Dielectric Solubility Profiles in Dioxane–Water Mixtures for Several Antipyretic Drugs

Effect of Substituents

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The solubilities of APAP, aminopyrine, and antipyrine have been determined in dioxane–water mixtures of known dielectric constants. The dielectric profiles varied considerably for the subject materials, acetaminophen showing a three-peak system and aminopyrine a single solubility peak. However, antipyrine showed a solubility isotherm running asymptotically toward maximum solubility in pure water. It is possible that solute polarity is the deciding factor in the solubility curves that have been observed.

IN A CONTINUING effort to illustrate the relationship of solubility and dielectric constants (1–6), a study was conducted on several more carefully chosen compounds. In this communication, the dielectric solubility profiles for *p*-hydroxy acetanilide (APAP), aminopyrine, and antipyrine were determined. Previous work (6) indicated a multipeak array or multiple dielectric requirements (DR) for acetanilide and several derivatives, those being the *p*-methyl and *p*-ethoxy (phenacetin) acetanilides. It was felt that APAP, as well as being an important antipyretic, would lend itself as a possible clue on the effect of polar substituents on both the magnitude of solubility and position of the solubility maxima on the dielectric constant scale.

Aminopyrine (dimethylaminoantipyrine) and antipyrine represent two chemical moieties differing only by a dimethylamino group. This difference should prove illustrative of the effect on dielectric solubility profiles. It was felt that the aforementioned compounds might allow for a qualitative picture in terms of substituent effects on solubility and DR shifts.

Thus, this present study was conducted with a view toward encompassing several more pharmaceutical solutes with respect to dielectric solubility profiles and an attempt of a preliminary evaluation of solute polarity.

EXPERIMENTAL

Materials.—The solutes used in this study were acetaminophen (APAP) N.F., aminopyrine U.S.P. (Penick Chemical Division, New York, No. 77414), antipyrine N.F. (Penick Chemical Division, New York, N. Y., No. 78093). The solvents used in this study were 1,4-dioxane (No. 9231, J. T. Baker Chemical Co., Phillipsburg, N. J.) and freshly boiled demineralized distilled water in order to maintain neutral pH.

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Equipment.—Bantam demineralizer model BD-1 (Barnstead Still and Sterilizer Co., Boston, Mass.) with mixed resin bed; Beckman model DU spectrophotometer; Bausch & Lomb Spectronic 505; Mettler Automatic Balance, type H 6T; heated vacuum desiccator, Precision Scientific Co.

Methods.—The protocol used in the analytical procedures has been described elsewhere (5). No pretreatment of the solutes was considered necessary, and they were used directly. The reported results are averages of at least three runs on each material (acetaminophen and certain portions of dielectric profile represent 14 runs). Each run was internally averaged for both the spectrophotometric and gravimetric procedures. The gravimetric results were only slightly higher (1–3%) than the spectrophotometric values, probably due to larger sample withdrawal.

RESULTS AND DISCUSSION

In Fig. 1, the solubility of APAP at 25° is plotted in mg./ml. as a function of v/v composition of dioxane–water mixtures. A three-peak array or three DR's are found occurring at 25, 43, and about 48%

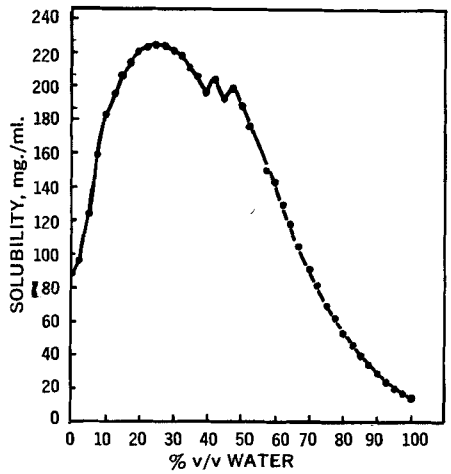


Fig. 1.—The solubility of APAP at 25° in mg./ml. as a function of composition (v/v) for dioxane–water mixtures.

