

Solubility Profiles for the Xanthenes in Aqueous Solutions of a Glycol Ether II

Ethyl Cellosolve

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The solubilities of the xanthenes were determined in ethyl cellosolve-water mixtures as a function of the dielectric constant of these solvent mixtures. This mixture of a glycol ether with water was chosen in order to contrast the dielectric requirements found with those observed in alcohol-water and dioxane-water mixtures. The dielectric requirements found for the ethyl cellosolve-water system correlate to a good degree with previous findings. A dielectric requirement of 40 was also found which was not found in dioxane-water mixtures but was present in the alcohol-water mixtures. These systems were experimentally designed so that solubility curves could be expressed in various concentration notations as well as mole fraction.

IN A CONTINUING effort of investigating the relative consistency of dielectric requirements (DR's) for a given solute(s) in various binary mixtures (1-3), the present study was undertaken. The dielectric requirement is defined as the dielectric constant of maximum solubility in a given solvent mixture.

It had been found (2, 3) that the DR's for the xanthenes in aqueous mixtures of a cyclic ether, dioxane, and normal alkyl alcohols, ethanol and methanol, were fairly consistent; however, in the aqueous alcoholic systems a new peak at a DR of about 40 was also found. It was felt important to see if this new peak at a value of 40 could be found in another aqueous mixture with a semi-polar solvent. In this case, a glycol ether was chosen considering this to be sufficiently different in nature from a cyclic ether and a normal alcohol. The solvent chosen was ethyl cellosolve since it had a dielectric constant intermediate between dioxane and the alcohols and also had the property of being infinitely soluble in water. The dielectric constant range produced by these mixtures would be about 15-78, and it was expected that this range should accommodate 4 of the 5 DR's found in dioxane-water mixtures having values of about 20, 30, 50, and 60.

These systems were experimentally designed through density measurements so that solubility could be expressed in various concentration notations as well as mole fraction. It had been shown that the observed DR's are concentration notation dependent (3) and it was felt that these systems should be similarly treated.

EXPERIMENTAL

Solubility Determination.—The protocol for solubility determinations has been described previously (1-3). All runs were done at 25°, and each of the three runs performed was subjected to both spectrophotometric and gravimetric analysis. Internal averaging was done for each run, and the results reported are for the three-run average.

Materials.—Caffeine was obtained from Nepera Chemical Co., theophylline from Matheson, Coleman and Bell, 7094Tx450, and theobromine N.F. from Penick, lot NBT 4092. Ethyl cellosolve was obtained from Union Carbide, 5753753. Distilled water was used throughout this study. All materials were used directly as supplied by the manufacturer.

Equipment.—A water bath with attendant controls was used as an equilibration environment at 25°. Twenty-four hours was the time allowed and found sufficient 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 in the various concentration conventions noted *versus* the dielectric constant of ethyl cellosolve-water mixtures is shown in Fig. 1. The concentration notation of mg./Gm. of solvent has been omitted from this figure and subsequent figures since the solubility curve coincides very closely to the mg./Gm. of solution solubility curve. In Figs. 2 and 3, the solubility of theophylline and theobromine plotted in the usual fashion are shown.

The DR's observed in the ethyl cellosolve-water system for the xanthenes have average values of about 30, 40, 48, and 60. The DR's in ethyl cellosolve-water mixtures and dioxane-water mixtures (2) have been summarized in Table I. The DR of 40, which was observed in alcohol-water mixtures (3), was also found in ethyl cellosolve-water mixtures; however, this DR of 40 was not found in the dioxane-water system. Thus, this new DR is not unique to alcohol-water mixtures since it has also been found in ethyl cellosolve-water mixtures. To illustrate this point, a composite figure has been prepared showing the solubility

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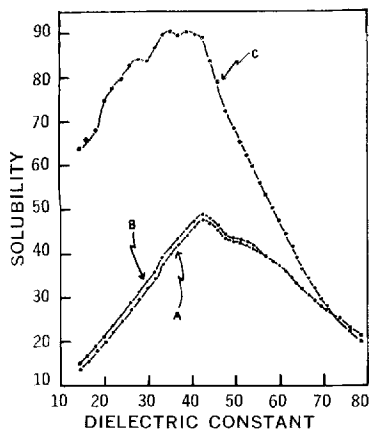


Fig. 1.—A plot of the solubility of caffeine at 25° vs. the dielectric constants of ethyl cellosolve-water mixtures. Key: A, solubility expressed as mg./ml.; B, solubility expressed as mg./Gm. of solution; C, solubility expressed as mole fraction (m.f. $\times 10^4$).

