coralyne salts. This formulation is presently being utilized and is prepared by dissolving Ib in sufficient aqueous sodium hydroxide to yield a final concentration of 25 mg/ml (calculated on the basis of Ib) at pH ~ 6.5. The solution obtained is sterile filtered, frozen, and lyophilized. The lyophilized product is stable, and reconstitution as a solution is easily accomplished upon the addition of water. Such a formulation affords good solubility and stability with respect to I and appears to be completely suitable for intravenous use.

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Micelle Formation and Its Relationship to Solubility Behavior of 2-Butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl Ketone Hydrochloride

LOUIS J. RAVIN ˣ, ELIE G. SHAMI ‡, and ELISABETH S. RATTIE

Abstract □ Micelle formation by 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride was studied by conductance measurements. The CMC was approximately 0.05% and was independent of temperature between 20 and 50°. The heat of formation for the micelle was calculated to be 6.9 kcal/mole. The unusual solubility behavior of the compound was attributed to its ability to form micelles. Ultracentrifuge studies indicate the molecular weight of the micelle to be approximately 100,000. Anions such as chloride, sulfate, acetate, tartrate, and citrate significantly affect the equilibrium solubility of the compound. NMR spectroscopic data indicate that the solubility behavior, in part, is related to an effect on the CMC of the compound by the anionic environment.

Keyphrases □ 2-Butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride—micelle formation, relationship to solubility □ Solubility—2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride, micelle formation □ Micelles—2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride, relationship to solubility

It was reported previously (1, 2) that 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride[1] (I) was capable of existing in the micellar state and that surfactants such as polysorbate 80, sodium lauryl sulfate, and cetyldimethylbenzylammonium chloride had a pronounced effect on its equilibrium solubility. This paper reports the results of studies on the micellar behavior of I, its relationship to the solubility characteristics, and the effect of various anions on its equilibrium solubility.

EXPERIMENTAL

Materials—Ultrapure water[2] was used. All other chemicals were of analytical reagent grade quality.

Equipment—A recording spectrophotometer[3] was used for UV absorption measurements. A conductivity bridge[4] and a conductivity cell[5] were used in the conductance experiments.

Equilibrium Solubility Studies—*Effect of Temperature*—Approximately 200 mg of I was added to screw-capped vials containing 15 ml of water. The vials were rotated for 24 hr at 20, 25, 30, 35, 40, 45, and 60°. The contents of the vials were filtered through syringes fitted with Swinney filter adapters containing a

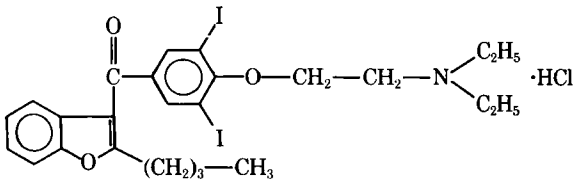
[1] SK&F 33134-A, marketed as Cordarone by Labaz Laboratories in several European countries.

[2] Harleco, Philadelphia, Pa.

[3] Cary model 15.

[4] Surfass model RCM 15B1, Arthur Thomas.

[5] K-1.00/CM, Beckman Instruments.



I

0.45-μm filter disk[6]. The resulting clear solutions were diluted with anhydrous methanol and assayed for I using a recording spectrophotometer.

Effect of Various Salt Solutions—Approximately 200 mg of I was added to screw-capped vials containing 15 ml of salt solutions of known concentrations. The vials were rotated for 24 hr at 30°. The contents of the vials were filtered as previously stated. The resulting solutions were diluted with anhydrous methanol and assayed for I.

Determination of Critical Micelle Concentration (CMC)—The CMC for I was determined by conductance measurements. A series of solutions of various concentrations was prepared and equilibrated at 20, 25, 30, 37, 45, and 50°. Conductance measurements were made on the solutions. The CMC was determined from a plot of equivalent conductance *versus* square root of concentration, using the point of intersection of the straight-line segments of the curve as the CMC value.

