Correlations between solubilities, heats of fusion and partition coefficients for barbituric acids in octanol + water and in aqueous micellar solutions

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Despite the success of recent theoretical approaches to the prediction of the solubility of non-polar solutes in aqueous solutions (Pierotti 1976), there remains a need for semi-empirical approaches that correlate their solubilities in aqueous solution of compounds of practical interest with their macroscopic (thermodynamic) or structural properties. This is particularly true for complex solvents such as aqueous surfactant solutions which are often used to solubilize drugs. The correlations using the boiling point (Almgren et al 1979), the melting point (Yalkowsky & Valvani 1979) or molecular surface area of the solute (Yalkowsky & Valvani 1976; Vaution et al 1981) have indicated that aqueous systems, as different apparently as octanol + water and aqueous micellar solutions, may be treated with respect to the solubilization phenomenon in a similar manner, i.e. as two-phase systems.

It is the purpose of this article to assess this point further in the case of the partition coefficients of barbituric acids solubilized at several temperatures in aqueous solutions of an anionic surfactant: sodium paraffin sulfonate, in relation to the heat of fusion of these drugs.

Methods

The distribution coefficient of thirteen barbituric acids in aqueous solution of sodium paraffin sulfonate ($C_{14}H_{29}SO_3Na$), the experimental procedure and physical properties of the compounds used have been published previously (Vaution et al 1981). The heat of fusion data were obtained from melting point peak areas using a differential scanning calorimeter Dupont de Nemours No. 990. The instrument was standardized using indium (melting point 429·6 K). The solubility of the barbituric acids in water at 298·16, 308·16 and 318·16 K, and the heats of fusion are shown in Table 1.

Discussion

The apparent distribution coefficient of a solute dissolved in dilute micellar solutions as determined from solubility measurements may be defined as:

$$K = \frac{S_m - S_w}{S_w C} \qquad (1)$$

where S_m is the molar solubility of the solute in an aqueous solution at molar concentration C of the ionic surfactant,

and S_w is the solubility in water. Fig. 1 shows that the logarithm of the rate of change of the barbituric acid solubility with surfactant concentration is a linear function of the heat of fusion ΔH^F:

$$\log \left(\frac{S_m - S_w}{C}\right) = a + b(\Delta H^F) \qquad (2)$$

Table 2 presents the values of the a and b coefficients of equation (2) calculated using solubility measurements of barbituric acids in aqueous sodium paraffin sulfonate solution at the three temperatures studied (Vaution et al 1981).

The ΔH^F value for allobarbitone was not used in the regression analysis as it was found at all temperatures systematically below the line corresponding to the other barbiturates. The heat of fusion for reposal and amobarbitone had not been measured and were calculated from the regression equations (2) at the three temperatures studied using the coefficients of Table 2.

Equation (2) may be rewritten as:

$$\log S_w = -\log K + a + b(\Delta H^F) \qquad (3)$$

It is instructive then to compare this equation with that

Table 1. Solubility in water and heat of fusion of barbituric acids.

		ΔH^F (kcal mol^{-1})*	S_w (mol litre^{-1})		
			298·16 K	308·16 K	318·16 K
1	Butobarbitone	4·01	0·0213	0·0243	0·0309
2	Reposal	5·42 ± 0·04 (a)	0·0017	0·0023	0·0025
3	Pentobarbitone	5·09	0·0041	0·0057	0·0069
4	Butabarbitone	5·51	0·0074	0·0099	0·0137
5	Barbitone	5·83	0·0401	0·0515	0·0680
6	Amobarbitone	6·15 ± 0·03 (a)	0·0022	0·0033	0·0043
7	Phenobarbitone	6·64	0·0052	0·0085	0·0113
8	Vinbarbitone	7·15	0·0049	0·0070	0·0080
9	Heptabarbitone	9·23	0·0010	0·0014	0·0018
10	Secobarbitone	4·15	0·0044	0·0063	0·0094
11	Aprobarbitone	5·11	0·0194	0·0260	0·0334
12	Itobarbital	5·45	0·0076	0·0103	0·0141
13	Allobarbitone	5·95	0·0087	0·0111	0·0169

* A cal = 4·184 joules.
(a) Calculated, average of three ΔH^F values: see text.

Table 2. Coefficients of the linear equation (2) at three temperatures.

