Solubility Profiles for the Xanthines in Aqueous Alcoholic Mixtures I

Ethanol and Methanol

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The solubilities of caffeine, theophylline, and theobromine were determined in two binary mixtures as a function of the dielectric constant. The binary mixtures chosen were water and two *n*-alkyl alcohols, ethanol and methanol. The alcohol was chosen on the basis of the dielectric constant range produced so that various "cuts" along the solubility curve could be obtained. The dielectric requirements (DR's) found in these systems could then be matched with previous findings. The DR's found in this study correlate to a fair degree with past work; however, a consistent new peak at a dielectric constant of about 40 was also found. These systems were experimentally designed so that solubility could be expressed in various concentration notations as well as mole fraction.

THE SOLUBILITY profile for the xanthine drugs in dioxane–water mixtures in terms of dielectric requirements has been given previously (1). It also had been shown the dielectric requirements (DR's) for salicylic acid (2) were relatively constant for a diverse spectrum of binary mixtures and that the magnitude of solubility at a given DR varied widely.

In a continuing effort to investigate the relative constancy of DR's in various binary mixtures, the present study on the xanthines was undertaken. In this case, the solubilities of the xanthines were determined in mixtures of two semipolar, *n*-alkyl alcohols with water. The two alcohols, ethanol and methanol, were chosen on the basis of giving a desired dielectric constant range so that isolation and limitation of a given number of the total DR's found in dioxane–water could be accomplished. The main purpose of this work was to determine if the DR's found with alcohol–water mixtures were the same as the DR's found in dioxane–water mixtures.

It should be noted that caffeine contains one more methyl group than the other xanthines, theophylline and theobromine, which are positional isomers. In the dioxane–water system, it was found that the first three DR's for caffeine were about 3–4 dielectric constant units below the first three DR's for the other xanthines. Whether this difference is due to the chemical difference noted above or experimental variation is not really known. However, it has been assumed that the latter was true and the xanthines show approximately the same DR's in dioxane–water

mixtures. Whereas previous data were presented only in a mg./ml. convention, the experimental system in this study was so designed through density measurements to allow for presentation of solubility in various concentration notations as well as mole fraction. It has been shown (3) that the DR's are concentration notation dependent and it was felt that these systems should be similarly treated.

EXPERIMENTAL

Solubility Determinations.—The protocol for solubility determinations has been described previously (4, 5). All runs were done at 25° and each of the three runs made were subjected to both spectrophotometric and gravimetric analysis. Internal averaging was performed and the results are reported for the three run average.

Materials.—Caffeine was obtained from Nepera Chemical Co., Inc., theophylline from Matheson, Coleman and Bell, 7094 TX450, and theobromine N.F. from Penick, lot NBT 4092. Ethanol was obtained from U. S. Industrial Chemical Corp., sealed absolute, methanol from Allied Chemical, reagent ACS code 1212. Distilled water was used throughout this study. All materials were used directly as supplied by the manufacturer.

Equipment.—A water bath and attendant controls were used as an equilibration environment at 25°. Twenty-four hours was the time allowed for equilibration. A Bausch & Lomb spectronic 505 was used for spectrophotometric analysis, and a vacuum desiccator was used to dry samples to constant weight.

RESULTS AND DISCUSSION

The solubility of caffeine at 25° in the various concentration notations given *versus* the dielectric constant of the binary mixtures studied is shown in Fig. 1.

In Figs. 2 and 3, the solubility of theophylline and theobromine at 25° in the mg./ml. of solution convention is illustrated as a function of the dielectric constant of the binary mixtures studied.

Since the solubility curves for theophylline and theobromine, in the mg./Gm. of solution and mole fraction conventions are analogous to those in Fig. 1 for caffeine they have been omitted from these figures. The variation of DR's with concentration notation has been summarized in Table II.

