# Application of the Potentiometric Method to the Study of Solubilization by Ionic Surfactants

By C. T. RHODES and M. DONBROW*

**The potentiometric method is applied to the study of the solubilization of benzoic acid by an ionic surfactant, sodium dodecyl sulfate. It is shown that the method is of value in evaluating the antimicrobial activity of acidic preservatives in surfactant solutions. Solubilization by ionic surfactants appears to be basically similar to solubilization by nonionic surfactants.**

THE POTENTIOMETRIC method, a well-established method of examining interaction between cosolutes and macromolecules (1), has been applied recently to the study of solubilization by surfactant solutions and emulsions (2–6). In all cases good agreement was obtained between results obtained potentiometrically and those obtained by other methods. This method enables direct measurements to be made of the chemical activity of acids, amines, and phenols in surfactant solutions. Since it appears that the antimicrobial activity of a preservative in a surfactant solution is equal to its chemical activity (7), this technique is likely to be of considerable use in the formulation of pharmaceutical products.

The presence of surfactant has characteristic effects upon the titration curves of organic acids and amines, elevating those of acids and depressing those of amines (2, 4, 8). In any $L_1$ surfactant solution (aqueous isotropic liquid phase) of an organic acid, the following equilibria will exist.

$$A_m^- \leftrightharpoons A_w^- \leftrightharpoons HA_w \leftrightharpoons HA_m \qquad \text{(Eq. 1)}$$

where HA represents the unionized and $A^-$ the ionized species, and the subscripts $w$ and $m$ indicate the aqueous and bound or micellar components.

It has been shown that when the lipophilic part of the ion is small, *e.g.*, acetate or benzoate, the salt form is not solubilized by nonionic surfactants (5, 6, 8, 9). In solutions of ionic surfactants of the same charge as the ionized species of the solubilizate, thermodynamic considerations indicate that the electrostatic repulsion between the ions of like charge disfavors binding of the ionized species, even when the lipophilic group is comparatively large (10). Dyer has shown that the ionized forms of acidic and basic cosolutes possessing large lipophilic groups are not bound by ionic micelles (11). His results also indicate that the pKa value of the cosolute is unaffected by the surfactant. The present authors have confirmed these findings (6). For such systems $A_m^-$ may be eliminated from Eq. 1; when the ionized form of an acid is not solubilized by the surfactant, the following form of the Henderson equation has been shown to govern the pH values measured when a weak acid is titrated in the presence of surfactant (6).

$$pH = pKa + \log [A^-]/[HA_w] + \log \gamma^{\pm} \qquad \text{(Eq. 2)}$$

where [A] is the salt concentration, $[HA_w]$ is the concentration of nonmicellar acid, pKa is the thermodynamic dissociation constant, pH the negative log of hydrogen ion concentration, and $\gamma^{\pm}$ represents the activity correction.

If the salt form of the acid is titrated with hydrochloric acid, the term $\log \gamma^{\pm}$ is very nearly constant, provided the volume of titrant added is small compared with the total volume of the system (12). Thus, Eq. 2 may be rearranged to Eq. 3:

$$pH = pKa' + \log [A^-]/[HA_w] \qquad \text{(Eq. 3)}$$

where pKa', the apparent dissociation constant, equals $(pKa + \log \gamma^{\pm})$. By substitution of appropriate pH, pKa', and $[A^-]$ values in Eq. 3, it is possible to evaluate $HA_w$.

Further, since

$$HA_t = HA_m + HA_w \qquad \text{(Eq. 4)}$$

where $HA_t$ is the total unionized acid in the system, the value $HA_m$ can be determined.

Two difficulties emerge when the potentiometric method is applied to systems of ionic surfactants. First, such surfactants are themselves salts and therefore can react with the titrant. Second, there is some difficulty in evaluating the ionic strength and thus appropriate pKa' values in solutions of ionic surfactants. It is normally possible to calculate $I$, the ionic strength of an electrolyte solution, by means of Eq. 5:

$$I = \frac{1}{2} \sum c_i z_i^2 \qquad \text{(Eq. 5)}$$

where $c_i$ is the molarity of ionic species, $i$, the valency of which is $z_i$.

However, the process of micellization will reduce the ionization of the surfactant, and thus Eq. 5 cannot be applied to such systems.

In the present paper, the solubilization of benzoic acid by an ionic surfactant, sodium dodecyl sulfate, is investigated potentiometrically. It is shown that when the difference between the dissociation constants of the solubilized material and surfactant is large, the effect of the titrant upon the surfactant may be neglected.

## EXPERIMENTAL

The sodium dodecyl sulfate used in this investigation was W.D. product.[1] Gas chromatographic analysis by Packter has shown that this material consists of about 92% of the dodecyl compound and 8% of the tetradecyl compound (13).