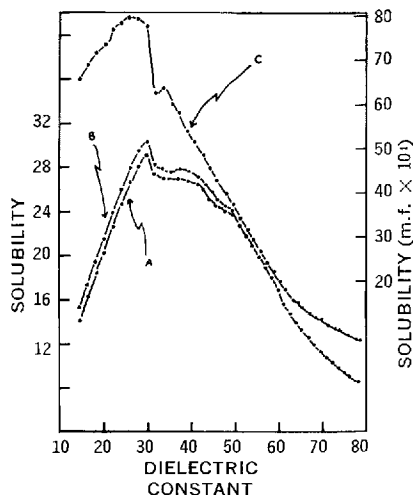


Fig. 2.—A plot of the solubility of theophylline at 25° vs. the dielectric constants of ethyl cellosolve-water mixtures. Key: A, solubility expressed as mg./ml.; B, solubility expressed as mg./Gm. of solution; C, solubility expressed as mole fraction (m.f. $\times 10^4$) using scale at right hand side of figure.

curves on a mg./ml. basis for caffeine in the four binary solvent systems studied. This is shown in Fig. 4. In the case of dioxane-water mixtures, a dielectric constant of 40 is seen to fall in a valley between the third and fourth DR's for this system. If a peak or shoulder does exist at about this value it would be, at best, difficult "to see" due to the nature of the curve and the inherent experimental variation involved. This figure also reveals another interesting point. At a dielectric requirement of 30, common to three binary mixtures, dioxane-water mixtures produce a strong peak, whereas both ethanol-water and cellosolve-water mixtures produce only a weak shouldering effect. At a di-

electric constant of about 50, common to all four binary mixtures, aqueous dioxane and aqueous methanol produce definite peaks; whereas, aqueous cellosolve and aqueous ethanol again produce a shouldering effect.

There is a probability that various hydrates/solvates (2), each with its own solubility characteristics, cause these complex individually overlapping solubility curves. It was thought that the production of a new peak (DR) in a given system would

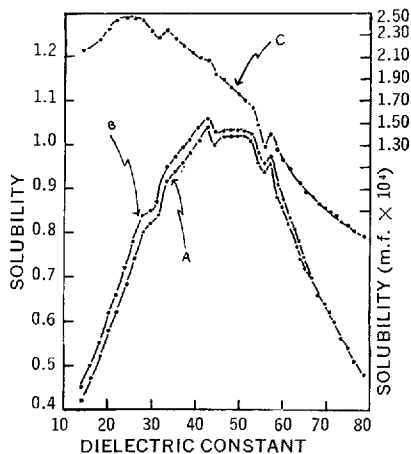


Fig. 3.—A plot of the solubility of theobromine at 25° vs. the dielectric constants of ethyl cellosolve-water mixtures. Key: A, solubility expressed as mg./ml.; B, solubility expressed as mg./Gm. of solution; C, solubility expressed as mole fraction (m.f. $\times 10^4$) using scale at right hand side of figure.

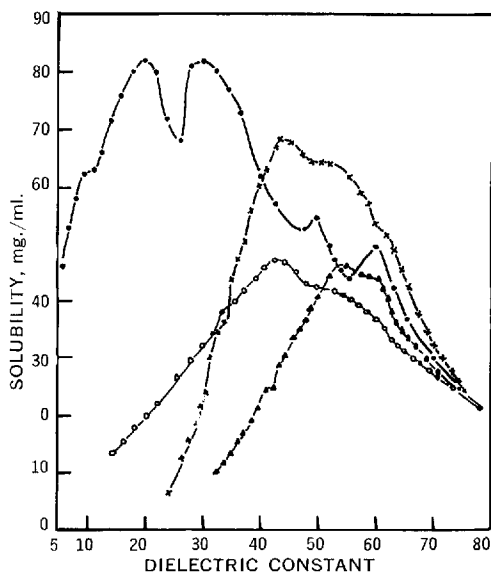


Fig. 4.—A plot of the solubility of caffeine at 25° in mg./ml. as a function of the dielectric constant of various binary mixtures. Key: ●, dioxane-water; ○, ethyl cellosolve-water; ×, ethanol-water; ▲, methanol-water.