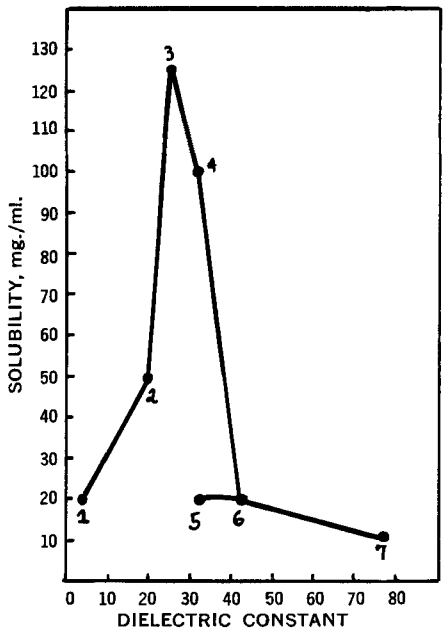


Fig. 2.—The solubility of APAP at 25° in mg./ml. for: *1*, chloroform; *2*, acetone; *3*, ethanol; *4*, methanol; *5*, propylene glycol; *6*, glycerin; *7*, water.

TABLE I.—COMPARISON OF THE DR'S AND RESPECTIVE SOLUBILITIES AND THEIR DIFFERENCES FOR ACETANILIDE AND *p*-HYDROXYACETANILIDE

	Acetanilide	APAP	Δ
	Dielectric Requirements		
DR_1	5	14	9
DR_2	18	28	10
DR_3	28	33–37	5–9
	Solubility, mg./ml.		
	304	224	80
	262	205	57
	244	198	46

v/v water. However, the determination of the third peak was experimentally extremely difficult, since after 14 replicates, nine runs indicated a peak at 48% v/v water. In the other five runs the water concentration varied but seemed to hover around 53% v/v. Thus, the reported values of the third peak are given as a range. Solubility maxima occurred at the following values of the dielectric constant: 14, 28, and 33–37.

In considering these values for the DR's, approximate solubility values from Smith and Mitchell (7) have been plotted in Fig. 2. Their work was essentially a pure solvent scan and when solubility was plotted as a function of the dielectric constant for the reported solvents, maximum solubility occurred in ethanol (ϵ = 25) and a shouldering effect somewhere between propylene glycol and glycerin (dielectric range of 32–42). Obviously, not enough solvents were tested to check out the DR of 14 in this study. The values of the pure solvent scan correlate with the DR's obtained in this study, *i.e.*, 25 versus 28 and 32–42 *versus* 33–37 for the former and latter, respectively.

At this point, it would be well to consider the effect of the *p*-hydroxy group upon the position of the DR and the magnitude of solubility. In Table I, the DR's and solubility in mg./ml. are given for the parent compound, acetanilide (6), and *p*-hydroxyacetanilide.

In each case the value has been listed and the differences noted by Δ-symbols. Again, it should be pointed out that the solubility values reported are at the respective DR's. It has, of course, been assumed that the three major solubility peaks for acetanilide and APAP are correlatable with one another in stepwise fashion. Thus, the DR shifts to higher polarity for APAP indicate the effect of the polar hydroxy substituent. As can be seen from Table I, the differences in DR's and magnitude of solubility are of the same order in value. This direction of change is for the *p*-hydroxy derivative to have larger values of DR's (higher polarity), and the solubility to be somewhat diminished. However, at higher DR's or higher water concentrations, the hydroxy group of the APAP molecule still carries the nonpolar portion of the molecule with it, and this may result in slightly diminished solubility. It is felt that there is a striking parallelism in contrasting the DR's and solubility for these two compounds.

The consideration of solute polarity can be observed from the composite plot in Fig. 3. In this case, the dielectric solubility profiles of acetanilide and APAP are plotted on common axes. From this figure, it can be seen that up to about 45% v/v water (ϵ range 2–35), the solubility of acetanilide is greater along the dielectric profile, whereas the solubility of APAP is greater along the dielectric profile from 45–100% v/v water (dielectric constant range of 35–80).

