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Physico-chemical properties of barbituric acid derivatives Part I. Solubility-temperature dependence for 5,5-disubstituted barbituric acids in aqueous solutions

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Summary

Solubility–temperature dependence data for four 5,5-disubstituted barbituric acids in 0.001 M HCl are presented. The solubility data were fitted to the Valentiner equation by the method of multiple linear regression and by the sigma plot method. Curvature in van 't Hoff (reciprocal temperature) plots for 5,5-diethyl- (**1**) and 5,5-diisopropyl- (**2**) barbituric acids indicated that the heat capacity change for the solution process has a finite value. The van 't Hoff plot for 5-ethyl-5-phenylbarbituric acid (**3**) was in two distinct sections. These corresponded to an anhydrous polymorph (Form II) and a monohydrate (Form XIII). Simultaneous solution of the equations for the two sections gave the transition temperature (38.2°C) for the two forms. For 5,5-dimethylbarbituric acid (**4**) above 15°C, the solubility–temperature dependence was very similar to (**1**) and (**2**). Below 20°C, non-linearity in the plot suggested the possibility of a change in the crystal structure for (**4**). Calculation of *apparent* thermodynamic functions for solution of (**1**), (**2**) and (**4**) from the equations of best fit showed that the apparent enthalpy changes for solution were linearly related to the melting points of the compounds. The apparent entropy and heat capacity changes for solution were linearly related to the size of the 5-alkyl substituents. Differences in the apparent thermodynamic functions for the two forms of (**3**) are expected to result solely from physical differences in the two crystalline forms. Introduction of the water molecule giving Form XIII of (**3**) brought about marked changes in the apparent enthalpy and entropy changes for solution of the two forms. These changes nearly cancel out so that the apparent free energies for the solution process (and hence the saturated solubilities) are nearly the same for the two forms.

Introduction

Solubility–temperature dependence data may be used in pre-formulation studies, e.g., for the prediction of solubilities for industrial processes and at physiological temperatures. The data may be used to recognize polymorphic transitions and for the estimation of thermodynamic quantities for the solution process. These may give insight into the crystalline state and into interactions of solutes with solvent molecules.

Polymorphism has been extensively studied in the barbituric acids using hot-stage microscopy (Brandstätter-Kuhnert and Aepkers, 1962, 1963)

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and X-ray powder diffractometry (Huang, 1951; Cleverley and Williams, 1959b). Single crystal X-ray diffraction studies of barbituric acid derivatives in polymorphic modifications have led to crystal structures being obtained for these polymorphs (Craven et al., 1969a and 1969b; Craven and Vizzini, 1971; Craven et al., 1973; Williams, 1973a and 1973b). Several infra-red spectroscopic studies on barbituric acid polymorphism have also been reported (Cleverley and Williams, 1959a and 1959b; Mesley et al., 1967a and 1967b; Mesley, 1970). At least four modifications of 5,5-diethylbarbituric acid and thirteen modifications of 5-ethyl-5-phenylbarbituric acid have been described. However, a number of these can only exist in the presence of a few percent of a different barbituric acid derivative. Five of the polymorphs of phenobarbitone (Forms I, II, III, V and XIII) were found to be sufficiently stable, in the absence of other barbituric acid derivatives, for determination of unit cell constants from single crystal X-ray diffraction data (Williams, 1973a).

The transition between an anhydrous form and a monohydrate form of 5-ethyl-5-phenylbarbituric acid (phenobarbitone, **3**) was first recognized by Eriksson (1961). These modifications were identified as Form II (anhydrous) and Form XIII (monohydrate) in the classification of Mesley (Mesley et al., 1967a and 1967b; Mesley, 1970), although the monohydrate should be strictly regarded as a pseudomorph, rather than as a polymorph (Williams, 1973a). It was initially considered (from infrared spectra) that a keto-enol tautomeric transition might have occurred to some extent in Form XIII (Cleverley and Williams, 1959b) and endotherms in differential scanning calorimetric data (Mesley et al., 1967a) were interpreted (Mesley, 1970) as supporting this postulate, rather than possible changes in hydration (Mesley et al., 1967a). However, thermogravimetric and single-crystal X-ray diffraction studies (Williams, 1973a) showed clearly that Form XIII was a monohydrate.

The solubility–temperature dependence for phenobarbitone in water has been determined over the temperature range 15–55 ° C (Sekiguchi et al., 1973). The transition temperature between the anhydrous and monohydrate forms was estimated to be 35.1° C. This value was in reasonable agreement with a range of values (36.4–47 ° C) obtained by several other methods (Sekiguchi et al., 1973). The heat of transition was reported to be in the range 1.48–1.87 kcal/mol. A recent solubility–temperature dependence study has reported transition temperatures and heats of transition for two polymorphs of phenobarbitone which are stable only in the presence of up to 10% of other barbituric acids (Kato et al., 1984). This study failed to recognize the reversible Form XIII–Form II transition of phenobarbitone that occurs in the presence of water. For a number of barbituric acids (including phenobarbitone), other solubility–temperature dependence studies so far performed (Treiner et al., 1982) provide base-line data for studies in surfactant solutions (Vaution et al., 1981) and are not suitable for the estimation of thermodynamic functions, as measurements were made at only three temperatures. Ionization of the barbituric acid derivatives (leading to the more water-soluble anionic forms) was not taken into account in studies performed in solutions that did not contain surfactants.

Theoretical

The criterion for equilibrium for a solid in contact with its saturated, non-ideal solution in a given solvent is shown by Eqns 1a, 1b and 1c:

$$\mu_i = \mu_i^\circ + RT\ \ln[\mathrm{x}_i] f_i \quad T \text{ and } P \text{ constant} \tag{1a}$$

$$\mu_{\text{solid}} = \mu_{\text{satd soln}} = \mu_i^\circ + RT\ \ln[\mathrm{x}_i] + RT\ \ln\ f_i \tag{1b}$$

$$\mathrm{a}_i = [\mathrm{x}_i] f_i \tag{1c}$$

where μ_i is the chemical potential of the species i; $[\mathrm{x}_i]$ is its mole fraction concentration; a_i is the activity; and f_i is the corresponding rational activity coefficient. The mole fraction concentration may be replaced by the corresponding molal ($[\mathrm{m}_i]$) concentration, and the rational activity coefficient by the molal activity coefficient (γ_i). The activity coefficient may be defined by choosing an arbitrary standard state in which the activity is unity. This may be the pure substance ($[x_i] = 1$), or a hypothetical solution state containing the solute at a concentration of 1 mol fraction or 1 molal, but behaving as though it was at infinite dilution ($[x_i] = 0$) (Davis et al., 1974; Grant et al., 1984). The use of the pure solute as the standard state for associated liquids, such as alcohols, has been criticised (Davis et al., 1974) on the grounds that the standard state is different from one compound to the next, so that molecular interactions are difficult to evaluate and correlations with biological data remain obscured. It is customary in solubility studies of solids to define the standard state as the pure super-cooled liquid solute. However, this choice of standard state may also be criticised when comparisons are made between the solution properties for several compounds, as the relevant standard states no longer correspond.

