Solubility Profiles for Antipyrine and Aminopyrine in Hydroalcoholic Solutions

By ANTHONY N. PARUTA

The solubilities of antipyrine and aminopyrine have been determined in binary mixtures of ethanol and water of known dielectric constants. The solubility curves produced in this solvent system were compared with the solubility curves found in dioxane–water mixtures. The dielectric requirements (DR's) are apparently not correlatable in these two solvent systems, and the constancy of DR's may be questioned. The solubility ratios of these 2 solutes in the binary mixtures studied is also discussed. In addition, the dielectric constants of the saturated solutions were determined and compared to the dielectric constants of the binary mixtures. It is felt that these data may lead to a consideration of "solute" or "inherent" polarity for these materials.

IT HAD BEEN shown previously (1) that antipyrine and aminopyrine produced rather unique solubility curves in dioxane–water mixtures. The highly water-soluble antipyrine was characterized by a solubility curve running asymptotically to pure water, whereas aminopyrine was characteristic of an ideal semipolar solute having only one maximum in the solvent mixture. The attributed variation in polarity between antipyrine and aminopyrine was felt to be due to the dimethylamino group in aminopyrine causing both a decrease in the magnitude of solubility and a substantially lower DR, or a shift to lower polarity. This rather large difference, while perhaps not too surprising, was somewhat perplexing. Thus, it was felt judicious that these two solutes should be tested in another solvent system, and in this case, ethanol–water mixtures were chosen. It was also expected that the DR's should also correlate and that the nature of the curves should be essentially similar.

Since it had also been observed (2) that the highly water-soluble antipyrine caused substantial dielectric constant changes in syrup vehicles, the dielectric constants of the saturated solutions were also determined. It is hoped that some useful information might be gained from a knowledge of these values.

EXPERIMENTAL

Materials—The solutes used in this study were aminopyrine USP[1] and antipyrine USP.[2] The solvents used were freshly boiled demineralized distilled water and absolute ethanol USP–NF.[3]

Methods—The protocol used in the analysis of solubility data has already been described (1). No pretreatment of the solutes was considered necessary, and they were used directly. The re-

ported results are the averages of at least 4 runs on each material. Each run was internally averaged for both gravimetric and spectrophotometric procedures. Dielectric constant values were determined from calibration curves as previously described (2).

Equipment—A WTW DK-06 multidekameter was used for dielectric constant determinations, a Bantam demineralizer, model BD-1 with mixed resin bed; Bausch & Lomb Spectronic 505, and a Mettler automatic balance, type H 6T, heated vacuum desiccator.[4] A water bath and attendant temperature controls were used for equilibration media.

RESULTS AND DISCUSSION

Solubility—In Fig. 1, the solubility of antipyrine in mg./ml. is plotted *versus* the dielectric constants of the binary mixture indicated. The solubility of aminopyrine in ethanol–water and dioxane–water mixtures (1) is also shown in Fig. 1.

The data for ethanol–water mixtures are from the present work, whereas that for the dioxane–water system has been taken from a previous communication (1). The dielectric requirement (DR) is seen to have a value of about 55 for antipyrine and about 35 for aminopyrine in ethanol–water mixtures. In dioxane–water mixtures, there may be a slight "shouldering" at a dielectric constant value of about 55 for antipyrine.

It was also shown in another communication (3) that changes, *i.e.*, "appearance" of shoulders, could occur upon changing the composition scale coordinate to a dielectric constant scale coordinate. Although this appearance allows for the correlation of the binary systems in the case of antipyrine, this correlation is considered to be vague. This is especially notable in the case of antipyrine in ethanol–water mixtures where a change in the plotting coordinate does not effect a change in the DR value for this solute.

The solubility curve for aminopyrine in dioxane–water mixtures does not indicate the occurrence of a shoulder, although one can "force" this occurrence, it is deemed as noncorrelation of the DR in these solvent mixtures for this solute.

