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DETERMINATION OF AQUEOUS SOLUBILITIES OF A SERIES OF 5-ETHYL-5-ALKYLBARBITURIC ACIDS AND THEIR CORRELATION WITH LOG P AND MELTING POINTS

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ABSTRACT

A rapid potentiometric method has been used to determine the aqueous solubilities of an homologues series of 5-ethyl-5-alkyl (n=0-9) barbituric acids. A plot of the logarithm of solubility against the number of carbon atoms in the side chain revealed two distinct linear regions with a definite break about the butyl compound. The solubilities of all the members of this series (except 5-ethyl barbituric acid) can be predicted from log P values and melting points by the semiempirical solubility equation of Yalkowsky.

INTRODUCTION

In drug development it is of interest to know not only how rapidly but also to which extend a drug can be absorbed. The maximal rate of absorption, which determines the maximum possible

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systemic drug concentration and effect, is primarily determined by both the lipophilicity and solubility of the drug (1). In order to assess the optimal balance of lipophilicity and solubility for maximal absorption it is of fundamental importance to know the exact relationship between these two parameters. The semiempirical relationship worked out by Yalkowsky et al. (2) is a very useful approach to assess the mutual influence between both parameters. In this paper we apply this approach to an homologeous series of 5-ethyl-5-alkylbarbituric acids and discuss the practical benefit of further refinements of the original approach, such as proposed by Chiou et al. (3). Furthermore we report a potentiometric method for the determination of aqueous solubilities of sparingly soluble weak acids and bases.

THEORETICAL

According to Chiou et al (3) the correlation between aqueous solubility (S) and the octanol-water partition coefficient (P) can be described by the following expression

$$\text{Eq. 1} \qquad \log S = -\log P + \log X_i - \log V_o^* + \log \frac{\gamma_w^*}{\gamma_w} - \log \gamma_o^*$$

where X_i represents the ideal solubility of a crystalline drug, at a given temperature, expressed in a mole fraction scale (4), and V_o is the molar volume (5) of water saturated octanol (0,12 l/mol) (6). The last two terms in Eq. 1, expressed by activity coefficients, designate respectively the possible deviation from an ideal solution caused by the dissolved water in the octanol phase and by the

dissolved octanol in the water phase. Here γ_w is the activity coefficient of the compound in pure water, and γo^* and γ_w^* are the respective activity coefficients in the octanol and water phases at equilibrium (mutual saturation). If it is assumed that the solute forms an ideal solution in the water-saturated octanol and that the solute solubility is the same in octanol-saturated water as in water, then Eq. 1 simplifies to

Eq. 2 $$\log S = -\log P + \log X_i - \log V_o^*$$

Substitution into Eq. 2 of $\log X_i$ by a modified Scatchard-Hildebrand expression (2,4) and of $\log V_o^*$ by its numerical value gives

Eq. 3 $$\log S = -\log P - \frac{\Delta Sf\ (MP-25)}{1364} + 0.92$$

which is identical to the relationship initially proposed by Yalkowsky and Valvani (2) (except that for the molar volume term in Ref. 2 a value of 0.8 is used for pure octanol). Here ΔS_f is the molar entropy of fusion and MP is the melting point on the centigrade scale.

The entropy of fusion for most rigid aromatic molecules is relatively constant and is essentially equal to 13,5 eu (7,8) which reduces equation 3 to

Eq. 4 $$\log S \simeq -\log P - 0.01\ MP + 1.17$$

For molecules having more than 5 non-hydrogen atoms (n>5) in a flexible chain the entropy of fusion can be approximated by (9)

Eq. 5 $$\Delta S_f = 13.5 + 2.5(n-5)\ \text{eu}$$

Experimental

Materials

The barbituric acid derivatives were prepared by condensation of urea with an appropriately substituted diethyl-malonate (10). The compounds with a 5-n-alkylsubstituent of three or less carbon atoms were recrystillized in water, the remaining more lipophilic compounds were crystallised in an ethanol-water mixture.

