameters to 3, namely a, b and c in Eqn. 7, from which the various thermodynamic functions, e.g. in Eqn. 5, can be derived with equal or greater ease. Only in a few instances is the data so accurate that more adjustable parameters are required.

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