# Drugs as Solubilizing Agents

## Solubilization of Acids by Water-Soluble Amine Salts

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**The solubilization of several aliphatic and aromatic acids in aqueous solutions of cyclopentamine hydrochloride, ephedrine sulfate, and propoxyphene hydrochloride has been investigated. At low concentrations of the amine salts, a limited solubilizing effect was observed, but as the concentration was increased, the pattern changed sharply so that the ratio of the acid in solution to the salt became many times greater than at lower concentrations. The degree of solubilization and the temperature range in which it occurs are dependent upon the structure of both the amine and the acid. The ratios of the moles of acid per mole of the amine salt follow the Arrhenius relationship to a maximum value which does not change with further elevation of the temperature.**

MANY MATERIALS have been incorporated into pharmaceutical preparations to increase the solubility of other ingredients. An extensive literature has been built up which covers the solubilization of materials in aqueous solutions using compounds designed specifically for that purpose (1–4). A number of materials, other than solvents, are known to increase the water solubility of other ingredients in the formulation in which this action is incidental to their therapeutic effect (5, 6). Many pharmacologically active amines have carbon chains of sufficient length to be effective solubilizing agents within the concentrations of the aqueous solutions which their acid salts are capable of forming. The solubilization of aromatic acids in amphetamine sulfate solutions has previously been described by Lippmann and Mattocks (7). Other effects due to solubilization by amine salts can be observed in dry products which are able to attract moisture from their surroundings. For example, the rate of decomposition of acetylsalicylic acid is accelerated because more acid is dissolved in the amine salt solutions which may be formed in the product than would be dissolved in an equal amount of water. This study covers observations made on the change in water solubility of a variety of organic acids in aqueous solutions of ephedrine sulfate, cyclopentamine[1] hydrochloride, and propoxyphene hydrochloride.[2]

### EXPERIMENTAL

**Solubility of Acids in Amine Salt Solutions.**—Solutions of the amine salts under study were prepared in the range from 0 to 4.5 Gm./10 ml. of the solution at 25°. Densities of the solutions were also determined at 25°. The solutions were then saturated with the acid by shaking an excess of the acid with the solution for 4 to 24 hr. in constant-temperature rooms controlled to ±1°. These mixtures were then rapidly filtered through medium porosity sintered-glass filters in the constant-temperature room. A sample of this solution was weighed and diluted to at least twice its volume with water, and then 0.25 ml. of diluted sulfuric acid was added. This mixture was then extracted three times with a volume of ether equal to about twice that of the aqueous phase. The combined ether extracts were washed with 10 ml. of water which in turn was re-extracted with 20 ml. of ether. To the combined ether extracts were added 2 drops of phenolphthalein T.S. and an excess of 0.1 *N* sodium hydroxide solution. The ether was removed *in vacuo* or on a steam bath. The excess base was then back titrated with 0.1 *N* hydrochloric acid. The weight of the acid in the sample was calculated, and from the density information the amount of the amine salt and water were determined. The molal concentration of the acid was then plotted against the molal concentration of the amine salt.

An alternative method for the determination of solubility was used for liquids and for the fatty acids at higher temperatures. A solution of the amine salt was equilibrated in a water bath controlled to ±0.1° by a mercury thermoregulator. The acid was added until an excess remained undissolved. The cloudy mixtures were then slowly back titrated with small amounts of the amine salt solution until the mixtures just became clear. A sample of each solution was then weighed in a tared glass-stoppered bottle and the acid in the sample determined as previously described. The pH of the solutions saturated at 25° and below were determined with a Beckman model G pH meter.

**Propoxyphene Salicylate–Salicylic Acid Complex.**—It was observed that in solutions saturated with salicylic acid containing between 1.75 and 3.5 Gm. of propoxyphene hydrochloride in 10 ml. of solution that a crystalline precipitate was deposited after the solution had been filtered. This material was isolated and found to have a melting point of 113–115°. Titration showed that the ratio of salicylic acid to propoxyphene was 2 moles to 1. No chlorine was present. An alternate method of preparation was to melt 1 molecular equivalent of propoxyphene with 2 molecular equivalents of salicylic acid. The resulting melt crystallized and was recrystallized from methanol.