Ultracentrifuge[7] Studies—The ultracentrifuge studies were conducted using the sedimentation equilibrium method (3). Samples containing 4.6, 3.5, and 1.5% of I were prepared. To effect solution, it was necessary to dissolve the drug at temperatures in excess of 60°. When cooled, I remained in solution. The samples were centrifuged at 38,000 rpm. Photographs were taken at intervals of 0, 15, 30, 47, 64, and 147 min to follow the movement of the front.

NMR Studies—The NMR spectrum of a solution of I (0.15% in 0.02% sodium sulfate solution) was run in deuterium oxide at 25 and 60°.

RESULTS

CMC—The CMC for I in aqueous solution was approximately 0.05%. Figure 1 shows a plot of the equivalent conductance *versus* the square root of concentration. The CMC was independent of temperature between 20 and 50°.

Effect of Temperature on Equilibrium Solubility—The equilibrium solubility of I in water at 25° was approximately 5.1×10^{-4} mole/liter, and showed a dramatic temperature dependency. Figure 2 shows a typical van't Hoff plot, illustrating the temperature dependency on solubility. The solubility increased gradually up to about 35°; the heat of formation for the micelle was calculated to be 6.9 kcal/mole. At 35°, there was a sharp increase in the solubility, apparently due to the appearance of a new species in solution. The concentration of I in solution at the inflection point corresponded to the CMC value determined by conductance measurements. The calculated apparent heat of formation for the micelle is high when compared to reported values (4). In the 35–60° range, the solubility remained temperature dependent. A sample

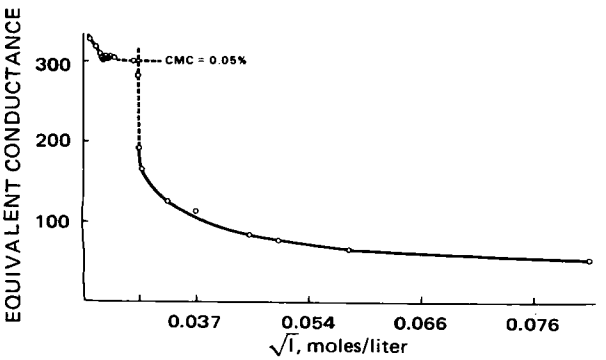


Figure 1—*Plot showing the CMC for I.*

[6] Millipore.
[7] Model E, Spinco Division, Beckman Instruments, Bellmont, California.

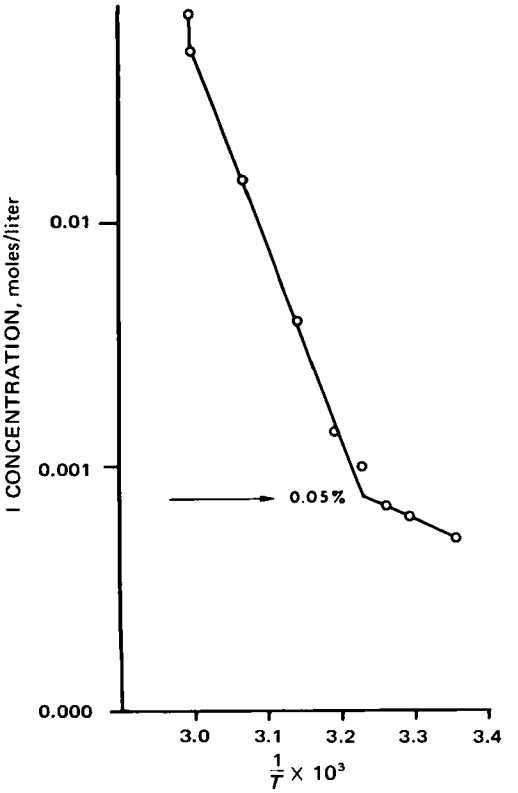


Figure 2—*Typical van't Hoff-type plot illustrating the effect of temperature on the aqueous solubility of I.*

equilibrated at 40° for 48 hr had a solubility of 1.4×10^{-3} mole/liter; however, when this solution was brought to 25° and equilibrated for 48 hr, the solubility approximated the value previously determined. Thus, in this temperature range, the solubility was reversible. However, above 60°, complete solution of the excess compound was achieved.