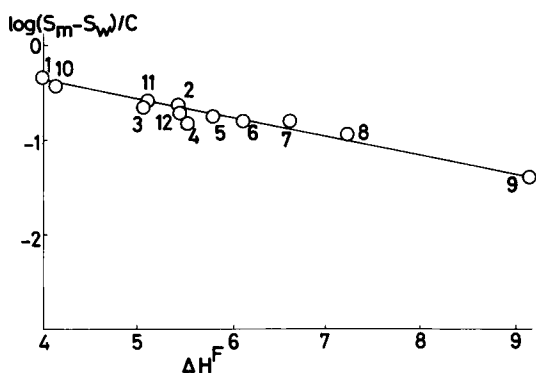| T/K	a	b	r^2
298·16	0·3863	−0·2040	0·974
308·16	0·3784	−0·1912	0·985
318·16	0·4505	−0·1932	0·987

* Correspondence.

FIG. 1. Variation of the rate of change with surfactant concentration (at 308·16 K) of the barbituric acids solubility with their heat of fusion.

found empirically for the partition coefficients of aromatic hydrocarbons in the octanol + water system (Yalkowsky & Valvavi 1976) and for benzoic and phenylacetic acids in the same two phase mixtures (Armstrong et al 1979):

$$\log S_w = \alpha \log K + \beta T_m + \gamma \qquad (4)$$

For a large variety of compounds, these authors found that $\alpha = -1\cdot0$ and $\beta = -0\cdot01$. The similarity of equations (3) and (4) is then obvious; the only difference between the two equations is that we found that the standard deviation of the linear regression (2) is much better with the heat of fusion as variable than with the melting point. This may explain the difference between the value of the b and β coefficients.
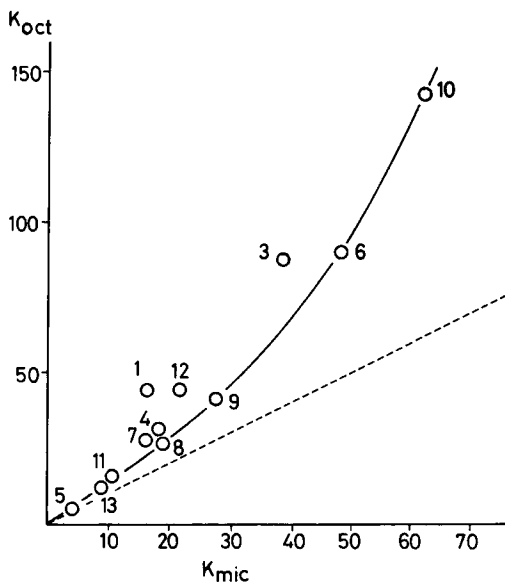

FIG. 2. Partition coefficients of barbituric acids in the octanol + water system (K oct) (Hansch & Anderson 1967) and in sodium paraffin sulfonate solutions (K mic) (Vaution et al 1981) at 308·16 K.

Note that ΔH^F and T_m are correlated through the so-called Walden rule.

It is not the logarithm of the partition coefficient but the logarithm of the relative increase of solubility with surfactant concentration that is linearly related to the heat of fusion.

Using the partition coefficient of the barbituric acids in the octanol + water mixtures (Hansch & Anderson 1967) and their solubility values in pure water, one may calculate with a good approximation the solubility of the solutes in the organic phase saturated with water. Again it is the logarithm of this solubility that is linearly correlated to the heat of fusion.

If, instead of the heats of fusion of the solutes, their molecular surface area is chosen as variable, then it is the partition coefficient that is linearly correlated in the octanol + water mixtures (Yalkowsky & Valvani 1976) or in the aqueous micellar solutions (Vaution et al 1981). These findings provide new arguments to the theoretical approach of the solubilization phenomenon in micellar solution as a two-phase equilibrium.

The similarities of the semi-empirical treatments of the partition coefficients in the octanol + water and the aqueous sodium paraffin sulfonate solutions prompted us to compare the K values of the barbituric acids in the two liquid systems (Fig. 2). There is a definite correlation between the two sets of partition coefficients; the dotted line presents the equal partition coefficient curve. This presentation emphasizes small uncertainties which are often hidden on a logarithm plot. For example, in the case of pentobarbitone (compound no. 3) a difference of 0·1 in log K of the Hansch calculated partition coefficient value would bring this compound on the line corresponding to the other barbiturates.

Fig. 2 indicates that the partition coefficients of the barbituric acids both in micellar or in octanol + water solutions increase with the number of carbon atoms on the side chain of the malonyl-urea framework; however the increase is less in the micellar solutions than that expected if the hydrocarbon groups were solubilized in a hydrocarbon-like environment (octanol). This supports the earlier suggestion (Vaution et al 1981) that barbituric acids are solubilized at the interface between the micelle surface and water through a partial adsorbtion phenomenum.

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