Research Papers

Physico-chemical properties of barbituric acid derivatives: IV. Solubilities of 5,5-disubstituted barbituric acids in water

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Abstract

Solubilities at 25°C in 0.001 M HCl were determined for a series of 29 barbituric acid derivatives with aliphatic or aromatic substituents. The range of solubilities spanned more than four orders of magnitude. Relationships between these solubilities and other structural and physico-chemical properties were investigated. The data were fitted to a predictive relationship between solubility (as dependent variable) and the melting points and partition coefficients first proposed by Yalkowsky. The predicted solubilities from this relationship were in very good agreement with the measured values for some derivatives. A few solubilities deviated significantly. Data for several 5-methyl substituted barbituric acid derivatives suggested that they are more hydrated in aqueous solution than the corresponding 5-ethyl derivatives.

Keywords: Barbiturate; Solubility; Partition coefficient; Melting point; Hydration

1. Introduction

1.1. Theoretical

The general expression for the chemical potential (μ_i) for a dissolved solute at constant temperature (T) and pressure consists of ideal and non-ideal contributions:

$$\mu_i = \mu_i^o + RT \ln a_i = \mu_i^o + \underset{\text{ideal}}{RT \ln x_i} + \underset{\text{non-ideal}}{RT \ln \gamma_i}$$

(1)

The standard chemical potential (μ_i^o) and activity coefficient (γ_i) are defined by choosing a standard state in which the activity $(a_i = x_i \cdot \gamma_i)$ is unity. This may be the pure substance $(x_i = 1)$ (used for the solvent and the solute if the two are completely miscible), or a hypothetical solution state containing the solute at a concentration of 1 mole fraction, 1 molal or 1 molar, but behaving as though it was at infinite dilution $(x_i = 0)$ (usually used for sparingly soluble solids). Even where the solvent and solute are completely miscible, the use of the pure solute as the standard state for associated liquids has been criticized on the grounds that the standard state is different from one compound to the next and molecular interac-

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tions are difficult to evaluate (Davis et al., 1974). This criticism would appear to have equal validity for solid solutes as well.

The activity of a solid (a^s) can be estimated by reference to the supercooled liquid from the enthalpy of fusion, ΔH^f (Eq. 2):

$$\ln a^s = -\frac{\Delta H^f}{R} \cdot \frac{T_m - T}{T_m T} \tag{2}$$

where T_m is the melting temperature, T denotes the experimental temperature (both in K) and it is assumed that ΔH^f is constant over the temperature range T to T_m. Eq. 2 is a truncation ($\Delta C_p^f = 0$) of the more general equation (Hildebrand and Scott, 1962; Moelwyn-Hughes, 1965; Acree, 1984) which may be used when the difference between molal heat capacities of the liquid and solid is known ($\Delta C_p^f = $ constant) (Eq. 3):

$$\ln a^s = -\frac{\Delta H_m^f}{R} \cdot \frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R} \cdot \frac{T_m - T}{T}$$

$$-\frac{\Delta C_p^f}{R} \cdot \ln \frac{T_m}{T} \tag{3}$$

where ΔH_m^f is the molar enthalpy of fusion of the solute at the melting point. Assumptions made in the derivation of Eq. 3 are that the melting temperature is not significantly different from the triple point, and that ΔH_m^f is not significantly different from the enthalpy of fusion at the triple point (Acree, 1984). Combining Eq. 1 and 3 then leads to Eq. 4, in which the non-ideal contribution ($-\ln \gamma_i$) accounts for departures from Raoult's law:

$$\ln x^s = -\frac{\Delta H_m^f}{R} \cdot \frac{T_m - T}{T_m T} + \frac{\Delta C_p^f}{R} \cdot \frac{T_m - T}{T}$$

$$-\frac{\Delta C_p^f}{R} \cdot \ln \frac{T_m}{T} - \ln \gamma_i \tag{4}$$

where x^s is the mole fraction solubility of the solute, ΔC_p^f denotes the heat capacity for fusion, T_m is the melting temperature and T represents the experimental temperature (both in K). A real solution may then be regarded as consisting of ideal (Eq. 3) and non-ideal ($\ln \gamma_i$) contributions to solubility (Yalkowsky and Valvani, 1980).

1.2. Experimental solubilities of 5,5-disubstituted barbituric acids (I)
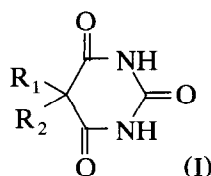
In an early study of structure-activity relationships in barbituric acids (Tabern and Shelberg, 1933), solubilities in water at 20°C were reported for several derivatives, although no experimental details were given. The inactive 5,5-dimethyl-barbituric acid was reported to be less soluble than the 5,5-diethyl derivative. This appeared to be paradoxical, given the increased hydrophobicity of the ethyl substituents. Biological activity data were primarily related to partition coefficients (Tabern and Shelberg, 1933).

Solubilities in water at 25°C were related to the number of carbons in the substituents for small subgroups of measured data for 14 derivatives, but no unifying predictive relationship was obtained (Breon et al., 1976). Measurements of the solubilities of hypnotically active barbituric acid derivatives in water have also been performed (Vaution et al., 1981) to provide baseline information for studies of their solubilization by surfactants. Although the effect of pH on barbituric acid solubility in the surfactant solutions was taken into account, pH effects on the solubilities in aqueous, non-surfactant solutions were not reported. Determination of the solubilities, both with and without surfactant at several temperatures, and the enthalpies of fusion for these derivatives, allowed estimation of linear regression equations which predicted the solubility in water at each temperature by extrapolation to zero surfactant concentration (Treiner et al., 1982).

In a further study (Summers, 1978), enthalpies of fusion and solubilities in methanol were deter-

mined for a number of barbituric acids, but no attempt was made to compare the solubilities with ideal mole fraction solubilities calculated using Eq. 2. Densities of the methanol solutions were not reported, so it was not possible to make these comparisons. The enthalpies of fusion were determined by differential scanning calorimetry (DSC), as in the study of Treiner et al. (1982). A comparison of the two sets of fusion data shows that there are differences between them. The differences between the reported values for compounds common to both sets of data range from 120–1942 cal/mol (502–8125 J mol^{-1}) and are often larger for compounds with greater values for ΔH^{f}. A study of some 5-ethyl-5-n-alkylbarbituric acids (Mayer and Rowland, 1984) used the Yalkowsky relationship (Yalkowsky and Valvani, 1980) to estimate their solubilities and then compared these with measured values.

