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SOLUBILIZATION OF PHENOBARBITAL IN SODIUM PARAFFINSULFONATE

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SUMMARY

The solubility behavior of phenobarbital in systems containing the anionic surfactant sodium paraffinsulfonate, is described. The occurrence of a 'second' inflection point in the solubility curves is explained by the formation of mixed micelles of main surfactant and chemically related impurities. A general model for the treatment of the solubilization of ionizable substances in anionic surfactants, sorting out pH effects, is described.

INTRODUCTION

Surface active agents are frequently used in pharmaceutical applications for the purpose of solubilizing poorly soluble substances. The literature is replete with reports describing this phenomenon and excellent reviews (e.g. Seiller et al., 1971, Puisieux and Cavé, 1975) exist. If a substance has a solubility, s' in water and in solutions below the critical micelle concentration, cmc, then at concentrations, c, above, cmc, the solubility, s, will increase linearly with concentration in excess of cmc, i.e. $s' - s = \alpha' [c - cmc]$. Solubilization in such cases is a distribution phenomenon where α' is a distribution coefficient.

Deviations from linearity have been reported. Markina et al. (1968) studied the solubilization of aliphatic and aromatic hydrocarbons in aqueous solutions of sodium oleate. Initially the solubility increased linearly with surfactant concentration, but at higher concentrations solubilities increased sharply. This was attributed to the occurrence of laminated micelles. A similar sharp increase was reported by DeLuca et al. (1973).

Deviations in the opposite sense have also been reported on occasion. Azaz and Donbrow (1976) reported this in the solubilization of phenolic compounds in non-ionic-surface active agents and attributed the phenomenon to adsorption rather than micellar solubilization. In the study to be reported here, such a negative deviation from linearity will be shown, but the explanation will differ from the quoted cases.

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The surfactants available commercially are never pure substances. The phenomena alluded to above are phenomena associated with pure surfactants. It shall be shown in the following, that impurities may give rise to *exactly* the same phenomena, and the occurrence of slope discontinuities *in general* are more likely attributable to impurities than to such esoteric phenomena as the micellar shape changes found in *some* pure systems.

EXPERIMENTAL

Sodium paraffinsulfonate was used as received from supplier [1]. It contains 87% monosulfonate, 10% di- and polysulfonates and 1% non-sulfonate. Phenobarbital was used as received from supplier [2].

Solutions of sodium paraffinsulfonate were prepared by weighing the desired amount and adjusting the volume with a weighed amount of water at the temperature in question. In this manner consistent weight/weight concentration and density figures are obtained and can be converted to other units as desired. The concentration units used for data presented here is always in g/100 ml total solution or in mole per mole when concentrations in surfactant are plotted.

Surface tension measurements were made conventionally using an automatic de Nouy tensiometer [3].

Solubility determinations were carried out by exposing an excess of phenobarbital to the surfactant solution in question and determining the concentration in solution after equilibrium had been attained. pH determinations were made of the saturated solutions using a direct-reading, three digit, temperature-compensated pH meter [4].

The pK of phenobarbital was determined at the temperatures in question by potentiometric titration.

RESULTS AND DISCUSSION

Plots of the solubility of phenobarbital versus concentration of paraffinsulfonate show concentration independence up to a particular surfactant concentration which coincides with the critical micelle concentration determined by surface tension measurements (0.125 ± 0.014 g paraffinsulfonate per 100 ml). Beyond this point (C_1), as shown in Fig. 1, the solubility increases linearly in a certain concentration range ($C_1 < C < C_2$). At a concentration C_2 there is an abrupt change in slope to a lower value, and the concentration of phenobarbital increases linearly, but to a lesser extent, above C_2.

As it is always the case with 'transition points' (Carstensen and Patel, 1975), care should be taken to demonstrate that the curve is actually two line segments and not, for instance, a smooth power or asymptotic exponential curve. The Durbin–Watson test

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[1] Produits chimiques de la Montagne Noire, 145 Avenue de Laveur 81100, Castres.

[2] Phenobarbital, Supplier: Pharmacie Centrale des Hopitaux de Paris, 7 Rue du Fer a Moulin, 75005 Paris, France.