Data-Fitting Methods

It has recently been advocated (Ives and Moseley, 1976) that for evaluation of thermodynamic functions from the temperature dependence of thermodynamic ionization constants, a return to the principles of the Everett and Wynne-Jones treatment (Everett and Wynne-Jones, 1939) be adopted. This leads to a temperature dependence equation of the form given in Eqn 2:

$$-\log K = A + \frac{B}{T} + C \log T = \left[\frac{\Delta C_p^\circ - \Delta S_0^\circ}{R \ln 10}\right] + \frac{\Delta H_0^\circ}{RT \ln 10} - \frac{\Delta C_p^\circ}{R} \log T \qquad (2)$$

In Eqn 2, known as the Valentiner equation (Blandamer et al., 1980a, 1981), K is an equilibrium constant; T is the absolute temperature; and A, B and C are constants which may be 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). This equation has also been applied extensively to describe the temperature dependence of rate constants (Moelwyn-Hughes et al., 1965; Blandamer et al., 1980a, 1980b, 1981). Eqn 2 may be derived from either the Gibbs-Helmholtz or van't Hoff equations and allows for the fact that the heat-capacity change (ΔC_p°) for any equilibrium process is not usually zero, especially in aqueous solution. It is an exact representation of the variation in the equilibrium constant with temperature, in any system for which the standard heat-capacity change for the equilibrium reaction is temperature-invariant ($\Delta C_p^\circ =$ constant). Allowance for the temperature variance in ΔC_p° may be made by expressing this function as a power series in $T(\Delta C_p^\circ = a' + b'T + c'T^2 + \ldots)$. However, since most equilibrium–temperature dependence data are not sufficiently precise to reveal the temperature dependence of ΔC_p° (Ramette, 1977), truncation of ΔC_p° to the constant term (a') is justified. If ΔC_p° is assumed equal to zero, then Eqn 2 reduces to the integrated van't Hoff equation, for which the experimental data ought to demonstrate a linear dependence of log K on $1/T$. This assumption is frequently made in reporting the temperature dependence of both equilibrium and kinetic data, particularly where the temperature range is not more than 20–30 °C.

Eqn 2 may be strictly applied only when the equilibrium constant (K) is derived from the thermodynamic activities (a_i) of the species involved. Use of the following thermodynamic identities, Eqns 3–6, allows derivation of the standard thermodynamic functions for the equilibrium process (Eqns 7–10):

$$\Delta G^\circ = -RT \ln K \qquad (3)$$

$$\Delta S^\circ = -(\partial \Delta G^\circ / \partial T)_p \qquad (4)$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \qquad (5)$$

$$\Delta C_p^\circ = \left(\frac{\partial \Delta H^\circ}{\partial T}\right)_p = T\left(\frac{\partial \Delta S^\circ}{\partial T}\right)_p = -T\left(\frac{\partial^2 \Delta G^\circ}{\partial T^2}\right)_p \qquad (6)$$

$$\Delta G^\circ = RL(B + AT + CT \log T) \qquad (7)$$

$$\Delta H^\circ = R(LB - CT) \qquad (8)$$

$$\Delta S^\circ = -R(LA + LC \log T + C) \qquad (9)$$

$$\Delta C_p^\circ = -RC \qquad (10)$$

For Eqns 3 and 7 to 10, R is the gas constant ($R = 1.98719$ cal $\cdot$ mol$^{-1} \cdot K^{-1}$), L denotes (ln 10 = 2.302585) and the subscript p denotes constant pressure. The constants A, B and C are the coefficients from Eqn 2. This thermodynamic treatment is of general application to any equilibrium process (Ives and Moseley, 1976), e.g., ionization constants, solubilities, partition coefficients or complexation constants. Equilibrium–temperature dependence data may be fitted to Eqn 2 by either of the following data-fitting methods. All computations were carried out with an Apple Macintosh SE microcomputer:

(i) the method of multiple linear regression (Eqn 2a),

$$y = a_0 + a_1[\mathrm{x}_1] + a_2[\mathrm{x}_2] \tag{2a}$$

for which the coefficients a_0, a_1 and a_2 are equated with A, B and C, respectively, in Eqn 2. The variables $[\mathrm{x}_1]$ and $[\mathrm{x}_2]$ are equated with $1/T$ and $\log T$, respectively; and y is equated with $-\log K$. The coefficients a_0, a_1 and a_2, and their associated standard errors, are obtained by the method of least-squares (Draper and Smith, 1966) which was computer programmed. The use of Eqn 2a in this way violates the assumption that the independent variables $[\mathrm{x}_1]$ and $[\mathrm{x}_2]$ (in this case $1/T$ and $\log T$) are truly independent.

(ii) the sigma plot method (Ives and Moseley, 1976; Ramette, 1977). In this procedure, $\Delta H°$ values are estimated from the finite difference form of the van't Hoff equation [$\Delta H° = -LRT_{\mathrm{av}}^2 \Delta pK/\Delta T$]. The $\Delta H°$ values are then plotted against $T(\Delta H° = \Delta H_0° + \Delta C_p° T)$ (from Eqn 6 above) and the slope is used to estimate the coefficient (C) for the log T term in Eqn 2 ($C = -\Delta C_p°/R$). The value of C is then used to calculate Σ, and to estimate the coefficients A and B by linear regression against $1/T$ (Eqn 11):

$$\sum = -\log K - C \log T = A + B/T \tag{11}$$

The calculations were verified by calculating the derived thermodynamic functions for: (a) the ionization of water (Harned and Robinson, 1940), as recalculated by Ramette (Ramette, 1977); (b) the ionization of cyanoacetic acid (Feates and Ives, 1956), as recalculated by Ives and Moseley (Ives and Moseley, 1976). No significant differences from the literature results for (a) and (b) were found. It is likely that even the best available equilibrium–temperature dependence data are not sufficiently accurate to reveal the temperature dependence of $\Delta C_p°$ (Timini, 1974; Ives and Moseley, 1976; Ramette, 1977).

Eqn 2 may be applied to the equilibrium process for saturated solubility ($\log K = \log m_i$) and its temperature dependence if the thermodynamic activity of the dissolved solute is available (Eqn 1c). In the present work, concentrations of saturated solutions were measured on the molal scale and activity coefficients have been assumed equal to unity. Consequently, the derived thermodynamic functions have apparent values and are denoted with an asterisk, e.g., ΔG^*.

