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Solubility of Sodium Salicylate in Mixed Solvent Systems

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Abstract □ The solubility of sodium salicylate was determined in aqueous mixtures of dioxane, acetone, 1-propanol, ethanol, and methanol. The solubility had fair parallelism to dielectric constants over a wide range of concentration, indicating adherence to the coulomb relationship. The solubility curves for sodium salicylate are examined from a suppressive dissociative point of view, insofar as ionization may be taking place without complete dissociation. Comparison of the solubility curves for an acid and its sodium salt is considered. The possibility that uni-univalent electrolytes in solutions below a dielectric constant of 30 are completely associated is shown for several systems in plots of various concentration notations. Adherence of the predicted linearity from the Born equation for these systems is discussed. However, the theoretical ionic radius is found to be about twice the expected value.

Keyphrases □ Salicylate, sodium, solubility—mixed solvent systems □ Alcohols, acetone, dioxane—water mixtures—sodium salicylate solubility □ Solubility, sodium salicylate—dielectric constant relationship □ Ion, radii—sodium, salicylate

The solubility of chemical compounds described as salts are normally thought of as having maximum solubility in water relative to other less polar solvents such as alcohols. The direction of decreasing solubility with decreasing polarity is generally based on the charge-separating ability of the solvent or the dielectric constant.

It is of interest to consider the solubility changes that occur as a function of the dielectric constant for a typical, useful pharmaceutical such as sodium salicylate. This pharmaceutical was also chosen because data are

available (1) on salicylic acid in the same solvent systems and a comparison could be made for an acid and its sodium salt.

The Born equation (2), which deals with the relationship between solubility and the reciprocal of the dielectric constant, was also tested in this study.

The diminution of solubility of a salt with a concomitant decrease in dielectric constant obviously would be related to the degree of dissociation of the particular salt and might be related to the water content of these binary mixtures.

EXPERIMENTAL

Reagents—The reagents used were methanol¹, 1-propanol¹, 1-pentanol², 1-octanol², 1-butanol³, 1-decanol⁴, ethanol⁵, and acetone⁶. Deionized water was used for all binary mixtures prepared. The sodium salicylate⁷ was USP grade. Dioxane⁸ (*p*-dioxane), stabilized, was also used in these studies.

The purity of the solvents was tested by the following procedure. The refractive indexes of each solvent were determined initially and throughout their use with a Bausch and Lomb Abbe-3 refractometer at 25°. The results are given in Table I.

The instrument was checked against 99 mole % free benzene (Fisher certified reagent), and the experimental value of 1.4983 was obtained at 25° versus the literature value of 1.498 at 25°.

¹ Fisher Certified, Fisher Scientific Co.

² Baker Analyzed, J. T. Baker Co., Phillipsburg, N. J.

³ Eastman Kodak No. 50, Eastman Kodak, Rochester, N. Y.

⁴ No. 5189, Matheson, Coleman & Bell, East Rutherford, N. J.

⁵ U. S. Industrial Chemical Corp.

⁶ Analytical Reagent, No. 2240, Mallinckrodt.

⁷ USP, J. T. Baker Co., Phillipsburg, N. J.

⁸ No. C 608258, Amend Drug and Chemical Co., Inc.

Table I—Refractive Index of Solvents Used

Solvent	Literature ^a	Determined	Percent Deviation
Methanol	1.326	1.3288	0.2
Ethanol	1.359	1.3640	0.4
1-Propanol	1.383	1.3840	0.1
1-Butanol	1.397	1.4025	0.4
1-Hexanol	1.416	1.4215	0.4
1-Octanol	1.427	1.4320	0.4
1-Decanol	1.4366 ^b	1.4410	0.3
p-Dioxane	1.4224 ^b	1.4024	0.1

^a "Handbook of Chemistry and Physics," 48th ed., The Chemical Rubber Co., Cleveland, Ohio, 1967. ^b Values at 20° from *a*.

Table II—Dielectric Constant of Solvents Used

Solvent	Literature ^a	Determined	Percent Water
Methanol	32.63	32.7	0.2
Ethanol	24.30	24.4	0.4
1-Propanol	20.1	20.2	0.5
1-Butanol	17.1	17.2	0.6
1-Hexanol	13.3	13.4	0.8
1-Octanol	9.86 ^b	9.9	0.4
1-Decanol	7.93 ^b	8.0	0.8
p-Dioxane	2.21	2.2	0.4

^a "Table of Dielectric Constants of Pure Liquids," U. S. Dept. of Commerce, NBS Circular 514. ^b Calculated from literature value at 20° and temperature coefficients to adjust value to 25°.