Since the dielectric constants of the saturated solutions in ethanol–water mixtures were deter-
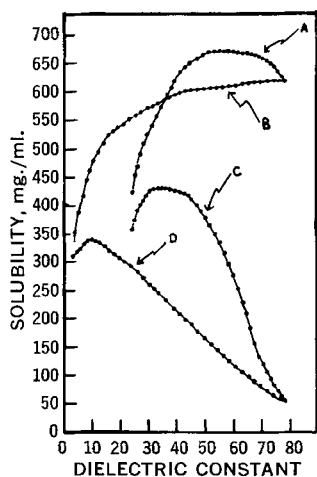
Fig. 1—A plot of the solubilities of antipyrine and aminopyrine in mg./ml. at 25° versus the dielectric constants of the solvent mixtures. Curves A and C are for antipyrine and aminopyrine in ethanol–water mixtures. Curves B and D are for antipyrine and aminopyrine in dioxane–water mixtures.

Fig. 3—The solubility of aminopyrine in mg./ml. at 25° versus the dielectric constant values of the respective saturated solutions.

mined, it was felt instructive that the solubility curves be plotted *versus* these values. As expected, the solubility curves obtained from this treatment were essentially the same as the curves produced when only the dielectric constants of the solvent mixtures (ϵ_{12}) were used. The solubilities of antipyrine and aminopyrine are plotted *versus* the dielectric constants of the saturated solutions (ϵ_{123}) and are shown in Figs. 2 and 3.

If it were found that the ϵ_{123} and the ϵ_{12} curves were plotted as a function of concentration and these dielectric curves intersected, it would imply
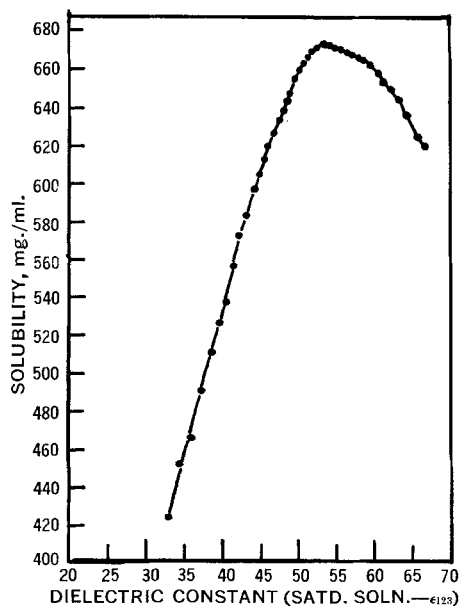

Fig. 2—The solubility of antipyrine in mg./ml. at 25° versus the dielectric constant values of the respective saturated solutions.
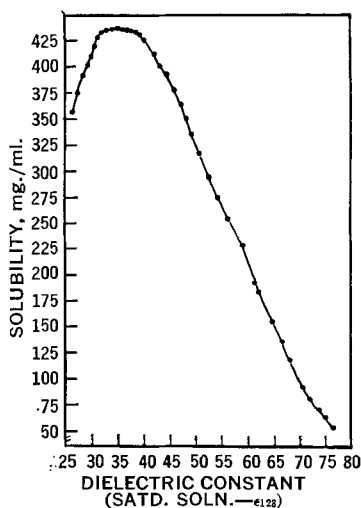
that the dielectric constant of the solute might occur at this point of intersection. In other words, the addition of solute to a given composition does not change the dielectric constant of the solvent mixture. Furthermore, were the point of intersection to lie close to the dielectric requirement, where maximum solubility occurs, it would further indicate that solute polarity and solvent polarity were equal in magnitude. This would probably indicate the essential embodiment of either the solubility parameter or dielectric requirement approaches since solubility is maximized when there is no difference in the polarity of the solute and solvent mixture. This is seen to be the case for antipyrine (Fig. 4) and for aminopyrine (Fig. 5) having points of intersection for antipyrine and aminopyrine at 51–53 and 35, respectively, whereas the dielectric requirements were 53–55 and 35, respectively. At any point away from the intersection, one observes either an increase or decrease in the dielectric constant of the saturated solution relative to the solvent system.