[3] Tensiometre DOGNON-ABRIBAT, No. 03, PROLABO, 12 Rue Pelee 75011 Paris.

[4] pHM 64 Research pH Meter, Radiometer, Copenhagen.

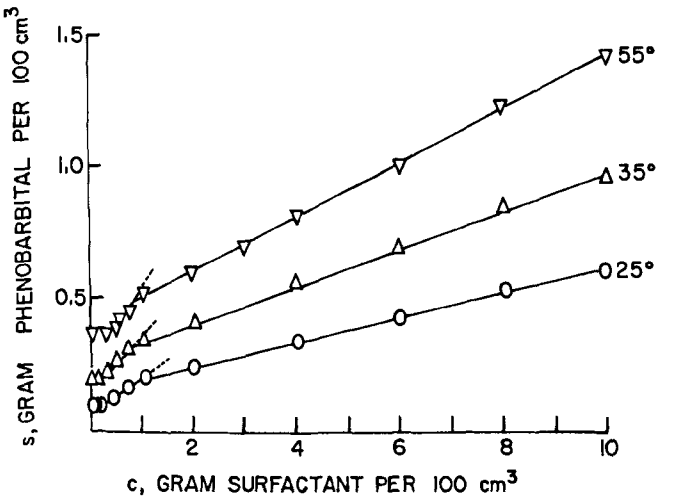

Fig. 1. Grams of phenobarbital solubilized as a function of amount of surfactant per 100 ml of solution. 45° data omitted for graphical clarity.

applied to the data here imply unmistakably ($P < 0.01$) that the situation is one of two line segments.

The surfactant used is a sodium salt of an anionic surfactant and direct plotting such as shown in Fig. 1 does not at all account for the pH effects. An increase in surfactant concentration will increase the pH, and with the increased pH there will be a larger amount of phenobarbital in the aqueous phase. It is for this reason that the pH of the micellar systems and the potentiometric titration curves were determined.

The pH was recorded in all systems at all temperatures, and a typical pH versus c curve is shown in Fig. 2. This curve resembles a typical titration curve such as might be expected (Yasunaga et al., 1967, 1969; Kale and Zana, 1977).

The amount of ionized plus unionized phenobarbital in the aqueous part of the system can be calculated from these types of curves and a knowledge of the pK of phenobarbital. Knowing the total solubility of phenobarbital in the system, the amount present in the aqueous phase can be subtracted to yield the amount of phenobarbital (L moles) dissolved in the micellar phase (C moles). This latter figure is the amount of surfactant in excess of that needed to attain the critical micellar concentration, divided by the molecular weight, 321. Details of the above calculations are outlined in Appendix I. Plots of L versus C are shown in Fig. 3. It is seen here that the same discontinuity exists as in Fig. 1.

To explain the above phenomenon it is, of course, not impossible to rule out change in micellar shape at a certain concentration, but another explanation is certain to apply (and is linked to impurity content). Prior to discussing this explanation, it might be worthwhile to dispose of some models which at first sight *might* apply, but which on further analysis will be found wanting.

One such possibility is linked to adsorption phenomena. The fact that s increases with temperature would seem to make this an unlikely explanation. Furthermore, this would

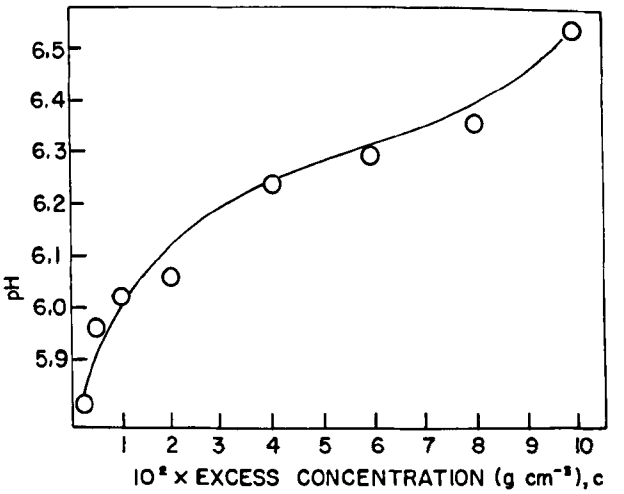

Fig. 2. pH of the solubilized phenobarbital system as a function of concentration of paraffinsulfonate in excess of the cmc. Temperature = 25°C.

dictate a smooth curve in contrast to the one found in Fig. 1 and Fig. 3.