The DR's found for the xanthines in these alcohol–water mixtures have been summarized in Table I. The values of the DR's for the xanthines in dioxane–water mixtures are also shown in order to contrast the various binary mixtures used. For theobromine in the methanol–water system, a shoulder at a

dielectric constant value of about 40 was not clear cut. Although slight shouldering can be seen at a dielectric constant value of about 38, the existence of this DR is questioned. There is some indication that shouldering occurs at a dielectric constant of about 42 on the mole fraction basis, but this also does not necessarily prove a DR existence with another concentration convention.

Although the DR's in these alcohol–water mixtures correlate well with the DR's previously found in dioxane–water mixtures (1), a new DR at a value of 42–44 was also found. No explanation for this new peak is given; however, were this peak to exist in dioxane–water mixtures, it would fall in the valley between the third and fourth DR's for these mixtures. It is possible that alcohol–water mixtures behave mechanistically different toward the xanthines, in so far as the extent of solvation and/or hydration is concerned relative to the cyclic ether, dioxane. This will be discussed in a latter portion of this communication.

These figures illustrate also a low degree of dielectric requirement sensitivity to concentration notation. A maximum change of about 2–5 dielectric constant units is found in going from the pharmaceutical convention to the mole fraction expression. The DR's found for the xanthines relative to concentration notation have been tabulated and summarized in Table II.

Since the solubility of the xanthines has been determined in several mixtures including dioxane–water mixtures (1), it was felt judicious to determine and compare the ratios of solubility of the xanthines to one another in each pure solvent and at the common dielectric requirements. It had been shown that the ratios of solubility for the xanthines (defining theobromine = 1) in dioxane–water mixtures at the DR's were closer to the ratios of solubility in water. This was felt to imply the importance of the aqueous hydration of the xanthines. The mag-
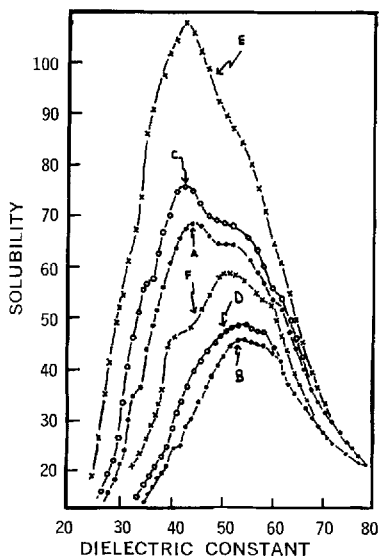

Fig. 1.—The solubility of caffeine at 25° as a function of the dielectric constant of ethanol–water and methanol–water mixtures. Key: A, aqueous ethanol; B, aqueous methanol; solubility expressed as mg./ml. of solution. C, aqueous ethanol; D, aqueous methanol; solubility expressed as mg./Gm. of solution. E, aqueous ethanol; F, aqueous methanol; solubility expressed as mole fraction ×10⁴.

Fig. 2.—The solubility of theophylline at 25° in mg./ml. of solution as a function of the dielectric constant of ethanol–water mixtures (A) and methanol–water mixtures (B).
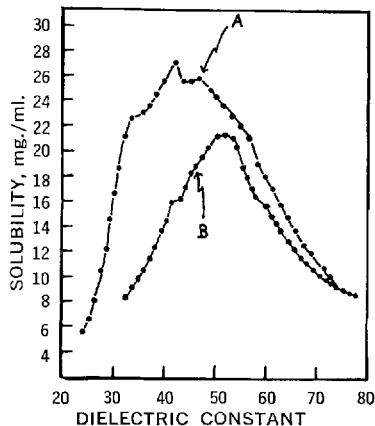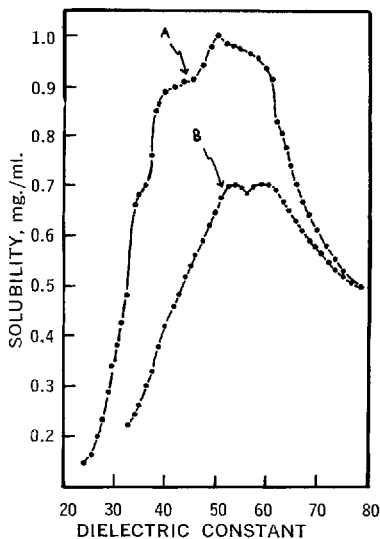

Fig. 3.—The solubility of theobromine at 25° in mg./ml. of solution as a function of the dielectric constant of ethanol–water mixtures (A) and methanol–water mixtures (B).