Melting points

The melting points were determined on a Köfler hot-stage apparatus and were corrected relative to a calibration chart for the instrument but uncorrected for emergent stem. For compound 6 a literature value (11) has been used.

Dissociation constants

The pKa values of the compounds were obtained by fitting equation 6 to the series of UV-absorbance/pH values using a nonlinear regression analysis programme (NONLIN) (10,12).

Eq. 6
$$A = \frac{Ai,_T\,(10^{pH\,-pKa}) + Au,_T}{1 + 10^{pH\,-\,pKa}}$$

where: A = total absorbance

$Ai,_T$ = absorbance of the total concentration in the ionized form, and

$Au,_T$ = absorbance of total concentration in unionized form

Partition coefficients

The experimental octanol-water partition coefficients of the compounds employed in this paper have been reported previously (13).

The log P of compound 6 has been calculated based on barbitone (log P = 0.66) considering the methylene contribution (f_{CH_2} = 0.519) of Nys and Rekker (14).

Aqueous solubilities

The aqueous solubilities of the compounds were determined by a potentiometric method, employing non-logarithmic linear titration curves. This method was originally proposed by Levy and Rowland (15) for the determination of the aqueous dissociation constants of sparingly soluble substances. They showed that the pKa of an acid can be calculated from the slope (equal to solubility x K_a) of the straight line, obtained when the number of millimoles of unknown neutralized (Z') is plotted against the reciprocal of the hydrogen-ion concentration (equation 7), and the solubility of the uncharged species, determined independently. Conversely, when the K_a is known, the solubility can be calculated by the same approach with the following equation valid any time after precipitation.

Eq. 7 $$Z' = A^o - Ka^c \cdot A_{sol} \cdot \frac{1}{[H^+]}$$

where:

$Z' = X^- + H^+ + OH^-$

X^- = absolute number of moles of acid added to the solution

H^+ = absolute number of moles of hydrogen ions present in solution

OH^- = absolute number of moles of hydroxyl ions present in solution

A^o = absolute number of moles of acid originally added to the solution (as salt)

A_{sol}=absolute number of moles of unionized species present in saturated solution

K_a^c=stoichiometric ionization constant

Method

A stock solution of the sodium salt of the barbiturate was prepared by dissolving the acid in a slight molar excess of NaOH and freshly distilled water or extemporaneously prepared KCl solution. 20-80 ml of this solution were used for the determination. The titration was performed under nitrogen in a water-jacked thermostated vessel (25±0.1°C). Hydrochloric acid was added from a 2.5ml micro burette[1] calibrated to 0.001 ml. The amount of added sodium salt of the barbiturate was calculated such that, after subtraction of the volume needed to neutralize the excess of NaOH, 1.5-2.0 ml of HCl was consumed. The normality of the HCl was adjusted (0.01-2.0 N) to minimise volume changes. During the precipitation phase a minimum of 10 additions was made in a single run, with a wait of 5 to 10 min after each addition of HCl in order to ensure a stable and accurate pH reading.

Compounds 1, 3 and 4 have also been determined by the classical method (16); an aqueous mixture containing approximately twice the expected amount required for saturation was equilibrated for 6h at 25±0.1°C. The suspension was then centrifuged, the supernatant diluted and the concentration of dissolved solute determined by UV spectroscopy[2].

1) Autoburette ABV 11 Radiometer, Copenhagen

2) Cecil Instruments CE 505

Results and Discussion

Partition coefficient, log P

The experimentally determined log P values of compounds 2 to 10 (Table 1) are linearly correlated with the number of carbon atoms in the side chain ($r = 0.9906$). The slope of the regression line is equal to 0.549, a value close to the methylene increment (0.519) proposed by Nys and Rekker (14). The experimental log P value of the first member of the series, 5-ethylbarbituric acid (-1.52) differs significantly from the extrapolated value (0.50). An experimental error in the determination of log P seems unlikely since this value can be predicted with good agreement from HPLC retention indexes of the series (13).