Another explanation could be that since the pH in the system changes, the micelles may exist as M^{n-}, $MH^{(n-1)-}$, $MH_2^{(n-2)-}$ etc, where M represents a fully ionized n-mer. It

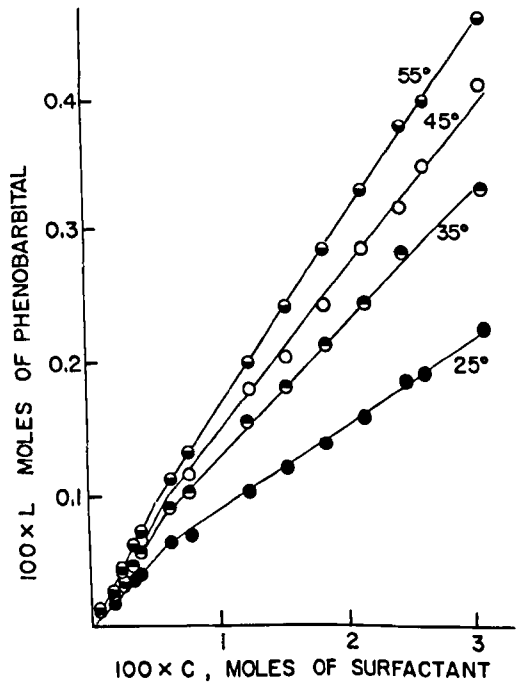

Fig. 3. Moles of phenobarbital in the micellar phase as a function of the number of moles of surfactant in the 100 ml system.

is unlikely in the pH range in question (Yasunaga et al., 1967, 1969; Kale and Zana, 1977) that more than two such species are involved. Assuming two different distribution coefficients, q_1 and q_2, in two such micellar species leads, as shown in Appendix II, to a smooth curve and not a biphasic curve as shown in Fig. 1 and Fig. 3.

A feasible explanation may be sought in the following: the surfactant is not entirely pure. This is very often the case with commercial surfactants. Surfactants containing polyoxyethylene or polyoxypyropylene groups, for instance, possess a spectrum of molecular weights, and distribution of chain lengths and position and number of sulfonate groups (as is the case here) represent impurity variations in sulfonic detergents.

When two similar surfactants are mixed, the critical micelle concentration (cmc) is usually lowered. The cmc, when the compounds are similar, is frequently a linear function of concentration of the additive. An example of this is the mixture of sodium dodecyl sulfate and potassium caprate quoted by Osipow (1962). In the case of sodium paraffinsulfonate (Vaution et al., 1978) there is a fixed amount of impurity so that the cmc values of pure sodium paraffinsulfonate probably is higher than those determined for the surfactant as used. Cases cited in literature apply to the cmc of the major component, C_1, and not to that of the additive (C_2). Usually this latter is present in small amounts ($100[1-f]\%$), so that a rather high concentration ($C_2/[1-f]$) would be necessary to attain a second break in a parameter curve (such as surface tension versus concentration curve). It shall be assumed in the following that at the *fixed* impurity concentration there are two distinct cmc values: C_1 and C_2. One, C_1, corresponds to the point where a pure (or predominant) A-micelle starts occurring, A being the surfactant species in abundance. C_2, then, is the point where pure (or predominant) B-micelles start occurring, B being the species not in abundance (the 'impurity'). If the micelles are pure A and B micelles. it is to be expected that there will be breaks in the solubility curve at:

$C = C_1/f$ (formation of A-micelles)

$C = C_2/(1-f)$ (formation of B-micelles).

The solubility behavior of a solute may therefore be written:

$$0 < C < C_1/f \qquad S = Q \tag{1}$$

$$C_1/f < C < C_2/(1-f) \qquad S = Q + \alpha(fC - C_1) \tag{2}$$

where α is a solubility constant for the solute in the A-micelle. This pattern is represented by the curve O–I–II in Fig. 4.