TABLE I.—SUMMARY OF THE DIELECTRIC REQUIREMENTS FOR THE XANTHINES IN ALCOHOL-WATER MIXTURES AND DIOXANE–WATER MIXTURES

System	Dielectric Constant Range	DR_1	DR_2	DR_3	DR_4	DR_5	DR_6
				Caffeine			
Dioxane–water	2.2–78.5	11	20	30	..	50	61
Ethanol–water	24.3–78.5	..	..	34	44	51	60
Methanol–water	32.4–78.5	..	..	..	42	54	60
				Theophylline			
Dioxane–water	2.2–78.5	14	20	34	..	50	61
Ethanol–water	24.3–78.5	..	..	34	41	48	58
Methanol–water	32.4–78.5	..	..	..	42	52	60
				Theobromine			
Dioxane–water	2.2–78.5	14	22	34	..	50	61
Ethanol–water	24.3–78.5	..	..	35	43	51	61
Methanol–water	32.4–78.5	..	..	..	38–42[a]	53	60

[a] See under *Results and Discussion.*

TABLE II.—SUMMARY OF THE DIELECTRIC REQUIREMENTS FOR THE XANTHINES AS A FUNCTION OF CONCENTRATION NOTATION

Concn. Notation	Caffeine				Theophylline				Theobromine				Solvent System
	DR_1	DR_2	DR_3	DR_4	DR_1	DR_2	DR_3	DR_4	DR_1	DR_2	DR_3	DR_4	
mg./ml.	..	42	54	60	..	42	53	60	..	40[a]	53	60	Methanol–water
	34	44	51	60	34	41	48	58	35	43	51	60	Ethanol–water
mg./Gm. of soln.	..	40	53	58	..	42	51	58	..	40[a]	51	60	Methanol–water
	35	42	49	60	34	40	48	58	35	43	50	60	Ethanol–water
mole fraction	..	42	52	58	..	42	50	59	..	42	53	59	Methanol–water
	33	43	50	60	34	40	47	58	33	43	51	62	Ethanol–water

[a] See under *Results and Discussion.*

TABLE III.—SUMMARY OF THE SOLUBILITIES AND SOLUBILITY RATIOS FOR THE XANTHINES AT THE OBSERVED DR's AS WELL AS EACH PURE SOLVENT

Substance	Solubility in 2nd Component mg./ml.	Ratio	DR 30–34 mg./ml.	Ratio	DR 40–43 mg./ml.	Ratio	DR 50–55 mg./ml.	Ratio	DR 58–61 mg./ml.	Ratio	Solubility in Water mg./ml.	Ratio
					Dioxane–Water							
Caffeine	21	23	82	41	..	..	55.0	32	50.0	42	21.8	39
Theophylline	9	10	29	15	..	..	21.0	12	15.7	14	8.3	13
Theobromine	0.9	1	2.0	1	..	..	1.7	1	1.2	1	0.6	1
					Ethanol–Water							
Caffeine	6.4	47	36	51	69	77	65	65	54	60	21.5	44
Theophylline	5.3	38	23	33	27	30	25	25	22	24	8.3	17
Theobromine	0.14	1	0.7	1	0.9	1	1.0	1	0.9	1	0.5	1
					Methanol–Water							
Caffeine	10.2	47	..	..	25	50	47	67	44	66	21.5	44
Theophylline	8.3	38	..	..	16	32	21	30	16	23	8.3	17
Theobromine	0.22	1	..	..	0.5[a]	1	0.7	1	0.7	1	0.5	1

[a] See under *Results and Discussion.* This value of solubility was chosen at a dielectric constant of 40, although no shouldering was evidenced.

nitudes of solubility and solubility ratios have been summarized as shown in Table III.