Since the dielectric constants and solubilities were known, it would then be possible to calculate the approximate change in the dielectric constant of the solvent system/mg. of solute added. Although it should be realized that the addition of 1 unit or mg. of a solute to a given solvent composition may not change the dielectric increment in a linear fashion when more units or mg. are added up to saturation, it may be assumed that on the average this linearity may be approximately correct.

In Tables I and II, the values for the dielectric constants of the binary solvent system and the saturated solutions are listed in columns 2 and 3. The dielectric increment, $\Delta\epsilon$, the solubilities, and the dielectric constant change/mg. of solute are listed in columns 4, 5, and 6.

In Table I, the data for antipyrine are given and several interesting observations can be made. Whereas antipyrine in pure water at a concentration of 620 mg./ml. decreases the dielectric constant substantially (11.8 units), the same concentration
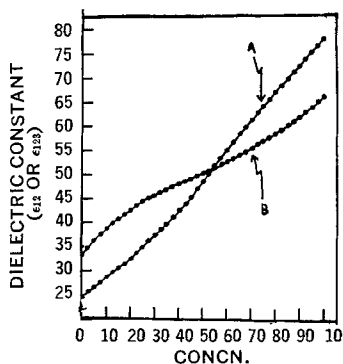
Fig. 4—A plot of the dielectric constants of the solvent mixture (curve A) and saturated solutions (curve B) of antipyrine versus the composition of the solvent mixtures.
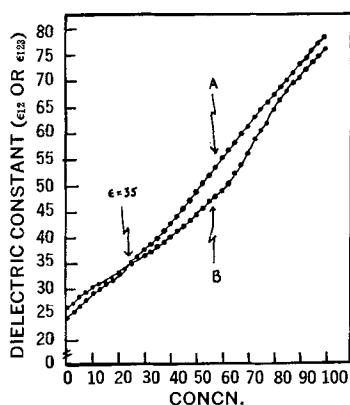

Fig. 5—A plot of the dielectric constants of the solvent mixture (curve A) and saturated solutions (curve B) of aminopyrine versus the composition of the solvent mixtures.

TABLE I—SUMMARY OF THE DIELECTRIC CONSTANTS OF SATURATED SOLUTIONS OF ANTIPYRINE, THE DIELECTRIC INCREMENT ($\Delta\epsilon$), THE RESPECTIVE SOLUBILITY, AND THE DIELECTRIC INCREMENT/mg. SOLUTE

% w/w Ethanol	ϵ_{12}	ϵ_{123}	$\Delta\epsilon$	Sol., mg./ml.	$\Delta\epsilon$/mg.
0	78.5	66.7	−11.8	620	−0.019
10	73.2	62.3	−10.9	650	−0.017
20	67.5	58.7	−8.8	665	−0.013
30	61.7	55.8	−6.9	670	−0.010
40	55.4	53.1	−2.3	671	−0.003
50	49.0	50.4	+1.4	660	+0.002
60	42.8	48.1	+5.3	638	+0.008
70	37.5	46.0	+8.5	620	+0.014
80	32.7	42.4	+9.4	573	+0.016
90	29.0	38.7	+9.7	510	+0.019
100	24.3	33.0	+8.7	425	+0.021

TABLE II—SUMMARY OF THE DIELECTRIC CONSTANTS OF SATURATED SOLUTIONS OF AMINOPYRINE, THE DIELECTRIC INCREMENT ($\Delta\epsilon$), THE RESPECTIVE SOLUBILITY, AND THE DIELECTRIC INCREMENT/mg. OF SOLUTE

