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Solid-state properties of drugs. I. Estimation of heat capacities for fusion and thermodynamic functions for solution from aqueous solubility-temperature dependence measurements

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Summary

A novel equation was developed to describe solubility-temperature dependence data for some polar solids (acetaminophen, barbiturates and parabens) in water. Fitting of data to the equation by non-linear regression was tested with error-free model data similar to the experimental data. All coefficients for the equation were recovered from error-free data with an accuracy of $\pm 0.04\%$ at best and $\pm 0.56\%$ at worst. The fitting procedure for real data estimated apparent thermodynamic functions (enthalpy, entropy and heat capacity) for the solution process (using the hypothetical one mole fraction solution behaving at infinite dilution as the standard state) and also the heat capacity change for fusion of the solid drugs. The apparent thermodynamic functions for real data were estimated with good precision, based on *t*-tests. The estimated changes in heat capacity for fusion were similar in magnitude to those obtained by an independent method. The thermodynamic functions for solution and for fusion displayed trends with molecular structure in some cases.

Introduction

The heat capacity at constant pressure (C_p) of a system is a temperature-dependent property (Shinoda, 1978) "which multiplied by the temperature change gives the quantity of energy which has entered or left... as heat" (Glasstone, 1972a). As ΔC_p is the first or second derivative with respect to temperature (T) of the standard enthalpy change ($\Delta H°$), entropy change ($\Delta S°$) or free energy change ($\Delta G°$) for transforming a system from one state to another (Eqn 1), any means by which ΔC_p can be estimated should facilitate the prediction of constants for reactions such as solubility, acid-base and complexation equilibria.

$$\Delta C_p = \left(\frac{\delta \Delta H°}{\delta T}\right)_p = T\left(\frac{\delta \Delta S°}{\delta T}\right)_p = -T\left(\frac{\delta^2 \Delta G°}{\delta T^2}\right)_p \quad (1)$$

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Quantum mechanical methods permit the estimation of heat capacities for ideal gases and for some elemental crystalline solids (Glasstone, 1972b). However, predicted heat capacity changes involving the liquid state (especially in polar liquids) are presently inaccessible and equilibrium constants for liquid phase reactions must be measured. The present paper attempts to show how changes in heat capacity for fusion and changes in heat capacity for solution of solid drugs can be estimated from their solubility-temperature dependences.

An important equation involving a change in heat capacity is that used for the estimation of activities or ideal solubilities of solid solutes at any absolute temperature, T (Eqns 2 and 3):

$$\ln a^s = \ln a_2 = \ln x_2^i$$

$$= -\frac{\Delta H_m^f}{R}\frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R} \times \frac{T_m - T}{T} - \frac{\Delta C_p^f}{R}\ln\frac{T_m}{T} \quad (2)$$

$$= -\frac{\Delta H_m^f}{R}\frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R}\left(\frac{T_m - T}{T} - \ln\frac{T_m}{T}\right) \quad (3)$$

where a^s is the activity of the solid, a_2 denotes the activity of the dissolved solute, x_2^i is the ideal mole fraction solubility of the solute, ΔH_m^f corresponds to the change in enthalpy for fusion of 1 mole of solute at the melting temperature, T_m, and ΔC_p^f is the change in heat capacity on transforming 1 mole of solute from the solid state to the hypothetical supercooled liquid standard state at temperature T (Hildebrand et al., 1970; Shinoda, 1978; James, 1986). Although this standard state has long been preferred for ideal and regular solutions, it has limitations (Grant and Higuchi, 1990).

A difficulty with Eqn 2 is that ΔC_p^f is not readily available, although ΔH_m^f can usually be obtained from differential scanning calorimetric measurements. It has often been assumed that either $\Delta C_p^f = 0$ or $\Delta C_p^f = \Delta S_m^f$, the molar change in entropy for fusion of the solute (Hildebrand et al., 1970; Hollenbeck, 1980; Neau and Flynn, 1990). These assumptions lead to simplified forms of Eqn 2, in which $\ln x_2^i$ is linearly related to either $1/T$ or $\ln T$, respectively. A recent study, in which ΔC_p^f for several *n*-alkyl *p*-aminobenzoates was determined by a direct calorimetric method (Neau and Flynn, 1990), indicated that ΔC_p^f ranged from 0 to 4 cal/mol per K for rigid, flat molecules (e.g., unsubstituted aromatic hydrocarbons). However, molecules with rotational degrees of freedom (e.g., alkanes and substituted aromatic hydrocarbons) were usually found to have ΔC_p^f in the range 7–15 cal/mol per K, i.e., nearer to ΔS_m^f. This valuable approach has, however, some limitations: (a) there did not appear to be a definite correlation between ΔC_p^f and ΔS_m^f; (b) the heat capacities for the liquid form are determined above the melting point, where thermal decomposition is likely; and (c) the formulation of Eqn 2 is based on the hypothetical pure supercooled liquid as the thermodynamic standard state, which is generally inaccessible. Also, the pure liquid standard state will be different for associated solutes, if comparisons between different drug entities are needed (Davis et al., 1974).

