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Equilibrium Dialysis of Barbituric Acids up to High Concentrations of Aqueous Sodium Alkylsulfonate Solutions

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Abstract □ The partition coefficient K of four barbituric acids has been determined by the equilibrium dialysis method in aqueous solutions of sodium alkylsulfonate at 25°C. The results obtained from dilute solutions to 0.3 M surfactant concentration are compared with solubility data for the same systems. The K values as deduced from Langmuir or Freundlich isotherms decrease with increasing surfactant concentration. The detergent used was an impure commercial product of known composition, which could be considered as a mixed surfactant. The change of partition coefficient with surfactant concentration as obtained from equilibrium dialysis experiments has been interpreted by assuming a continuous change of micelle composition.

Keyphrases □ Barbituric acids—equilibrium dialysis up to high concentrations of aqueous sodium alkylsulfonate solutions, solubility □ Sodium alkylsulfonate—aqueous solutions, equilibrium dialysis of barbituric acids up to high concentrations, solubility □ Equilibrium dialysis—barbituric acids up to high concentrations of aqueous sodium alkylsulfonate solutions, solubility □ Solubility—equilibrium dialysis of barbituric acids up to high concentrations of aqueous sodium alkylsulfonate solutions

The solubility of 13 barbituric acids as a function of sodium alkylsulfonate concentration between 25°C and 55°C shows a rather sharp change in slope at low surfactant concentrations (~0.05 mol/L); the solubility increases less rapidly above this concentration than below it (1, 2). The ionic surfactant used was not pure but was a typical commercial product mixture consisting of 91% monosulfonated and 9% disulfonated ions. A model was suggested (1) to explain the solubility profile, which assumed two types of mixed micelles: predominantly monosulfonated mixed micelles at low surfactant concentration and predominantly disulfonated micelles at high concentrations. To further investigate this micellar system, we decided to study the solubilization behavior at 25°C of four typical barbituric acids (amobarbital, phenobarbital, secobarbital, and allobarbital) with the same surface-active agent using equilibrium dialysis instead of the solubility method.

Table I—Characteristics of Barbituric Acids

Barbituric Acid	Solubility, mol/L[a]	Melting Point, °C
Amobarbital	0.0022	157
Phenobarbital	0.0052	174
Allobarbital	0.0087	172
Secobarbital	0.0044	98

[a] Solubility in water at 25°C.

EXPERIMENTAL

Materials—The barbituric acids[1] were used without further purification. The melting points and the solubility in water at 25°C are presented in Table I. The sodium alkylsulfonate was a commercial product[2] containing monosulfonated ion–disulfonated ion–polysulfonated ion (90.7:8.8:0.5, v/v/v). The monosulfonated product was a mixture of $C_{14}H_{29}SO_3Na$ and $C_{15}H_{31}SO_3Na$, whose average molecular weight was 321.

Methods—The equilibrium dialysis experiments were performed using dilute to saturated solutions of barbituric acids at 25°C thermostatically controlled to within ±0.1°C with polytef cells and a cellulose acetate membrane. The equilibrium was attained in ~4 h. Barbituric acid concentrations were analyzed using a UV spectrophotometer. Each experiment was repeated five times, and at least six barbiturate concentrations were studied for each surfactant concentration.

The solubility of the barbituric acid is dependent on the pH of the medium. The pH of the solutions was measured at each concentration, and a correction applied to the concentration of barbituric acid on both sides of the dialysis using:

$$S_T = S_0(1 + 10^{pH-pK}) \qquad \text{(Eq. 1)}$$

where S_T and S_0 are the total concentration and the concentration of undissolved barbituric acid of a given pK, respectively.

RESULTS

Sodium alkylsulfonate showed a very high degree of adsorption onto the cellulose acetate membrane (Fig. 1). This adsorption was reproducible, and a systematic correction was applied. The barbituric acids were also partially adsorbed onto the membrane. A correction was also applied which amounted at most to 5% of the total concentration of the drug dissolved in the solution.

Two types of isotherms were used to obtain the partition constants. The Freundlich isotherm may be written as:

$$\log r = \log K + \frac{1}{n_f}\log B_{aq} \qquad \text{(Eq. 2)}$$

[1] Amobarbital and secobarbital obtained from: Expandia, 13 Avenue de l'Opéra, 75001 Paris, France. Allobarbital obtained from: Soprotec, 144 Avenue de Malakoff, 75116 Paris, France. Phenobarbital obtained from: Coopération Pharmaceutique Française, 66 Rue du Chemin Vert, 75001 Paris, France.

[2] Société des Produits Chimiques de la Montagne Noire, 81100 Castres, France.