This solution remained clear after shock-cooling and crystal seeding to induce crystallization and formed a metastable micellar solution. Subsequent dilutions of this metastable solution remained clear until the effective concentration on dilution approached the CMC. Below this concentration, the compound precipitated from solution.

Determination of Micelle Molecular Weight—To characterize the system further, sedimentation equilibrium studies were conducted to determine the approximate size and molecular weight of the micelle. Figure 3 shows a series of ultracentrifuge patterns, illustrating the approach to sedimentation equilibrium for a 4.6% solution of I. The character of the curves suggests that the system is heterogeneous. The distance the front moved with time was determined, and a plot of the log of this distance against time is shown in Fig. 4. The slope of the line was determined and

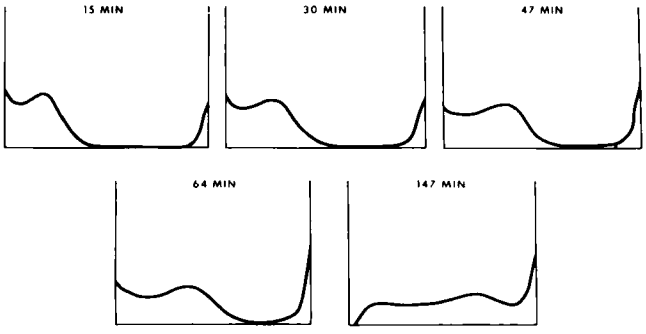


Figure 3—*Representative ultracentrifuge patterns illustrating the approach to sedimentation equilibrium for a micellar solution of I.*

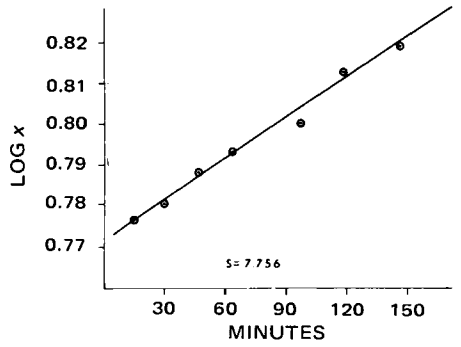


Figure 4—*Determination of sedimentation coefficient from a plot of log* x (*distance of boundary to axis of rotation*) versus *time for a micellar solution of I.*

used in the following equation to calculate the apparent sedimentation coefficient:

$$S = \frac{2.303\ d\ \log x/dt}{60(\omega)} \qquad \text{(Eq. 1)}$$

where S = sedimentation coefficient, and ω = angular velocity.

A sedimentation coefficient of 7.756 was calculated for the system. When utilizing this value and extrapolating from a plot for protein compounds in the literature (5), it appears that the micelle is composed of approximately 150 monomeric units having a molecular weight in excess of 100,000.

Effect of Various Anions—Previously it was reported that chloride ion depressed the solubility of I (2); therefore, it was decided to investigate the effect of some commonly used buffer salts on the equilibrium solubility. Figure 5 illustrates the effect of citrate and tartrate ions on the equilibrium solubility of I. The solubility increases rapidly and then suddenly decreases to a constant value below the equilibrium solubility previously determined.

The pH of these solutions ranged from 4.3 to 5.4. To eliminate the possible effect of pH with increasing salt concentrations, several neutral sulfate salts were studied. The pH of these solutions remained relatively constant at pH 4.3. The effect of these salts on the solubility of I is shown in Fig. 6. Again there are a sharp increase and the sudden drop to a constant value.

Another anion, acetate, was utilized in the solubility studies. The pH of these solutions ranged from 4.0 to 4.7. The effect (Fig. 7) was similar to that previously observed with the chloride ion (2). The solubility was depressed by the addition of increasing amounts of acetate ions. Apparently, the effect on solubility was not due to an ionic strength effect. When solubility was plotted as a function of increasing normality, these data were superimposable.