Further, a sample of each solvent was tested initially and throughout its use by measuring its dielectric constant value on a Sargent model V oscillometer. Deviations from literature values of the dielectric constant were considered to be due to the water content. The results are given in Table II.

Procedure—Solubilities were determined by either a spectrophotometric or gravimetric determination in a manner previously given (3). Spectrophotometric⁹ determinations were done at 231 nm. Densities were determined by weighing the withdrawn samples previous to drying. In the case of the pure solvent scan, for the higher membered alcohols, the solubility was determined after 24-hr. equilibration in a 25° bath. Twenty-four hours was chosen since the equilibrium value of solubility occurred in about 10 hr. for the slowest rate in 1-decanol.

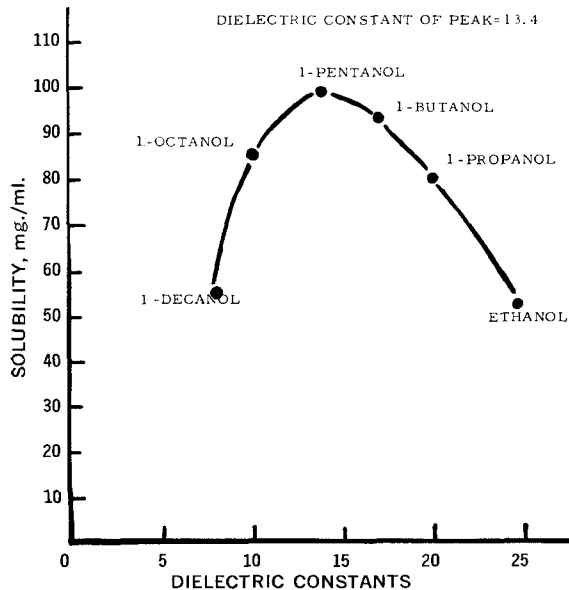


Figure 1—Solubility of sodium salicylate in milligrams/milliliter at 25° versus the dielectric constants of pure alcohols.

⁹ Cary model 16 spectrophotometer.

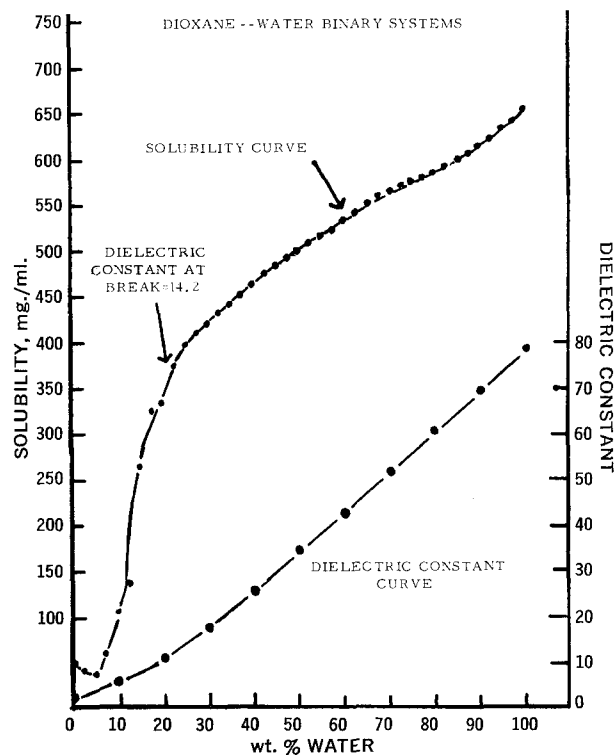


Figure 2—Solubility of sodium salicylate in milligrams/milliliter versus the percent w/w water in dioxane-water mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

In the cases of alcohol-water, dioxane-water, and acetone-water systems, the solubility was tested at various concentrations, especially high nonpolar components, at 15-min. intervals for several