The present work follows from previous studies of the solubility (Prankerd and McKeown, 1990) and partitioning (Prankerd and McKeown, 1992a,b) equilibria of a large series of barbituric acid derivatives. In this work, solubilities were determined in 0.001 M hydrochloric acid at 25°C for 29 barbituric acids with widely varying hydrocarbon substituents. These were compared, where possible, with solubilities from earlier work (Breon et al., 1976; Vaution et al., 1981) and the differences examined critically. The experimental results were examined for methylene group contributions to solubility in a series of cycloalkane-1′,5-spirobarbituric acids. By comparing the solubilities of pairs of derivatives in which one substituent (R_1) was methyl, ethyl, allyl, phenyl or 3-methylbut-2-enyl (3MBE) and the other (R_2) was either methyl or ethyl, further evidence was sought for an earlier proposal that hydration was more highly developed in 5-methyl substituted barbituric acids than in 5-ethyl substituted barbituric acids (Prankerd, 1977; McKeown, 1980b; McKeown and Prankerd, 1981). Solubilities have been previously related to partition coefficients and other physical properties, e.g., the melting point (Yalkowsky et al., 1972; Yalkowsky and Valvani, 1980, 1981; Chiou et al., 1981; Yalkowsky, 1981), and these predictive relationships were also investigated in the present work.

2. Materials and methods

2.1. Instrumental techniques

High-performance liquid chromatography (HPLC) was performed on Waters Associates Liquid Chromatographs using ODS (C18) packings in stainless-steel or radially compressed columns (Waters 8C1810 Radial Pak Cartridge) and filtered (Millipore 0.45 μm), degassed aqueous methanol (20–80% v/v) as mobile phase. Detection was by UV at 210, 214 or 280 nm. UV absorbance measurements were made in 10 or 20 mm Spectrosil (far UV) cuvettes with either a Hilger and Watts Uvispek H700 Mk IX single-beam spectrophotometer or a Shimadzu UV 240 recording spectrophotometer. Both instruments were equipped with temperature-controlled cuvette holders which were maintained at 25.00 ± 0.02°C. Temperatures were monitored with fully immersed thermometers calibrated to an accuracy of ±0.02°C (Physics and Engineering Laboratory, Department of Scientific and Industrial Research, Gracefield, New Zealand).

2.2. Materials

The source of each compound has been previously reported (Prankerd and McKeown, 1992a,b). All materials were recrystallized to constant melting point. For compounds 1, 5, 6, 9, 10, 12–15, 25–30, 33, 34 and 48, single peaks were observed on HPLC with a non-specific UV detector (λ = 214 nm) (Prankerd and McKeown, 1990). The remaining compounds gave single spots on thin-layer chromatography (McKeown, 1980a). In addition, mol% purity was estimated for several compounds (nos 11, 12, 26, 27) using a Perkin-Elmer DSC7 differential scanning calorimeter (Perkin-Elmer, Danbury, CT). Purities were > 99.0% in all cases. Water was double distilled, the second distillation being from alkaline potassium permanganate as described before (Prankerd and McKeown, 1992a). The water was used to prepare 0.001 M HCl by dilution of standard HCl. Standard solutions of the barbituric acid derivatives in 0.001 M HCl were prepared in volumetric flasks calibrated at 25.0°C.

2.3. Determination of equilibrium solubilities

An excess of the barbituric acid was powdered and weighed into a vial with a screw-cap and a parafilm liner, then HCl (0.001 M) was added. The vials, capped and sealed with paraffin wax, were attached by spring clips to a vertical disc which could be rotated in a waterbath controlled at $25.00 \pm 0.05°C$. Duplicate samples of the solution were taken at intervals with a glass syringe, filtered under positive pressure with a 0.45 μm filter (Millipore), and the barbituric acid deriva-

Table 1
Molar and mole fraction solubilities of 5,5-disubstituted barbituric acid derivatives (I) in 0.001 M HCl at $25.0 \pm 0.05°C$

Compound	R_1	R_2	Solubility		
			$M (\times 10^4)$	$x_i (\times 10^5)$	Log x_i
1	Me	Me	181.2 ± 1.5	32.73 ± 0.3	− 3.485
2	Me	Et	591.2 ± 0.7	106.7 ± 0.1	− 2.972
3	Me	allyl	692 ± 11	125 ± 2	− 2.904
4	Me	phenyl	41.70 ± 0.7	7.53 ± 0.1	− 4.123
5	Me	3MBE [a]	25.03 ± 0.04	4.522 ± 0.006	− 4.345
6	Et	Et	401.8 ± 1.6 [e]	72.55 ± 0.3	− 3.139
7	Et	i-Pr	71.11 ± 0.13 [f]	12.85 ± 0.02	− 3.891
8	Et	allyl	243.3 ± 2.7	43.94 ± 0.48	− 3.357
9	Et	phenyl	47.61 ± 0.15 [g]	8.602 ± 0.03	− 4.065
10	Et	3MBE [a]	55.83 ± 0.06	10.09 ± 0.01	− 3.996
11	Phenyl	phenyl	0.637 ± 0.007	0.115 ± 0.001	− 5.939
12	i-Pr	i-Pr	17.15 ± 0.02	3.099 ± 0.005	− 4.509
13	i-Pr	allyl	196.0 ± 0.8 [h]	35.40 ± 0.14	− 3.451
14	i-Pr	3MBE [a]	25.55 ± 0.1	4.616 ± 0.02	− 4.336
15	t-Bu	3MBE [a]	2.81 ± 0.03	0.508 ± 0.006	− 5.294
16	allyl	allyl	83.81 ± 0.04 [i]	15.14 ± 0.007	− 3.820
17	allyl	phenyl	42.72 ± 0.06	7.718 ± 0.011	− 4.113
19	Et	Et [b]	68.1 ± 0.4	12.30 ± 0.08	− 3.910
20	Et	1MB [b,c]	2.094 ± 0.002 [j]	0.378 ± 0.0004	− 5.422
24	$(CH_2)_2$		130 ± 10	23.5 ± 1.8	− 3.629
25	$(CH_2)_3$		221.3 ± 0.3	39.97 ± 0.05	− 3.398
26	$(CH_2)_4$		44.76 ± 0.34	8.087 ± 0.06	− 4.092
27	$(CH_2)_5$		8.70 ± 0.06	1.57 ± 0.01	− 4.804
28	$(CH_2)_6$		6.79 ± 0.02	1.227 ± 0.004	− 4.911
29	$(CH_2)_7$		10.42 ± 0.02	1.883 ± 0.004	− 4.725
30	$(CH_2)_{10}$		0.26 [k]	0.047	− 6.33
33	$(CH_2)_5$ [b]		3.45 ± 0.01	0.623 ± 0.002	− 5.205
34	$(CH_2)_{11}$		0.016 [k]	0.0030	− 7.54
48	Et	CHE [d]	2.96 [k]	0.535	− 5.272