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[1] Marketed as Clopane by Eli Lilly and Co.
[2] Marketed as Darvon by Eli Lilly and Co.

*Anal.*—Calcd. for $C_{36}H_{41}NO_8$: C, 70.22; H, 6.71; N, 2.28. Found: C, 70.01; H, 6.28; N, 2.30.

**Levopropoxyphene Salicylate–Salicylic Acid Complex.**—Three and four-tenths grams of levopropoxyphene[3] was melted with 2.76 Gm. of salicylic acid on a steam bath. The resulting oil crystallized and was then recrystallized from methanol to give 4.2 Gm. of crystals melting at 114–116°. Titration indicated that there was 1 mole of levopropoxyphene present for 2 moles of salicylic acid.

*Anal.*—Calcd. for $C_{36}H_{41}NO_8$: C, 70.22; H, 6.71; N, 2.28. Found: C, 70.46; H, 6.84; N, 2.00.

**Hydrolysis of Acetylsalicylic Acid in Propoxyphene Hydrochloride Solution.**—The acetylsalicylic acid was determined by a modification of the U.S.P. XVI (8) assays for acetylsalicylic acid tablets. Five milliliters of propoxyphene hydrochloride solution at each of several concentrations was placed in screw-capped bottles containing 400 mg. of acetylsalicylic acid and stored at 25°. Blanks containing only the propoxyphene hydrochloride solutions were also prepared. The samples were assayed periodically over a 50-day period to determine the amount of acetylsalicylic acid present. Following the addition of 10 ml. of alcohol to dissolve the undissolved acid, the samples were immediately titrated with 0.5 *N* sodium hydroxide solution to pH 9 using a glass electrode pH meter. Then 35 ml. of 0.1 *N* sodium hydroxide solution was added, and the mixture was heated on a steam bath for 15 min. The sample was allowed to cool and was then back titrated to pH 9.0 with 0.1 *N* hydrochloric acid. The blank was treated in the same way, and the titration values were corrected for the amount of sodium hydroxide required to saponify the acid blank. Each milliliter of 0.1 *N* sodium hydroxide required to saponify the acid is equivalent to 18.01 mg. of acetylsalicylic acid. During the titration, propoxyphene base precipitated and crystallized. It collected on the glass electrodes but did not otherwise interfere with the assay.

**Materials.**—U.S.P. grade propoxyphene hydrochloride, ephedrine sulfate, acetylsalicylic acid, benzoic acid, and salicylic acid were used. Commercial grade cyclopentamine hydrochloride was washed with ether and then dried *in vacuo*. The following acids were also used: cinnamic acid, recrystallized from ether, m.p. 133–134°; hydrocinnamic acid, recrystallized from *n*-hexane, m.p. 47–48°; cyclohexanecarboxylic acid, m.p. 29.5–30.5°; sorbic acid[4]; decanoic acid, m.p. 31–32.5°; neut. equiv. 173.7; lauric acid, m.p. 42–43°, neut. equiv. 200.9; myristic acid, m.p. 52–53°, neut. equiv. 228.3; palmitic acid, m.p. 61–62°, neut. equiv. 256.4; stearic acid, m.p. 68–69°, neut. equiv. 283.65; and caproic acid, neut. equiv. 117.4.

The straight-chain amine hydrochlorides were prepared by adding with stirring a solution of the amine in dry ether below the surface of a 10% solution of dry hydrogen chloride in ether. The resulting salt was collected, washed with dry ether, and dried under reduced pressure over a desiccant.