Eqn 2 has not been generally recognized as contributing to the non-linear solubility-temperature dependence of a solid solute. Temperature dependence of solubilities (or other equilibria) has usually been described by the integrated van't Hoff or Hildebrand (linear) equations. When non-linear dependence of ln solubility on $1/T$ (van't Hoff) or ln T (Hildebrand) is recognized, the following more general expression (Eqn 4) has been found to be appropriate (Grant et al., 1984; Prankerd and McKeown, 1990):

$$-\log K = -\log s_2 = A + \frac{B}{T} + C \log T$$

$$= \frac{\Delta C_p^\circ - \Delta S_0^\circ}{R \ln 10} + \frac{\Delta H_0^\circ}{RT \ln 10} - \frac{\Delta C_p^\circ}{R}\log T \quad (4)$$

where s_2 represents the saturated solubility and A, B and C are constants which are related to the thermodynamic functions ($\Delta C_p^\circ - \Delta S_0^\circ$), ΔH_0° and ΔC_p°, respectively (Ives and Moseley, 1976; Ramette, 1977). In principle, ΔH_0° and ΔS_0° should be the hypothetical standard enthalpy and entropy changes for solution at $T = 0$ K, and ΔC_p° the heat capacity change that relates these quantities to experimental temperatures. However, the extrapolation to 0 K from real experimental temperatures is extremely long, so that these quantities are better regarded as integration constants or fitting parameters. In this paper, they are referred to (for want of better terminology) as the zero point enthalpy and entropy changes, respectively. They can be used to calculate the quantities ΔH_T° and ΔS_T° at a physically meaningful temperature T (i.e., from 273.15 to 373.15 K for aqueous solutions). They may still be related to the molecular structure of the solutes, as shown previously for the apparent thermodynamic quantities ΔH^*, ΔS^* and ΔC_p^* (Prankerd and McKeown, 1990). In Eqn 4, substitution of $\Delta C_p^\circ = 0$ leads to the integrated Van't Hoff equation, while $\Delta C_p^\circ = \Delta S_0^\circ$ leads to the Hildebrand equation. Eqn 4 may be strictly applied only when the solubility (s_2) is equal to the thermodynamic activity (a_i) of the species involved. By making this assumption, Eqn 4 was used to predict solubilities and estimate apparent thermodynamic functions for solution (Grant et al., 1984; Prankerd and McKeown, 1990).

A consideration of the fundamental definition of equilibrium for the solution process allows Eqns 2 and 4 to be combined. Equilibrium at fixed temperature and pressure is defined by Eqn 5:

$$\sum \mu_i \, dN_i = 0 \tag{5}$$

where μ_i is the chemical potential and dN_i denotes a small increase in the number of molecules of type 'i' (Moelwyn-Hughes, 1961). For a solid in contact with its saturated, non-ideal solution in any solvent, Eqns 6 and 7 hold:

$$\mu_i = \mu_i^\circ + RT \ln a_i \tag{6}$$

$$a_i = x_i f_i \tag{7}$$

where μ_i is the chemical potential (partial molar free energy, $\Delta\bar{G}$) of the species i, μ_i° corresponds to the chemical potential of the species i in its standard state (standard partial molar free energy, $\Delta\bar{G}^\circ$), x_i is its mole fraction concentration, a_i represents the activity and f_i is the corresponding rational activity coefficient (Prankerd and McKeown, 1990). This leads to the following, given that the criterion for equilibrium is $\mu_{solid} = \mu_{satd\ soln}$.

$$\mu^\circ_{solid} + RT \ln a_{solid} = \mu^\circ_{satd\ soln} + RT \ln a_{satd\ soln} \tag{8}$$

therefore

$$\mu^\circ_{satd\ soln} - \mu^\circ_{solid} = RT \ln \frac{a_{solid}}{a_{satd\ soln}} \tag{9}$$

therefore

$$\mu^\circ_{satd\ soln} - \mu^\circ_{solid} = -RT \ln \frac{a_{satd\ soln}}{a_{solid}}$$

$$= -RT \ln K = \Delta G^\circ_{soln} \tag{10}$$

For ideal or regular solutions, e.g., naphthalene in benzene, it is reasonable to suppose that the standard chemical potentials in each phase ($\mu^\circ_{satd\ soln}$ and μ°_{solid}) are identical or nearly identical. This leads to the commonly used definition for solubility equilibrium (Hildebrand et al., 1970) of equality of activities, $a_{solid} = a_{satd\ soln}$. However, this definition is limited (Grant and Higuchi, 1990) and it seems unreasonable to make its underlying assumption for the case of real solutions of polar solids in polar liquids. Assuming that the activity coefficient (Eqn 7) is unity (i.e., $f_2 = 1$):

$$-RT \ln K = -RT \ln x_{satd\ soln} + RT \ln a_{solid} \tag{11}$$

therefore

$$\ln x_{satd\ soln} = \ln K - \ln a_{solid} \tag{12}$$

The first term of this expression is given by Eqn 4 and the second by Eqn 2 (Eqn 13):