Determination of solubilities

The potentiometric method for determination of solubility has some potential advantages over the classical method, which consists of preparing a saturated aqueous solution by shaking an excess of solute followed by separation and appropriate determination of the concentration in the supernatant (16). The potentiometric method combines achievement of saturation and analytical method, without the need for such physical separation of undissolved solid in a saturated solution.

In the classical method, periods from 6 hours up to several days, for very sparingly soluble substances, are necessary to achieve saturation, whereas the titrimetric method is much more rapid. The linearity of the plot of the number of millimoles of unknown neutralized versus the reciprocal of the hydrogen- ion concentration

during the precipitation suggests that a thermo-dynamic equilibrium is probably achieved and maintained with the potentiometric method. Furthermore each run gives 10 to 20 measurements, in contrast to the classical method were only one measurement is obtained per experiment.

The danger of erroneous results due to supersaturation, a common problem with the classical procedure, is also much less likely with the titrimetric method because the addition of the titrant produces a high local concentration of substance which favours precipitation.

Comparison with classical method

The solubilities of compounds 3, 4 and 5 determined by the potentiometric method are in good agreement with those determined by the classical method, whether reported or experimentally obtained by us (Table 1). These results suggest that the thermodynamic equilibrium achieved during the titration is close to the equilibrium obtained by the usual saturation process.

Limits of the potentiometric method

It is obvious that with this method only solubilities of weak acids and bases, whose salt is much more soluble than the unionised species, can be determined. Other limitations inherent to this present method have already been outlined by Levy and Rowland (15). An additional restriction applies to comparatively soluble compounds (>0.1mol/l) for whom the activity effects on the dissociation constant can no longer be neglected. In the current series this last limitation only applies to the 5-ethyl barbituric acid, the first homologue.

Correlations between solubility and number of carbon atoms

Breon et al. (11) reported a linear relationship between solubility and number of carbon atoms from the ethyl to pentyl compounds. But the extension of the series up to 10 compounds, by including both lower (hydrogen and methyl) and higher (hexyl to nonyl) homologues, reveals a sigmoidal-like shape of this plot. If instead of solubilities their logarithms are represented as a function of the number of carbon atoms the plot (Figure 1) shows two distinct lines, with the change taking place at the butyl compound. The slope of the first part of the curve is equal to -0.178 and that of the second part -0.536. A similar observation has been made by Yalkowsky et al. (17) for a series of alkyl p-amino benzoates. These authors propose that the nonlinearity of the curve is due to a change in crystal structure with chain length. The crystal structure of the lower homologues is probably determined primarily by the properties of the nucleus, in our case the barbiturate ring, whereas the higher homologues ($n>5$) the contribution of the linear aliphalic chain to overal properties of the compound dominates. A definite break in the melting point-chain length profile about the butyl compound (Figure 2), tends to confirm this theory. Its principle was described by Flynn and Yalkowsky (18) in a very figurative way: "The molecular tail becomes sufficiently large to wag the molecular dog.".

Comparison of predicted and observed solubilities

Provided that the experimental data are accurate and the theory behind equations 1 to 5 is correct, the comparison of calculated (by