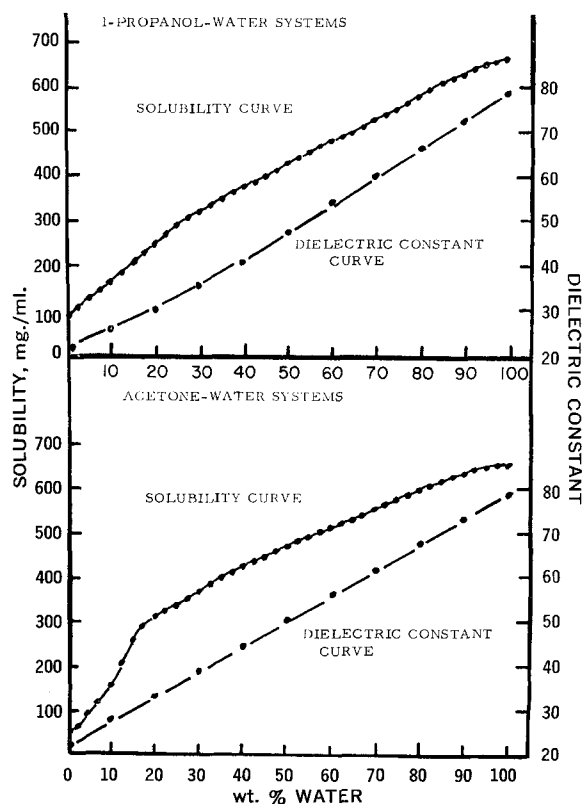


Figure 3—Solubility of sodium salicylate in milligrams/milliliter at 25° versus the percent w/w water for the acetone-water and 1-propanol-water binary mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

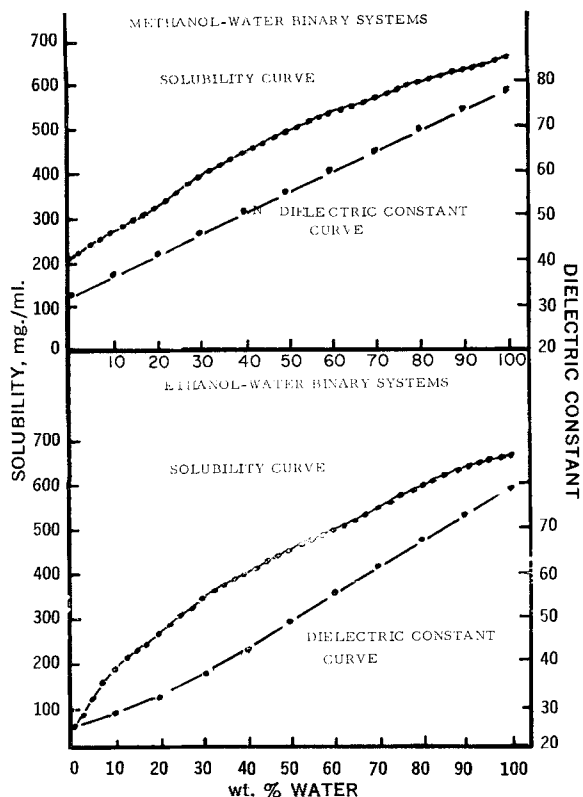


Figure 4—Solubility of sodium salicylate in milligrams/milliliter at 25° versus the percent w/w water for the ethanol-water and methanol-water binary systems. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

hours. In no case did asymptotic solubility values occur after 2 hr. Since solutions of sodium salicylate are known to be light sensitive, the experimentally determined equilibrium solubility occurred in

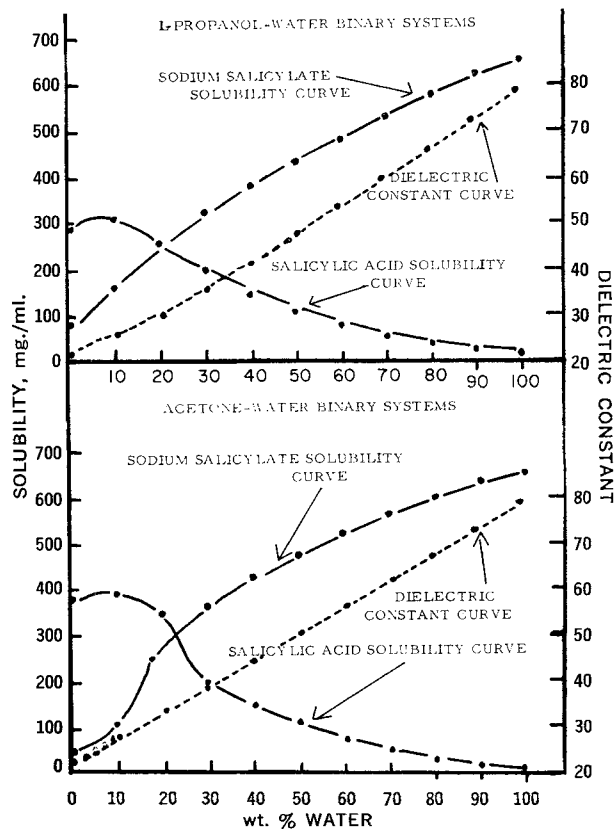


Figure 6—Solubility of salicylic acid and sodium salicylate in milligrams/milliliter at 25° for acetone-water and 1-propanol-water mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

about 2 hr., and 4 hr. was chosen as the end-point. No discoloration of these solutions was noted during the procedure.