therefore

$$\ln x_{\text{satd soln}} = -\left(\frac{\Delta C_p^\circ - \Delta S_0^\circ}{R} + \frac{\Delta H_0^\circ}{RT} - \frac{\Delta C_p^\circ}{R}\ln T\right) - \left(-\frac{\Delta H_m^f}{R}\frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R}\frac{T_m - T}{T} - \frac{\Delta C_p^f}{R}\ln\frac{T_m}{T}\right) \quad (13)$$

which may be rearranged (Eqn 14):

therefore

$$-\ln x_{\text{satd soln}} = \frac{1}{R}\left(\Delta C_p^\circ - \Delta S_0^\circ + \frac{\Delta H_0^\circ}{T} - \Delta C_p^\circ \ln T - \frac{\Delta H_m^f}{T_m}\frac{T_m - T}{T} + \Delta C_p^f\left[\frac{T_m - T}{T} - \ln\frac{T_m}{T}\right]\right) \quad (14)$$

Eqn 14 should be a generally applicable description of the solubility-temperature dependence of any solid, provided that the activity coefficient of the dissolved solute is unity. This is the case when the thermodynamic standard state is taken as the hypothetical 1 mole fraction solution behaving as if it were infinitely dilute. This standard state is adopted for the present study.

The present study is an exploration of Eqn 14 in treating solubility-temperature dependence data. This approach has the benefit of giving estimated values for ΔC_p^f. This may be of value in situations where this quantity is inaccessible by other means, such as the direct calorimetric method (Neau and Flynn, 1990). The use of Eqn 14 also leads to apparent thermodynamic functions for solution which (in principle) are corrected for any variable effects of the solid state. The study employs literature experimental solubility data for aqueous solutions as well as model error-free data generated from Eqn 14, using coefficients which were similar to those from real solubility data.

Methods and Data

Precise aqueous solubility-temperature dependence data (Prankerd, 1985; Chow, 1987; and Mehdizadeh and Grant, unpublished observations) previously described in the literature (Grant et al., 1984; Prankerd and McKeown, 1990) were used in the study. Van't Hoff plots for these data are non-linear and are given in the original references. The data were fitted to Eqn 14 with MacMULTI (adapted by R. Rajewski, Department of Pharmaceutical Chemistry, University of Kansas, from Yamaoka et al., 1981) on a Macintosh SE computer. MacMULTI is a non-linear regression analysis program which provides several minimization algorithms. In this study, the damping

TABLE 1

Model solubility data from Eqn 14, based on experimental data for acetaminophen and for 5,5-diethylbarbituric acid

Temperature (K)	Acetaminophen model −ln(mole fraction)	5,5-Diethylbarbituric acid model −ln(mole fraction)
273.15	6.999887170	8.306187808
278.15	6.900779130	8.199811703
283.15	6.789588973	8.088326630
288.15	6.667216063	7.972152399
293.15	6.534489179	7.851674930
298.15	6.392172898	7.727249359
303.15	6.240973315	7.599202818
308.15	6.081543182	7.467836929
313.15	5.914486523	7.333430048
318.15	5.740362796	7.196239278
323.15	5.559690650	7.056502293
328.15	5.372951311	6.914438975
333.15	5.180591657	6.770252897
338.15	4.983026998	–
T_m (K)	443.15	463.15
$\Delta H_m^f / T_m$ (cal/mol per K)	16.28778585	12.32861928

Gauss-Newton algorithm was used. Weighting was not applied to the data, as there was no reason to suppose that points at one end of the temperature scale were more precise than at the other. The program was tested for its ability to recover known model values of ΔH_0°, ΔS_0°, ΔC_p° and ΔC_p^f from error-free solubility data generated by Eqn 14 from absolute temperatures and the model values. The model values were similar in magnitude to those found in the present study from the actual data sets. The model data in Table 1 and raw experimental data in Table 2 were used for curve fitting. It must be stressed that the large number of significant figures in Table 1 does not imply physical exactitude, but rather the correct mathematical representation of the model solubility data on conversion to logarithms.

Enthalpies of fusion (ΔH_m^f) were taken from the literature or measured with a Perkin-Elmer DSC 7 differential scanning calorimeter (Perkin-

TABLE 2

Mole fraction solubility of (a) parabens in water (Mehdizadeh and Grant, unpublished observations), (b) 5,5-dialkylbarbituric acids in 0.001 M HCl (means of two determinations) (Prankerd, 1985) and (c) acetaminophen in water (Chow, 1987)