## RESULTS AND DISCUSSION

**Effect of the Solubilizing Agent on Solubility.**—Although the solubility data on a three-component system may be expressed in several ways, one of the clearest methods is to show the effect of the concentration of the solubilizing agent (amine salt) upon the solubility of the solute (acid) in a constant amount of water. This may be done by using molal concentrations. Solubilization of a very modest sort occurs at the lower concentrations of the salts. As the concentration of the amine salt is increased, a change in the properties of the solution suddenly occurs and the acid becomes much more soluble. The concentration at which this change occurs will be referred to as the solute critical micelle concentration (SCMC), and it may be quite different from the critical micelle concentration obtained on solutions which do not contain a third component (9). In order to define the SCMC, reference must be made to the temperature and the nature of the third component. The solubilities of the acids in the amine salt solutions can be expressed by two relationships, one for that above the SCMC and another for that below the SCMC:

$$K = \frac{\Delta C_A}{\Delta C_S} \qquad K' = \frac{\Delta C_A}{\Delta C_{S'}}$$

where $K$ is the ratio of the change in concentration of the acid, $\Delta C_A$, to the change in the concentration of the amine salt below the SCMC, $\Delta C_S$. $K'$ is the ratio of the change in the concentration of the acid, $\Delta C_A$, to the change in the concentration of the amine salt above the SCMC, $\Delta C_{S'}$. The behavior of these solutions of amine salts is similar to that of a system of two immiscible solvents. The micelle interior behaves in the same way as an organic phase. When the amount of water is constant and there is an excess of the third component, the amount of the third component dissolved in the water-immiscible

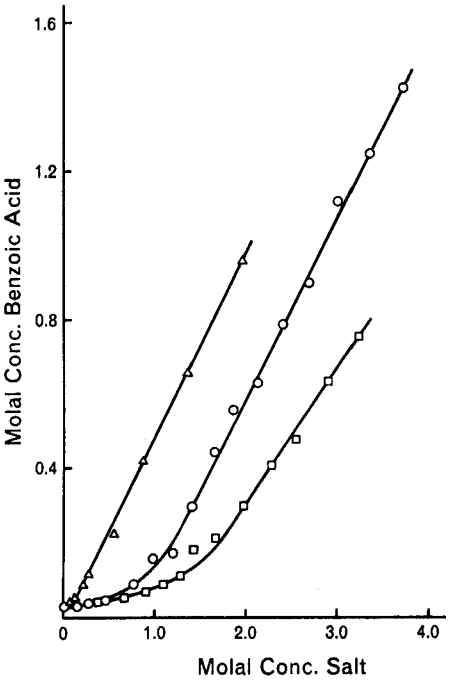



Fig. 1.—Solubility of benzoic acid at 25°C. *in* aqueous solutions of amine salts. Key: △, *d*-propoxyphene HCl; ○, cyclopentamine HCl; □, ephedrine sulfate.

[3] Marketed as Novrad by Eli Lilly and Co.
[4] Marketed as Sorbistat by Chas. Pfizer and Co., Inc

solvent or the micelle is proportional to the amount of solvent or micelle present. The amount of acid extracted into the micelle can then be expressed as the increase in its solubility in the system over that at the SCMC. An example of this behavior is the solubility of benzoic acid in aqueous solutions of three amine salts at 25° which is illustrated in Fig. 1.