The possibility of interconversion of the hydrochloride salt to

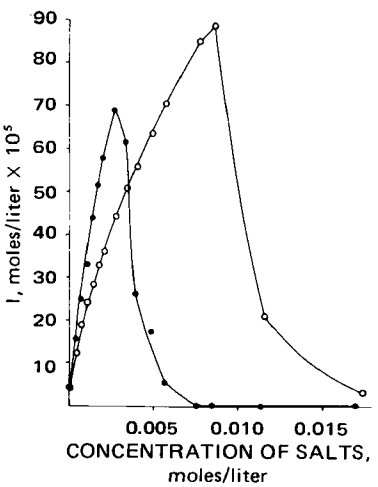


Figure 5—*Plot showing the effect of sodium citrate* (●) *and sodium tartrate* (○) *on the equilibrium solubility of I.*

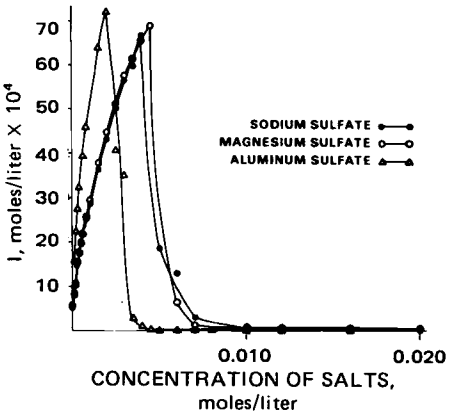


Figure 6—*Plot showing the effect of various sulfate salts on the equilibrium solubility of I.*

the citrate salt being responsible for the solubility behavior was considered. The citrate salt of I was prepared. The equilibrium solubility of this salt at 25° was 9.1×10^{-5} mole/liter, which is not in agreement with the solubility values achieved during the studies with the citrate ion.

NMR Spectroscopy—It was previously reported that the NMR spectrum of I in micellar solution had broad resolution bands at 25°; however, when the temperature was increased, the resolution became sharp and reached a maximum at 60° (1). The conclusions were that the micellar system was completely disrupted at 60° and that the resulting spectrum was of the monomer of I.

To explain the dramatic increase in solubility, a solution isolated from the sulfate solubility studies was investigated using this technique. This solution showed behavior similar to that of the micellar solution. At 25°, there was no apparent resolution. However, when the temperature was raised to 60°, the resolution bands became sharper (Fig. 8). Apparently, the various ions exert an effect on the equilibrium solubility of I by affecting its CMC. The NMR data confirm this observation. This finding is not surprising since ionic environment has been shown to affect CMC values (6, 7).

CONCLUSION

The pharmaceutical importance of this study is apparent, and the implications of equilibrium solubility and dissolution rate to drug availability in a dosage form are obvious. When formulating this drug, the development pharmacist must exercise extreme care in the selection of the proper excipients and/or buffer systems and also in the concentration of these ingredients. A study of this type points out that a thorough understanding of the physical–chemical behavior of complex drug molecules is extremely important.

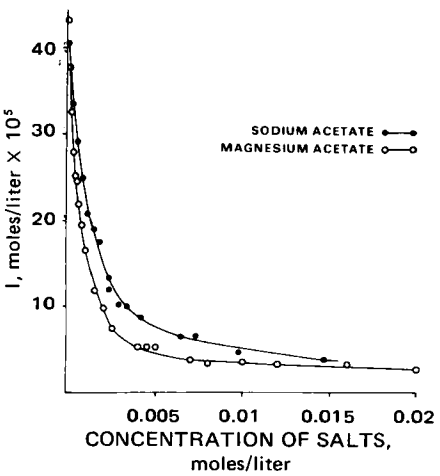


Figure 7—*Plot illustrating the effect of acetate salts on the equilibrium solubility of I.*

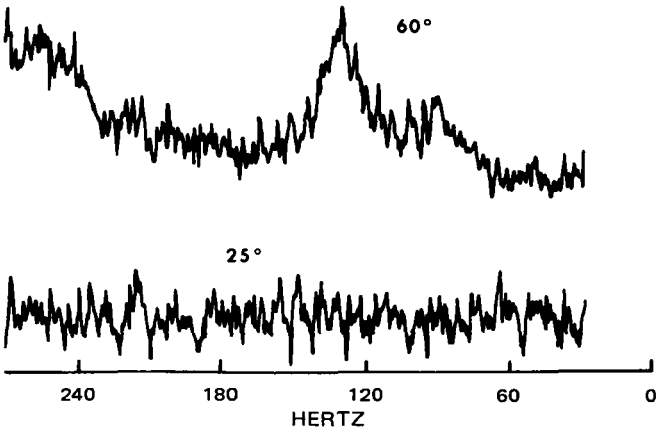


Figure 8—*NMR spectra for I (0.15% in 0.02% sodium sulfate solution) at 25 and 60°.*