(a)	Temperature (K)	Methyl paraben mole fraction $\times 10^4$	Ethyl paraben mole fraction $\times 10^5$	Propyl paraben mole fraction $\times 10^5$	Butyl paraben mole fraction $\times 10^5$
	273.15	1.0877	4.238	1.3175	0.9860
	278.15	1.2667	4.800	1.5880	1.0976
	283.15	1.5433	5.566	1.9307	1.3819
	288.15	1.7856	6.499	2.2486	1.6332
	293.15	2.1537	7.891	2.7195	1.9596
	298.15	2.6670	9.918	3.1817	2.2862
	303.15	3.1238	10.323	4.0655	2.5485
	308.15	3.7432	13.554	5.5164	3.5017
	310.15	4.0503	15.606	6.2766	–
	313.15	4.5298	17.140	8.5245	–
	318.15	5.6349	21.125	9.5012	–
	323.15	6.8287	27.312	12.9076	–
	328.15	–	33.191	–	–
	331.65	9.3746	39.329	–	–
	T_m (K)	404.15	389.15	369.65	341.65
	$\Delta H_m^f/T_m$ (cal/mol per K)	15.19846993	16.27564344	18.10408784	16.85947093

(b)	Temperature (K)	5,5-Diethyl-barbituric acid mole fraction $\times 10^4$	5,5-Diisopropyl-barbituric acid mole fraction $\times 10^5$	5-Ethyl-5-phenyl-barbituric acid [a] mole fraction $\times 10^4$
	283.15	4.895	2.075	–
	288.15	5.485	2.390	–
	293.15	6.185	2.735	–
	298.15	6.990	3.095	0.995
	303.15	8.070	3.750	1.180
	308.15	9.215	4.355	1.370
	313.15	10.50	5.180	1.610
	318.15	12.15	6.165	1.910
	323.15	13.85	7.220	2.330
	T_m (K)	463.15	496.15	450.15
	$\Delta H_m^f/T_m$ (cal/mol per K)	12.32861928	16.07968229	13.45760087

TABLE 2 (continued)

(c)	Temperature (K)	Acetaminophen mole fraction $\times 10^3$
	278.15	0.9716
	283.15	1.125
	288.15	1.285
	293.15	1.544
	298.15	1.728
	303.15	1.965
	304.65	2.049
	310.15	2.305
	312.15	2.572
	314.65	2.899
	316.65	3.058
	321.65	3.585
	324.65	4.041
	331.65	5.218
	332.65	5.649
	340.15	7.451
	343.15	8.653
	T_m (K)	443.15
	$\Delta H_m^f / T_m$ (cal/mol per K)	16.28778585

[a] Form II polymorph.

Elmer, Danbury, CT) as described elsewhere (Prankerd and Ahmed, 1992).

Results

Use of error-free model data sets

MacMULTI recovered the model values for the coefficients ΔH_0°, ΔS_0°, ΔC_p° and ΔC_p^f from the error-free data in Table 1 without difficulty, if the true value of either ΔH_0° or ΔC_p^f was included in Eqn 14 as a constant. However, if all four coefficients were allowed to 'float', convergence to a consistent solution was not easy. The principal difficulty was to find an adequate estimate of ΔC_p^f. This could vary widely, thus forcing the other coefficients to adopt incorrect values as well. To solve this problem, use was made of the ΔC_p^f values reported in Neau and Flynn (1990). These range from 0.04 to 18.12 cal/mol per K. The data in Table 1 were fitted to Eqn 14 three times, defining $\Delta C_p^f = 4$, 11 or 18 as a constant in each case. Initial estimates for the three coefficients (ΔH_0°, ΔS_0° and ΔC_p°) were always chosen to be very different from the true values, simulating the usual situation in which the true values are not known. This resulted in three sets of values for ΔH_0°, ΔS_0° and ΔC_p° which were within $\pm 20\%$ of their true values, as well as the corresponding standard deviations (SD), and the sum of squares of residuals (SSR) for the regression. The set with the smallest values for the SDs and SSR was then used as the basis for further analysis. Two further values for ΔC_p^f (± 1 from the best value so far) were again incorporated into Eqn 14 and the best result again selected, based on SD and SSR values. At this stage, the initial estimates for the coefficients were taken from the previously estimated coefficients with the lowest SD and SSR values. ΔS_0° and ΔC_p° were now within $\pm 3\%$ of the correct values and ΔH_0° was within $\pm 7\%$ at worst. The value for ΔC_p^f was then left undefined in Eqn 14 and the best estimates for all four coefficients used as initial esti-

TABLE 3

Estimated thermodynamic values from fitting data in Table 1 to Eqn 14

Quantity	Acetaminophen model (% deviation)	5,5-Diethylbarbituric acid model (% deviation)
ΔC_p° (actual)	105.10	68.00
ΔC_p° (estimated)	105.14 (0.038%)	67.93 (0.10%)
ΔS_0° (actual)	−580.84	−381.00
ΔS_0° (estimated)	−581.07 (0.040%)	−380.57 (0.11%)
ΔH_0° (actual)	−20026	−12165
ΔH_0° (estimated)	−20042 (0.080%)	−12132 (0.27%)
ΔC_p^f (actual)	7.559	12.50
ΔC_p^f (estimated)	7.597 (0.50%)	12.43 (0.56%)