In order to gain a perspective into what the solubilizing effects of these salts are in relationship to very simple structures, the solubility of benzoic acid at 25° in solutions of straight-chain amine hydrochlorides of even-numbered carbon chain lengths from 4 to 12 are given in Fig. 2. It can be seen that ephedrine sulfate (I) acts somewhat less effectively than *n*-hexylamine hydrochloride on a mole-to-mole basis. Cyclopentamine hydrochloride (II) falls between *n*-hexylamine and *n*-octylamine hydrochloride, and propoxyphene hydrochloride (III) falls between *n*-octylamine and *n*-decylamine hydrochloride in solubilizing effect. Examination of the structures of these amines reveals that their solubilizing effects can be correlated with the length of carbon chain to which the amino group is terminally attached. It has been previously reported that the phenyl group is equivalent to a chain of about 3.5 carbon atoms (10). I contains phenyl and two carbons, 5.5; II contains seven carbon atoms including the ring; III can be calculated to be either 7.5, 7.0, or 6.5, but the combined effect is probably greater since the phenyl, benzyl, and propionoxy groups are all attached to the carbon $\gamma$ to the amino group. The position of attachment of the polar group in the carbon chain plays a role in this solubilizing effect. Winsor has indicated that in the tetradecane sodium sulfates, as the sulfate was moved toward the middle of the chain, the CMC rises (11). Little effect on solubilization has been found to result by changing from one anion to another as long as the resulting

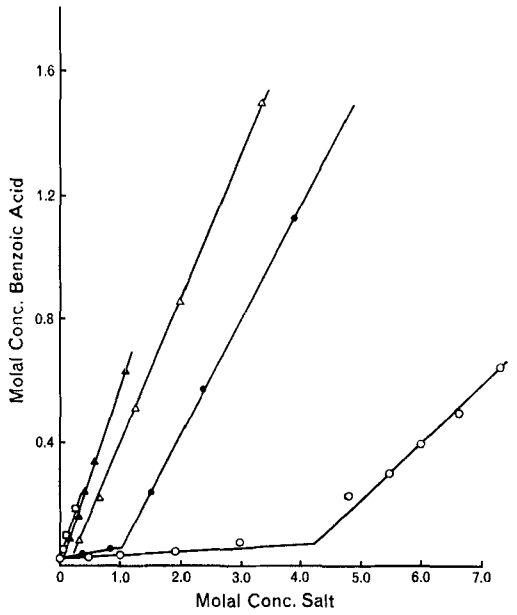
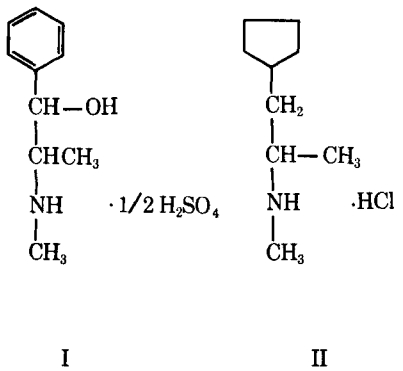



Fig. 2.—Solubility of benzoic acid at 25°C. in aqueous solutions of straight-chain amine salts. Key: ○, *n*-butylamine HCl; ●, *n*-hexylamine HCl; △, *n*-octylamine HCl; ▲, *n*-decylamine HCl; □, *n*-dodecylamine HCl.

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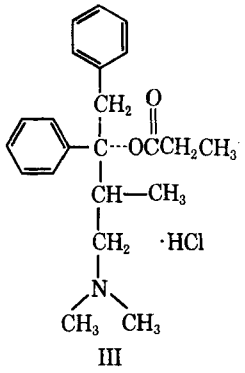



III

TABLE I.—SOLUBILIZATION OF ACIDS IN AMINE SALT SOLUTIONS AT 25°C.