When the concentration is higher than $C_2/(1-f)$ there are several possibilities. It shall at first be assumed that a pure B-micelle forms, and it shall be shown that this has as a consequence that the solubility curve will have the profile O–I–II–III. This contrasts with the experimental findings. It shall next be shown that if a mixed AB-micelle (predominantly B) is formed then a curve of the type O–I–II–IV is possible. This profile is in accordance with experimental findings. It should be noted that this does not constitute proof of a mixed micelle but simply implies that a mixed micelle will explain the experimental findings where a 'pure' micelle will not.

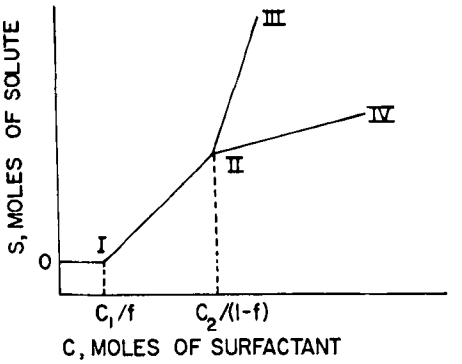

Fig. 4. Schematic of dissolved amount as a function of moles of surfactant according to Eqns. 3 and 8.

In the simplest case described above, B-micelles start occurring at an amount of surfactant of $C > C_2/(1 - f)$ and the solubility will then be given by:

$$S = \alpha\{fC - C_1\} + \beta\{(1 - f)C - C_2\} + Q = Q + (\alpha f + \beta - \beta f)C - (\alpha C_1 + \beta C_2) \quad (3)$$

where β is the solubility constant of the solute in B-micelles. Eqn. 3 represents a linear relation of either type II–III or type II–IV in Fig. 4. The slope of line II–III is larger than that of line I–II if:

$$\text{Slope} = \alpha f + \beta - \beta f > \alpha f \quad (4)$$

since the slope of line I–II is αf. Eqn. 4 may be reduced to

$$\beta(1 - f) > 0 \quad (5)$$

and since both β and $(1 - f)$ are larger than zero, this is always true. Hence in a simple situation such as A-micelles forming after addition of C_1 moles to the system and B-micelles forming after addition of C_2 moles to the system, there will always be an augmentation of slope after C_2.

Since A and B are similar type compounds there is another likely explanation for changes in slope, i.e. one where the micelles formed above C_2 are mixed micelles. In this case they contain a fraction ϕ of B and a fraction $(1 - \phi)$ of A. The amount of B in the mixed micelle is therefore: $\{(1 - f)C - C_2\}$, and hence the amount of A in the mixed micelle is $\{(1 - f)C - C_2\}(1 - \phi)/\phi$.

The amounts of A-micelles and mixed micelles are hence given by:

$$fC - C_1 - \{(1 - f)C - C_2\}\frac{1 - \phi}{\phi} \quad \text{A-micelles} \quad (6)$$

$$\{(1 - f)C - C_2\}/\phi \quad \text{mixed micelles} \quad (7)$$

The solubility can now be expressed in the following form, reserving the notation for

solubility in the mixed (predominantly B) micelle:

$$S = Q + \alpha[fC - C_1 - \{(1-f)C - C_2\}] \frac{1-\phi}{\phi} + \frac{\beta}{\phi}[(1-f)C - C_2] =$$

$$= Q + \left[\alpha f - \frac{1-\phi}{\phi}(1-f) + \frac{\beta}{\phi}(1-f)\right] C - \left[\alpha(C_1 + C_2)\frac{1-\phi}{\phi} + \frac{\beta}{\alpha}C_2\right] \quad (8)$$

This line (II–IV in Fig. 4) will have a slope smaller than the slope of line I–II in Fig. 4 if:

$$\alpha f - \frac{1-\phi}{\phi}(1-f) + \frac{\beta}{\phi}(1-f) < \alpha f \quad (9)$$

i.e. if

$$1 - \phi > \beta \quad (10)$$

Eqn. 10 is a condition which may or may not hold depending on the particular surfactant and the particular impurity. A model in which two mixed micelles, one predominantly A and one predominantly B will give a similar result.