TABLE 4

Contributions of each term in Eqn 14 for 5,5-diethylbarbituric acid model data

T(K)	$-\frac{\Delta H_m^f}{RT_m}\frac{(T_m - T)}{T}$	$\frac{\Delta C_p^f}{R}\frac{(T_m - T)}{T}$	$\frac{\Delta C_p^f}{R}\ln\frac{T_m}{T}$	$\frac{\Delta H_0^\circ}{RT}$	$\frac{\Delta C_p^\circ}{R}\ln T$	$-\ln x_2$ (model)
273.15	−4.3154635	4.37550	−3.32149	−22.4115	−191.9703	8.306187808
278.15	−4.1263657	4.18377	−3.20739	−22.0087	−192.5910	8.199811703
283.15	−3.9439462	3.99881	−3.09532	−21.6200	−193.2007	8.088326630
288.15	−3.7678575	3.82027	−2.98521	−21.2449	−193.7996	7.972152399
293.15	−3.5977756	3.64783	−2.87700	−20.8825	−194.3883	7.851674930
298.15	−3.4333982	3.48116	−2.77061	−20.5323	−194.9671	7.727249359
303.15	−3.2744432	3.31999	−2.66600	−20.1937	−195.5362	7.599202818
308.15	−3.1206465	3.16406	−2.56309	−19.8660	−196.0959	7.467836929
313.15	−2.9717611	3.01310	−2.46185	−19.5488	−196.6467	7.333430048
318.15	−2.8275554	2.86689	−2.36220	−19.2416	−197.1888	7.196239278
323.15	−2.6878122	2.72520	−2.26411	−18.9439	−197.7224	7.056502293
328.15	−2.5523275	2.58783	−2.16753	−18.6552	−198.2478	6.914438975
333.15	−2.4209096	2.45459	−2.07241	−18.3752	−198.7652	6.770252897

R = 1.98719 cal/mol per K; T_m = 463.15 K; ΔH_m^f = 5710.0 cal/mol; ΔC_p^f = 12.50 cal/mol per K; ΔH_0° = −12165.0 cal/mol; ΔS_0° = −381.00 cal/mol per K; ΔC_p° = 68.00 cal/mol per K. Some figures have been deleted for clarity.

mates in fitting the model data. It was necessary to use a range of step sizes to be certain of converging to the best result, once adequate initial estimates of the coefficients were available. The results for the two model sets of data are given in Table 3.

In each example, ΔC_p° and ΔS_0° were estimated from the model data with similar accuracy, ΔH°_0 had slightly poorer accuracy, and estimation of ΔC_p^f was least accurate. The deviations from the true values are probably due to computer round-off error. These accuracies are in agreement with the rank order of the magnitudes of the terms in Eqn 14, shown in Table 4 for the 5,5-diethylbarbituric acid model. The model based on acetaminophen solubility data gave a similar rank order of contributions. The ΔC_p^f term is smallest (i.e. hardest to estimate), as it is made up of two terms with opposite signs, which tend to cancel each other out. The ΔC_p° and ΔS_0° terms are large (i.e., easiest to estimate) and the ΔH_0° term is intermediate in its contribution to the model values for $-\ln x_2$. The term containing ΔH_m^f, although small, is not estimated, as the coefficient is fixed in magnitude.

Use of model data sets with introduced errors

The effect of introduced errors in the acetaminophen model data was examined. The model $-\ln x_2$ value (in Table 1) for either 273.15, 303.15 or 338.15 K was increased by 1% in separate experiments. This approach has been de-

TABLE 5

Estimated values from fitting acetaminophen model data to Eqn 14 after introduction of a +1% error into a single data point

Quantity	273.15 K (% deviation) [a]	303.15 K (% deviation)	338.15 K (% deviation)
ΔC_p° (estimated)	100.84 (−4.22%)	120.43 (+14.54%)	101.71 (−3.37%)
ΔS_0° (estimated)	−558.14 (+4.07%)	−672.44 (−15.57%)	−562.76 (+3.21%)
ΔH_0° (estimated)	−19350.7 (+3.49%)	−26143.2 (−30.55%)	−19471.1 (+2.85%)
ΔC_p^f (estimated)	12.519 (+65.61%)	18.084 (+139.2%)	10.620 (+40.50%)
SSR	0.002334	0.003016	0.001362

[a] Percent deviations are from the true values in Table 3.

TABLE 6

Estimated thermodynamic values from fitting model data with alternate positive and negative deviations from the acetaminophen model data to Eqn 14

Quantity	Modified acetaminophen model (SD; % deviation)
ΔC_p° (actual)	105.10
ΔC_p° (estimated)	104.99 (4.68; 0.105%)
ΔS_0° (actual)	−580.84
ΔS_0° (estimated)	−580.33 (26.79; 0.088%)
ΔH_0° (actual)	−20026
ΔH_0° (estimated)	−20037 (1422.6; 0.055%)
ΔC_p^f (actual)	7.559
ΔC_p^f (estimated)	8.000 (3.21; 5.83%)

scribed previously for the temperature dependence of very precise acid dissociation constants (Ives and Moseley, 1976). The results of fitting the modified data according to the procedure above are summarized in Table 5.