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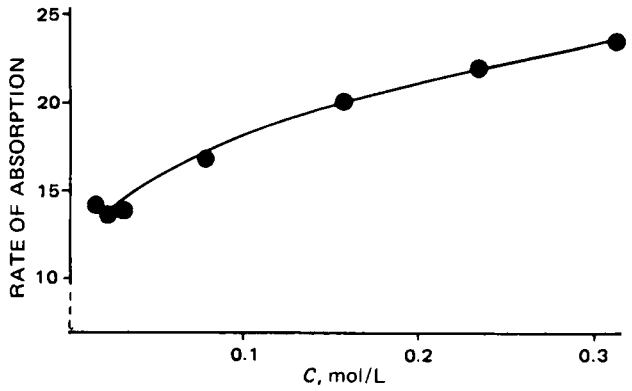

Figure 1—*Rate of adsorption of sodium alkylsulfonate onto the acetate cellulose membrane.*

where $r = B_{mic}/C$; B_{mic} and B_{aq} are the molar concentrations of barbituric acids within the micelles and in the aqueous phase, respectively; and C is the surfactant molar concentration. B_{aq} is assumed to be equal in both compartments of the cell. Figure 2A illustrates the corresponding curves for amobarbital. The Langmuir isotherm is presented for the same barbiturate in Fig. 2B:

$$\frac{1}{r} = \frac{1}{n} + \frac{1}{Kn}\left(\frac{1}{B_{aq}}\right) \qquad \text{(Eq. 3)}$$

Both isotherms suffer from a number of well-known deficiencies. They involve long linear extrapolations to obtain K or n, depending on which isotherm is used, although it is known at least in a few cases that they are not valid when a large concentration domain is investigated (3) (Freundlich isotherm). Furthermore, the intercept usually being very small, the n value of the Langmuir isotherm is known to have poor accuracy (4, 5). Finally, both equations are applicable only to dilute solutions. Thus, the slopes of Eqs. 2 and 3 can be better determined than their intercepts with the ordinate axis.

Table I compares, for the most dilute surfactant concentration studied, the values of the parameters obtained from the dialysis method according to the Freundlich and Langmuir methods, together with the solubility results at 25°C taken from our previous work. The apparent partition constant as obtained from the solubility data may be defined in dilute surfactant solutions by:

$$K = \frac{B_m - B_{aq}}{B_{aq} \cdot C} \qquad \text{(Eq. 4)}$$

There is no way of calculating with any confidence the individual values of n from the Langmuir isotherm. For each concentration of surface-active agent at least six dialysis experiments were performed ranging from very dilute to saturated concentrations of the barbituric acid. The correlation factors were excellent in all cases (in the range $0.994 < r^2 < 0.999$); thus, the intercepts and slopes were obtained with the highest accuracy compatible with the systems under investigation. This is the most complete set of data obtained from equilibrium dialysis experiments in the case of a single micellar system.

As can be seen from the data in Table II, n values ranging from 0.99 to 1.38 are necessary in order to match the solubility and dialysis results with the same isotherm. The n values are slightly >1 with the Freundlich isotherm, and the K values differ widely from those derived from the solubility data for those barbituric acids that showed good agreement

Table II—Comparison of Partition Constants as Deduced from Solubility or Equilibrium Dialysis Experiments at 25°C at Low Sodium Alkylsulfonate Concentrations [a]

Freundlich, K	n_F [b]	Langmuir, Kn	Solubility K	n_L [c]	Barbituric acid
27.4	1.07 ±0.02	51.5	51.6	0.99	Amobarbital
14.4	1.03 ±0.02	19.2	22.7	1.18	Phenobarbital
10.6	1.00 ±0.01	11.7	9.2	1.27	Allobarbital
82.4	1.04 ±0.01	119.9	80.6	1.38	Secobarbital

[a] $C = 0.0201$ mol/L. [b] Values of n deduced from the Freundlich isotherm. [c] Values of n deduced from the Langmuir isotherm.