TABLE I.—SUMMARY OF DR'S FOR XANTHINES IN AQUEOUS ETHYL CELLOSOLVE AND AQUEOUS DIOXANE^a

System	Dielectric Constant Range	Caffeine					
		DR ₁	DR ₂	DR ₃	DR ₄	DR ₅	DR ₆
Dioxane-water	2-78	11	20	30	..	50	61
Cellosolve-water	14-78	..	? ^b	32	43	50	62
Theophylline							
Dioxane-water	2-78	14	20	34	..	50	61
Cellosolve-water	14-78	..	? ^b	30	37	46	61
Theobromine							
Dioxane-water	2-78	14	22	34	..	50	61
Cellosolve-water	14-78	..	? ^b	32	42	48	58

^a Data from Reference 1. ^b See under Results and Discussion and Table II.

TABLE II.—SUMMARY OF FIRST OR EXPECTED DR FOR XANTHINES IN BINARY MIXTURES STUDIED^a

Systems	ϵ_2	DR	DR - ϵ_2	Peak or Shoulder Observed
Dioxane-water	2.2	13	10.8	Yes
Ethanol-water	24.3	34.5	10.2	Yes
Methanol-water	32.4	42.0	9.6	Yes
Ethyl cellosolve-water	14.5	20.7 ^b	6.2	No

^a Data from References 2 and 3. ^b Expected DR of about 20-22 found in dioxane-water mixtures.

be possible at the expense of DR's close to this new value. In other words, a given species could exist in two different solvent mixtures, depending on the composition of the mixtures and each component's contribution to the solvated state of that species. This does not seem to be the case in alcohol-water or cellosolve-water mixtures. Although a new DR of about 40 is found, the DR's of about 30 and 50 are also present which indicate that the DR of 40 is not a mixture of the two DR's surrounding it. However, it can also be seen that the strong peak at a DR of 30 in dioxane-water is reduced to a

slight shouldering effect in aqueous ethanol and aqueous ethyl cellosolve. It would seem that this is partially due to the dielectric constant range of the solvent system chosen. The co-solvency efficiency has been discussed previously (3) and will be further elucidated in a latter portion of this communication.

Table I also shows that a DR of about 20 found in dioxane-water mixtures was not found in ethyl cellosolve-water mixtures. The dielectric constant range of aqueous cellosolve, *i.e.*, 14.5-78, certainly encompasses a dielectric constant of 20, but the solubility curves did not indicate any peaks or shoulders in this dielectric constant area. Upon re-examination of the data for the four binary mixtures studied, it was noted that the first DR observed starting from the second or semipolar component was a certain number of dielectric constant units above the value for the second component. Table II summarizes the first average DR found or expected and the difference between this value and the dielectric constant of the second component.

It is apparent that the first or expected DR resides at a definite value above the dielectric constant of the second component. The DR observed for the first three binary mixtures is seen to be about 10-11

TABLE III.—SUMMARY OF DR'S FOR XANTHINES IN ETHYL CELLOSOLVE-WATER MIXTURES IN VARIOUS CONCENTRATION CONVENTIONS NOTED

Concn. Notation	Caffeine				Theophylline				Theobromine				
	DR ₁	DR ₂	DR ₃	DR ₄	DR ₁	DR ₂	DR ₃	DR ₄	DR ₁	DR ₂	DR ₃	DR ₄	DR ₅
mg./ml.	32	43	50	62	30	37	46	61	..	32	42	49	57
mg./Gm. soln.	32	43	50	62	30	37	48	61	..	30	42	49	57
mole fraction	19	28	35	39	..	20	26	33	25	33	43	50	57