The present work was performed after consideration of several observations:

(i) It has been observed that 5,5-dimethylbarbituric acid is markedly less soluble in 0.001 M HCl at 25 °C than the diethyl derivative (Prankerd, 1985). This is most likely to relate to the extremely high melting point of the dimethyl derivative (284–286 °C). It was of interest to examine the effect of this high melting point on the thermodynamic functions for the solution process.

(ii) 5,5-Dimethylbarbituric acid is the weakest acid in a series studied by McKeown (1980a). A linear free-energy relationship disclosed an acid-strengthening steric effect for the series (McKeown, 1980b). A study of the first ionization constants for some cycloalkane-1′,5-spirobarbituric acids (McKeown and Prankerd, 1981), in which the C5 substituents are restricted in motion, confirmed the observed steric acid-strengthening effect. An explanation for the steric effect was proposed in terms of differential forces for hydration of the ionized and molecular forms of the barbituric acids and the size of the C5 substituents. An earlier investigation of the pK_1-temperature dependence for 5,5-dimethylbarbituric acid (Prankerd, 1977) showed that this compound had a more positive value for $\Delta H°$, a less negative value for $\Delta S°$ and a more negative value for $\Delta C_p°$ for the ionization reaction than had other barbituric acids (Manov et al., 1952). The less negative value for ΔS° for ionization was consistent with the proposed explanation for the steric effect.

(iii) Other extreme or anomalous properties have been noted for 5,5-dimethylbarbituric acid (McKeown, 1976; Prankerd, 1985). These include extremely rapid base-catalyzed hydrolysis (McKeown, 1976), a very low octan-1-ol/water partition coefficient (Prankerd, 1977, 1985), extremely low solubilities in ethanol/water mixtures (Prankerd, 1985) and an unusual (although not unique) hydrogen-bonding arrangement in the X-ray crystal structure (Prankerd, 1985). In addition, it is not hypnotically active (Fischer and von Mering, 1903).

(iv) Diisopropylcyanoacetic acid has been used in a pK temperature-dependence study (Ives and Marsden, 1965) as a model compound which should exhibit marked steric hindrance to solvation. 5,5-Diisopropylbarbituric acid (**2**) was synthesized in this laboratory for similar model studies (Wong, 1979). It is structurally similar to diisopropylcyanoacetic acid, and is also expected to exhibit steric hindrance to hydration. The role of solvation of both ionic and molecular species in ionization equilibria has been discussed recently (McKeown, 1980b; McKeown and Prankerd, 1981; McKeown et al., 1986). Thermodynamic functions for solution for **2**, under conditions involving only the molecular species, may demonstrate interesting features related to hydration, compared to those for other barbituric acid derivatives.

The present study was performed to see whether the extreme properties exhibited by 5,5-dimethylbarbituric acid extended to its solid-solute equilibria, and to compare the solution properties of this derivative with other barbituric acids. The solubility–temperature dependence equations would also allow calculation of thermodynamic functions which could be used in further elucidating the nature of the acid-strengthening steric effect (McKeown, 1980b; McKeown and Prankerd, 1981; McKeown et al., 1986). It was of interest to evaluate the multiple linear regression and sigma plot methods described above by comparison of the derived coefficients for the Valentiner Eqn 2.

Materials and Methods

Materials

The barbituric acids were obtained from previous studies (McKeown 1980a; Wong, 1979). 5,5-Diethylbarbituric acid (**1**) (British Drug Houses, Poole, U.K.) was recrystallized from ethanol, m.p. 191–193° C, and 5-ethyl-5-phenylbarbituric acid (**3**) (donated by Kempthorne-Prosser & Co. Ltd., Dunedin, New Zealand) was recrystallized from ethanol/water (1 : 4), m.p. 176.5–177.5° C (McKeown 1980a). **1** and **3** were identified as the respective Form II polymorphs by comparison of their infrared spectra with authentic spectra in the literature (Mesley, 1970). Form XIII of **3** was prepared by grinding Form II with an agate mortar and pestle in water (Williams, 1959b) and the structure identified by comparison of its infrared spectrum with authentic spectra from the literature (Williams, 1959b; Mesley, 1970). 5,5-Dimethylbarbituric acid (**4**) was synthesized by condensation of diethyl dimethylmalonate with urea in the presence of ethanolic sodium ethoxide (McKeown, 1980a) and recrystallized to constant melting point from water, m.p. 286–288° C (McKeown, 1976). After storage for 12 months, the melting point had changed to 273–274° C (McKeown, 1976; McKeown, 1980a). 5,5-Diisopropylbarbituric acid (**2**) was synthesized by condensation of diethyl diisopropylmalonate with urea in dimethylsulphoxide, using potassium *t*-butoxide as the base (Wong, 1979), m.p. 227–228° C. All barbituric acid derivatives gave a single peak when examined by high-performance liquid chromatography, using the conditions given below. Water was double-distilled, the second distillation being from alkaline permanganate in an all-glass still fitted with a partial reflux still-head and a fractionating column (1300 × 38 mm) packed for 1100 mm of its length with Raschig rings (7 × 7 mm). Hydrochloric acid (0.001 M) was prepared by dilution from standard acid (0.1 M).

Solubility determinations

Molal (m_i) solubility–temperature dependence data for the 5,5-disubstituted barbituric acids were obtained in 0.001 M HCl. A large excess of each powdered derivative was weighted into separate vials with screwcaps and parafilm liners. The solvent was added, then each vial was capped and sealed with paraffin wax. For **1**, **2** and **3** (Form II), the vials were then attached by spring clips to a vertical disc which was rotated in a water-bath at the required temperature ±0.05 °C. The samples were equilibrated at each temperature for 24 h, starting at 50 °C, then at 5C° intervals down to 10 °C. The temperature was then raised in 5C° steps back to 50 °C. For studies on **4**, this apparatus was not available. A teflon-coated stirring bar was placed in the vial containing the barbituric acid and the solvent. The vial was then sealed and immersed in water in a water-jacketed cell on a magnetic stirrer. The system was equilibrated at 5 °C for several days, then solubilities were determined at 5 °C intervals (24 h equilibration times) until 50 °C was reached, then the temperature lowered in 5C° steps back to 5 °C. After equilibration for a further 48 h, the solubility at 5 °C was redetermined. The temperature was then increased and solubilities were again determined at 10 and 15 °C after 24 h at each temperature. Temperatures were determined with a thermometer recently calibrated under total immersion to ±0.02 °C (Physics and Engineering Laboratory, Department of Scientific and Industrial Research, Wellington, New Zealand) (McKeown, 1980a). For **1**, **2** and **3**, temperature measurements were made under total immersion. For **4**, emergent stem corrections (t_c) were made to the readings according to $t_c = n(t - \bar{t}) \times 0.00016$, where t is the observed temperature, $\bar{t}$ is the 'average column temperature' (estimated by placing a secondary thermometer at one third the height of the exposed mercury column of the primary thermometer) and n is the height of the exposed column in °C.