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Solvolysis of a Substituted Imidazoline, Mazindol

H. V. MAULDING[x], P. TURI, D. GROSSMAN*, and J. P. NAZARENO

Abstract □ Hydrolysis of mazindol to form 2-(2-aminoethyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine was followed spectrophotometrically in aqueous solutions at temperatures between 37 and 70°, pH values up to 7.6, and an ionic strength of 0.2. The effects of acetate, formate, and phosphate buffers as well as ionic strength on the observed rate constants were investigated. An interesting nonlinear dependency of the k_{obs} with buffer concentration was noted. The velocity constants declined with increasing hydrogen-ion concentration; the log k–pH profile and rate law are given along with other relevant data.

Keyphrases □ Solvolysis—mazindol, a substituted imidazoline, pH values up to 7.6 □ Mazindol—solvolysis in aqueous solutions, pH up to 7.6

The chemical stability of organic medicinal agents from the viewpoint of the finished dosage forms and the kinetic aspects of the pertinent drugs are of great interest.

The transformation of the nonphenethylamine anorexigenic, mazindol[1] [5-(*p*-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol] (I), to its hydrolysis product, 2-(2-aminoethyl)-3-(*p*-cholorophenyl)-3-hydroxyphthalimidine (II), was practically quantitative under the conditions employed as monitored by spectrophotometric and TLC methods. The process is somewhat analogous to the hydrolysis of 1,3-diphenyl-2-imidazolinium chloride recently reported (1).

EXPERIMENTAL

Kinetic Studies—A stock solution was prepared by dissolving 90 mg (3.16×10^{-4} mole) of I in 5 ml of 0.1 *N* HCl, and water was added to 50 ml. Two-milliliter aliquots were added to 200-ml volumetric flasks, equilibrated at various temperatures, containing 198 ml of the acidic or buffer solution. Ten-milliliter samples were withdrawn periodically and scanned[2] from 210 to 350 nm. The absorbance readings at 272 ± 1 nm were used to evaluate the rate of conversion of I to II.

A stock solution of II containing 95.5 mg (3.16×10^{-4} mole) in 50 ml of 0.01 *N* HCl was prepared. Two-milliliter aliquots were added to 198 ml of acidic or buffer solution previously equilibrated at various temperatures. Samples (10 ml) were taken periodically, and their UV spectra were scanned from 210 to 350 nm to monitor possible degradation of II.

Preparation of II from I—Two grams of I was refluxed in 100 ml of 48% aqueous ethanol for 2 hr until the solution became almost clear. The solvent was removed *in vacuo*. The resultant white solid dissolved in 50 ml of benzene with heating. Petroleum ether was added until the point of slight turbidity, and the compound was allowed to crystallize overnight at room temperature. The yield after two recrystallizations was 1.5 g (71%) of II, mp 170–171°.

Determination of pKa Values—A stock solution of 6.3×10^{-3} *M* I was prepared and added to 0.01 *M* tromethamine buffers (pH 7.8, 8.0, 8.2, and 8.4) along with 0.1 *N* HCl and 0.09 *N* NaOH to give a final concentration of 6.3×10^{-5} *M*. The samples were quickly read[2] at 272 nm. The pKa was calculated to be 8.55 ± 0.05 by the procedure of Albert and Sergeant (2).

Compound II (151.4 mg, 0.005 *M*) was dissolved in 95 ml of boiled water with the aid of 5 ml of 0.1 *N* HCl. The solution was titrated with 0.5-ml increments of 0.1 *N* KOH, giving a pKa value of 8.53 ± 0.05 at 25° (2).

[1] Sandoz Pharmaceuticals, East Hanover, N.J.

[2] Cary model 14 recording spectrophotometer.