Least square fits values of αf, α, C_2 and the slope of line II–IV are shown in Table I. It is noted that this latter is given by:

$$\text{Slope(II–IV)} - \alpha f = \left[\frac{\beta}{\phi} - \frac{1-\phi}{\phi}\right](1-f) \quad (11)$$

This quantity is dependent on both β and ϕ neither of which is known a priori, and hence the values of the slope of line II–IV cannot be used to separate the values of β and ϕ. Although the intercept provides another equation, the intercept value (in Eqn. 8) is always rather small in magnitude, and hence afflicted with a large coefficient of variation, and

TABLE I

SLOPES AND LINE INTERSECTIONS FROM FIG. 3. LEAST SQUARES FIT VALUES

Temperature (°C)	Slope of line I–II	α [a]	100 C_2 (moles) [b]	Slope II–IV	1000/T °K^{-1}
25	0.11	0.12	0.54	0.066	3.354
35	0.15	0.17	0.35	0.10	3.245
45	0.18	0.21	0.35	0.18	3.182
55	0.20	0.23	0.39	0.20	3.047

[a] Slope of I–II divided by 0.87. α is the amount of phenobarbital per amount of micelle in this region. The amount of micelle is the amount of surfactant added beyond C_1 multiplied by 0.87 (because only 87% is micelle forming in this region).

[b] From solving the least squares fit equations for lines I–II and II–IV.

attempts to resolve β and ϕ values by these simultaneous equations have been unsuccessful in this study. It is noted that both β and ϕ may be temperature-dependent, but to differing degrees, and that therefore no trends in intercept (C_2) and slope values with temperature can be predicted.

The critical micelle concentration for A occurs at 0.125 g/100 ml i.e. at $C = 3.9 \times 10^{-4}$ mol/100 ml, so that $C_1 = 0.83 \times 3.9 \times 10^{-4} = 3.2 \times 10^{-4}$ mol/100 ml. Table I shows C_2 to occur at $C = 5.4 \times 10^{-3}$ mol/100 ml, i.e. $C_2 = 5.4 \times 10^{-3} \times 0.13 = 7 \times 10^{-4}$ mol/100 ml (since there is 13% of disulfonate in the surfactant). In other words, C_1 and C_2 are of a similar order of magnitude, and this lends credence to the proposed model. It should be noted that this feature could be utilized as an analytical method for purity for surfactants of this type.

The temperature dependence of α is that which can be expected from a solubility parameter, as shown in Fig. 5. The least squares fit equation for this latter is

$$\ln(\text{Slope I–II}) = 4.584 - \frac{2.016}{T} \tag{12}$$

so that the heat of solution of the phenobarbital in the A-micelle is R times the slope (where R is the gas constant), i.e. of the order of 4200 cal/mol.

The model explained above explains both solubility curves that increase and solubility curves which decrease their slope above a higher critical micelle concentration than the principal one. Since most commercial surfactants are of the type described here, it is well possible this model explains phenomena previously attributed to other features of micelle formation.

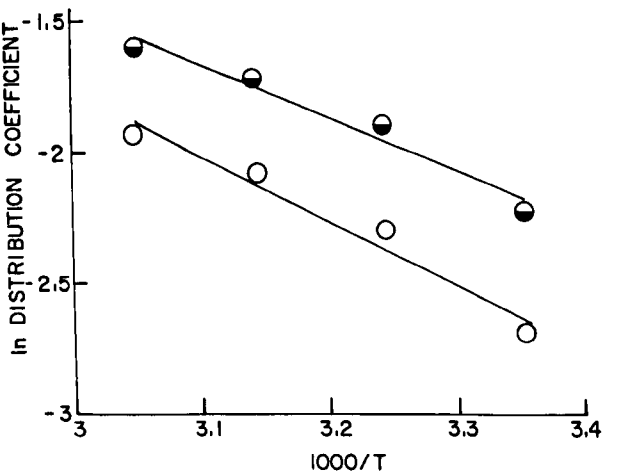

Fig. 5. Temperature dependence of the distribution coefficient, ● in the A-micelle and ○ in the B-micelle.