These ratios have been plotted and are shown in Fig. 4. In the dioxane–water system, the ratios of solubility at the DR's found are seen to approximate the ratios in water. However, both the ethyl and methyl alcohol show different patterns. For theophylline, the ratios in going from pure water to pure ethanol or pure methanol increase linearly as the DR's decrease and approach the dielectric constant of the alcohol. For caffeine, the ratios in

going from pure water to pure ethyl or methyl alcohol go through a maxima. Obviously, there is a potentiation effect for caffeine in the co-solvency of alcohol–water mixtures which does not occur with dioxane–water mixtures.

The linear increase for theophylline and the curve for caffeine may imply more effective and/or different hydration or solvation leading to the various hydrates or solvates having their own solubility characteristics. These effects may aid in explaining the multiplicity of peaks obtained in these co-
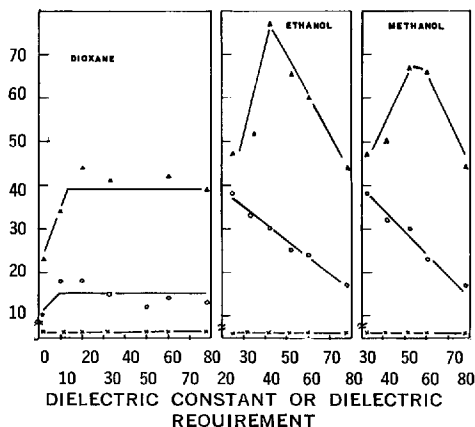
Fig. 4.—A plot of the solubility ratios (theobromine = 1) for the xanthines at the DR's found and in the pure solvents used. Key: $\times$, theobromine; $\bigcirc$, theophylline; $\blacktriangle$, caffeine.

solvent mixtures and the newly observed peak at a dielectric constant value of about 40.

It was felt to be instructive to view these solubility curves from the point of view of co-solvency. Ideally, a co-solvent effect would deal with a solubility curve having only one maximum. In this case, co-solvency efficiency could be expressed as the ratio of the magnitude of solubility at the maximum to the magnitude of solubility in either pure solvent.

Such, however, is not the case with the xanthines where a multiplicity of maxima occur. In order to determine the co-solvency efficiency of a given mixture, it would be necessary to determine the ratios of solubility at each dielectric requirement for a given xanthine relative to a pure solvent. Further, were one to compare the xanthines and solvent systems relative to one another, it would also be necessary to determine the co-solvency efficiency at each dielectric requirement relative to the pure solvent where the magnitude of solubility is the same, *i.e.*, water. In Table IV, the co-solvency efficiency for the xanthines in alcohol–water mixtures and dioxane–water mixtures is presented. The co-solvency efficiency has been defined as the solubility at a given dielectric requirement for each xanthine relative to the solubility in water for each xanthine. In other words, the co-solvency efficiency

is the number of times the solubility of a given xanthine is increased over the solubility in pure water at a given dielectric requirement.

From inspection of Table IV, several approximate trends can be delineated. The efficiency of increasing solubility relative to water can be obtained for the solvent systems under consideration from Table IV. For a dielectric requirement of 30, common to dioxane–water and ethanol–water only, dioxane is seen to cause the greatest co-solvent effect. At a dielectric requirement of 40, common to ethanol–water and methanol–water mixtures, ethanol shows the largest co-solvent effect. At DR's of 50 and 60, common to all three solvent systems, ethanol has the highest efficiency at both values, whereas dioxane is better than methanol at DR 50 and slightly better than methanol at DR 60. Furthermore, at the common DR of 50 and 60, ethanol and methanol discriminate the xanthines to a larger extent. For example, at a DR of 50, the solubility ratios for the xanthines vary about 0.3 in dioxane–water mixtures, about 1.0 in ethanol–water mixtures, and 1.1 in methanol–water mixtures. This also indicates that dioxane increases the solubility of the xanthines to about the same extent at a given DR, whereas both ethanol and methanol increase the solubility to varying extents at a given DR.