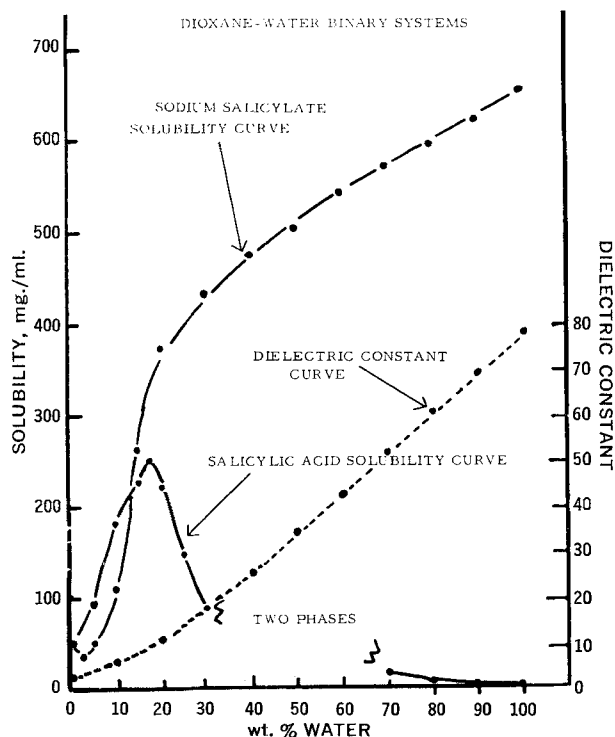


Figure 5—Solubility of both salicylic acid and sodium salicylate in milligrams/milliliter at 25° for dioxane-water mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

RESULTS AND DISCUSSION

The solubility of sodium salicylate was initially determined in a series of pure alcohols and is shown in Fig. 1. The solubility is plotted in milligrams/milliliter versus the dielectric constants of the pure solvents. Sodium salicylate dissolves to the greatest extent in 1-pentanol, producing a peak in this pure solvent scan. The dielectric requirement over this limited range of alcohols is equal to the dielectric constant of 1-pentanol or 13.9, which is strikingly similar to that observed for salicylic acid (1) which was found to have a value of about 15. This could indicate that at this relatively low value of the dielectric constant, sodium salicylate is essentially undissociated and acts as a neutral molecule or nonelectrolyte. It has been stated (4) that in media of dielectric constants below 60, divalent ions will be associated; and below a dielectric constant of 30, univalent ions will be undissociated. It may be assumed that a uni-univalent salt would then behave as a nonelectrolyte possessing semipolar character and inherent polarity.

The solubility of sodium salicylate was also determined in binary mixtures of water with dioxane, acetone, 1-propanol, ethanol, and methanol. The data obtained are plotted in Figs. 2-4 as the solubility in milligrams/milliliter versus the weight percent of water. The dielectric constants of the binary mixtures are also shown in these figures, being drawn below the solubility curve. In the case of dioxane, a fair degree of parallelism is seen to exist between dielectric constants and solubility over the range of about 25% w/w water to pure water. The solubility curve deviates at about 25% w/w water, possessing a dielectric constant value of 14; again there is good agreement with the value of 15 for salicylic acid. In the case of the alcoholic systems, 1-propanol, ethanol, and methanol, a fair degree of parallelism is observed for the solubility curves. Only in the case of acetone-water mixtures does a deviation seem to exist at about a 20% w/w concentration of water. This occurs at a dielectric constant value of about 31, which supports the pre-

vious contention of complete association at a dielectric constant value of 30.

A comparison of the solubility curves observed for a weak acid and its sodium salt was of interest. Thus, the solubility data obtained are replotted in Figs. 5-7 as the solubility in milligrams/milliliter versus the weight percent of water. Included in these figures is the solubility of salicylic acid in the same solvent mixtures obtained previously (1).

In the case of the dioxane-water mixtures shown in Fig. 5, the solubility profile for sodium salicylate gives a sharp change of slope at approximately the same point as the peak observed for salicylic acid in the same mixture. Since the solubility profile for sodium salicylate is a repressive ionization curve, the "salt" acts as if it was completely associated at low dielectric constant values. The decrease in dielectric constants with increasing nonpolar solvent concentration causes the solubility to decrease, since the work required to separate the charges (ionization \rightleftharpoons dissociation) becomes larger.