In agreement with the results of Tables 3 and 4, Table 5 shows that the estimated values for ΔC_p^f are very sensitive to experimental error. The other estimated values are less sensitive. It should be pointed out that the situations examined here are at an extreme, in that all error is in only one data point. Real data should have a more or less random distribution of positive and negative errors, which will provide a smoother response. This is illustrated by the data in Table 6, which were obtained by analysis of a set of acetaminophen model data in which alternate points were increased by 0.25%, while the remaining points were decreased by 0.25%, simulating real data. This modified data set had a total SSR of 0.00323 for 10 degrees of freedom (DF). As expected, the calculated values for $-\ln x_2$ at each temperature, from the estimated coefficients in Table 6, were very close to the unmodified acetaminophen model data. A further model set of data, in which the introduced error in each point was $\pm 0.5\%$, could not be fitted to give a repro-

TABLE 7

Estimated thermodynamic quantities from fitting solubility data as a function of temperature for acetaminophen and 5,5-diethyl-, 5,5-diisopropyl- and 5-ethyl-5-phenylbarbituric acids to Eqn 14

	5,5-Diethylbarbituric acid (SD)	5,5-Diisopropylbarbituric acid (SD)	5-Ethyl-5-phenylbarbituric acid (SD)	Acetaminophen (SD)
ΔC_p°	66.44 (2.83)	89.19 (1.21)	105.85 (9.40)	111.09 (2.34)
ΔS_0°	−370.35 (16.34)	−498.25 (6.87)	−592.49 (41.46)	−617.04 (11.48)
ΔH_0°	−11411.3 (902.8)	−14632.8 (360.7)	−21027.2 (908.7)	−22582.0 (92.7)
ΔC_p^f	11.25 (0.18)	7.033 (0.32)	4.660 (0.991)	12.93 (5.41)
SSR	0.000204	0.00103	0.000365	0.01201
DF [a]	5	5	2	17

[a] DF, number of degrees of freedom (= number of experimental temperatures − 4).

TABLE 8

Estimated thermodynamic quantities from fitting solubility data as a function of temperature for alkyl p-hydroxybenzoates to Eqn 14

	Methylparaben (SD)	Ethylparaben (SD)	Propylparaben (SD)	Butylparaben (SD)
ΔC_p°	79.62 (1.37)	128.39 (3.43)	196.58 (5.29)	79.84 (11.62)
ΔS_0°	−437.35 (7.72)	−714.85 (19.39)	−1099.1 (285.1)	−438.70 (65.95)
ΔH_0°	−12606.5 (382.2)	−26467.8 (989.4)	−45118.6 (1120.8)	−11940.4 (3392.4)
ΔC_p^f	14.35 (0.36)	12.53 (0.965)	18.53 (10.8)	8.25 (1.81)
SSR	0.00191	0.0151	0.0129	0.01204
DF [a]	10	10	8	4

[a] DF, number of degrees of freedom (= number of experimental temperatures − 4).

ducible set of coefficients. The total SSR for this set was 0.013 for 10 DF, at best.

Table 6 demonstrates, as was seen with Table 3–5, that the estimation of ΔC_p^f is most subject to errors in the data. However, the difference between the actual and estimated coefficients is much less than 1 SD, in all cases.

Use of Eqn 14 to describe experimental data

The experimental data in Table 2 were fitted to Eqn 14, using the procedures described above, except that ΔC_p^f was fixed with a value of 4, 8, 11, 14 or 18, to find the best initial estimates of the quantities in Eqn 14. The thermodynamic quantities and their standard deviations for 5,5-diethylbarbituric acid, 5,5-diisopropylbarbituric acid, 5-ethyl-5-phenylbarbituric acid and acetaminophen are reported in Table 7. Corresponding thermodynamic quantities for the parabens are listed in Table 8.

All the coefficients in Tables 7 and 8 have small standard deviations and are statistically significant at least at the 95% confidence level (*t*-test), except for the ΔC_p^f values for 5-ethyl-5-phenylbarbituric acid and propylparaben (90% c.i.). The estimated ΔC_p^f values are in agreement with the range of values reported by Neau and Flynn (1990).

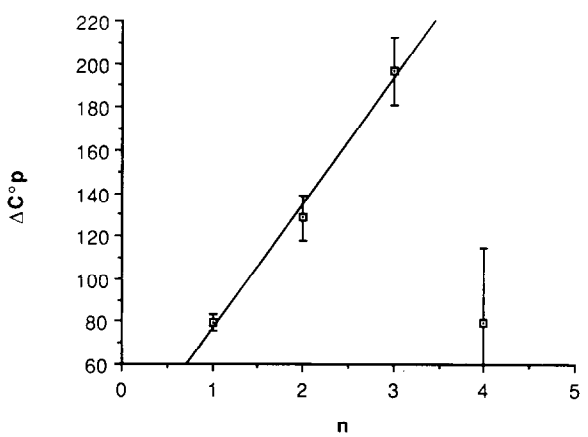

Fig. 1. Plot of change in heat capacity for solution, ΔC_p° (cal/mol per K) for parabens in water as a function of chain length, n. The point for BP ($n = 4$) was omitted from the best straight line. Error bars are three times the standard deviations listed in Table 8.