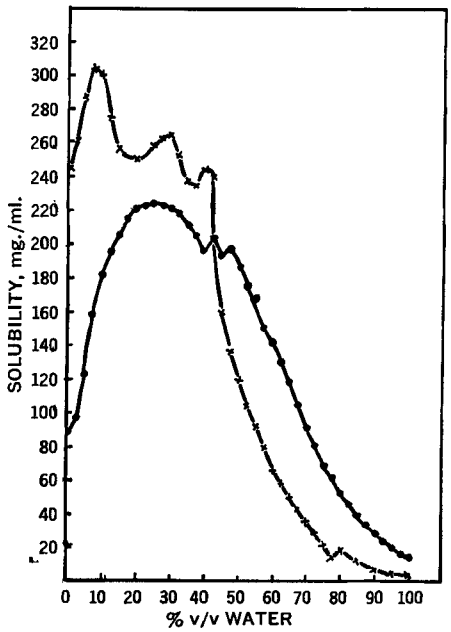


Fig. 3.—The dielectric solubility profiles for acetanilide (×) and APAP (●).

TABLE II.—COMPARISON OF THE DIELECTRIC SOLUBILITY PROFILES OF ACETANILIDE AND APAP RELATIVE TO THE RATIOS OF SOLUBILITY AND POLARITY (ϵ_{12}) OF SOLVENT MIXTURES

% Water	Solubility, mg./ml. Acetanilide	Solubility, mg./ml. APAP	ϵ_{12}	Acetanilide/ APAP	APAP/ Acetanilide
0.0	240	90	2.2	2.67	...
10.0	300	185	5.6	1.62	...
20.0	250	225	10.7	1.10	...
30.0	265	225	17.7	1.18	...
40.0	245	195	25.9	1.26	...
50.0	120	190	34.3	...	1.6
60.0	70	145	43.0	...	2.0
70.0	35	85	51.9	...	2.4
80.0	20	55	60.8	...	2.7
90.0	10	30	69.7	...	3.0
100.0	5	15	78.5	...	3.0

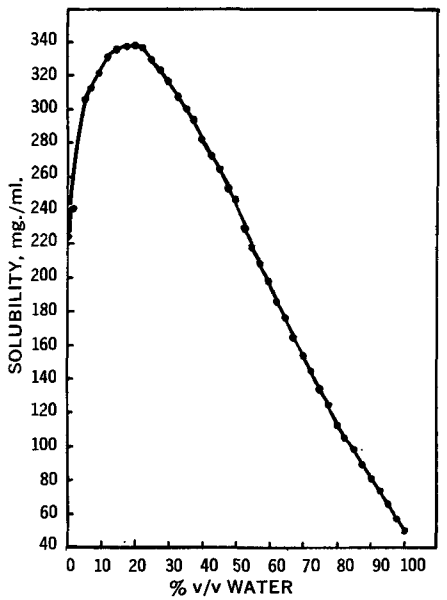


Fig. 4.—The solubility of aminopyrine at 25° in mg./ml. as a function of composition (v/v) for dioxane–water mixtures.

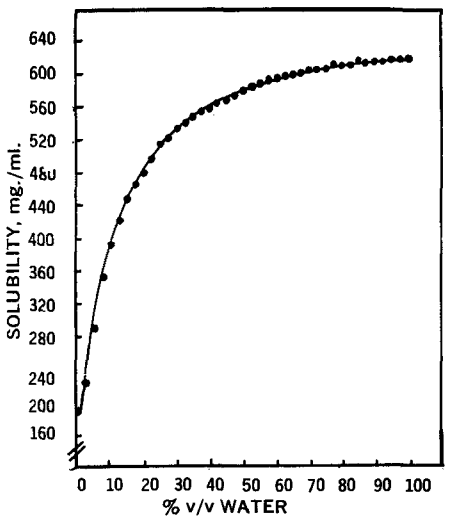


Fig. 5.—The solubility of antipyrine at 25° in mg./ml. as a function of composition (v/v) for dioxane–water mixtures.