| | *K* | *K'* | Intercept Molal Concn. Salt | Acid |
|---|---|---|---|---|
| **Ephedrine Sulfate** | | | | |
| Sorbic acid | 0.009 | 0.070 | 1.55 | 0.034 |
| Caproic acid | 0.03 | 2.75 | 1.06 | 0.098 |
| Cinnamic acid | 0.0075 | 0.135 | 1.60 | 0.015 |
| Hydrocinnamic acid | 0.027 | 2.02 | 1.03 | 0.08 |
| Benzoic acid | 0.0575 | 0.36 | 1.45 | 0.11 |
| Cyclohexane carboxylic acid | 0.0375 | 2.02 | 1.00 | 0.09 |
| Salicylic acid | 0.049 | 0.36 | 1.40 | 0.095 |
| Acetylsalicylic acid | 0.0475 | 0.114 | 1.38 | 0.090 |
| CMC (freezing point depression) | | | 1.44 | |
| **Cyclopentamine Hydrochloride** | | | | |
| Salicylic acid | 0.052 | 0.41 | 1.08 | 0.074 |
| Acetylsalicylic acid | 0.042 | 0.19 | 1.20 | 0.07 |
| Benzoic acid | 0.062 | 0.50 | 0.97 | 0.068 |
| CMC (freezing point depression) | | | 1.14 | |
| **Propoxyphene Hydrochloride** | | | | |
| Acetylsalicylic acid | 0.16 | 0.265 | 0.31 | 0.074 |
| Benzoic acid | 0.14 | 0.50 | 0.14 | 0.0475 |
| CMC (freezing point depression) | | | 0.14 | |

salts are studied at the same molal concentrations (12).

**Effect of the Solute on Solubility.**—A correlation can be drawn between the structure of the acid and its solubility in the amine salt solutions. $K$ and $K'$ values for a variety of acids with the amine salt solutions and the intercepts of the two linear portions of the solubility curves are listed in Table I.

The aromatic acids and sorbic acid (2,4-hexadienoic acid) which have double bonds or aromatic systems conjugated with the carboxyl group and which have high melting points are much less soluble than the corresponding aliphatic acids. This is in contrast to a generalization that unsaturated compounds are more soluble than the corresponding saturated compounds (4). However, it is in agreement with a report that compounds with higher melting points are less soluble than lower melting compounds of closely related structures and molecular weights (13). The explanation presented for this is that more energy is required for solubilization because the latent heat of fusion of the crystal opposes a change of state.

Of particular interest are three pairs of compounds which are identical except for the amount of saturation. At higher concentrations the ratio of the solubility of caproic acid in ephedrine sulfate solution is 39 times that of sorbic acid (Fig. 3). The solubility ratio of hydrocinnamic acid is 15 times that of cinnamic acid, and the solubility ratio of cyclohexane carboxylic acid to benzoic acid is 5.6 at 25°.

The homologous series of fatty acids containing an even number of straight chain carbon atoms from 10 to 18 were studied to determine the effect of chain length upon the solubility of the acids in cyclo-

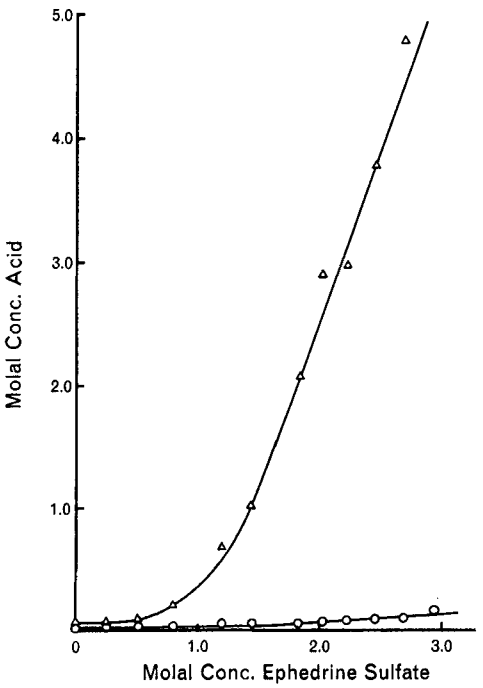



Fig. 3.—Solubility of acids at 25°C. in aqueous ephedrine sulfate solutions. Key: ○, sorbic acid; △, caproic acid.