[a] 3MBE = 3-methylbut-2-enyl.
[b] 2-Thio derivative.
[c] 1MB = 1-methylbutyl.
[d] CHE = cyclohexylidene-2-ethyl.
[e] Lit. 401 (Vaution et al., 1981); 397 (Breon et al., 1976).
[f] Lit. 59.5 (Breon et al., 1976).
[g] Lit. 51.7 (Vaution et al., 1981); 52.1 (Breon et al., 1976).
[h] Lit. 194 (Vaution et al., 1981).
[i] Lit. 86.5 (Vaution et al., 1981).
[j] Lit. 3.3 (Breon et al., 1976).
[k] Single determination.

tive concentration determined by spectrophotometric or HPLC methods (i) or (iii) as described previously for aqueous phases (Prankerd and McKeown, 1992a). 2-Thiobarbituric acid derivatives were determined by a previously described spectrophotometric method (Prankerd and McKeown, 1992b). When solutions showed no further increase in concentration with time, it was taken that equilibrium had been reached (usually 24 h). The aliquots were taken by volume and concentrations were calculated on the molar scale. Mole fraction concentrations were estimated by dividing the molar concentrations (M) by $(M + 55.346)$. The molarity of water at 25°C is 55.346 and it was assumed that the saturated solutions were sufficiently dilute that no error was incurred by the use of this value.

3. Results and discussion

The measured solubilities and precision for duplicate determinations are given in Table 1. The precision of the solubility measurements ranged from ± 0.05 to $\pm 1.7\%$, although in one case (no. 24), it was $\pm 7.7\%$. The mean precision for all compounds was $\pm 0.8\%$. For the spectrophotometric analyses, correlation coefficients for Beer's law plots were ≥ 0.999 and all plots passed through the origin. The accuracy of the solubilities determined in the present work can be estimated in most cases at $\pm 2\%$.

3.1. Equilibrium solubilities

Previous solubility studies of barbituric acids in water (Breon et al., 1976; Vaution et al., 1981; Treiner et al., 1982; Tabern and Shelberg, 1933) have ignored the role of ionization in determining equilibrium solubilities. The ionized forms (e.g., as 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 (at a particular pH value), and therefore its contribution to the total solubility, depends on the temperature (298.15 K), concentration and the pK_1 value of the derivative. The pK_1 values range from 7.30 (compound 11, 5,5-diphenyl-

barbituric acid) (McKeown, 1980a) to 8.88 (compound 27, cyclohexane-1',5-spirobarbituric acid) (McKeown and Prankerd, 1981) for the compounds examined in this work. Solubilities were determined in 0.001 M HCl to give conditions which would suppress ionization but not be of high enough ionic strength to significantly change activity coefficients (referred to the infinitely dilute solution as standard state) from unity. The solubilities determined in the present work (Table 1) for 5-allyl-5-isopropylbarbituric acid (compound 13) and for 5,5-diethylbarbituric acid (compound 6) are in excellent agreement with those from the literature (Vaution et al., 1981; Treiner et al., 1982; Mayer and Rowland, 1984). The solubility for 5,5-diallylbarbituric acid (compound 16) is in good agreement, although the literature value (Vaution et al., 1981; Treiner et al., 1982) is a little higher than the present value. Agreement between the values for 5-ethyl-5-phenylbarbituric acid (compound 9) is not particularly good. The literature solubility for compound 9 has been reported as 5.22 mM (Breon et al., 1976) or 5.17 mM (Vaution et al., 1981), whereas the present value is 4.76 mM. The solubility reported in the literature (0.33 mM) (Breon et al., 1976) for 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid (compound 20) is about 50% higher than that found in the present work (0.209 mM).

The lower solubilities reported in the present work, with the exception of that for compound 20, may all arise from the suppression of ionization with added HCl (0.001 M). The deviations are seen to be progressively greater for derivatives of lower pK_1 values. Also, samples were removed from the equilibrated system with a glass syringe and filtered with 0.45 μm Millipore filters, whereas in earlier work (Paruta et al., 1965; Breon et al., 1976) samples were removed with a glass wool-tipped pipette. This method has the disadvantage that fine particles may be withdrawn with the saturated solution, resulting in higher apparent solubilities. This may account for the discrepancy found in the solubility for compound 20. No details were given for the range of possible experimental errors of the equilibrium aqueous solubilities of barbituric acids deter-

mined in earlier work (Breon et al., 1976; Vaution et al., 1981; Treiner et al., 1982).

3.2. Prediction of solubilities

Although some advances have been made in the theoretical prediction of solubilities of nonpolar solutes in aqueous solution (Pierotti, 1976), empirical approaches to prediction of aqueous solubilities of polar compounds, especially crystalline solids, are still required (Adjei et al., 1980; Martin et al., 1980; Treiner et al., 1982). Solubilities calculated from regular solution theory require estimates of the solubility parameters for the solvent and solute, as well as the solute molar volume and its enthalpy or heat capacity change for fusion. Solubility parameters for organic solvents are easily calculated from the enthalpy (ΔH) or energy (ΔE) of vaporization (Hildebrand and Scott, 1962). However, the solubility parameter for water has been assigned a wide range of values (Chertkoff and Martin, 1960; Davis et al., 1972, 1974), and enthalpies of vaporization for crystalline solids are determined from the temperature dependence of their (low) vapor pressures (Davies and Thomas, 1959; Davies et al., 1959; Moelwyn-Hughes, 1965). Molar volumes may be obtained from additive relationships (Yalkowsky et al., 1972), but enthalpy and heat capacity changes for fusion (referred to the hypothetical supercooled liquid at the temperature of the solubility measurement) are usually determined by extrapolation of thermal data from above the melting point of the solid (where errors may be large, due to decomposition).