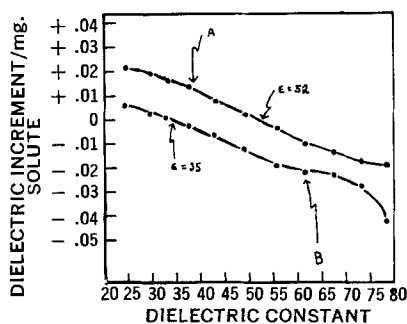| % w/w Ethanol	ϵ_{12}	ϵ_{123}	$\Delta\epsilon$	Sol., mg./ml.	$\Delta\epsilon$/mg.
0	78.5	76.3	−2.2	53	−0.042
10	73.2	70.7	−2.5	92	−0.027
20	67.5	63.9	−3.6	157	−0.023
30	61.7	56.2	−5.5	253	−0.022
40	55.4	49.2	−6.2	335	−0.019
50	49.0	44.5	−4.5	389	−0.012
60	42.8	40.9	−2.7	425	−0.006
70	37.5	36.6	−0.9	435	−0.002
80	32.7	33.2	+0.5	435	+0.001
90	29.0	29.8	+0.8	409	+0.002
100	24.3	26.4	+2.1	357	+0.006

Fig. 6—A plot of the dielectric increment/mg. for antipyrine (curve A) and aminopyrine (curve B) versus the dielectric constant value for the solvent mixture.

in 70% w/w ethanol–water raises the dielectric constant by 8.5 units.

This may indicate that at these high concentrations of solute, antipyrine and its inherent polarity dominates, and the effect would be one of altering or changing its environment to conform more closely to its own nature.

The dielectric constant increment/mg. of solute has been plotted *versus* the dielectric constant of the solvent system and is shown in Fig. 6 for antipyrine (A) and aminopyrine (B).

In Table II, the data for aminopyrine are given in the same fashion as above, and again there are several interesting observations. It can be seen that although the dielectric increment caused by aminopyrine in pure water is only −2.2 units, the dielectric increment/mg. is 0.042 units which is greater than twice the dielectric increment/mg. for antipyrine which has a value of only 0.019 units. One can also observe that the magnitude of solubility for antipyrine is almost 12 times that of aminopyrine, and thus, the effective dielectric increment of aminopyrine is about 24 times that of antipyrine. The dimethylamino group present in aminopyrine, while causing a diminution of solubility, may also,

because of spacial requirements "thrust" into the hydrogen bonded structure of water more effectively and cause the larger decrease in the dielectric constant. From a mechanistic point of view, one can conceive of the solute "melting," and the liquid produced being miscible with water to a certain extent. Thus, this second "liquid" should lower the dielectric constant of water depending upon its own magnitude. If it is assumed that aminopyrine as the second liquid has an approximate polarity value or dielectric constant of about 35, it should have a

more decided effect of lowering the dielectric constant of water relative to antipyrine which has a value of about 53–55. This would be analogous to the case of adding 2 solvents of differing polarity or dielectric constants. Therefore, methanol should be more effective in lowering the dielectric constant of water, having a dielectric constant value of 33, than glycerin with a value of about 43 at the same concentration. It can be presumed that aminopyrine may be operating through two mechanisms: the first by having an inherent polarity lower than antipyrine, and the second by the side chain thrust into the bonded structure of water.

Although antipyrine is more effective in reducing the dielectric constant of water and ethanol–water mixtures up to about 40% w/w ethanol, antipyrine is also far more effective in increasing the polarity or dielectric constant of ethanol and water–ethanol mixtures up to about 20% w/w water. The dielectric increment/mg. of solute has been summarized in Table III. In this case, the composition for the binary mixtures is given in the first column. The dielectric increment/mg. solute and the ratios of the increments, where their value is greater than unity, are also shown. It can then be seen that the polarity adjustment for any given solvent composition by a given solute probably depends on the inherent polarity of that solute.