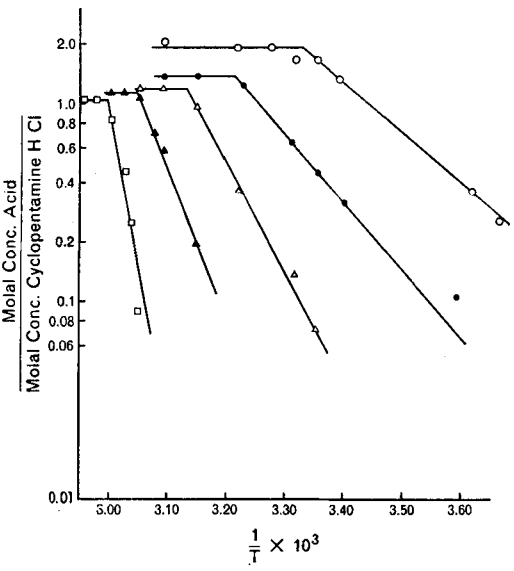



Fig. 4.—Semilog plot of $K'$, the moles of acid dissolved per mole of cyclopentamine hydrochloride above the SCMC, *vs.* the reciprocal of the absolute temperature. Key: ○, decanoic acid; ●, lauric acid; △, myristic acid; ▲, palmitic acid; □, stearic acid.

TABLE II.—MAXIMUM SOLUBILIZATION OF FATTY ACIDS IN CYCLOPENTAMINE HYDROCHLORIDE SOLUTION

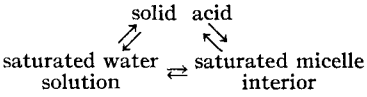
| Acid | Temp. of Max. Solubilization, °C. | Max. Concn., $M/M$ | Carbon Atoms, No. | Measure of Mol. Vol. |
|---|---|---|---|---|
| Decanoic | 27 | 1.93 | 10 | 19.3 |
| Lauric | 38 | 1.39 | 12 | 16.7 |
| Myristic | 46 | 1.19 | 14 | 16.7 |
| Palmitic | 55 | 1.14 | 16 | 18.3 |
| Stearic | 61 | 1.04 | 18 | 18.7 |

pentamine hydrochloride solutions. Only decanoic, lauric, and myristic acids had measurable concentrations at 25°. A more complete picture was gained when the solubilities were determined at several temperatures. As the temperatures of the solutions were increased, a maximum ratio for the molal concentration of the acid to the amine salt was obtained. These molal ratios were plotted on a semilogarithmic scale against the reciprocals of the absolute temperature (Fig. 4). The Ahrrenius relationship exists until the maximum ratio is reached. The maximum ratios of the acid to amine salt necessary to saturate the solution are listed in Table II. Also reported are measures of molecular volume of the amine salt obtained by multiplying the chain length of the acid by the maximum molal concentration of the acid solubilized by 1 mole of the amine salt. These values are reasonably constant which suggests that there is a maximum amount of hydrocarbon which can be solubilized by the amine salt. The temperatures at which the solubility plateaus begin are from 4 to 7° below the melting points of the acids. It has been suggested that the solubilization of crystals is more difficult than that of liquids of approximately the same molecular weight because the latent heat of

fusion opposes the change of state (13). The change in solubility which occurs as the temperature changes is a measure of the energy necessary to bring the acid to a state where a change from the crystalline to the liquid state is possible. Once the acid is in the liquid state, no further change in the solubility is observed in the system.

The point at which the linear portion of the solubility curve, such as in Figs. 1 and 2, intercepts the base line (no acid in solutions) is an approximation of the SCMC determined by the measurement of a third component in the system. Actually, the SCMC should be at the intercept of the two linear portions of the solubility curve, but because of the very slight solubility of the fatty acids in water, the point of interception with the base line serves as a close approximation. As the ratio of the acid solubilized to the amount of amine salt increases with temperature, there is a corresponding decrease in the value obtained for the SCMC. These data are summarized in Fig. 5, and a minimum SCMC is obtained which corresponds to the appearance of the maximum solubility ratio in Fig. 4.

The mechanism of solubilization which seems to fit these data best is that of the pseudo two-phase system (3) in which both the water and the micelle interior are saturated by mixing in the presence of excess acid.