The surfactant was titrated potentiometrically with 0.5 $N$ hydrochloric acid at 25°. The techniques and apparatus used have been described previously (2).

An attempt was made to measure the sodium ion activity of sodium dodecyl sulfate solutions by use

Received December 14, 1964, from the School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind.
Accepted for publication March 16, 1965.
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[1] Supplied by Sipons Ltd., London, England.

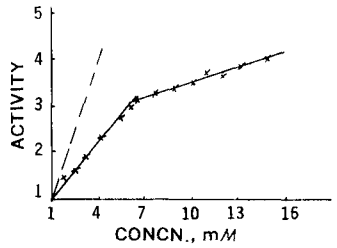


Fig. 1.—Sodium dodecyl sulfate activity concentration curve.

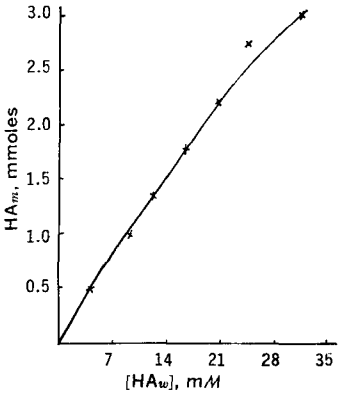


Fig. 2.—Solubilization isotherm benzoic acid in sodium dodecyl sulfate solution.

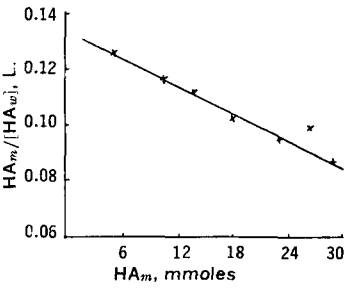


Fig. 3.—Langmuir isotherm plot.

of a sodium ion responsive glass electrode (E.I.L. type GEA 33).[2]

Sodium benzoate, 0.2 *M*, was titrated with 0.5 *N* hydrochloric acid alone and in the presence of 0.2358 *M* sodium dodecyl sulfate.

## RESULTS AND DISCUSSION

From the titration of the surfactant alone the pKa′ of dodecyl sulfonic acid was found to be less than 1. The observed value showed variation; this was attributed to the effect of micellization upon the surfactant.

When sodium benzoate is titrated in the presence of sodium dodecyl sulfate, the benzoate ion will react preferentially with the titrant hydrochloric acid since its pKa′ value (4.20) is considerably higher than that of the surfactant. By substitution in the Henderson equation, it is possible to evaluate the relative amount of surfactant which has reacted with the titrant. Thus, at pH 4, the lowest value used for calculation purposes, the relative amount of surfactant ion neutralized may be calculated as follows:

$$\text{pH} = \text{pKa}' \log [\text{A}^-]/[\text{HA}_w]$$

$$4 = 1 + \log [\text{A}^-]/[\text{HA}_w]$$

$$\therefore [\text{A}^-]/[\text{HA}_w] = 1{,}000$$

*i.e.*, about 0.1% of the surfactant has reacted with the titrant.

The attempts made to evaluate mean ion activity coefficients of solutions of sodium dodecyl sulfate and thereby obtain a direct measurement of ionic strength, *I*, were not entirely successful. It was found that though the plot of salt activity against surfactant concentration was of the expected form, even below the CMC the value of $\gamma^{\pm}$ determined potentiometrically showed a very marked deviation from ideality. It has been suggested that in measuring pNa values great care must be taken to reduce liquid junction potential (14). The unsatisfactory nature of the pNa results may be due in part at least to this cause (Fig. 1).

An alternative method was therefore used to reduce errors due to the uncertainty of the ionic strength of the surfactant solution. Sodium benzoate, 0.2 *M*, was titrated with hydrochloric acid instead of sodium benzoate, 0.1 *M*, as used in previously reported work (6). It was thought that titration at this comparatively high ionic strength would reduce the effect of uncertainty of *I* since the value of the term log $\gamma^{\pm}$ for organic acids appears to show little change above *I* values of about 0.1 (15) and thus above this value the pKa′ value of benzoic acid is constant.

Figure 2 shows the solubilization isotherm obtained by use of Eq. 3; $HA_w$ represents the fraction of total benzoic acid bactericidally active; $HA_m$, the benzoic acid bound by the micelles, may be regarded as an inactive reserve of drug.