As can be seen, as the dielectric constant of the second component (alcohol, dioxane) increases, the greatest co-solvency efficiency occurs at higher dielectric requirement values. In the dioxane–water system, the maximum co-solvency effect (C.E.$_{max.}$) for the xanthines is seen to occur in the dielectric constant range of 20–30. By defining a term DR$_{max.}$, the dielectric constant of maximum co-solvency and taking the difference between this value and the dielectric constant of the second component, values of DR$_{max.}$ $-$ ϵ_2 can be obtained. These values are simply the number of dielectric constant units above the dielectric constant of the second component where co-solvency efficiency is maximized. By taking the average C.E.$_{max.}$ for the three xanthines in a given solvent system, values for DR$_{max.}$ $-$ ϵ_2 are determined as shown in Table V.

It is obvious that for each of these systems, the average co-solvency efficiency is maximized at a dielectric constant value of 21–23 units greater than the dielectric constant of the pure second component. Furthermore, as the DR$_{max.}$ increases in value with an increase in the dielectric constant of the second component, the DR$_{max.}$ value gets closer and closer to the dielectric constant of the common component of these solvent systems, *i.e.*,

TABLE IV.—SUMMARY OF THE CO-SOLVENT EFFICIENCY [SOLUBILITY (DR; mg./ml.)/(WATER mg./ml.)] FOR THE XANTHINES IN VARIOUS BINARY MIXTURES

System	DR 11–14	DR 20–22	DR 30–34	DR 41–43	DR 50–55	DR 58–61	Substance
Dioxane–water	2.9	3.8[b]	3.8[b]	...	2.5	2.3	Caffeine
	4.0	4.5[b]	3.5	...	2.5	1.9	Theophylline
	3.0	3.3[b]	3.3[b]	...	2.8	2.0	Theobromine
Ethanol–water	...	...	1.6	3.2[b]	3.0	2.5	Caffeine
	...	...	2.8	3.1[b]	3.1[b]	2.7	Theophylline
	...	...	1.6	1.8	2.0	1.8	Theobromine
Methanol–water	...	...	...	1.2	2.2[b]	2.1[b]	Caffeine
	...	...	...	1.9	2.5[b]	1.9	Theophylline
	...	...	...	1.0[a]	1.4[b]	1.4[b]	Theobromine

[a] See under *Results and Discussion.* [b] These values have been used to determine the average co-solvency efficiency.

TABLE V.—SUMMARY OF THE MAXIMUM AVERAGE CO-SOLVENT EFFICIENCY ($DR_{max.}$) FOR THE VARIOUS BINARY MIXTURES STUDIED AND THE DIFFERENCE, $DR_{max.} - \epsilon_2$

System	DR_{max}	ϵ_2	$DR_{max.} - \epsilon_2$	$DR_{max.} - \epsilon_1$
Dioxane–water	25	2	23	53
Ethanol–water	45	24	21	33
Methanol–water	55	32	23	23

TABLE VI.— SUMMARY OF THE $DR_{max.} - \epsilon_2$ FOR EACH OF THE XANTHINES IN THE BINARY MIXTURES USED

System	$DR_{max.} - \epsilon_2$ Caffeine	Theophylline	Theobromine
Dioxane–water	23[a]	18	26[a]
Ethanol–water	22	17	26
Methanol–water	22	20	24[a]