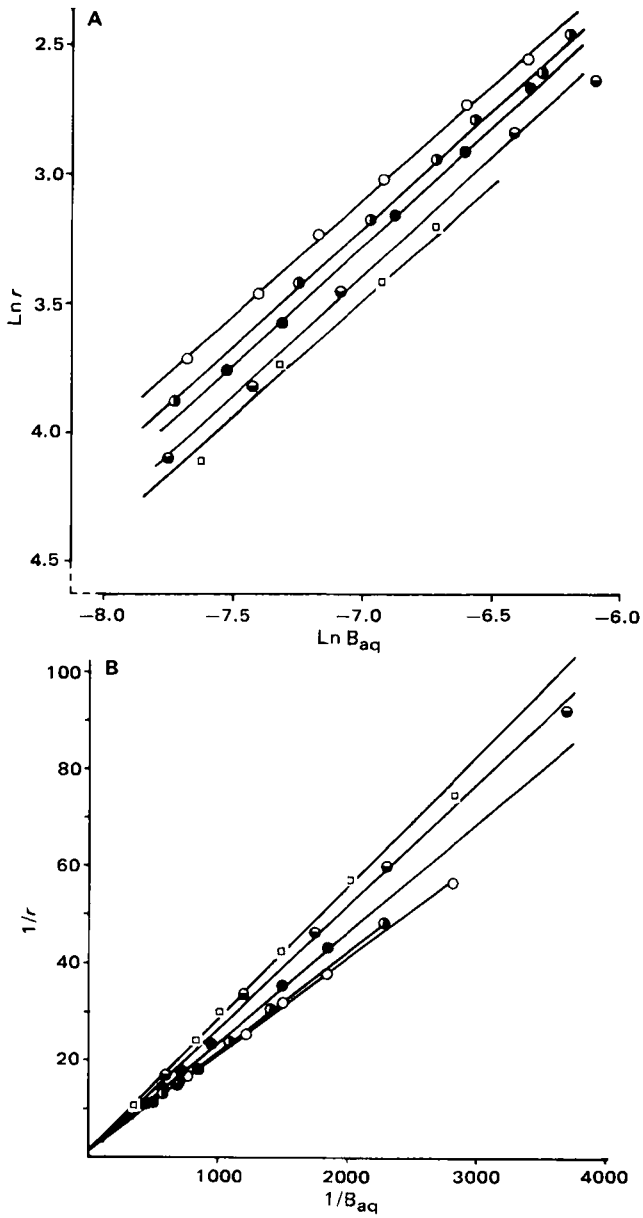

Figure 2—*Freundlich (A) and Langmuir (B) isotherms for amobarbital in aqueous sodium alkylsulfonate solutions. Key: (○) 0.020 mol/L; (◑) 0.065 mol/L; (●) 0.125 mol/L; (◒) 0.182 mol/L; (□) 0.239 mol/L.*

with the solubility results when using the Langmuir isotherm. The results are satisfactory in the other two cases.

The results of the analysis of the dialysis experiments with both kinds of isotherm do not agree with each other whatever barbituric acid is considered. Considerable care must be exercised when using these isotherms—the fact that $n \cong 1$ is obtained from the Freundlich plot does not ensure that the K values are necessarily correct. There is no reason for the n values obtained from the Freundlich or Langmuir isotherms to be equal, as can be inferred from their very different (3) theoretical derivation.

The Langmuir isotherm which has the soundest theoretical basis has been chosen (Table III). We think that the long extrapolation involved in the determination of K with the Freundlich isotherm is inappropriate. Table II shows the results obtained for all the solutions studied. It has been assumed that the n values are characteristic of the behavior of each barbituric acid. Thus, the K values have been calculated using the n values deduced from the comparison between the Langmuir isotherm and the solubility results at low surfactant concentrations.

DISCUSSION

It has been assumed previously (1) that the solubility profile for the barbituric acids in aqueous sodium alkylsulfonate solutions could be

Table III—Partition Constants of Barbituric Acids (Langmuir Isotherm) in Aqueous Sodium Alkylsulfonate Solutions

Barbituric Acid	Concentration of Sodium Alkylsulfonate, mol/L				
	0.0201	0.0646	0.1246	0.1822	0.2386
Amobarbital					
Kn	51.5	48.4	44.0	39.1	39.0
r^2	0.9996	0.9990	0.9998	0.9999	0.9968
Phenobarbital					
Kn	19.2	17.8	14.3	12.9	11.1
r^2	0.9893	0.9998	0.9986	0.9999	0.9999
Allobarbital					
Kn	11.7	8.0	6.9	5.8	5.3
r^2	0.9986	0.9997	0.9995	0.9999	0.9986
Secobarbital					
Kn	111.9	106.0	100.7	96.0	91.9
r^2	0.9992	0.9999	0.9996	0.9997	0.9999

described from dilute to concentrated surfactant solutions ($C \leq 0.3$ M or 10% w/v) by two partition coefficients, corresponding to two types of micelle. In the low concentration region, predominantly monosulfonated micelles would be formed, and a change in the slope of the solubility *versus* surfactant concentration curve might indicate the formation of disulfonated micelles.