In the case of acetone-water mixtures, the solubility of the salt continuously decreases to the lowest value in pure acetone, whereas the salicylic acid shows a peak at a dielectric constant value of 25. However, after about 20% w/w water, there seems to be a fair degree of symmetry for these solubility curves about the line drawn through about 310 mg./ml.

Thus, the approximate solubility of salicylic acid and sodium salicylate is a fairly constant amount below and above this line at each concentration increment. The decrease in solubility of the sodium salt is due to the decrease in the charge-separating ability of the solvent mixture, whereas the increase in solubility of salicylic acid is due to the more favorable semipolar environment produced by the solvent blends.

With the three alcohols studied, although there is no line of symmetry between the solubility curves, the aforementioned statement still obtains. In the case of 1-propanol, a peak is observed for salicylic acid at a dielectric constant value of 22.

In the acetone, 1-propanol, and ethanol systems, the sodium salicylate intersects the salicylic acid solubility curve at the respective dielectric constants of 33, 30, and 34, whereas in methanol-water

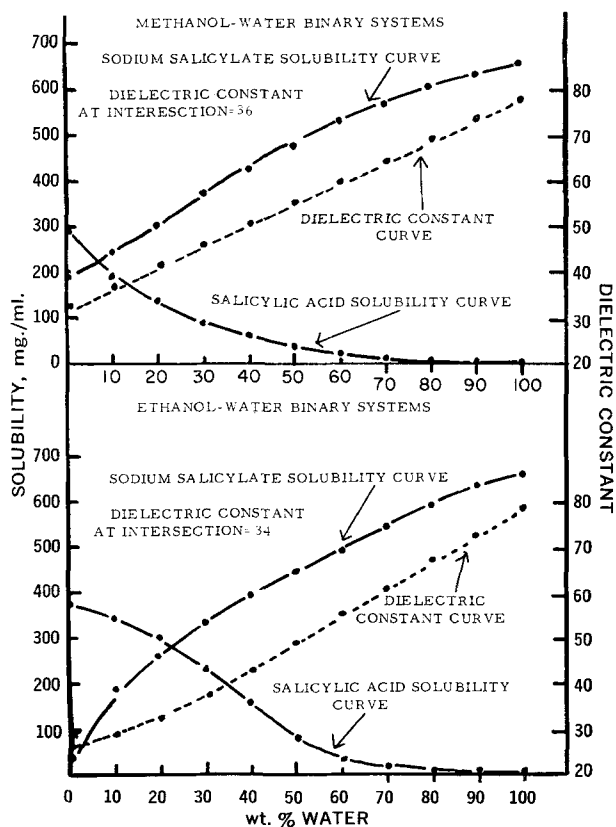


Figure 7—Solubility of both salicylic acid and sodium salicylate in milligrams/milliliter at 25° for ethanol-water and methanol-water mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

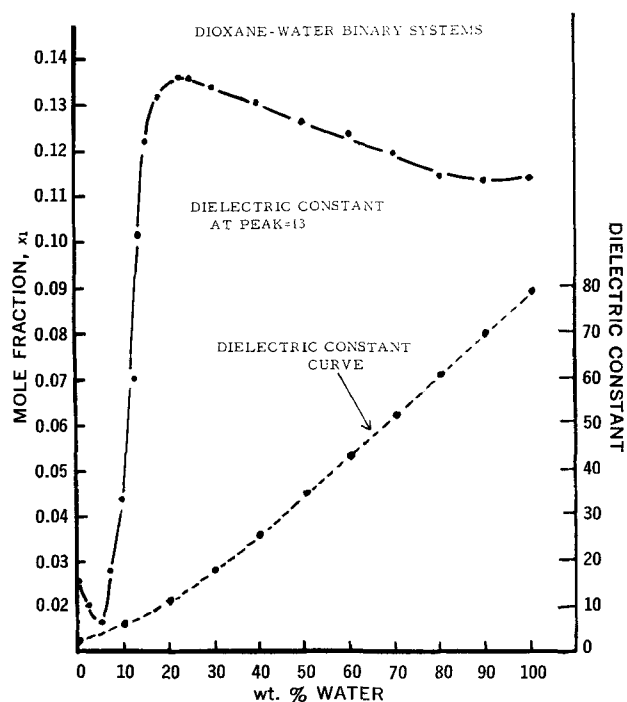


Figure 8—Mole fraction solubility of sodium salicylate as a function of the percent w/w composition of dioxane-water mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

systems the value is 36. This supports the value of about 30 being the point where uni-univalent electrolytes become completely associated. Further, sodium salicylate becomes isodielectric with salicylic acid. That is, it possesses the same solubility as salicylic acid.