These requirements have led to numerous assumptions (Hollenbeck, 1980) and simplifications, e.g., Eq. 2. A recent study addresses these concerns to some degree and suggests relationships between fundamental thermodynamic functions and molecular structure (Prankerd, 1992). Solubility parameters for crystalline solids of low vapor pressure have been estimated from their solubilities in solvent mixtures of known solubility parameter (Chertkoff and Martin, 1960; Hildebrand and Scott, 1962), including those for some barbituric acids (Khalil et al., 1976). Ideal solubilities of barbituric acids have been calculated from their molar enthalpies of fusion (ΔH^f), using Eq. 2 with the tacit assumptions that activity coefficients were unity (implying that the solubility of a given derivative would be identical for all solvents) and that $\Delta C_p^f = 0$ (Eq. 3) (Summers, 1978). Solubilities in water have been estimated by correlation of solubilities in surfactant solutions with ΔH^f (Treiner et al., 1982). It was stated that correlation of the solubilities in surfactant solutions were better correlated with ΔH^f than with melting points (Treiner et al., 1982).

In view of the uncertainties associated with estimating solubilities from regular solution theory, especially of polar compounds in polar solvents, other methods for solubility estimation or for describing relationships between series of

Table 2
Limiting activity coefficient and melting point data for cycloalkane-1',5-spirobarbituric acids

Compounds		n_a	n_b	Log γ^∞		m.p. (°C)		Δ log γ^∞ (a − b)	Δ m.p. (°C) (a − b)
a	b			a	b	a	b		
25	24	3	2	3.398	3.63	257	325	− 0.232	− 68
26	25	4	3	4.094	3.398	271.5	257	0.694	14.5
27	26	5	4	4.804	4.094	288	271.5	0.710	16.5
28	27	6	5	4.911	4.804	266	288	0.107	− 22
29	28	7	6	4.725	4.911	228	266	− 0.186	− 38
30	29	10	7	6.33	4.725	209.5	228	1.605	− 18.5
34	30	11	10	7.54	6.33	231.5	209.5	1.21	22

n_a and n_b are the numbers of methylene groups in compounds a and b.

compounds have been proposed. Hildebrand and Scott (1962) have stressed the inapplicability of regular solution theory to polar solutions.

3.3. Methylene group contributions

3.3.1. Cycloalkane-1',5-spirobarbituric acids

Group contributions to solubility have been calculated for homologous series of compounds by plotting the log mole fraction solubility (log x_i) or the log limiting activity coefficient (referred to the pure solute as the standard state, log $\gamma^\infty = -\log x_i$), against the number of methylene groups in each compound (Davis et al., 1972, 1974). The only set of compounds in this study that could be considered a homologous series are the cycloalkane-1',5-spirobarbituric acids. A plot of log γ^∞ vs the number of methylene groups (Table 2) as independent variable is given in Fig. 1. This shows that the relationship between the log γ^∞ values and the number of methylene groups is not the linear relationship frequently observed with other homologous series (Davis et al., 1974). This suggests that the crystal lattice energies for the series change in a complex fashion. An approximation of the crystal lattice energies may sometimes be obtained from the melting points for the derivatives (Lewis and Randall, 1961; Ubbelohde, 1965). Crystal lattice energies for a few barbituric acid derivatives have previ-
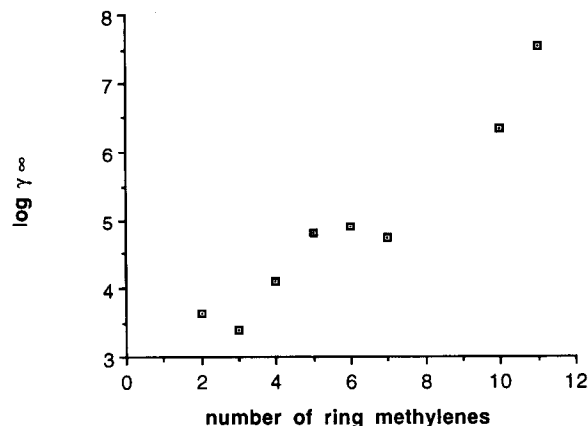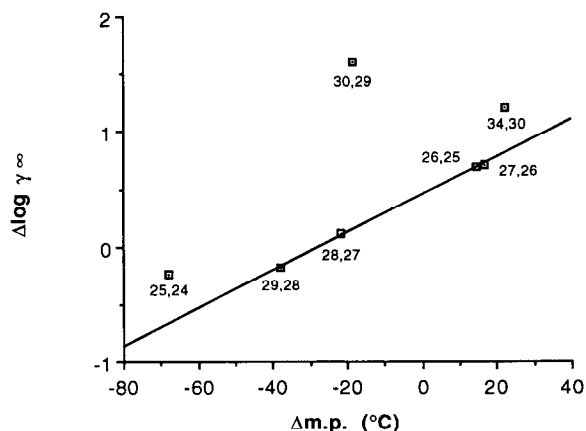
Fig. 2. Plot of differences in log limiting activity coefficients ($\Delta\log \gamma^\infty$) as a function of melting point differences (Δm.p.) for pairs of cycloalkane-1',5-spirobarbituric acids. The regression line is plotted through points 29,28, 28,27, 27,26 and 26,25 only.

ously been found to be in the same order as their melting points (Caillet and Claverie, 1980). On this basis, the differences in the melting points may be compared with the differences between the log γ^∞ values for pairs of cycloalkane-1',5-spirobarbituric acids which differ by one methylene group (Table 2 and Fig. 2). Fig. 2 shows a linear relationship for several of the cycloalkane-1',5-spirobarbituric acid pairs. Data for the large ring members, compounds 30 and 34 (10- and 11-membered rings) and the smallest member, compound 24 (three-membered ring) do not fall on the line. The large ring compounds are likely to show more hydrocarbon character than derivatives with smaller rings. Conversely, compound 24 is the most polar of all the barbituric acid derivatives studied in this paper and does not melt before it decomposes near 325°C. Evidence for the high polarity of compound 24 is given by its octanol-water partition coefficient ($P = 0.280 \pm 0.002$, log $P = -0.533$), which was the lowest observed for 25 substituted barbituric acids (Prankerd and McKeown, 1992a,b).