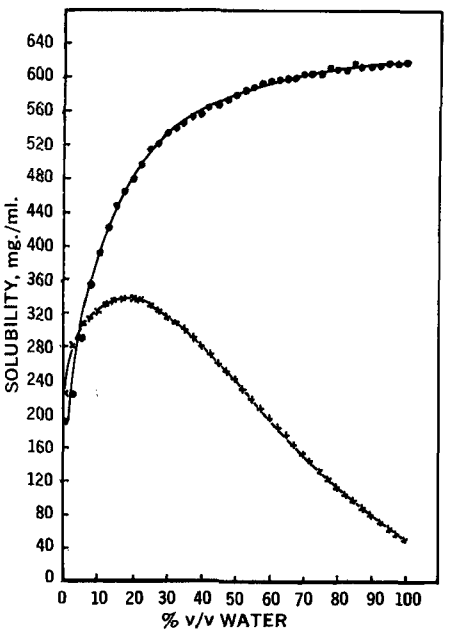


Fig. 6.—The dielectric solubility profiles for antipyrine (●) and aminopyrine (×).

It is interesting to note in this respect that the greatest pharmaceutical utility of dielectric constants would be in the range of about 30–80, encompassing hydroalcoholic mixtures, glycols, glycerin, syrup, and aqueous solutions of said materials.

In Table II, the approximate solubility of acetanilide and APAP are given in mg./ml. at 10% volume increments of added water and the respective dielectric constants of the solvent mixtures.

Since the solubility of acetanilide and APAP supersede each other over a certain portion of the dielectric constant scale, the solubility ratio has been included in this table. The solubility of acetanilide is greater than the solubility of APAP up to about 40% water, whereas the opposite is true after 40% water. Thus, these ratios are given when they are greater than unity. The values of these ratios for APAP/acetanilide are seen to increase as a function of polarity in going toward pure water. As the solvent system becomes more polar, the ratio of solubility increases smoothly to a ratio in pure water of 3:1. The solubility ratios of acetanilide/

TABLE III.—COMPARISON OF THE SOLUBILITY DIELECTRIC PROFILES OF ANTIPYRINE AND AMINOPYRINE RELATIVE TO THE RATIOS OF SOLUBILITY AND POLARITY (ϵ_{12}) OF SOLVENT MIXTURES

% v/v Water	Solubility, mg./ml.		ϵ_{12}	Antipyrine/ Aminopyrine
	Antipyrine	Aminopyrine		
0.0	185	220	2.2	0.84
2.5	220	280	3.0	0.79
5.0	290	310	3.7	0.93
10.0	390	320	5.6	1.2
20.0	480	340	10.7	1.4
30.0	540	320	17.7	1.7
40.0	560	280	25.9	2.0
50.0	580	240	34.3	2.4
60.0	600	200	43.0	3.0
70.0	605	155	51.9	3.9
80.0	610	110	60.8	5.5
90.0	615	80	69.7	7.8
100.0	620	50	78.5	12.4

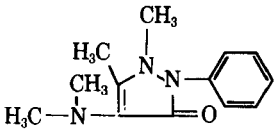
APAP are also seen to decrease smoothly to 40% water; however, these ratios are complicated by the fact that some of these values are solubility peak or solubility valley values.

The solubility of aminopyrine at 25° in mg./ml. as a function of v/v composition of dioxane–water mixtures is shown in Fig. 4. The dielectric solubility profile illustrates only one solubility maxima occurring at a dielectric constant value of about 11. In the case of aminopyrine, it is interesting to note that the solubility from about 35% v/v water to about 90% v/v water is an approximately linear function of composition. In the range of 90–100% v/v water, the solubility is positively and slightly deviated from linearity. The rate of change in the range of 35–90% v/v water is −4 mg./1% change in solvent composition. Further, since the dielectric constant of dioxane–water mixtures in this range is approximately linear, the solubility of aminopyrine is a linear function of the dielectric constant. The dielectric constant range of these mixtures is about 27–70. The noteworthy point is that these trends have been observed by other workers (8, 9), but only when solubility was plotted in mole fraction. It may further imply the usefulness of dioxane–water mixtures as being representative of polarity in a continuous fashion rather than discrete polarity increments in a family of related solvents (8, 9).