[a] Co-solvency maximum is equal at 2 DR's, thus average $DR_{max.}$ used.
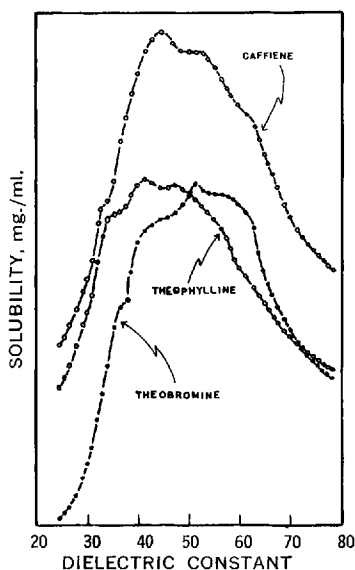

Fig. 5.—A plot of the solubility of caffeine, theophylline, and theobromine at 25° in mg./ml. *vs.* the dielectric constant of ethanol–water mixtures. Solubility magnitudes on overlapping uncommon scales. (See Figs. 1–3.)

water. Of course, these values should have different magnitudes, shown in column four, but they are proportionately related to the dielectric constant of the second component. Interesting enough, the average $DR_{max.}$ in methanol–water mixtures is equidistant between the dielectric constants of the pure components. It would be of more interest to view the xanthines in a comparative sense since in the xanthine drugs there exists a chemical difference (for caffeine) and theophylline and theobromine are positional isomers. Each xanthine in the three solvent systems under consideration can be handled separately relative to the dielectric constant

of maximum co-solvency. In this case, the exact value of the DR (Table I) at maximum co-solvency has been used or when the co-solvency efficiency was equal at 2 DR's, an average value of the exact DR was used. Thus, the $DR_{max.} - \epsilon_2$ for each xanthine in the solvent systems used have been summarized in Table VI.

In order to illustrate the variation of $DR_{max.} - \epsilon_2$ found for the xanthines, a composite figure is given (Fig. 5) of the solubility of each xanthine in mg./ml. for ethanol–water mixtures.

Although caffeine on an individual basis is the same as the average value, *i.e.*, 21–23, theophylline falls below the average range, while theobromine falls above the average range. Furthermore, the variation of theophylline and theobromine from the average value is about the same, theophylline being 3–4 units below the average, whereas theobromine is 3–4 units above the average. The order of the xanthines with respect to the increasing magnitude of $DR_{max.} - \epsilon_2$ is theophylline, 18 < caffeine, 22 < theobromine, 25. As has been noted previously, the magnitude of the co-solvency efficiency (Table IV) for theophylline was equal to or greater than that of either caffeine or theobromine in the solvent systems studied.

The DR's obtained in this study for the xanthines in alcohol–water mixtures showed good correlation with the DR's obtained previously with dioxane–water mixtures. A consistent new peak at a dielectric constant of about 40 was also found for these alcohol–water mixtures. In this regard, the solubilities of the xanthines are being determined in a glycol ether (ethylcellosolve)–water mixtures to see if the DR of 40 is unique to the alcohols.

The xanthines show a low degree of DR sensitivity to concentration notation for the alcohol–water mixtures.

The solubility ratios, defining theobromine as unity, in the pure solvents and at the dielectric requirements found showed a linear trend for theophylline and a curve having a maxima for caffeine.

The co-solvency efficiency, defined as the ratio of the magnitude of solubility at a given DR to the magnitude of solubility in water, showed maximum efficiency on the average at about 20 dielectric constant units above the dielectric constant of the pure second component. For the individual xanthines, the $DR_{max.} - \epsilon_2$ was seen to be in the order, theophylline < caffeine < theobromine; however, the co-solvent efficiency for theophylline was equal to or greater than either caffeine or theobromine in all the solvent systems studied. This would imply that the solubility of theophylline is affected to a greater degree in contrast to caffeine or theobromine and the dielectric constant of maximum co-solvency may lie closer to the dielectric constant of the pure second component.

The solubilities of the xanthines are being studied in ethylcellosolve–water mixtures relative to the above points and the authors' results will be the subject of future communications.

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