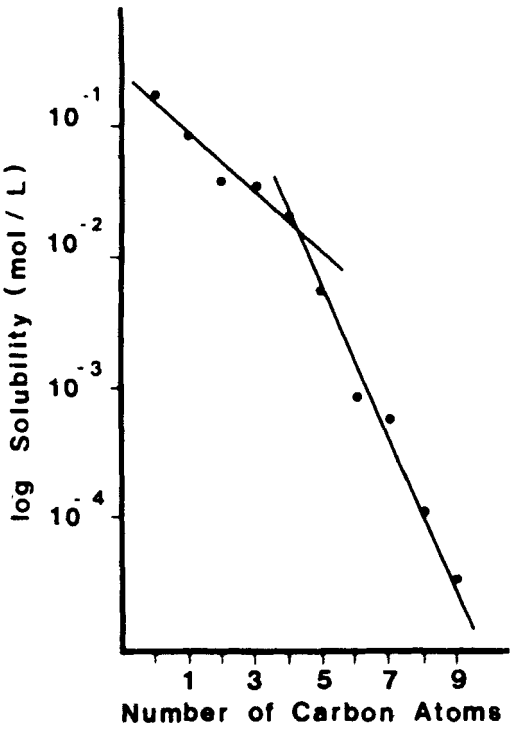

Figure 1.

Correlation between solubility and number of carbon atoms in the side chain

Eq. 4) and experimental solubilities should allow one to detect nonideal behaviour. After substraction of the effect of the entropy of fusion, approximated by Eq. 5, it should be possible to estimate the deviation caused by liquid-solute incompatibility in the water-saturated octanol phase and the effect of dissolved octanol on water solubilities, both contributions expressed in terms of their activity coefficients.

The logarithms of the solubilities have been calculated from log P and melting points (Table 1) using Eq. 4. The plot of observed

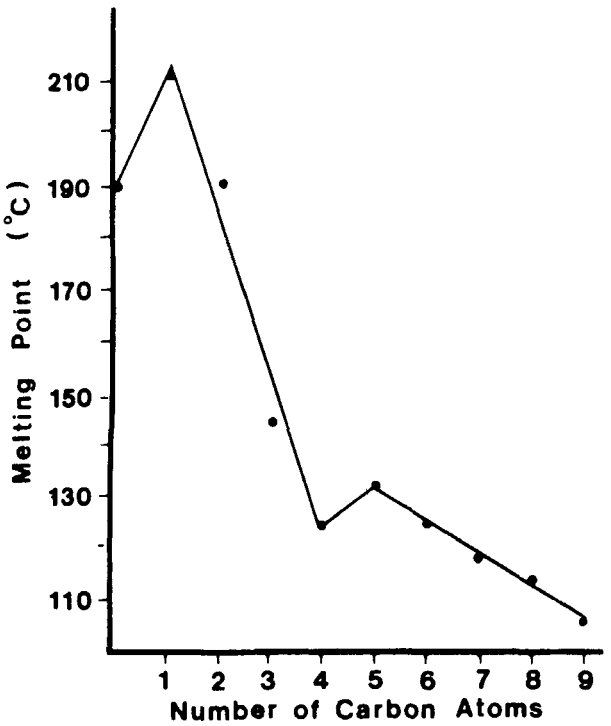

Figure 2.

Change in melting point with the number of carbon atoms in the side chain

against calculated log solubilities (Figure 3) shows that the predictions using Eq.4 are acceptable and that the residuals are randomly distributed. The scatter is partly due to the imprecision in the experimental log P values and can therefore be reduced by using calculated log P values.

The solubility of 5-ethylbarbituric acid cannot be predicted by Eq.4. For compounds of appreciable water solubility the effect of dissolved octanol is, according to Chiou et al. (3), negligible. Consequently the difference between calculated and observed value