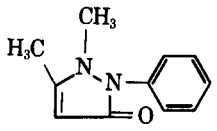
The solubility of antipyrine at 25° in mg./ml. as a function of the v/v composition of dioxane–water mixtures is shown in Fig. 5. The immediate and striking observation is the nature of the dielectric solubility profile. For antipyrine no peaks are observed, but a solubility isotherm rising continuously and asymptotically toward pure water. Thus, the DR for antipyrine cannot be delineated from this curve. However, assuming that water is the practical maximum attainable polarity, the DR in this case would be about 80.

The contrast of these two compounds with respect to DR's is rather notable. The DR of aminopyrine is 11, whereas the DR of antipyrine is about 80, a difference of about 70 dielectric constant units. It should be noted again that the introduction of a polar hydroxy group in acetanilide causes a shift of about 5–10 units with respect to the DR. As stated previously, the difference between aminopyrine and antipyrine is a dimethylamino group.

The formulas are given below.



Aminopyrine



Antipyrine

In considering the magnitude of solubility for antipyrine, the same type of striking differences are noted. In Fig. 6, a composite figure has been prepared by plotting the dielectric solubility profile of each compound on common axes. From this figure, it can be seen that the magnitude of solubility for antipyrine becomes significantly larger after about 5% v/v water and increases rapidly toward the solubility in pure water. While the solubility of antipyrine is increasing asymptotically, the solubility of aminopyrine is decreasing at a rapid rate which results in very large differences. In Table III, the approximate solubility of aminopyrine and antipyrine are listed in 10% volume increments of water, and the respective ratios at each composition change as well as the respective dielectric constants. The values of solubility at 2.5 and 5% water have also been included to show the ratios of solubility at very low polarity.

As can be seen from Table III, the solubility ratios increase smoothly and dramatically to a high of about 12:1 in pure water.

In the foregoing discussion, it is not implied that substituents such as hydroxy or dimethylamino groups will always tend to greater or lesser solubility effects, respectively. Each of these pairs of compounds may only be typical in so far as their nature, polar–nonpolar ratios, and other properties are concerned. It would be of interest to determine dielectric solubility profiles for a series of compounds in which the difference is a methylene group such that *n*-alkyl substitutions are stepwise. It might

then be possible to predict the effect of chain length on solubility with respect to the dielectric constant.

It is felt that these rather simply determined dielectric solubility profiles may have the characteristic of being able to give significant and interpretable results with respect to solubility phenomena. Only after a large number of type compounds and derivatives have been studied can trends be established in the position of solubility maxima and the concomitant magnitude of solubility.

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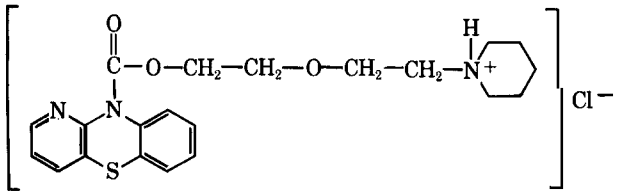
Drug Standards

Qualitative and Quantitative Tests for Pipazethate Hydrochloride

Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.

2-(2-PIPERIDINOETHOXY)ETHYL-10 H-[3,2-*b*][1,4] pyridobenzothiazine-10-carboxylate hydrochloride; $C_{21}H_{26}ClN_3O_3S$; mol. wt. 435.97. The structural formula of pipazethate hydrochloride may be represented as



Physical Properties.—Pipazethate hydrochloride occurs as a white crystalline powder and melts at about 162° (U.S.P. XVI, class I). It is very soluble in water, and freely soluble in alcohol, and in methanol. The pH of a 2% aqueous solution of pipazethate hydrochloride is about 5.4.

Identity Tests.—Dissolve about 100 mg. of pipazethate hydrochloride in 3 ml. of water and add 1 ml. of nitric acid: a reddish color, gradually changing to amber and to yellow, is produced.

Dissolve about 100 mg. of pipazethate hydrochloride in 3 ml. of water, add ammonia T.S. until basic,

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E. R. Squibb and Sons, New York, N. Y., has cooperated by furnishing samples and data to aid in the development and preparation of this monograph.