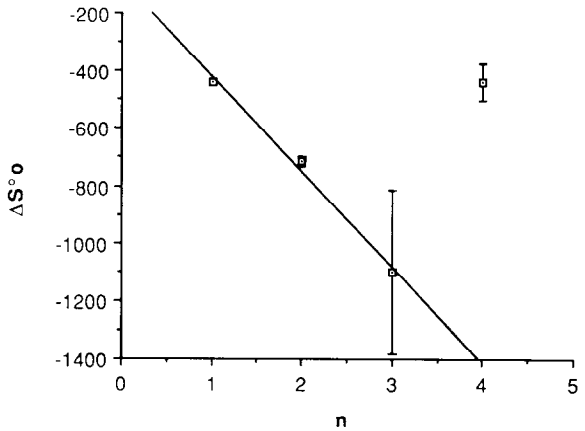

Fig. 2. Plot of change in zero point entropy for solution, ΔS_0°, (cal/mol per K) for parabens in water as a function of chain length, n. The point for BP ($n = 4$) was omitted from the best straight line. Error bars are three times the standard deviations listed in Table 8.

Discussion

Solution thermodynamic functions

The solution thermodynamic quantities (ΔC_p°, ΔS_0° and ΔH_0°) for the parabens in Table 8 demonstrate trends with increasing chain length that are followed for the methyl, ethyl and propyl derivatives, but are then broken for the butyl derivative (Figs 1–3). This probably results from a change in the behavior of the alkyl chain, such as the increase in chain flexibility proposed by Yalkowsky and Valvani (1980), based on entropies of fusion.

There are insufficient barbituric acid derivatives to find trends in their zero point thermodynamic functions. The values for ΔH_0°, ΔS_0° and ΔC_p° were used to calculate apparent free energy (ΔG_{25}^*), enthalpy (ΔH_{25}^*) and entropy (ΔS_{25}^*, $T\Delta S_{25}^*$) changes for solution of all compounds at 25°C (298.15 K), using previously reported equations (Prankerd and McKeown, 1990). These are listed in Table 9. The enthalpy changes for the parabens have the same sign and magnitude as those reported by Grant et al. (1984), but the

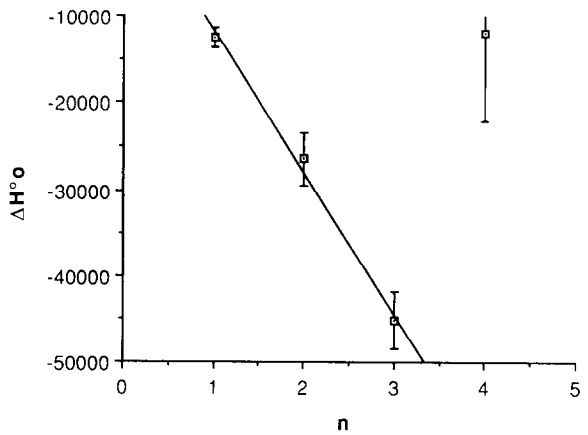

Fig. 3. Plot of change in zero point enthalpy for solution, ΔH_0°, (cal/mol) for parabens in water as a function of chain length, n. The point for BP ($n = 4$) was omitted from the best straight line. Error bars are three times the standard deviations listed in Table 8.

actual values differ, due to the additional terms in Eqn 14 which correct for solid-state behavior. The values for the barbituric acids are also of the same sign and magnitude as those reported by Prankerd and McKeown (1990), and differ in the actual values for this reason also, as well as the fact that a different concentration scale was previously used.

Enthalpy-entropy compensation plots have been used to attempt to demonstrate the role of hydration in observed acid-base equilibrium or kinetic reactions (Ives and Marsden, 1965; Carpenter, 1984). A difficulty with this approach for saturated solubility equilibria is that the effects of variable solid-state properties may be superimposed on the hydrational properties of different dissolved solutes. The use of Eqn 14 to correct the solution thermodynamic behavior for solid-state effects should result in a clearer demonstration of the relationship between enthalpy and entropy changes for solution, if such relationships exist. A plot of the ΔH_{25}^* and ΔS_{25}^* values from Table 9 did not display an unequivocal enthalpy-entropy compensation relationship for all the solutes. However, the barbiturates were clearly separated from the parabens and acetaminophen, suggesting that the former compounds are hydrated differently in solution compared to the latter. The two groups displayed approximately linear trends between the ΔH_{25}^* and ΔS_{25}^* values, and also between the ΔH_{25}^* and ΔG_{25}^* values. The failure to display a single relationship may be because such a relationship really does not exist for the group of solutes examined, or else the estimated thermodynamic functions are not sufficiently accurate to reveal them.