TABLE 1 - SOME PHYSICAL PROPERTIES OF BARBITURIC ACIDS

Key	5-ethyl-5 substituted barbituric acids	MP °C	pKa	log P	S x10^{-3}(mol/l)	log S obs.	log S calc.(Eq.4)
1	Hydrogen	191	6.89	-1.52 e)	120.0 h)	-0.92	+0.78
2	Methyl	211	8.11 8.14 d)	0.02 e)	80.1	-1.10	-0.96
3	Ethyl	190 a)	7.75 7.90 d)	0.66 e)	40.5 36.1 h) 39.7 b) 40.1 g)	-1.39	-1.38
4	n-Propyl	144 146 b)	7.75 7.92 d)	0.87 c)	36.1 35.0 h) 29.5 b)	-1.44	-1.14
5	n-Butyl	125 c) 127 b)	7.81 7.87 d)	1.70 c)	23.0 19.5 b) 21.3 g)	-1.64	-1.78
6	n-Pentyl	135 b)	-	2.22 f)	5.88 b)	-2.23	-2.39
7	n-Hexyl	125	7.74 7.96 d)	3.08 c)	0.893	-3.05	-3.16
8	n-Heptyl	118	7.78 7.94 d)	3.64 c)	0.605	-3.21	-3.65
9	n-Octyl	113	7.78	3.85 c)	0.114	-3.94	-3.81
10	n-Nonyl	105	7.82	4.13 c)	0.345	-4.46	-4.03

a) (BDH) manufacturers quoted value; Breon et al. (11); c) Yih (19); d) titrimetric determ. (20);
e) Toon et al. (13); f) calculated (14); g) Treiner et al. (21); h) classical method (16)

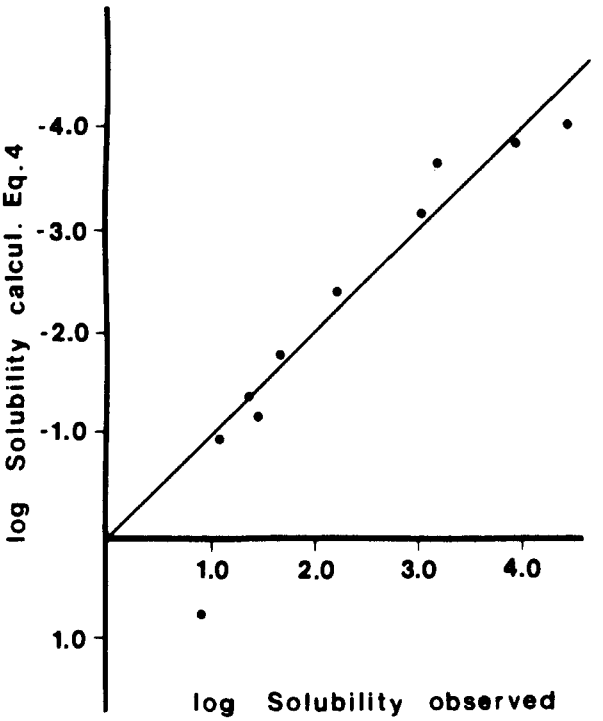

Figure 3.

Plot of predicted against observed solubilities

is simply a measure of log γ_o^*, where γ_o^* represents the activity coefficient in the water-saturated octanol phase. In the case of 5-ethylbarbituric acid log γ_o^* should be equal to 1.7. The resulting high value of the activity coefficient in the water-saturated octanol phase ($\gamma_o^* = 50.1$) should be regarded with suspicion. It appears that 5-ethylbarbituric acid is atypical for the series, its log P value and melting point (Figure 2) are not in line with those of the higher homologues. This difference in behaviour of the lowest homologue may be associated with the fact that the proton in position 5 has acidic properties. For the rest of the series, the lack of systematic

deviation in Figure 3 doesn't allow to a definitive conclusion as to the need for any correction in terms of either activity coefficients or entropy of fusion. For compounds 2 to 4 the assumptions of entropy of fusion equal to 13.5eu and activity coefficients equal to unity are quite reasonable. For higher homologues however we would expect the influence of activity parameters and entropy of fusion to increase with chain length. The fact that the results of the present series doesn't enable us to detect a clear trend of deviation for the higher homologues is due to the relative ratio of the "background noise" created by the imprecision of the experimental data and the magnitude of the expected deviation. Even for the nonyl compound the expected contribution of entropy of fusion on log solubility is 0.56, a value little different from the residual variance.

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