NOMENCLATURE

A principal micelle;
B impurity or mixed micelle;
c g of sodium paraffinsulfonate per 100 g of solution;
C moles of sodium paraffinsulfonate per 100 g of solution (c/321);
C_1,C_1 moles of sodium paraffinsulfonate per 100 g of solution corresponding to the critical micelle concentration of A or B (or mixed micelle);
C* amount of sodium paraffinsulfonate in excess of that needed for micellization (moles);
f fraction of A in surfactant;
1−f fraction of B in surfactant;
[HP] phenobarbital concentration;
K equilibrium constant of micellar species;
L $S - P_a$ = total number of moles of phenobarbital in solution;
n number of monomers in a micelle (A);
M,MH micelles of A;
[P] concentration of phenobarbital anion;
P_a $[HP] + [P] = [HP]_0(1 + 10^{pH-pK})$;
pK pK of phenobarbital;
Q amount of phenobarbital and phenobarbital anion in the aqueous phase;
q_1,q_2 distribution coefficients of phenobarbital in M and MH micelles;
s′ solubility of phenobarbital in mg/100 ml below the critical micelle concentration;
s solubility of phenobarbital in mg/100 ml of micellar system above the critical micelle concentration;
S solubility of phenobarbital in mol/100 ml of micellar system above the critical micelle concentration;
V volume of water in the system;
W monomer molecular weight;
α distribution coefficient of phenobarbital between water and micelle A;
β distribution coefficient of phenobarbital between water and micelle B or mixed micelle;
ρ density of solution at T°K;
ρ' density of water at T°K;
ϕ fraction of B in mixed micelle.

APPENDIX I

The nomenclature in the nomenclature list is used in the following. The weight fraction of surfactant is $c/(100\rho)$, so that the mass of water in the 100 ml is $100\rho - c$. The volume of water then is

$$V = [100\rho - c]/\rho'$$

The concentration of phenobarbital in the aqueous phase is given in the nomenclature list, and the amount of phenobarbital per V ml then is

$$Q = \frac{V}{100}[HB](1 + 10^{pH-pK})$$

The amount of phenobarbital in the micellar phase then is

$$L = S - Q$$

moles dissolved in the micellar phase. This is the quantity which is plotted versus C (the number of moles of surfactant in the (100 ml system) in Fig. 3.

APPENDIX II

If one assumes an equilibrium of the type in Eqn. A1 below then there will be associated with it an equilibrium constant as shown in Eqn. A2:

$$MH \rightleftharpoons M + H^+ \tag{A1}$$

$$K = [M][H^+]/[MH] \tag{A2}$$

This is in accordance with the curve in Fig. 2.

The concentration units are in g per 100 ml. Density measurements and weighed-in amounts allow conversion of these figures as desired. One hundred ml of solution contain c grams of surfactant with a monomer molecular weight of W. The molar concentrations of surfactants are then related to c, W and n by the equation:

$$\frac{[M]}{10} + \frac{[MH]}{10} = \frac{c}{W_n} \tag{A3}$$

c is actually the concentration above the cmc but since the latter is low in comparison with the former, c is used interchangably for concentration and for concentration above cmc in the following.

The total amount of phenobarbital, L, dissolved in the two species of micelle is given by their distribution coefficients (q_1 and q_2) and their amounts times the concentration of uncharged phenobarbital in the aqueous phase, i.e.

$$L = q_2[HP]\frac{[M]^{W_n}}{10} + q_1[HP]\frac{[MH]^{W_n}}{10} \tag{A4}$$

Eqns A2 and A3 may be combined to yield:

$$[M] + [MH] = [M]\left(1 + \frac{[H^+]}{K}\right) = \frac{10c}{W_n} \tag{A5}$$

and introducing this into Eqn. A4 then yields:

$$L = [HP]\, c\, q_1 \frac{([H^+]/K) + (q_2/q_1)}{([H^+]/K) + 1} \tag{A5}$$

This is a smooth curve without discontinuities in slope.

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