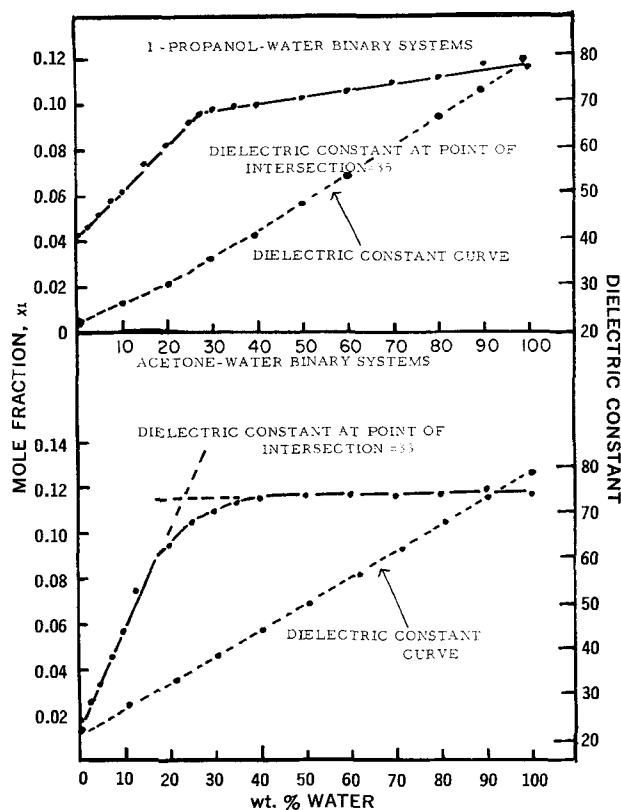


Figure 9—Mole fraction solubility of sodium salicylate as a function of the percent w/w composition of acetone-water and 1-propanol-water binary mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

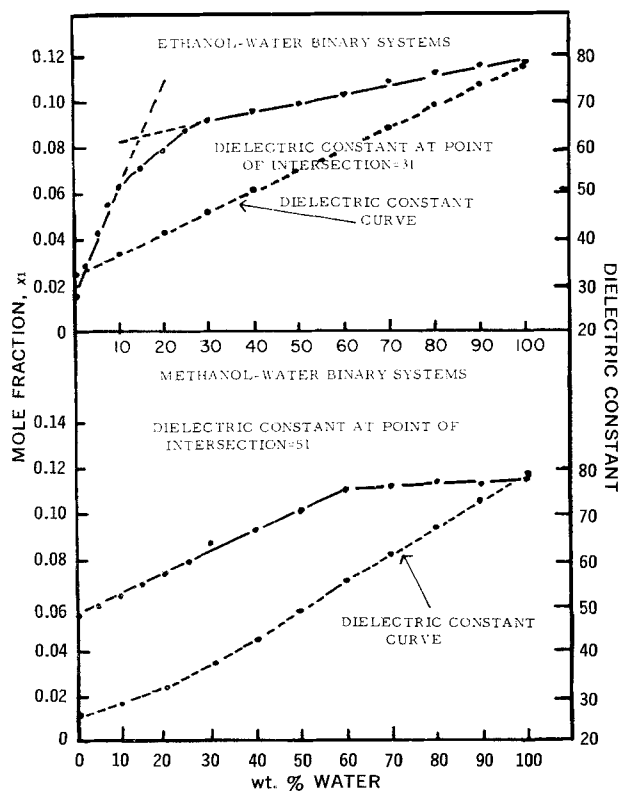


Figure 10—Mole fraction solubility of sodium salicylate as a function of the percent w/w composition of ethanol-water and methanol-water binary mixtures. The dielectric constants of the binary solvent systems are also shown using the right-hand scale.

At the point of intersection, it might be assumed that the inherent polarities of salicylic acid and sodium salicylate are similar in magnitude. When the sodium salicylate values become less than salicylic acid, the sodium salicylate might act as a neutral molecule or nonelectrolyte possessing an inherent polarity below that of salicylic acid. This might be due to the presence of the sodium in the salt.

The solubility of sodium salicylate was also considered from a mole fraction point of view, and the results obtained were plotted in Figs. 8-10. In the case of dioxane, a peak is observed at a dielectric constant value of about 13. For acetone, 1-propanol, ethanol, and methanol systems, two essentially linear portions are evidenced which indicate "breaks" at dielectric constant values at 33, 35, 31, and 51, respectively. Further, the mole fraction solubility of sodium salicylate is essentially invariant over the range of 40% w/w water to pure water in acetone-water systems and from 60% w/w water to pure water in methanol-water systems.