Since the fatty acids are of such limited solubility in water, all the soluble acid can be considered to be in the micelle interior. The apparent heat of solubilization, $\Delta H$, can then be approximated from the following equation:

$$\log\left[\frac{K'_2}{K'_1}\right] = \frac{\Delta H}{2.303\ R}\left[\frac{T_2 - T_1}{T_2 T_1}\right]$$

$K'_1$ and $K'_2$ are the amounts of acid solubilized by 1 mole of the amine salt at temperature $T_1$ and $T_2$. The calculated values for the apparent heat of solubilization are given in Table III. The apparent heat of solubilization in the plateau region would be very close to zero since little or no increase in solubilization occurs in this region as the temperature is raised. The acids with the shorter chain lengths have lower apparent heats of solubilization than those with longer chains. They also show less change in molal solubility with changes in temperature.

TABLE III.—APPARENT HEAT OF SOLUBILIZATION

| Acid | Apparent Heat of Solubilization, Kcal./mole |
|---|---|
| Decanoic | 13.97 |
| Lauric | 15.3 |
| Myristic | 24.2 |
| Palmitic | 34.2 |
| Stearic | 64.3 |

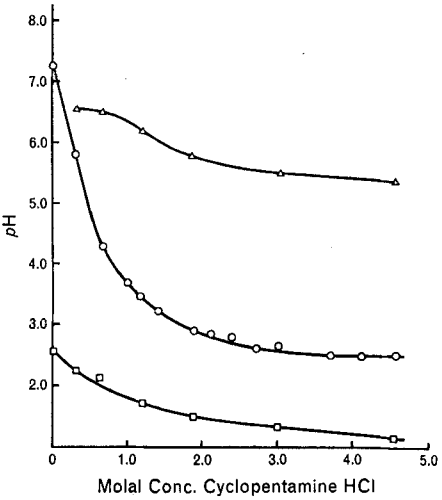



Fig. 6.—Change in pH with concentration of cyclopentamine hydrochloride. Key: △, cyclopentamine hydrochloride alone; ○, lauric acid; □, salicylic acid.

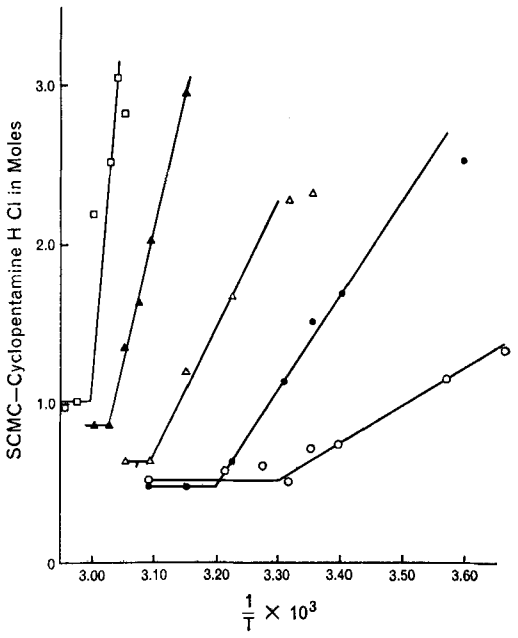



Fig. 5.—Plot of SCMC, molal concentration of cyclopentamine hydrochloride, *vs.* the reciprocal of absolute temperature. Key: ○, decanoic acid; ●, lauric acid; △, myristic acid; ▲, palmitic acid; □, stearic acid.