3.3.2. 5,5-Disubstituted barbituric acids

The relationship between acid strength and structure for the 5,5-disubstituted barbituric acids has been reported to depend on the steric effect

Fig. 1. Plot of log limiting activity coefficient (log γ^∞) as a function of ring size for the cycloalkane-1',5-spirobarbituric acid derivatives.

of the substituents as well as on their electronic effects (McKeown, 1980b; McKeown and Prankerd, 1981). The steric effect was envisaged as affecting both the un-ionized (initial state) and the ionized (final state) forms of the molecule through steric inhibition of hydration of the barbituric acid nucleus, depending on the size of the substituents. It was proposed that the methyl substituent had a smaller effect on desolvation of the un-ionized nucleus by comparison with the effect of the ethyl group. This hypothesis is still held for the acid-strengthening initial state steric effect (steric hindrance of weaker dipole-dipole solvation), but a different explanation has been given to account for final state effects (McKeown et al., 1986). It is relevant to the present study, where solubilities are for the un-ionized species only. Comparison of the values of log γ^∞ for the 5-methyl- and 5-ethyl-5-R_2-barbituric acids from Table 3 shows that the effect on mole fraction solubility of substituting a methyl group with an ethyl group (effectively the same as inserting a methylene group) is highly variable (from 0.514 to -0.454 log units). This variable effect may be examined by comparing the differences in values of log γ^∞ with the differences in melting points for pairs of 5,5-disubstituted barbituric acids which differ by a single side-chain methylene group (Table 3).

The data in Table 3 were plotted in Fig. 3 and show that, with the exception of the differences between the 3-methylbut-2-enyl substituted derivatives (compounds 5 and 10), there is a nearly linear relationship between the differences in the values for log γ^∞ and the differences in melting points. Where the difference in the melt-
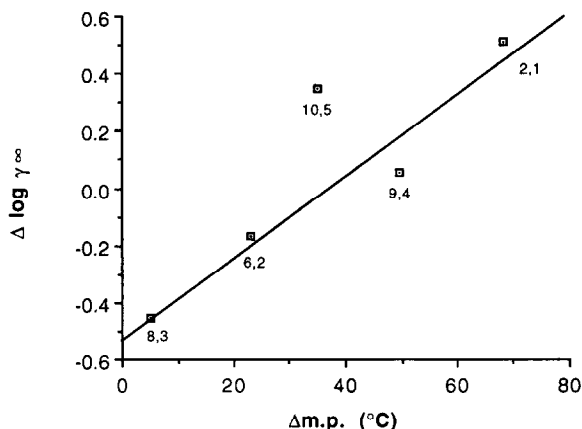

Fig. 3. Plot of differences in log limiting activity coefficient (Δlog γ^∞) as a function of melting point differences (Δm.p.) for pairs of 5-alkyl substituted barbituric acids. Point 10,5 was excluded from the regression line.

ing points is minimal (compounds 3 and 8) and the intermolecular cohesive forces might be expected to be similar, the observed solubility difference is large, with compound 3 ($R_1 = Me$) being nearly 3 times as soluble as compound 8 ($R_1 = Et$). These data are interpreted in terms of more extensive hydration of the dissolved 5-methyl derivative than for the 5-ethyl derivative. A priori, it might seem reasonable that the more soluble of two compounds would be the more highly solvated in aqueous solution. Therefore, the energy of hydration will dominate the solubility difference for these two compounds. However, this behavior will only be apparent when the cohesive forces, or crystal lattice energies, are very similar for the two species being compared. Conversely, where R_2 is Me (compounds 1 and

Table 3
Limiting activity coefficient and melting point data for pairs of 5,5-disubstituted barbituric acids

Compounds		$R_{a,1}$	$R_{a,2}$	$R_{b,1}$	$R_{b,2}$	Log γ^∞		m.p. (°)		Δ log γ^∞	Δ m.p. (°C)
a	b					a	b	a	b	(b − a)	(b − a)
2	1	Et	Me	Me	Me	2.972	3.485	216	284	0.513	68
6	2	Et	Et	Me	Et	3.139	2.972	193	216	− 0.168	23
8	3	Et	allyl	Me	allyl	3.357	2.904	162	167	− 0.453	5
9	4	Et	phenyl	Me	phenyl	4.065	4.123	179	228.5	0.058	49.5
10	5	Et	3MBE [a]	Me	3MBE [a]	3.996	4.345	158	193	0.349	35

[a] 3MBE = 3-methylbut-2-enyl.

2), the intermolecular cohesive forces, as approximated by the melting points, are very different and the solubility is now greater for compound 2 (R_1 = Et) than for compound 1 (R_1 = Me). Hence, the energy of hydration contribution to the differences in the solution energies is dominated by the crystal lattice energy for the higher

melting derivative (compound 1). For the 3-methyl-but-2-enyl derivatives (compounds 5 and 10), the large difference in the values of log γ^∞ suggests that either compound 5 (R_1 = Me) is less soluble than it ought to be, or else compound 10 (R_1 = Et) is more soluble than expected from the plot in Fig. 3. The discussion in the next section

Table 4
Partition coefficients, melting points and aqueous solubilities for barbituric acid derivatives