Born (2) and Larson and Hunt (4) developed a theory which relates the solubility of a weakly ionized, relatively insoluble salt to the dielectric constant. This theory can be further broadened to relate the ratio of solubilities for a solute in two solvents to the differences of the reciprocals of the dielectric constant, as given in Eq. 1:

$$\log \frac{S_1}{S_2} = \frac{e^2}{(2.303)2rkT} \left(\frac{1}{D_2} - \frac{1}{D_1} \right) \quad (\text{Eq. 1})$$

where S_1 and S_2 are the molar solubilities at the respective dielectric

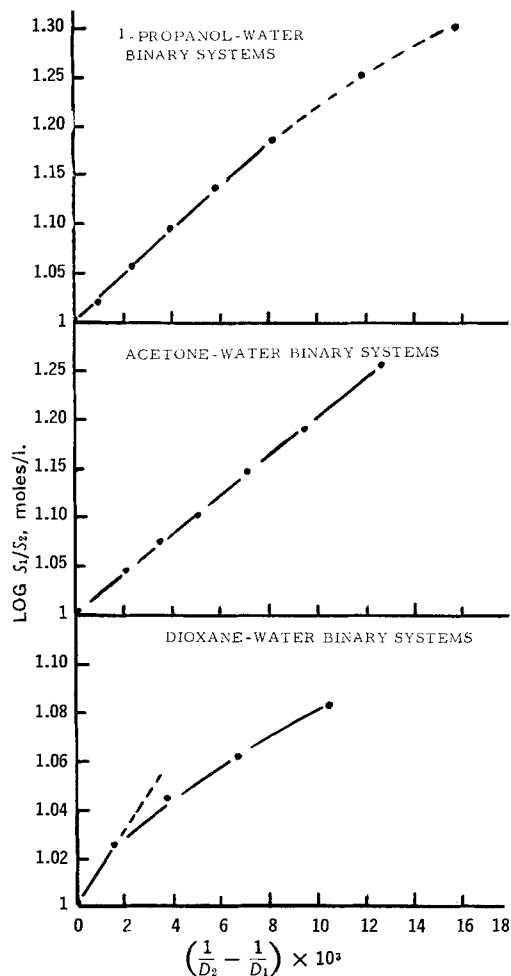


Figure 11—Logarithm of the ratio of the molar solubility (S_1/S_2) versus the differences of the reciprocals of the dielectric constants for the systems shown.

constants D_1 and D_2 . The charge on an electron e is taken in e.s.u., r is an effective ion radius, k is Boltzman's constant, and T is the absolute temperature. Obviously, a straight line having a slope of $0.4343e^2/2rkT$ should be observed when the $\log S_1/S_2$ is plotted versus $(1/D_2 - 1/D_1)$. A theoretical slope can be calculated by assuming an average ion radius of 2.6 Å in the following manner. By inspection, the slope has no units when r is used in centimeters:

$$\text{slope} = \frac{e^2}{(2.303)2rkT} \quad (\text{Eq. 2})$$

slope =

$$\frac{(4.8 \times 10^{-10} \text{ stat coulomb})^2}{(4.606)(2.6 \times 10^{-8} \text{ cm.})(298 \text{ deg.})(1.38 \times 10^{-16} \text{ ergs/deg.})} \quad (\text{Eq. 3})$$

By converting stat coulomb to dyne-centimeters, squaring, and collecting constants:

$$\text{slope} = \frac{23 \times 10^{-20} \text{ dyne-cm.}^2}{4930 \times 10^{-24} \text{ cm.-ergs}} \quad (\text{Eq. 4})$$

Table III—Elements Generated from the IBM 360/50 Least-Squares Program and the Ranges of Concentration and Dielectric Constants for the Systems Given

System	Slope	Y-Intercept	Correlation Coefficient	Range	
				Concentration	Dielectric Constants
Acetone-water	19.6	0.004	0.9994	30-100% water	39.3-78.5
1-Propanol-water	21.5	0.002	0.9957	40-100% water	35.0-78.5
Ethanol-water	21.3	0.002	0.9982	30-100% water	37.5-78.5
Methanol-water	25.5	0.001	0.9992	30-100% water	46.4-78.5