**pH Changes Due to Solubilization of Acids.**—The apparent pH of saturated solutions of the acids in the amine salt solutions were determined, and examples are shown in Fig. 6. The pH of the solutions drop well below that of a saturated solution of the acid in water. Lauric acid solutions reach pH 2.5 at the highest concentration. Solutions of acetic acid in water equal to the molal concentration of the lauric acid were about 0.2 pH units below that for the lauric acid solutions. This confirms that the increased concentration of the lauric acid is sufficient to produce the pH drop. Salicylic acid, the strongest acid used in this study, lowered the pH to 1.2 at its highest amine salt-solubilized concentration com-

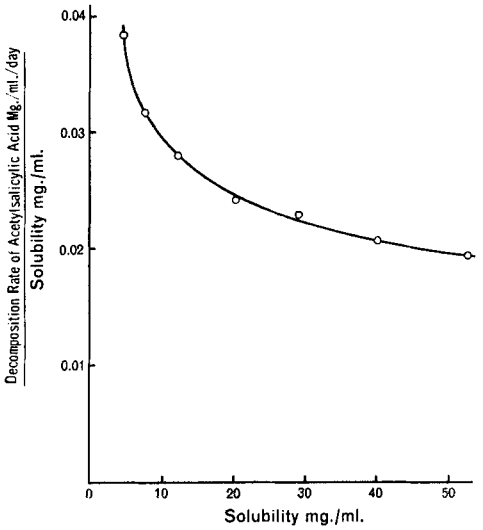



Fig. 7.—Rate of hydrolysis of dissolved acetylsalicylic acid *vs.* the solubility of acetylsalicylic acid in propoxyphene hydrochloride solution at 25°C.

pared with 2.6 for the saturated solution in water. The fact that the pH continues to drop with an increase in concentration of the solubilized acid indicates that dissociation of the additional acid must occur.

**Propoxyphene Salicylate–Salicylic Acid Complexes.**—The formation of a crystalline complex was observed in solutions of propoxyphene hydrochloride which had been saturated with salicylic acid. The conditions were such that the weaker acid, salicylic, was able to displace the stronger hydrochloric acid. The complex was also prepared by melting 2 mole equivalents of salicylic acid with 1 equivalent of propoxyphene. The complex of levopropoxyphene was also prepared. No crystalline complexes of any of the other acids and amines studied were observed. There is no evidence that complexes of this type are responsible for the increased solubility of organic acids in aqueous solutions of amine salts.

**Hydrolysis of Acetylsalicylic Acid in Propoxyphene Hydrochloride Solutions.**—The amount of hydrolysis of acetylsalicylic acid dissolved and suspended in propoxyphene hydrochloride solutions was measured by direct titration. From these data, the hydrolysis rates for each concentration of the amine salt were determined. Because there was always an excess of acetylsalicylic acid suspended in the saturated solutions, the reaction rates were zero order. Figure 7 is a plot of the decomposition rate per ml. divided by the solubility of acetylsalicylic acid per ml. of solution. Although more acetylsalicylic acid is hydrolyzed in solutions of higher concentrations of propoxyphene hydrochloride because of its greater solubility, the hydrolysis rate of acetylsalicylic acid in solution decreased as the concentration of the amine salt increased. This could result from the lower pH of the more concentrated solutions (14) or from the stabilizing effect observed by Nogami and co-workers (15). In aqueous solutions of acetylsalicylic acid in surface-active agents, the increased stability was attributed to the extraction of acetylsalicylic acid into the lipophilic micelle interior. No data were obtained in this study which permit a choice to be made between these two mechanisms if they are not both involved.

In dry unit dosage forms, such as tablets and capsules, the solubilization and subsequent hydrolysis of acetylsalicylic acid are dependent upon the ease with which the dosage form can attract and hold moisture. The source of water may be from one of the ingredients of the preparation itself, such as starch, the gelatin capsule body, or tablet coating solutions, or from the surrounding atmosphere. Whenever a small amount of moisture is taken up by the pharmaceutical dosage form, highly concentrated solutions of the amine salt may be formed. These are capable of dissolving many times the amount of acetylsalicylic acid that could be dissolved in an equivalent amount of water. The maintenance of an atmosphere of very low relative humidity will, however, minimize the hydrolysis rate of acetylsalicylic acid when it is in the presence of water-soluble amine salts.

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