Figure 3, a Langmuir isotherm plot, shows that the solubilization of benzoic acid by sodium dodecyl sulfate is similar to the solubilization of benzoic acid by nonionic surfactants previously examined (3, 4) in that it is governed by the Langmuir equation. It is noteworthy that Kostenbauder and his collaborators have also reported solubilization governed by the Langmuir isotherm (16). From Fig. 3, the value of *K*, the binding constant (the negative slope) and $\sigma_i$ (the intercept on the $HA_m$ axis) the amount of acid bound at monolayer saturation, have been determined. *K* equals 16.2 $M^{-1}$ and $\sigma_s$/mole 1.4 mole. It is significant that *K* is similar in values measured in systems of nonionic surfactants. Thus, the free energy change involved in the transfer of benzoic acid from an aqueous environment to a sodium dodecyl sulfate micelle is of the same order as that involved in the transfer of benzoic acid from water to a nonionic surfactant micelle. Recent studies of the thermodynamics of micellization (10) have indicated that the structure of the hydrocarbon nucleus of micelles formed by ionic, nonionic, and amphoteric surfactants is essentially the same. The above results support this finding.

Langmuir isotherm observance by the solubilization process lends support to the hypothesis advanced by Lawrence (17) in 1937 that solubilized

[2] Supplied by Electronic Instruments Ltd., London, England.

o-amphiphiles are located at the periphery of the micelle with the lipophilic tail of the molecule within the hydrocarbon nucleus and the hydrophilic carboxylic acid group protruding into the palisade layer.

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# Toxicities of Peppermint and *Pycnanthemun albescens* Oils, fam. *Labiateae*

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**The oral $LD_{50}$ of peppermint oil U.S.P. in fasted Wistar male rats using death after 24 hr. as the end point was found to be 4441 ± 653 mg./Kg. After 48 hr., the oral $LD_{50}$ was 2426 ± 329 mg./Kg. The intraperitoneal $LD_{50}$ of peppermint oil U.S.P. in Wistar male rats similarly after 24 hr. was determined to be 819 ± 126 mg./Kg. This latter was compared with a similar volatile oil, *Pycnanthemum albescens*. It was found to have an intraperitoneal $LD_{50}$ in male Wistar rats similarly after 24 hr. of 1383 ± 172 mg./Kg., which was only approximately 60 per cent as toxic as peppermint oil U.S.P. The oral $LD_{50}$ of *P. albescens* oil in fasted Wistar male rats after 24 hr. was 5309 ± 818 mg./Kg. After 48 hr., the oral $LD_{50}$ was 3147 ± 362 mg./Kg.**

PEPPERMINT oil enjoys very popular use as a flavoring agent and as an occasionally used carminative and anticolic aid. The list of preparations in which peppermint oil is used is extensive.

The U.S.P. XVI defines peppermint oil as containing not less than 5% of esters, calculated as menthyl acetate, and not less than 50% of total menthol, free and as esters.

The toxicity of peppermint oil is generally accepted as not being very great, and little reference is made to it. However, the LD of natural menthol, one of its major constituents, is stated to be 1000–2500 mg./Kg. in the rat administered subcutaneously in an oil vehicle (1).

*Pycnanthemum albescens* oil, having odor-blocking properties and antifungal activity, is composed of terpenes and apparently lacks any menthol content; but the exact chemical composition has not been determined. It is, however, a volatile oil, like peppermint oil from the family *Labiateae*.

It was, therefore, the purpose of this study to compare the oral and intraperitoneal toxicities between peppermint oil and *P. albescens* oil.

Received April 8, 1965, from the Department of Pharmacology, School of Pharmacy, Northeast Louisiana State College, Monroe.
Accepted for publication May 13, 1965.
The *Pycnanthemum albescens* oil for this study was provided by Dr. J. T. Goorley, Associate Professor of Pharmaceutical Chemistry, Northeast Louisiana State College, Monroe.
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## EXPERIMENTAL

Male rats of the Wistar strain received 0.5, 1.0, and 2.0 ml./Kg. of peppermint oil intraperitoneally. The peppermint oil was U.S.P., double distilled [Penick and Co., New York, N. Y., control No. LCX-69, W84050 (sp. gr. 0.9021)].

Twenty animals were used at each dosage, and the $LD_{50}$ after 24 hr. was determined using the Reed-Muench method (2). All animals in these studies were observed for a period of 30 days to include any possible latent effects.

Male rats, Wistar strain, in groups of 20 received, respectively, 0.5, 1.0, and 2.0 ml./Kg. of *P. albescens* oil intraperitoneally, and the $LD_{50}$ after 24 hr. was calculated using the Reed-Muench method (2). The *P. albescens* oil was obtained by steam distillation from the stalks, leaves, and tops of the fresh plant (sp. gr. 0.9219).

Male rats of the Wistar strain were fasted at least 20 hr. but not longer than 24 hr., water given *ad libitum*. The animals were fasted in screen-bottom cages such that there was no access to feces or litter.

The fasted rats in groups of 20 received, respectively, 2.0, 4.0, and 8.0 ml./Kg. of peppermint oil orally by means of stomach intubation. The oral $LD_{50}$ was calculated after both 24 and 48 hr. using the Reed-Muench method (2).

Additional fasted rats in groups of 20 received, respectively, 2.0, 4.0, and 8.0 ml./Kg. of *P. albescens*