Heat capacities for fusion

The estimated changes in heat capacity for fusion of the solutes reported in Tables 7 and 8 are similar in magnitude to those previously reported (Neau and Flynn, 1990). The values of ΔC_p^f for propyl paraben and 5-ethyl-5-phenylbarbituric acid (PEBA) seem to be higher and lower than anticipated, respectively. However, the standard deviations for these compounds were substantially larger than for the others. In particular, the data for PEBA had only two remaining degrees of freedom.

There appears to be an inverse linear relationship between the ΔC_p^f values and alkyl chain length for the parabens (Fig. 4). Omission of the point for PP ($n = 3$) gave a straight line which passed almost perfectly through the other three points. PP lies off the best line by less than 1 SD. Data for other homologs would be very useful in

TABLE 9

Estimated apparent thermodynamic quantities for solution of barbituric acids and alkyl p-hydroxybenzoates in aqueous systems at 25.00°C (298.15 K)

Compound [a]	ΔH^*_{25} (cal/mol)	ΔS^*_{25} (cal/mol per K)	$T\Delta S^*_{25}$ (cal/mol)	ΔG^*_{25} (cal/mol)
DEBA	8146	7.518	2241	5905
DIPBA	11952	9.926	2959	8993
PEBA	10533	10.624	3168	7365
AM	10538	15.890	4738	5801
MP	11131	16.264	4849	6282
EP	11814	16.704	4980	6834
PP	13493	20.913	6235	7258
BP	11863	16.182	4825	7039

DEBA, 5,5-diethylbarbituric acid; DIPBA, 5,5-diisopropylbarbituric acid; PEBA, 5-ethyl-5-phenylbarbituric acid (form II); AM, acetaminophen; MP, methyl paraben; EP, ethyl paraben; PP, propyl paraben; BP, butyl paraben.

confirming this apparent trend. No similar trend for ΔC_p^f values was previously reported for a similar series of compounds, the alkyl *p*-aminobenzoates (Neau and Flynn, 1990). The data of Neau and Flynn (1990) do indicate a reasonably smooth chain-length-dependent trend for the heat capacities of the liquid forms of the alkyl *p*-aminobenzoates, but to a lesser extent for the solid forms. The resultant differences between solid and liquid forms are thus somewhat irregular. This discrimination between solid and liquid states is not possible in the present analysis. It could be achieved by using the direct calorimetric approach of Neau and Flynn (1990) to determine the heat capacity of the solid form alone at the temperature of interest and calculating that for the liquid form by difference from the estimated ΔC_p^f value. This would circumvent the possibility of thermal degradation in attempting to measure the heat capacities of liquid forms at elevated temperatures.

Activity coefficients

It has been suggested that an equation similar to the following extended form of Eqn 2 could also be used to account for the saturated solubility of real solutions (Prankerd, 1985) (Eqn 15):

$$\ln x_2 = -\frac{\Delta H_m^f}{R}\frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R}\frac{T_m - T}{T} - \frac{\Delta C_p^f}{R}\ln\frac{T_m}{T} - RT \ln f_i \qquad (15)$$

for which f_i is an activity coefficient. The solubility data in Table 2 were successfully fitted to Eqn 15, giving activity coefficients which were close, although not identical, to unity. However, there was always a systematic trend in the residuals when the calculated and experimental data points were compared. Eqn 15 always overestimated the solubility in the middle of the temperature range and underestimated it at either end of the range. Thus, the non-ideal character of these solutions could not be adequately estimated by a term in $RT \ln f_i$ alone. Part of the reason why Eqn 15 is not successful is that its two heat capacity terms must account for changes in heat capacity for both the fusion and the solution processes. ΔC_p^f values estimated using Eqn 15 were always much greater in magnitude than those estimated using Eqn 14, which gave values similar to those measured by independent calorimetric measurements. The use of Eqn 14 has assumed that the activity coefficients for these aqueous solutions are unity, and gave random distributions of residuals between experimental and calculated solubilities.

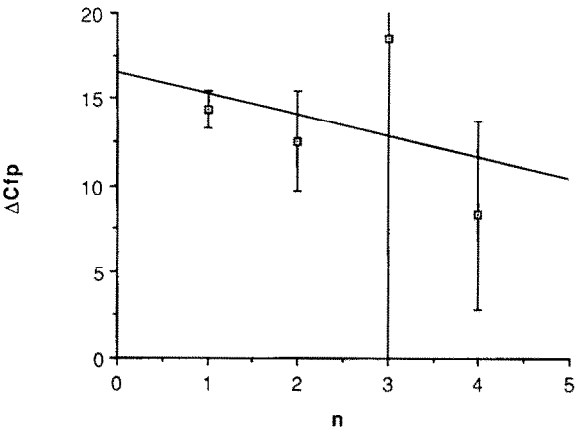

Fig. 4. Plot of change in heat capacity for fusion, ΔC_p^f, (cal/mol per K) for parabens as a function of chain length, *n*. Error bars are three times the standard deviations listed in Table 8.

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