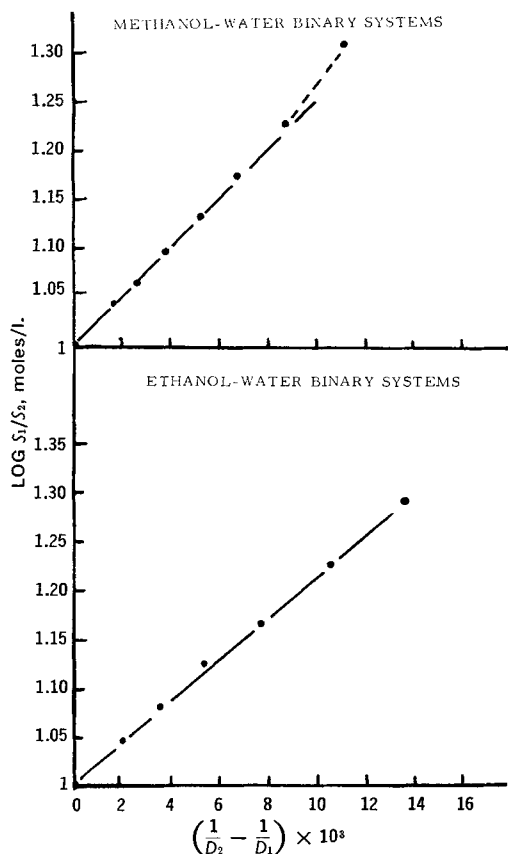


Figure 12—Logarithm of the ratio of the molar solubility (S_1/S_2) versus the differences of the reciprocals of the dielectric constants for ethanol–water and methanol–water binary mixtures.

Since an erg is a dyne-centimeter,

$$\text{slope} = \frac{23 \times 10^{-20} \text{ dyne-cm.}^2}{0.493 \times 10^{-20} \text{ dyne-cm.}^2} = 47.2 \quad (\text{Eq. 5})$$

Thus, the sodium salicylate systems were treated in this manner and the data were plotted as shown in Figs. 11 and 12. It is rather amazing that linearity is observed for the acetone, 1-propanol, ethanol, and methanol systems from about 30–40% w/w water up to pure water while dioxane–water systems show only limited linearity. Sodium salicylate possesses solubility in the range of about 1.0–4.1 M in these systems, and its adherence to the linearity in the Born equation is interesting.

The slopes of these lines were handled by a least-squares method programmed on an IBM 360/50 digital computer; the characteristics are shown in Table III. From the slopes generated from the experimental data, the average radius r is calculated to be about 5.6 Å, which is about two times too large for the average ion radius. The value of the average ion radius was calculated from the ionic size of sodium possessing a water number of 4 and the salicylate anion from molecular models with a monomolecular sheath of water molecules surrounding the polar functions. The hydrated sodium ion was calculated to be about 2.4 Å and the hydrated salicyl anion about 2.8 Å or an average value of 2.6 Å. The results are summarized in Table IV. With this value of r in the Born equation, the theoretical slopes are about two times too great, having a value of about 47.

Table IV—Average Ionic Radius from the Born Equation (Theoretical) and the Calculated Average Ionic Radius

System	A, Calculated Radius	B, Theoretical Radius	Ratio A/B
Acetone–water	6.2 Å	2.6 Å	2.4
1-Propanol–water	5.7 Å	2.6 Å	2.2
Ethanol–water	5.7 Å	2.6 Å	2.2
Methanol–water	4.8 Å	2.6 Å	1.9

Although the activity factor of Debye–Huckel can be included as an extension of the Born equation, that being the mean ionic activity coefficient, $\log \gamma_{\pm}$, the value of the coefficient of the ionic strength varies from about -0.51 in water to -2.98 in alcohols and -3.83 in acetone; no improvement was noted in the ionic size in the Born relationship in systems with high water concentration.

The actual effect of the Debye–Huckel correction is probably small and approximately cancels each other out in the solubility term of the Born equation. It has been stated (5, 6) that the “mean activity coefficient in a saturated solution is almost independent of the dielectric constant of the media.”

While this situation may be expected for relatively insoluble compounds, there may be a rather substantial effect for highly soluble substances such as sodium salicylate.

At this point, the rather large deviation between calculated and theoretical ionic size cannot be resolved.

CONCLUSIONS

1. An alcohol solvent scan of the solubility of sodium salicylate indicates a dielectric requirement of 14, which is the maximum solubility at a particular dielectric constant value, remarkably similar to that observed for salicylic acid.
2. The solubility of sodium salicylate in mixed systems of varying dielectric constants shows a fair parallelism over a wide range of concentration of the nonpolar solvent added. This indicates general adherence to the coulomb relationship or the work required to separate a charge.
3. The solubility curves observed are considered to be repressive dissociation effects, and general correlation is found at a dielectric constant value of 30 where uni-univalent electrolytes may be completely associated. Mole fraction solubility plots, being essentially two linear curves, also support this postulation in several systems.

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