After equilibration at each temperature, duplicate aliquots were filtered under positive pressure (0.45 μMillipore filter) into tared flasks, weighed, and then the barbituric acid concentration determined. Syringes and filters used for manipulating solutions equilibrated at temperatures above ambient were warmed before use. **1**, **2** and **3** were determined spectrophotometrically at 240 nm after diluting with borate buffer at pH 10.4. Beer's law plots obtained for all compounds passed through the origin and had correlation coefficients not less than 0.9990. **4** was determined by high-pressure liquid chromatography (Waters M6000 pump, U6K injector and Model 441 detector), using **1** as an internal standard. Chromatograms were run on reverse-phase octadecylsilyl columns (Waters 8C1810 Radial-Pak Cartridge) using filtered (0.45 μMillipore filter), degassed 25% (v/v) aqueous methanol as the mobile phase and an analytical wavelength of 214 nm (fixed wavelength zinc lamp). Injection volumes were 20–25 μl. Concentrations were determined by the method of peak height ratios.

Melting points

Melting point ranges were determined in washed capillary tubes with an Electrothermal Melting Point Apparatus 1A 6304 Mark II equipped with a thermometer calibrated to compensate for emergent stem exposure.

Infrared spectra

Infrared (IR) spectra were recorded in potassium bromide discs, using a Shimadzu IR-400 grating spectrophotometer. About 80 mg of a KBr (IR Spectroscopy Grade, Fluka AG, Buchs, Switzerland) dispersion containing 0.8 mg of the derivative was compressed in a stainless steel die. The KBr was finely ground with an agate mortar and pestle prior to introduction of the barbituric acid derivative, which was then gently crushed and incorporated. This was to minimise the possibility of disrupting the crystal structure of the sample. It has been shown that polymorphic changes can take place on grinding samples for KBr disc preparation for barbituric acid infrared spectral determination (Cleverley and Williams, 1959a), and also for spectra of other drugs (Kaneniwa and Otsuka, 1985).

Results and Discussion

Accuracy

Of the compounds examined in the present study, solubility data for **1** and **3** have previously been obtained. Previous studies of barbituric acids in water (Sekiguchi et al., 1973; Vaution et al., 1981; Treiner et al., 1982) have ignored the role of ionization in determining solubilities. The ionized forms (e.g., the alkali metal salts) are generally much more soluble in water than the un-ionized free acids. The proportion of the ionized form present in water (without additional buffer for pH maintenance) depends on the concentration and the pK_1 value, which ranges from 7.4 (**3**) to 8.5 (**4**) at 25 °C (McKeown 1980a), for the compounds examined in this work. Solubilities were determined in 0.001 M HCl to provide conditions which would suppress ionization but not be of high enough ionic strength to significantly change activity coefficients (referred to the 1 molal solution behaving as though it were infinitely dilute as the standard state) from unity. The solubilities determined in the present work for **1** are in good agreement with those in the literature (Vaution et al., 1981; Treiner et al., 1982). For **3**, the solubilities in 0.001 M HCl at 25, 35 and 45 °C were found to be significantly less than in the literature (Vaution et al., 1981; Treiner et al., 1982). The lower solubilities for **3** may be accounted for by the suppression of ionization, due to the added HCl, so that the measured solubilities are for the un-ionized molecule only. Solubilities for all compounds were estimated to have an accuracy of ±1%.

Data fitting

Experimental plots of $-\log m_i$ vs. reciprocal temperature for **1** and **2** over the whole temperature range (10 – 50 °C) and for **4** over the range 20 – 40 °C were the same when equilibration was approached from either over-saturation or from under-saturation (Fig. 1, **1**, **2** and **4**). This indicated that the equilibration time between sampling for measurements (24 h) was sufficient and that appearance of hydrolysis products (if any) had not interfered with the analyses. An earlier study (Sekiguchi et al., 1973) indicated that for **3**, equilibrium was achieved in less than 4 h, when a two-fold excess of the derivative was used. The time for equilibration is dependent on the degree of agitation and the surface area of the excess finely powdered solid barbituric acid. The solubility data is presented in van't Hoff plots (Fig. 1) and was fitted to the Valentiner Equation by methods 1 and 2 given in the Data Fitting Methods section of the Introduction. The coefficients found for the Valentiner equation are given in Tables 1 and 2. They were used to calculate the apparent thermodynamic functions ΔH^*, ΔS^* and ΔC_p^* for solution which are reported in Tables 3 and 4. These thermodynamic functions were then examined for their dependence on: (a) the melting point or (b) steric substituent constants for the 5,5-dialkyl derivatives **1**, **2** and **4** (Fig. 2a–c).

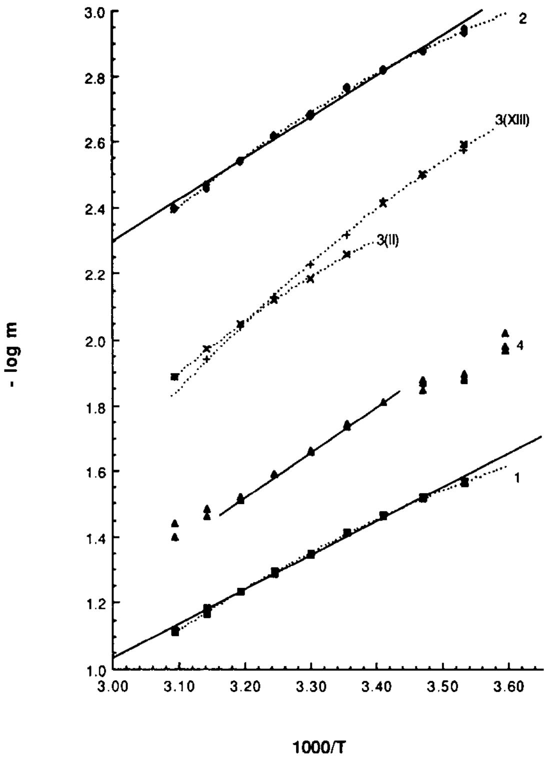

Fig. 1. Plots of the negative log molal solubilities in 0.001 M HCl of 5,5-diethylbarbituric acid (**1**) (■), 5,5-diisopropylbarbituric acid (**2**) (◆), 5-ethyl-5-phenylbarbituric acid (**3**) (x temperature decreasing; + temperature increasing) and 5,5-dimethylbarbituric acid (**4**) (▲) as a function of reciprocal temperature. Solid lines denote linear least-squares fitting of data to the van't Hoff equation and dotted lines were calculated from Eqn 2, using the coefficients in Table 1. For (**4**), only the data from 20 to 40 °C were fitted.