TABLE III—SUMMARY OF THE DIELECTRIC INCREMENTS/mg. OF SOLUTE FOR AMINOPYRINE AND ANTIPYRINE, AND THE RATIOS OF DIELECTRIC INCREMENTS/mg. IN THE RESPECTIVE SOLVENT MIXTURES

% w/w Ethanol	$\Delta\epsilon_1$ Aminopyrine	$\Delta\epsilon_2$ Antipyrine	$\dfrac{\Delta\epsilon_1}{\Delta\epsilon_2}$	$\dfrac{\Delta\epsilon_2}{\Delta\epsilon_1}$
0	−0.042	−0.019	2.2	...
10	−0.027	−0.017	1.6	...
20	−0.023	−0.013	1.8	...
30	−0.022	−0.010	2.2	...
40	−0.019	−0.003	6.3	...
50	−0.012	+0.002	...	...
60	−0.006	+0.008	...	...
70	−0.002	+0.014	...	...
80	+0.001	+0.016	...	16
90	+0.002	+0.019	...	9.5
100	+0.006	+0.021	...	3.5

Magnitude of Solubility—There are several ways in which the solubilities of these compounds in 2 solvent mixtures can be viewed. The solubility of antipyrine and aminopyrine in each solvent mixture at common dielectric constant values is shown in Tables IV and V. In this case, the solubilities of the solutes in mg./ml. for dioxane–water and ethanol–water is given in the first 2 columns. The last column shows the solubility ratio, the solubility of the solute in ethanol–water mixtures relative to dioxane–water mixtures.

In Table IV, the data for antipyrine illustrate that ethanol–water mixtures over the dielectric constant range of 35–75 are more efficient cosolvents but only to the extent of 5–10%. Furthermore, at dielectric constant values below 35, dioxane–water mixtures are more efficient cosolvents.

However, in Table V, the aminopyrine data show that ethanol–water mixtures possess far greater cosolvency than dioxane–water mixtures. This greater cosolvency is also seen to occur over the

TABLE IV—SUMMARY OF THE SOLUBILITY OF ANTIPYRINE IN DIOXANE–WATER AND ETHANOL–WATER MIXTURES AT SPECIFIED DIELECTRIC CONSTANT VALUES AND THE RATIO OF SOLUBILITY IN THE NOTED SOLVENT MIXTURES

Dielectric Constant	Sol., mg./ml. Dioxane–Water (A)	Ethanol–Water (B)	Ratio B/A
24.3 (Ethanol)	556	424	0.76
30	573	537	0.94
35	583	610	1.05
40	592	633	1.07
45	603	645	1.07
50	605	662	1.09
55	606	667	1.10
60	610	671	1.10
65	613	666	1.09
70	616	658	1.07
75	619	641	1.04
78.5 (Water)	620	620	1.00

TABLE V—SUMMARY OF THE SOLUBILITY OF AMINOPYRINE IN DIOXANE–WATER AND ETHANOL–WATER MIXTURES AT SPECIFIED DIELECTRIC CONSTANT VALUES AND THE RATIO OF SOLUBILITY IN THE NOTED SOLVENT MIXTURES

Dielectric Constant	Sol., mg./ml. Dioxane–Water (A)	Ethanol–Water (B)	Ratio B/A
24.3 (Ethanol)	287	370	1.29
27.5	276	401	1.45
30	264	428	1.62
35	242	435	1.80
40	216	434	2.01
45	191	413	2.16
50	165	378	2.30
55	141	333	2.36
60	120	277	2.31
65	100	195	1.95
70	80	119	1.49
75	63	77	1.22
78.5 (Water)	50	50	1.00

TABLE VI—SUMMARY OF THE SOLUBILITY RATIO (ANTIPYRINE/AMINOPYRINE) IN DIOXANE–WATER AND ETHANOL–WATER MIXTURES

ϵ_{12}[a]	Solubility Ratio (Antipyrine/Aminopyrine) Dioxane–Water	Ethanol–Water
78.5	12.4	12.4
69.7	7.8	4.8
60.8	5.5	2.3
51.9	3.9	1.8
43.0	3.0	1.5
34.3	2.4	1.4
25.9	2.0	1.2

[a] Values of dielectric constants used from *Reference 1*.

given range of dielectric constant values, 25–75. The increase in solubility caused by the ethanol–water cosolvents is seen to span a range of 22–230%.