Compound	R_1	R_2	Log P (oct./H_2O)	m.p. (°C)	Log S_w (M; obs.)	Log S_w (M; calc.)	Δ (obs. – calc.)
1	Me	Me	− 0.440	278	− 1.742	− 1.538	− 0.204
2	Me	Et	0.0808	216	− 1.228	− 1.319	0.091
3	Me	allyl	0.363	167	− 1.160	− 1.009	− 0.151
4	Me	phenyl	0.911	228.5	− 2.380	− 2.355	− 0.025
5	Me	3MBE [a]	1.171	193	− 2.602	− 2.189	− 0.413
6	Et	Et	0.666	192	− 1.396	− 1.641	0.245
7	Et	i-Pr	1.102	204	− 2.148	− 2.253	0.105
8	Et	allyl	0.867	162	− 1.614	− 1.481	− 0.133
9	Et	phenyl	1.434	179	− 2.322	− 2.294	− 0.028
10	Et	3MBE	1.725	158.3	− 2.253	− 2.345	0.092
11	phenyl	phenyl	1.957	288	− 4.196	− 4.203	0.007
12	i-Pr	i-Pr	1.634	227.5	− 2.766	− 3.109	0.343
13	i-Pr	allyl	1.366	142.7	− 1.708	− 1.770	0.062
14	i-Pr	3MBE	2.234	131.3	− 2.593	− 2.549	· − 0.044
15	t-Bu	3MBE	2.563	212	− 3.551	− 3.900	0.350
16	allyl	allyl	1.146	172	− 2.077	− 1.901	− 0.176
17	allyl	phenyl	1.692	158.5	− 2.369	− 2.312	− 0.057
19	Et	Et [b]	1.566	177.5	− 2.167	− 2.415	0.248
20	Et	1MB [b,c]	3.026	162	− 3.679	− 3.770	0.091
24		$(CH_2)_2$	− 0.533	325	− 1.886	− 2.024	0.138
25		$(CH_2)_3$	− 0.266	257	− 1.655	− 1.461	− 0.194
26		$(CH_2)_4$	0.242	271.5	− 2.349	− 2.180	− 0.169
27		$(CH_2)_5$	0.913	288	− 3.060	− 3.096	0.036
28		$(CH_2)_6$	1.363	266	− 3.168	− 3.300	0.132
29		$(CH_2)_7$	1.786	228	− 2.982	− 3.276	0.294
30		$(CH_2)_{10}$	3.148	209.5	− 4.585	− 4.490	− 0.095
33		$(CH_2)_5^b$	1.775	247.5	− 3.462	− 3.507	0.045
34		$(CH_2)_{11}$	3.51	231.5	− 5.796	− 5.147	− 0.649
36	Et	1MB [c]	2.10 [d]	125	− 2.387 [e]	− 2.328	− 0.059
37	Et	3MB [f]	2.07 [g]	156.8	− 2.658 [h]	− 2.692	0.034
48	Et	CHE [i]	2.82 [j]	167	− 3.529	− 3.614	0.085

[a] 3MBE = 3-methylbut-2-enyl.
[b] 2-Thio derivative.
[c] 1MB = 1-methylbutyl.
[d] Hansch and Leo (1979).
[e] Vaution et al. (1981).
[f] 3MB = 3-methylbutyl.
[g] Hansch and Leo (1979).
[h] Vaution et al. (1981).
[i] CHE = cyclohexylidene-2-ethyl.
[j] Estimated from HPLC capacity factor data (Prankerd, 1985).

suggests that compound 5 has an abnormally low solubility. The limited predictive ability of methylene group contributions for the solubility of these crystalline solids requires more general methods.

3.4. Relationship of solubilities with melting points and partition coefficients

Yalkowsky and Valvani (1980) have made some assumptions allowing estimation of the ideal and non-ideal contributions to the solubility of crystalline solids as indicated in Eq. 3 and 4. This has led to a simple predictive relationship between the molar aqueous solubility, as dependent variable, and the octan-1-ol/water partition coefficient (log P) and melting point (m.p. in °C) as independent variables (Yalkowsky and Valvani, 1980) (Eq. 5):

$$\log S_w = -1.05 \log P - 0.012 \text{ m.p.} + 0.87 \quad (5)$$

where S_w is the molar aqueous solubility and the coefficients were obtained by multiple linear regression of data for 155 conformationally rigid compounds, including aromatics, aliphatic alcohols and steroids. Assumptions made in deriving Eq. 5 are:

(i) That ΔC_p^f is small and that $(T_m - T)/T$ is approximately equal to $\ln(T_m/T)$, allowing the heat capacity terms in Eq. 3 and 4 to be ignored without any significant loss in accuracy;

(ii) That ΔS^f and the melting point can be used to estimate the ideal contribution to the solubility of a compound in water;

(iii) That log P provides an approximation to the log activity coefficient (referred to the pure solute as the standard state), or non-ideal contribution to the solubility;

(iv) For rigid molecules, ΔS^f can be regarded as a constant, so that the ideal contribution can be estimated from the melting point alone.

Recent studies (Neau and Flynn, 1990; Prankerd, 1992) indicated that ΔC_p^f is > 0, and contributes significantly to the solubility (Prankerd, 1992). This challenges assumption (i). Enthalpies of fusion at the melting point (ΔH_m^f) have been reported for some barbituric acids (Summers, 1978; Treiner et al., 1982). This allows assumption (ii)

to be tested, as ΔS^f may be calculated from the Gibbs-Helmholtz equation for the condition that the free energy of fusion is zero ($\Delta G_m^f = 0$; $\Delta H_m^f = T\Delta S_m^f$). Calculated entropies of fusion (Summers, 1978; and Prankerd, unpublished results) indicate that this quantity is quite variable for the barbituric acids ($\Delta S_m^f = 4.64$–19.90 cal mol^{-1} K^{-1} = 19.4–83.3 J K^{-1} mol^{-1}). Criticism of the use of the pure solute as the standard state has been made in the Introduction. Recent work (Prankerd and McKeown, 1990) using the hypothetical 1 molal solution behaving as though it were at infinite dilution as the standard state indicated that activity coefficients for aqueous barbituric acid solutions would be close to unity.