The Valentiner Eqn 2 is derived on the basis that ΔC_p° for the equilibrium process has a value which is finite and independent of temperature. If ΔC_p^* for solution were to have a linear depen-

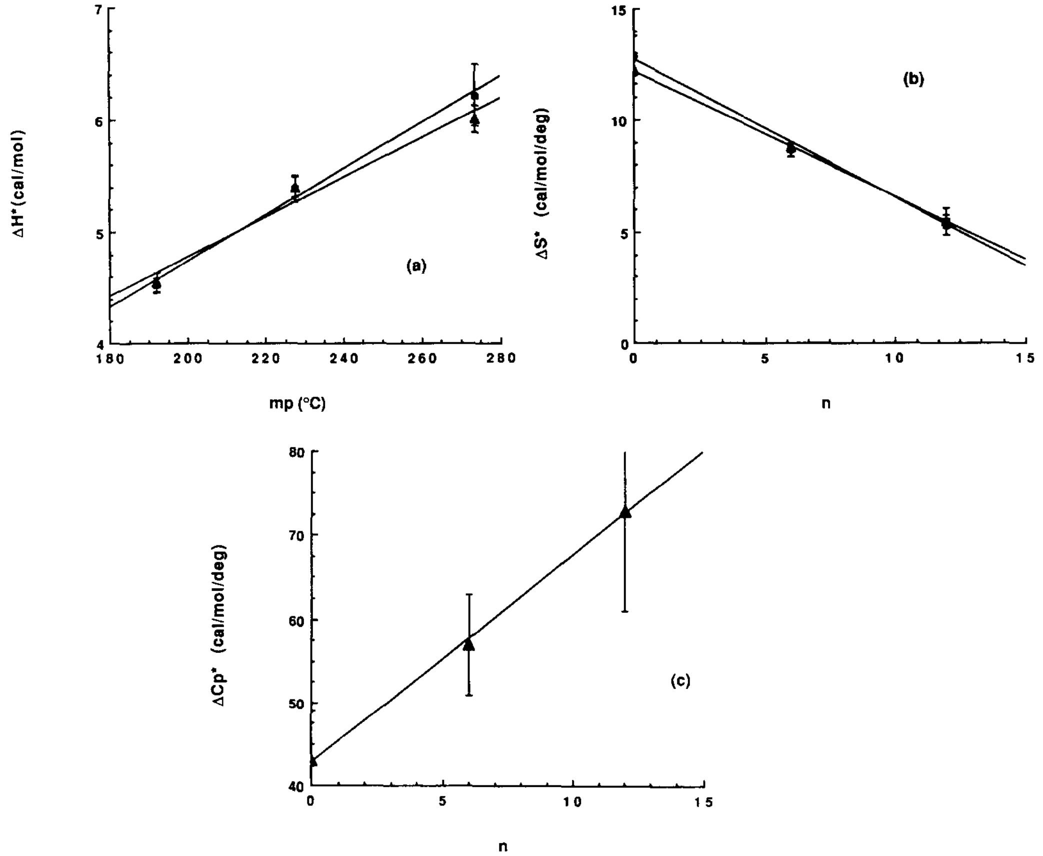

Fig. 2. Plots of apparent thermodynamic functions at 25 °C for solution of 5,5-diethylbarbituric acid (**1**), 5,5-diisopropylbarbituric acid (**2**) and 5,5-dimethylbarbituric acid (**4**) in 0.001 M HCl as a function of (a) melting point, m.p. (°C), (ΔH^*) or as a function of (b) and (c) the substituent size as given by the Newman six-number, *n*, (ΔS^*, ΔC_p^*). Values for the apparent thermodynamic functions were taken from Table 3 (■) or Table 4 (◆). Straight lines (———) are linear least-squares fits of the data. Error bars are the estimated errors in the values for the thermodynamic functions and are taken from Tables 3 and 4, respectively.

dence on temperature, i.e., $\Delta C_p^* = a + bT$, the addition of a linear term in T to Eqn 2 is required. This was tested with the most precise set of data (**1**) from this study. When the data for **1** was fitted to Eqn 2 with an additional linear term ($+DT$), a regression equation was obtained in which the standard errors for all coefficients were much larger than those obtained in the absence of such a linear term. The coefficients (A, B, C and D) for all terms were not significantly different to zero, despite a correlation coefficient (r) and an overall F-ratio which were quite acceptable. Hence, this solubility–temperature dependence data support a value for $\Delta C_p^* \neq 0$, but do not permit speculation into the temperature dependence of ΔC_p^*. The solubility temperature-dependence data for **2** were a little less precise than those for **1**, suggesting that a lack of significance would also result if an additional linear term in T for Eqn 2 was used with the data for this derivative. More accurate solubility data and a wider temperature range than in the present work would be needed for the temperature dependence of ΔC_p^* for solution to be apparent.

Form II of **3** was added to the vials at the beginning of the experiments ($T = 50$ °C). A discontinuity in the solubility-reciprocal temperature plot resulted (Fig. 1, **3**). This corresponds to the enantiotropic transition between the anhydrous polymorph (Form II) and a monohydrate (Form

TABLE 1

Coefficients for the Valentiner Eqn 2 from multiple linear regression $-\log m_i = A + B/T + C \log T$ (2)

Compound	A	B	C	R[a]	F[b]
1	79.481817	−2633.997	−27.981947	0.9996	9979.8
	(8.7479)[c]	(394.03)	(3.00088)		
1[d]	788.80961	−21404.362	−313.92346	0.9997	6786.2
	(622.486)	(16475.4)	(250.927)		
2	117.92850	−4126.4175	−40.952443	0.9994	6609.1
	(12.9288)	(582.799)	(4.43850)		
3 (II)	151.17842	−5669.8875	−52.499547	0.9997	3353.3
	(33.3637)	(1539.82)	(11.3973)		
3 (II)[e]	−2.505502	1422.5779	–	0.9981	1325.5
	(0.125219)	(38.84)	–		
3 (XIII)	131.98551	−4394.3432	−46.44456	0.9997	5817.4
	(21.0075)	(937.848)	(7.21777)		
4[e,f]	−2.820001	1358.545	–	0.9992	4988.3
	(0.0635)	(19.2352)	–		

[a] R is the multiple correlation coefficient.

[b] Overall F-ratio.

[c] Figures in parentheses are the standard errors for the coefficients A, B and C. Student's t values calculated from these indicate that the coefficients are all significant at least at the 99% confidence interval, except those for **3** (II) and **4**, which are significant at the 98% confidence interval.

[d] An additional term, $+DT$, is included in Eqn 2. $D = 0.20517487$ (0.1800381). See discussion for assessment of this additional coefficient.

[e] Data fitted to the van't Hoff equation; i.e., C in Eqn 2 defined as zero.

[f] For **4**, only the solubilities between 20 and 40 °C were fitted.