This would then lead to the consideration of the ratio of solubility of antipyrine relative to aminopyrine in the 2 binary solvent systems studied. These data are shown in Table VI, where at various dielectric constant values the ratio of the solubility of antipyrine relative to aminopyrine is given for dioxane–water and ethanol–water mixtures. The

far greater cosolvency effect of ethanol–water on aminopyrine is seen in the smaller ratios in this solvent mixture.

SUMMARY

It can be observed from Fig. 1 that in both cases the polarity of antipyrine is greater than aminopyrine by virtue of possessing both higher DR's and magnitude to solubility. Furthermore, the solubility curve for aminopyrine moves closer with respect to both DR and magnitude in the solvent mixture of higher polarity. It would be interesting to note how these differences in DR and magnitude would change by the use of more polar binaries such as methanol–water mixtures and less polar binaries such as propanol–water mixtures.

It may be assumed for this particular pair of solutes in the systems studied that from the differences in the position of the DR's and the concomitant magnitude that antipyrine is inherently more polar than aminopyrine. This is further substantiated by the characterization of solute polarity from dielectric constant studies of saturated solutions.

The rather obvious noncorrelation of DR in the 2 solvent systems for aminopyrine and the vague correlation in the case of antipyrine may imply that the concept of DR agreement, irrespective of the solvent system, is suspect.

Although previous publications (4, 5) had assumed that this concept was true, and at times tenuously true, it is now reasonable to postulate that the solubility profiles and respective DR(s) may be considered unique unto themselves in any given solvent system, a situation previously reported (6–9).

It is felt that this does not obviate either the usefulness or application of this knowledge, and that the cosolvency phenomena relative to dielectric constants has been amply illustrated. It is hoped that continuing studies on solutes of pharmaceutical interest relative to the above points will allow amplification and reinterpretation of past experiences in this area.

Presently, the author's research interests are concerned with the parabens and barbiturates, and these will be the subject of future communications.

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Pharmaceutical Heterogeneous Systems I

Hydrolysis of Aspirin in Combination with Tablet Lubricants in an Aqueous Suspension

By S. S. KORNBLUM and M. A. ZOGLIO

The chemical mechanism that explains the accelerated hydrolysis demonstrated by aspirin when in combination with an alkali stearate, *i.e.,* calcium stearate, in a solid dosage form has been elucidated by employing a suspension technique. The mechanism primarily involves a reaction of the alkali cation with aspirin in a solution to form a salt of aspirin which, in the presence of solvated aspirin, comprises a buffer system at a pH detrimental to the stability of aspirin. Using the kinetic data obtained from the suspension study, an attempt was made to predict aspirin stability in a solid dosage form. There is evidence presented to support the concept that stearic acid will serve as a medium for aspirin degradation at temperatures slightly above room temperature.

PREVIOUS RESEARCHERS (1–4) studying the hydrolysis of aspirin in either a homogeneous or heterogeneous aqueous system have demonstrated that decomposition is a function of water content, pH, and temperature. An aspirin

tablet can be identified as a heterogeneous system. One may compare an aspirin tablet with an aqueous aspirin suspension in order to facilitate an explicit definition of the hydrolysis phenomena. The effect of antacids in mixtures with aspirin has been studied in the presence of moisture and has been demonstrated to increase decomposition rate (5, 6). Some substances employed as tablet lubricants can effectively act as antacids, *e.g.*, stearate salts. The purpose of this study was to evaluate the commonly used tablet lu-