Fundamental relationships involving solubilities and other physico-chemical quantities are usually based on the dimensionless mole fraction scale. In the present work, solubilities were measured on the molar scale, as Eq. 5 was previously defined for this scale. Multiple linear regression of the log molar solubilities (log S_w) against the melting point and log P values in Table 4 gave the following regression equation, Eq. 6, and statistical data:

$$\log S_w = -1.060 \log P - 0.0124 \text{ m.p.} + 1.451$$

$$(6)$$

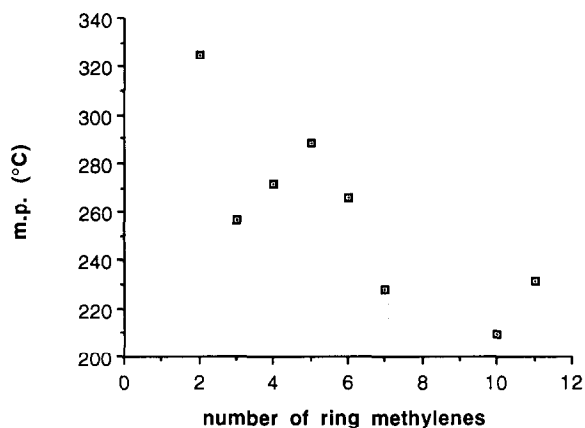$S.E.(\log P) = 0.043 \quad S.E.(\text{m.p.}) = 0.00085$

$S.E.(c) = 0.212$

Fig. 4. Plot of melting point (m.p.) as a function of ring size for the cycloalkane-1′,5-spirobarbituric acids.

$t(\log P) = -24.7$ $t(\text{m.p.}) = -14.6$ $t(c) = 6.8$
$R = 0.9787$ $F = 318$ degrees of freedom $= 28$

The t values derived from the standard errors for the coefficients (S.E.(log P), S.E.(m.p.) and S.E.(c)) and the overall F ratio show that the equation is statistically significant ($p < 0.01$). Correlation of the measured log S_w values with log P alone ($R = 0.796$; $F = 50.2$) led to a poorer relationship, while there was no correlation at all with m.p. ($R = 0.178$; $F = 0.95$).

The increase in measured solubility (Fig. 1 and Table 4) for compound 29 over that for com-

pounds 27 and 28 was unexpected, as solubilities normally decrease on addition of further methylene groups in a homologous series. In this case, the addition of the methylene groups also gave a marked decrease in the melting points from 288°C (compound 27) to 228°C (compound 29). Although the melting point for compound 28 was also lower (266°C) than for compound 27, this was not sufficient to offset the reduced solubility resulting from the introduction of the extra methylene group. Fig. 4 shows the relationship between the number of CH_2 groups in each cy-
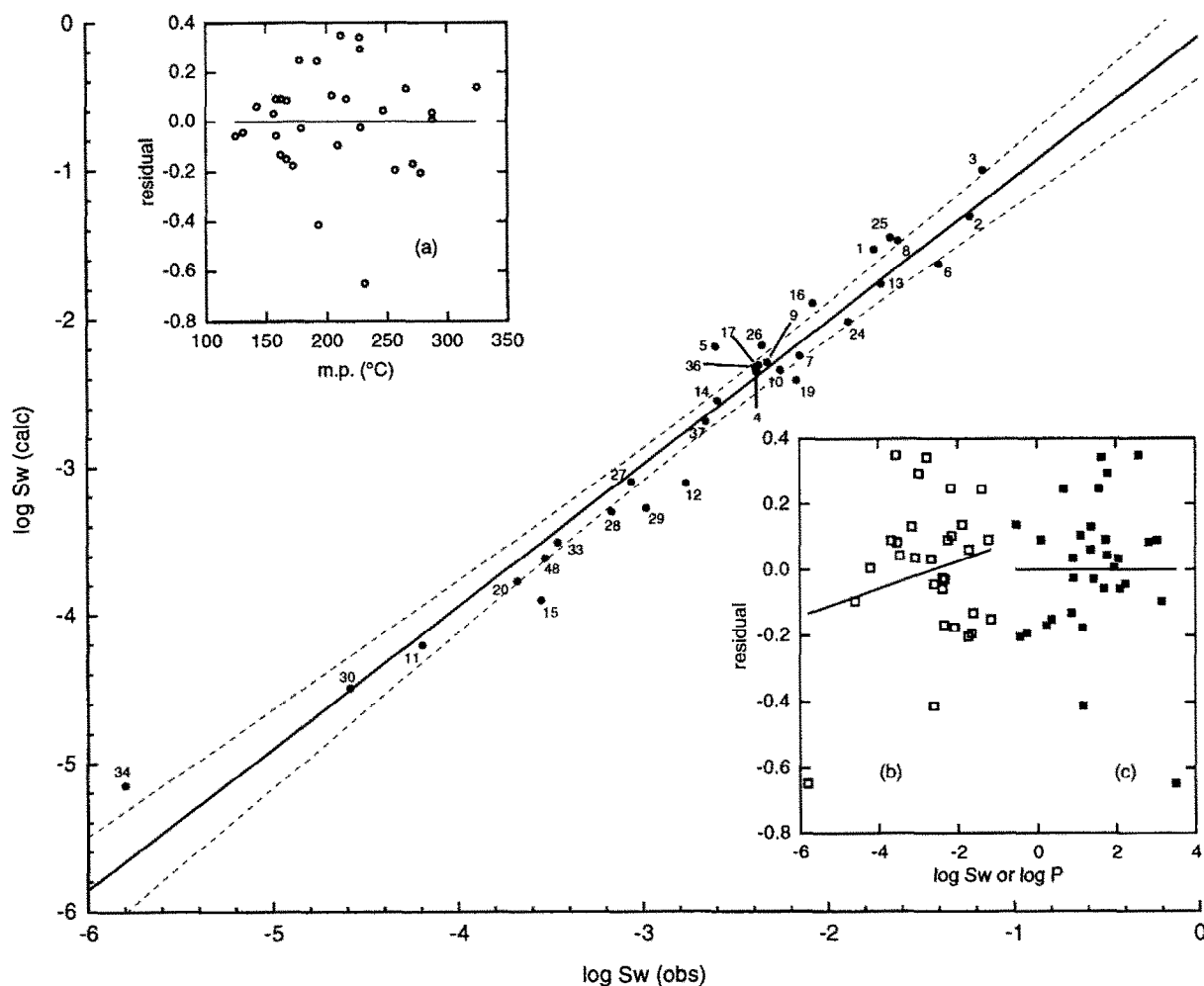
Fig. 5. Plot of the calculated log S_w values for all compounds vs their observed values. Dotted lines are 99% confidence intervals for the fitted line. Insets show plots of the residuals (Δ, differences between observed and calculated log S_w values) as a function of the observed values for (a) melting point (m.p.); (b) log S_w; and (c) log P.

cloalkane spiro-ring and their melting points. The solubilities calculated from Eq. 6 for compounds 27–29 are in the same rank order as the measured solubilities, indicating the usefulness of both melting points and partition coefficients as predictors of aqueous solubility in these compounds.