XIII). Form II is stable above the transition temperature, while Form XIII is stable below it. The compound added at the beginning of the experiment had an IR spectrum corresponding to the Form II polymorph, Fig. 3. However, crystalline material isolated from the experimental system at 10 °C had an IR spectrum which was identical to that of an authentic specimen of Form XIII, prepared and characterized as in the literature (Cleverley and Williams, 1959b; Mesley, 1970), Fig. 3. The solubility–temperature dependence plot for Form II (Fig. 1, **3**) could be fitted by either the Valentiner equation or by the van't Hoff equation (Eqn 2 with the coefficient for the log T term equal to zero). The overall F-ratios for the fits showed that the Valentiner equation gave the better fit. The plot for Form XIII showed curvature in the van't Hoff plot and this data was best fitted by Eqn 2. Iterative simultaneous solution of the equations (Eqn 2, Tables 1 and 2) for the two plots for **3** gave the thermodynamically controlled transition temperature (38.2 °C) for the two forms. This temperature was in good agreement with that previously determined (Eriksson, 1961; Sekiguchi et al., 1973). The data in Fig. 1 (**3**) indicates that the transition is reversible and that the higher temperature form (**3**, Form II) is metastable at temperatures below the transition temperature, whereas the transition from Form XIII to Form II, above the transition temperature, is more rapid. The earlier study of Sekiguchi et al. (1973) did not demonstrate this metastable behavior.

The coefficients derived for Eqn 2 from the two calculational methods are in agreement with each other, within the limits of the calculated errors. Finite errors in the experimental data and assumptions made in the data treatments are responsible for the deviations between the coeffi-

TABLE 2

Coefficients for the Valentiner Eqn 2 from the sigma plot method
$-\log m_i = A + B/T + C \log T$ (2)

Compound	A	B	C
1	81.491809 (2.5)	−2719.79417 (110)	−28.677989 (0.9)
2	104.96069 (6)	−3546.77329 (250)	−36.497908 (2)
3 (II)	148.50808 (6.3)	−5550.90777 (310)	−51.581716 (2.5)
3 (XIII)	126.549181 (11)	−4149.50930 (512)	−44.579826 (4)
4 [b]	60.067718 (3)	−1478.70921 (233)	−21.568625 (1)

[a] Figures in parentheses are the errors for the coefficients A, B and C. These were obtained by fitting the equation using the worst possible combinations of the solubility–temperature dependence data and their experimental errors. This corresponds to graphical plotting of 'lines of worst fit'.

[b] For **4**, only the solubilities between 20 and 40 ° C were fitted to Eqn 2.

cients A, B and C, as calculated by the two methods for each compound. For more precise equilibrium-temperature dependence data, e.g., ionization of cyanoacetic acid (Feates and Ives, 1956), the coefficients obtained by the two calculational methods are in much better agreement. It must be emphasized that the large number of significant figures in Tables 1 and 2 does *not* imply physical significance. They are necessary to preserve calculational accuracy (Ives and Moseley, 1976), particularly where small differences between large numbers are required, as in the estimation of the transition temperature for the two forms of **3**.

For **4** between 20 and 40 ° C, the solubility–temperature dependence is very similar to **1** and **2** (Fig. 1, **4**). The data points at 45 and 50 ° C were reproduced poorly and were not included in data-fitting procedures. Below 20 ° C, unusual non-linearity in the van't Hoff plot and poorer experimental precision indicated the possibility of a change in crystal structure for **4**. This was supported by an earlier observation of melting point differences for material which had been (i) freshly recrystallized from ice-cold water and dried, giving m.p. 284–286 ° C, and then (ii) stored for several months at room temperature, giving m.p. 273–274 ° C (McKeown, 1976). A high melting point (m.p. 283–284 ° C) was found in this work for **4** which had been equilibrated with water at low temperatures (5 ° C). However, in an earlier study, in which **4** was recrystallized from water at room temperature (Atkinson, 1984), the material

TABLE 3

Thermodynamic functions for solution of 5,5-disubstituted barbituric acids at 25 ° C. (Calculated from coefficients in Table 1.)

Compound	ΔG^* (kcal/mol)	ΔH^* (kcal/mol)	$T\Delta S^*$ (kcal/mol)	ΔS^* (cal/mol per deg)	ΔC_p^* (cal/mol per deg)
1	1.921 (0.006) [a]	4.53 (0.06)	2.61 (0.06)	8.7 (0.3)	56 (18)
2	3.757 (0.006)	5.38 (0.12)	1.62 (0.12)	5.5 (0.6)	81 (33)
3 (II)	3.076 (0.012)	5.16 (0.87)	2.09 (0.84)	7.0 (3.0)	104 (66)
3 (XIII)	3.169 (0.009)	7.41 (0.06)	4.24 (0.06)	14.2 (0.3)	92 (42)
4	2.373 (0.012)	6.22 (0.27)	3.85 (0.27)	12.9 (0.9)	–

[a] Figures in parentheses are the estimated errors in the thermodynamic functions. These were calculated by substituting the maximum and minimum values for A, B and C in Table 1 into Eqns 7 to 10, and taking half of the difference between the estimated maximum and minimum values for the thermodynamic functions.

TABLE 4

Thermodynamic functions for solution of 5,5-disubstituted barbituric acids at 25 °C. (Calculated from coefficients in Table 2.)

Compound	ΔG^* (kcal/mol)	ΔH^* (kcal/mol)	$T\Delta S^*$ (kcal/mol)	ΔS^* (cal/mol per deg)	ΔC_p^* (cal/mol per deg)
1	1.921	4.55	2.63	8.8	57
	(0.003) [a]	(0.09)	(0.09)	(0.15)	(6)
2	3.756	5.40	1.64	5.5	73
	(0.003)	(0.09)	(0.09)	(0.3)	(12)
3 (II)	3.076	5.16	2.09	7.0	103
	(0.012)	(0.36)	(0.36)	(1.2)	(13)
3 (XIII)	3.167	7.43	4.26	14.3	89
	(0.009)	(0.09)	(0.09)	(0.3)	(24)
4	2.371	6.01	3.64	12.2	43
	(0.003)	(0.12)	(0.18)	(0.6)	(6)

[a] Figures in parentheses are the estimated errors in the thermodynamic functions. These were calculated by substituting the maximum and minimum values for *A*, *B* and *C* in Table 2 into Eqns 7 to 10, and taking half of the difference between the estimated maximum and minimum values for the thermodynamic functions.

had m.p. ≈ 278 °C. Apart from very minor differences in the 1460–1420 cm^{-1} region, the main difference between the IR spectra of high- and low-melting forms of **4** was a loss of definition in the carbonyl stretching region (Fig. 4). This may indicate that the spectrum for the high-melting