The nonlinearity of a plot of the solubility of a solute *versus* surfactant concentration concerns only mixed systems, *e.g.*, 1-[(2-methylphenyl)-azo]-2-naphthylamine (Color Index No. 11390), in mixed anionic and nonionic surfactants (6, 7). Nishikido (7) attributed the nonlinear plot at low surfactant concentration to a variation of the micelle composition with the total surfactant concentration; the linearity observed at higher concentration was interpreted as evidence for a constant micelle composition. The previous model also assumed constant micelle composition (1). However, these conclusions were deduced solely from solubility measurements. The present equilibrium dialysis data suggest that these models might be too restrictive. In effect, a continuous change of the partition coefficient is observed from dilute to concentrated alkylsulfonate solutions with a levelling off at the highest concentrations (Fig. 3). The general pattern is observed whatever isotherm is employed to obtain the partition coefficients. Thus, the dialysis data are more compatible with a model of gradual change in micelle composition with total surfactant concentration.

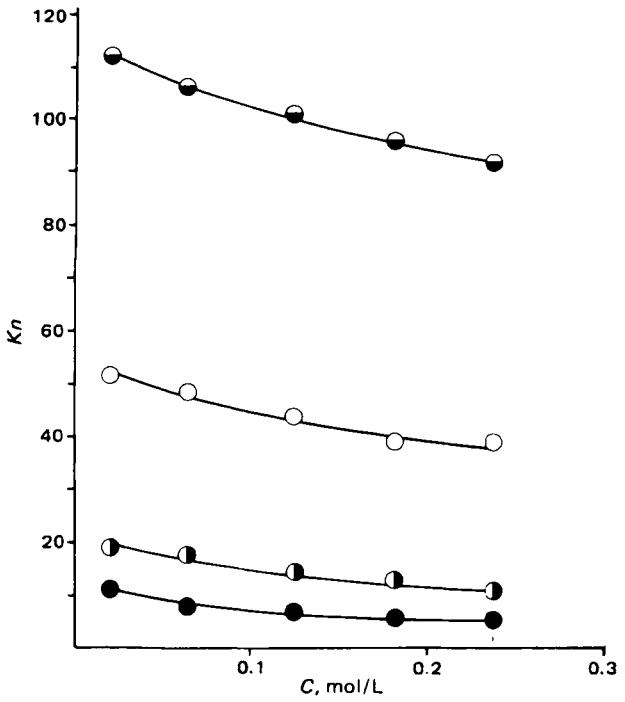

Figure 3—*Variation of partition constants with sodium alkylsulfonate concentration for different barbiturates. Key: (◒) secobarbital; (○) amobarbital; (◑) phenobarbital; (●) allobarbital.*

The following considerations indicate possible reasons for the decrease of K with surfactant concentration. It is known that the critical micelle concentration (CMC) of alkylsulfate surfactants increases when the sulfate group moves from the terminal to a median position along the hydrocarbon chain (8–10). In the case of the sodium tetradecanemonosulfate series quoted by Klevens (10), the CMC changes from 1.65×10^{-3} to 3.26×10^{-3} mol/L when the sulfonate group moves from the terminal position 1 to position 2. This situation is somewhat different from that of the present study, where the sulfonate group of the monosulfonated ions is on the terminal 1 position, while the second sulfonate group of the disulfonated ions is located somewhere on the hydrocarbon chain. However, a simple calculation may be used as a qualitative argument. The CMC of the compound used was 3.72×10^{-3} mol/L. Assuming an ideal behavior of the mixed micelles, the CMC of the pure sodium alkylmonosulfonated product would be 3.3×10^{-3} mol/L when taking into account the composition of the mixed surfactant. Thus, the CMC of the pure sodium alkyldisulfonated compound would be equal to 5.0×10^{-3} mol/L (the breaking point of the solubility curve is in most cases $\sim 5.0 \times 10^{-2}$ mol/L). Therefore, the progressive incorporation of the disulfonated ions in the monosulfonated micelles will increase the CMC of the mixed compound.

The increase in the CMC in a surfactant series is usually related to a decrease in the solubilization properties of the micelles. The appearance of mixed micelles with predominantly monosulfonated ions at low surfactant concentration with gradual incorporation of disulfonated ions at higher concentration may have the same effect: a decrease in the solubilization properties of the micellar solution; hence, the observed decrease of the partition coefficients with increasing surface active concentration for the four barbituric acids.

Finally, some aspects of the contradictions pointed out in this study between conclusions deduced from the solubility and from the equilibrium dialysis results have been discussed before, in particular by Donbrow *et al.* (3). It stresses the need for parallel studies using several solubilization methods to deduce nonequivocal conclusions about the behavior of complex molecules in micellar systems.

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