Inspection of the deviations between calculated and observed log solubilities in Table 4 shows that in only one case (compound 34) was the deviation greater than 0.5 log units. In the previous study (Yalkowsky and Valvani, 1980), the log P values were largely obtained by calculation from Hansch additivity relationships, leading to a significant level of uncertainty in the real log P values. In addition, the solubilities were literature values reported over the temperature range 20–30°C. The use of carefully measured log P values and solubilities obtained at a single temperature, as in the present study, might be expected to provide a more severe test of Eq. 5. The standard error of estimate for Eq. 5 obtained in the present work (0.216) was less than for the earlier study (Yalkowski and Valvani, 1980) (0.308). However, the excellent agreement between the regression coefficients for the log P and m.p. terms obtained previously (Yalkowsky and Valvani, 1980) and in the present study suggests that the assumptions made were reasonable for both sets of data. The large difference in the constant term is not easily explained, although the earlier report (Yalkowsky and Valvani, 1980) also gave several different values for this term, depending on the type(s) of compounds fitted to Eq. 5.

Fig. 5 shows a graph of the calculated solubilities (log S_w(calc)) plotted against the observed solubilities (log S_w(obs)), including 99% confidence limits for the linear regression (assuming that there is no error in the x values). Numerous observations lie outside the 99% confidence band. It is clear that Eq. 6 does not always calculate accurate estimates of the observed solubilities. The inset graphs show plots of the residuals (log S_w(obs) − log S_w(calc)) against the observed values for m.p., log P and log S_w. Although there is a small positive slope for the plot of residuals vs the observed log S_w values, it is not statistically significant. Omission of the most seriously de-

viant point (compound 34) from the data fit did not significantly alter the statistics of the fitted lines for all four plots in Fig. 5. Hence, no points were omitted in the final data-fitting process. Explanations for some of the more deviant points are now considered.

The calculated solubility for cyclododecane-1',5-spirobarbituric acid (compound 34) deviated considerably from the observed value. However, the observed value was the lowest measured in this work and the most difficult to determine. It is possible that adsorption onto filters may account for the low observed solubility, however, similarly low values should then have resulted for other hydrophobic compounds (e.g., compounds 20 and 30). This did not occur. Also, the log P value for compound 34 was estimated rather than measured (Prankerd, 1985), and may be less accurate. An alternative method of estimating log P for this compound leads to a value of ~ 3.60, with a consequent reduction in the deviation and an improvement in the fit to Eq. 6.

The compound with the next largest deviation between calculated and observed solubilities was 5-methyl-5-(3-methylbut-2-enyl)barbituric acid (compound 5). It was suggested from the data in Fig. 3 and Table 3 that this derivative might be anomalous, due to a low aqueous solubility. The data in Table 4 also suggest that this derivative is less soluble than expected (Eq. 6). It indicates that the deviation for differences in log γ^∞ and melting point (Fig. 3) result from a lower than expected solubility for compound 5, rather than from a higher than expected solubility for its 5-ethyl homologue, compound 10. The poor predictability of Eq. 6 for compound 5 is due to either: (i) the melting point fails to provide an adequate estimate of the ideal solubility (crystal lattice energy); (ii) the octanol/water partition coefficient is not accurate, or does not adequately account for departures from ideality in this case; (iii) the measured solubility is in error. The observed log P value for compound 5 was found with excellent reproducibility (± 0.0004 log units) and recovery (100.1 $\pm$ 0.1%) (Prankerd and McKeown, 1992a). It is not likely to be in error by the amount suggested by the large deviation from Eq. 6. Inaccuracy in the measured solubility is un-

likely to account for the deviation observed from Eq. 6, since the precision for the solubility determination was excellent ($\pm 0.16\%$). Also, the equilibration time (21 days in this case) and the excess of solid derivative (700%) were sufficient to ensure saturation of the solution. It is concluded that experimental errors do not acount for the deviations between measured and calculated solubilities for compound 5. Calculated solubilities for other derivatives (e.g., compounds 12 and 15) are also in error by more than the standard error of estimate (0.216), but in the opposite direction. It is likely that these errors arise from assumptions (i) or (ii) above. Yalkowsky has also advocated the use of the entropy change for the fusion process (ΔS^f) as a predictor for the ideal solubility, although usually only in the case of flexible molecules. It is concluded that the use of Eq. 6 may give good estimates of the solubilities of the barbituric acids. However, individual compounds can show significant deviations, especially in view of the high precision of the measured solubilities.

Although Eq. 6 ranked compounds 27–29 in the correct solubility order, it did not rank compounds 1 and 6 correctly. The difference in log P for these compounds (1.106) is close to that expected from the linear Hansch relationship. The melting point difference is very large and should increase the solubility of compound 6 compared to compound 1. A similar incorrectly predicted ranking is given for compounds 5 and 10. However, the melting point coefficient in Eq. 6 does not compensate sufficiently for the log P values in these cases. In terms of the original derivation of Eq. 6 (Yalkowsky and Valvani, 1980), the coefficient for log P (as an estimator of the non-ideal or activity coefficient contribution to Eq. 1) has a greater effect than is needed for the two more soluble compounds.

The partition coefficient and solubility data used in the present work might be expected to be a severe test of the Yalkowsky relationship, as all partition coefficients and solubilities were carefully determined at a single temperature. This is in contrast to the data used in the original development of the relationship, for which the solubilities were evaluated over a 10°C temperature range and the partition coefficients were mainly ob-

tained by estimation using additive relationships. Solubility-temperature dependence studies (Grant et al., 1984; Prankerd and McKeown, 1990) show that solubilities may easily increase 10–20% with a 5°C temperature rise. In this study, the deviations observed between measured and calculated solubilities for some derivatives are most likely to have their origins in difficulties in using melting points to estimate crystal lattice energies. The use of thermodynamic functions for fusion in predictive relationships may also be questioned, as there is usually a high degree of association within the liquid phases produced by fusion of hydrogen-bonded solids. This may then lead to the problem of non-corresponding standard states for each compound in a series.

Acknowledgements

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