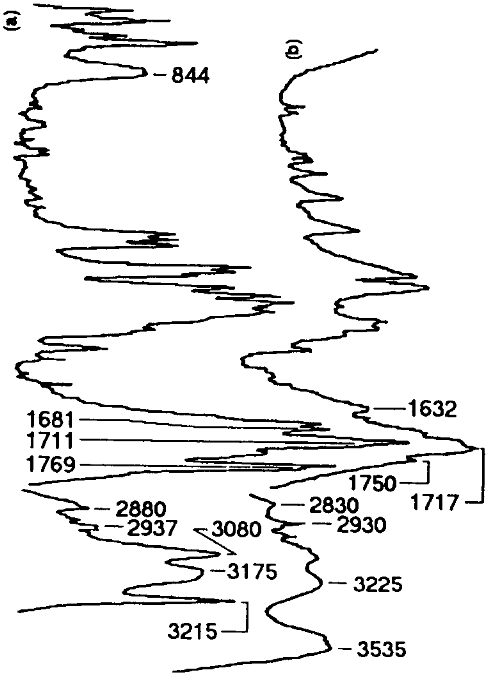

Fig. 3. Infrared spectra of phenobarbitone (**3**) (a) Form II (anhydrous); (b) Form XIII prepared by grinding Form II with water at *RT*. Excess solid material recovered from a saturated solution of **3** at 10 °C had a spectrum which was identical to (b).

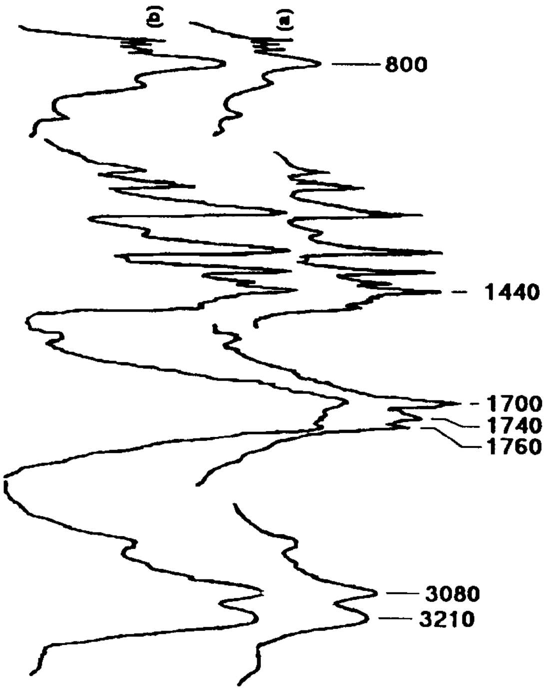

Fig. 4. Infrared spectra of **4** (a) low melting (273–274 °C) and (b) high melting (283–284 °C).

material (m.p. 283–284 °C) was obtained from a sample in which the transition to another polymorph was incomplete. The absence of O–H stretching and bending bands in IR spectra of the high-melting crystalline material excluded the possibility of hydrate formation (compare Fig. 4 with Fig. 3b, which shows typical O–H stretching and bending bands for a monohydrate). It had also been previously reported that elemental analysis of the high melting form of **4** gave percentages of carbon, hydrogen and nitrogen which correspond to the anhydrous derivative (McKeown, 1976). Polymorphism has not previously been observed for this barbituric acid derivative. Only the data between 20 to 40 °C were used for estimation of the thermodynamic functions. The data for **4** were better fitted by the van't Hoff equation (Table 1), although the sigma plot method was used to fit the data to the Valentiner equation (Table 2).

Apparent thermodynamic functions for solution

Statistically significant curvature in the plots of $-\log m_i$ vs $1/T$, compared to least-squares straight lines (Fig. 1), indicated a finite value for the apparent heat capacity change (ΔC_p^*) for the solution process for **1**, **2**, **3** (II) and **3** (XIII). Such curvature has been reported very infrequently. Curved plots were reported for a series of alkyl *p*-hydroxybenzoates (Grant et al., 1984). In that paper, the curvature was ascribed to the finite value of ΔC_p^* for solution, which in turn was attributed to changes in solvent structure brought about by the solute molecules (Tanford, 1980). An alternative explanation, that such curvature results from polymorphic or hydrational changes in the crystal state, was rejected (Grant et al., 1984). A report of curvature in the van't Hoff plot for the solubility of gepirone hydrochloride in pentanol (Behme et al., 1985), however, is questionable. Although the reported data could be fitted to the Valentiner equation, with a multiple correlation coefficient that was reasonable, the precision of the data is not sufficient to establish statistically significant values for the coefficients in Eqn 2. This is an example of the danger of reliance on correlation coefficients without further tests of statistical significance.

Calculation of apparent thermodynamic functions for solution for all derivatives was performed in the present work, as activity coefficients were not calculated, but were assumed to be equal to unity. This is equivalent to defining the standard state as a hypothetical 1 molal solution behaving as though it were at infinite dilution. As the concentrations of the barbituric acid derivatives ($<$ 0.0015 mol fraction) and the ionic strengths (0.001 M) of the solutions were low, it was reasonable to assume that the activity coefficients would not be very different from each other, and be close to unity. In another study (Grant et al., 1984), in which solute concentrations were more than an order of magnitude greater than in the present work, similar assumptions were used. Also, it is conventional in electrolyte chemistry to regard neutral species in aqueous media of ionic strengths of less than 0.1 M to have activity coefficients of unity on the molar or molal scales (Gold, 1956). Consequently, comparisons between the derived apparent thermodynamic functions for different compounds could be expected to be valid. Tables 3 and 4 report the apparent thermodynamic functions (calculated from Eqns 7 to 10) for solution for **1**–**4** at 25 °C.

For all compounds, the positive apparent entropy change (ΔS^*, increased disorder) increases the solubility by decreasing the apparent free energy (ΔG^*) in accordance with the Gibbs-Helmholtz equation. Conversely, the positive apparent enthalpy change (ΔH^*, endothermic) acts to decrease the solubility. There was no relationship between the ΔG^* values for solution at 25 °C and parameters related to intermolecular crystal forces (melting point) or C5-substituent size, as estimated by Newman's six-number (Newman, 1950), or by the steric parameter *S*(R) (Beckhaus, 1978; Isaacs, 1987) which are reported in Table 5. The derived apparent thermodynamic functions for each compound reported in Tables 3 and 4 are in good agreement with each other, within the estimated errors given in the tables. In all cases, the apparent enthalpy change for solution (ΔH^*) is positive (endothermic). For the 5,5-dialkyl derivatives **1**, **2** and **4**, ΔH^* values for solution exhibited a fairly good linear relationship with the melting points of the compounds (Fig. 2a). This

TABLE 5

Melting points and steric constants for 5,5-dialkylsubstituted barbituric acids

Compound	m.p. (° C)	n [a] (six-number)	S(R) [b] (10^4 J/mol)
1	192	6	3.29
2	227.5	12	5.61
4	273.5	0	2.29

[a] Newman (1950).

[b] Beckhaus (1978); Isaacs (1987).

suggests that the energy required to disrupt the crystal lattice of the compound in its solid state dominates the apparent enthalpy changes for solution.

There was no relationship between melting points and the ΔS^* or ΔC_p^* values for solution. However, these values for solution demonstrated a good *inverse* relationship to the size of the alkyl substituents, Table 5 and Figs. 2b or 2c, as estimated by Newman's six-number (Newman, 1950). A similar relationship was seen with a steric constant derived from molecular mechanics (Beckhaus, 1978; Isaacs, 1987). Assuming that each of the compounds in its crystal state has the same entropy (over the temperature range under study), the apparent increase in disorder on dissolution is seen to be greatest for the 5,5-dimethyl derivative and least for the 5,5-diisopropyl derivative. This result is not in conflict with current theories on the ordering of water molecules around dissolved hydrocarbon chains. The very good relationship between ΔC_p^* and Newman's six number is likely to be fortuitous, as ΔC_p^* has a large associated error. This is a consequence of the fact that this quantity is a second derivative of ΔG^*. Exact linear relationships would not be expected for ΔH^*, ΔS^* or ΔC_p^*, as these apparent thermodynamic functions are the sums of the functions for the two steps illustrated in Eqn 12 below. The apparent thermodynamic functions for **4** are seen to be at one extreme for these compounds, as was found earlier for the functions for ionization (McKeown et al., 1985). For thermodynamic functions for ionization, the ΔS° values were in the *same* rank order as the size of the substituents.

Differences in the apparent thermodynamic functions for solution of the two forms of **3** are expected to result solely from differences in the solid state. The X-ray crystal structure determined by Williams (1973a) for **3** (XIII) showed that each water molecule in the unit cell was hydrogen bonded to four phenobarbitone molecules (two hydrogen bond donors and two hydrogen bond acceptors) and that each phenobarbitone molecule was hydrogen bonded to four water molecules (there were no water–water or phenobarbitone–phenobarbitone hydrogen bonds). The data from the present study shows that introduction of water molecules into the crystal structure to give Form XIII brings about marked differences in the apparent enthalpy and entropy changes for solution of Form XIII compared to Form II (Tables 3 and 4). Over the temperature range of the study, these changes nearly cancel out so that the apparent free energy changes for the solution process (and hence the corresponding saturated solubilities) are similar for the two forms. The data in Table 3 gives a heat of transition at 298.15 K between the two forms of 2.25 ± 0.96 kcal · mol^{-1}, while the value from Table 4 is 2.27 ± 0.45 kcal · mol^{-1}. These two values are in excellent agreement, and are similar to a previously reported value (Sekiguchi et al., 1973). At the transition temperature (38.2° C), the heat of transition is 2.09 kcal · mol^{-1}.

It is not clear why the relationships between the apparent thermodynamic functions for solution and the crystal or molecular properties for **3** do not conform to those for the other barbituric acid derivatives. Two possible reasons are:

(i) **3** is an unsymmetrically disubstituted derivative, whereas the other compounds are symmetrically substituted at C5. Molecular symmetry can play an important role in delineating crystal properties. For example, adamantane is a C_{10}-saturated hydrocarbon ($M_r = 136.23$) which has a very high order of symmetry. Despite the fact that it is non-polar, and therefore has no intermolecular attractive properties apart from London forces, it is a crystalline solid with m.p. 269.6–270.8° C (Windholz, 1983). However, another C_{10} saturated hydrocarbon is decalin, which has a lower order of symmetry, and for which the *cis*- and *trans*-isomers have m.p. values of −43.3 and −30.4° C, respectively (Windholz, 1983). It is possible that the intermolecular crystal forces and the entropy in the crystal state for **3** are significantly different compared to **1**, **2** or **4**. The lower m.p. for **3** (II) (m.p. 178–179 ° C) tends to support this suggestion.

(ii) the C5 phenyl substituent may introduce additional interactions with water in the aqueous solution state.

An on-going study of the physicochemical properties of 5,5-diphenylbarbituric acid (which is symmetrically substituted, but with C5 phenyl groups), m.p. 287–288 ° C, may help to decide between these alternatives.

Thermodynamic functions for hydration

The solution process in water may be envisaged as follows, Eqn 12:

$$\underset{\text{(solid phase)}}{\text{molecule in crystal}} \rightarrow \underset{\text{(gas phase)}}{\text{isolated molecule}} \rightarrow \underset{\text{(solution phase)}}{\text{hydrated molecule}} \qquad (12)$$

Thermodynamic functions for the solution process may be regarded as the sums of the thermodynamic functions for these two steps. If activity coefficients on the molal scale were available for the barbituric acids whose solubilities have been reported above, *standard* thermodynamic functions could be calculated. These could be used according to Hess's Law, allowing calculation of the standard enthalpy change for hydration ($\Delta H^\circ_\mathrm{H}$) of the un-ionized derivatives, Eqn 13:

$$\Delta H^\circ_{\mathrm{H\,(un\text{-}ionized)}} = \Delta H^\circ_{\mathrm{solution}} - \Delta H^\circ_{\mathrm{sub}} \qquad (13)$$

This would also require the standard enthalpy change for sublimation ($\Delta H^\circ_\mathrm{sub}$), or as a first approximation, the standard enthalpy change for fusion ($\Delta H_\mathrm{f}{}^\circ$) from differential scanning calorimetry measurements. $\Delta H^\circ_\mathrm{sub}$ values may be estimated from the temperature dependence of the sublimation (or vapour) pressures of the compounds. $\Delta H^\circ_\mathrm{H}$ values, and the corresponding $\Delta S^\circ_\mathrm{H}$ values, would be useful for estimation of the extent of hydration of un-ionized molecules, and in estimating the changes in hydration occurring on ionization. These estimated thermodynamic functions may then show features which relate to the steric acid-strengthening effect reported previously (McKeown, 1980b; McKeown and Prankerd, 1981; McKeown et al., 1985). The state of hydration of bioactive molecules may also be of importance in characterizing the way in which they interact with biomembranes, with respect to transport properties across the membranes and in receptor interactions leading to a pharmacological response. Estimates of heats of solvation of aliphatic dicarboxylic acids in benzene, using the approach depicted in Eqn 12, have been previously reported (Davies and Thomas, 1960). Also, the estimation of thermodynamic functions for sublimation has been reported for a series of aliphatic amides (Davies et al., 1959). The techniques described in these papers gave highly reproducible estimates of the thermodynamic functions for sublimation from two independent methods for determination of the dependence of vapour pressures on temperature. Should measured activity coefficients for the solutes examined in the present study become available, then calculation of the *standard* thermodynamic functions for solution, based on activities, would be a simple process. Activity coefficients for aqueous solutions could be measured by determination of the activity coefficients for water, followed by application of the Gibbs-Duhem-Margules equation (Moelwyn-Hughes, 1965).

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