TABLE IV.—SUMMARY OF SOLUBILITY OF XANTHINES (IN mg./ml.) IN EACH PURE SOLVENT AND AT COMMON DR'S AND SOLUBILITY RATIOS DEFINING THEOBROMINE AS UNITY

	Solubility, mg./ml.					
	Ethyl Cellosolve	DR 30	DR 40	DR 50	DR 60	Water
Caffeine	13.6	35	48	43	36	21.5
Theophylline	14.1	29	27	25	16	8.3
Theobromine	0.41	0.84	1.04	1.02	0.96	0.50
	Solubility Ratios					
	Ethyl Cellosolve	DR 30	DR 40	DR 50	DR 60	Water
Caffeine	33	42	46	42	37	42
Theophylline	34	35	26	24	16	17
Theobromine	1	1	1	1	1	1

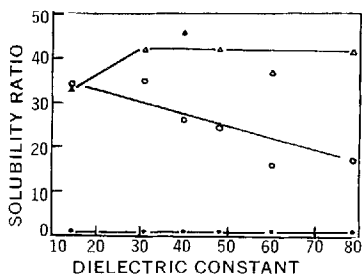


Fig. 5.—A plot of the solubility ratios for theophylline and caffeine relative to theobromine (unity) in each pure solvent and at the common dielectric requirements. Key: ●, theobromine; O, theophylline; ▲, caffeine.

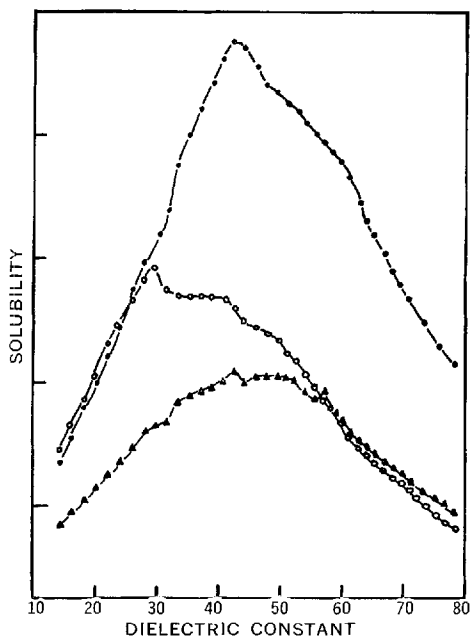


Fig. 6.—A plot of the solubility curves for caffeine (●), theophylline (O), and theobromine (▲) vs. the dielectric constants of ethyl cellosolve-water mixtures. The solubility scale does not describe magnitude since only the nature of the curves is being compared.

units above ϵ_2 . Thus, a peak or shoulder may not be found unless the second component has a dielectric constant about 10–11 units below the expected DR. This approximate value of 10–11 units is, of course, only operative for the range and systems studied, and may only apply for the solutes under consideration.

It is interesting to note in this regard, that the suspected shouldering for theobromine at a dielectric constant of 38 in methanol-water mixtures (3) resides only 5.6 dielectric constant units above ϵ_2 and this probably indicates it cannot be seen.

Since there can be a variation of 3–4 dielectric constant units (2) in any given DR for these solutes, it is possible that theobromine falls below this approximate difference ($DR - \epsilon_2$) of 10–11 units. The very low solubility of theobromine also miti-

gates easily detecting shouldering in the solubility curve.

It has previously been shown (3) that the value of the DR was sensitive to concentration notation. In the case of succinic acid, there was greater DR sensitivity for dioxane (mol. wt. = 88) than for ethanol (mol. wt. = 46) in going from the pharmaceutical convention to mole fraction. For the xanthines (3), it was shown there was low DR sensitivity to methanol (mol. wt. = 32) and ethanol (mol. wt. = 46). In Figs. 1–3, it can be seen that there is high DR sensitivity for caffeine and theophylline, but low sensitivity for theobromine. It is felt that the very low solubility of theobromine and very small incremental changes of solubility with varying composition damps the possible shifting with a high molecular weight solvent such as cellosolve (mol. wt. = 90). This could also possibly account for the new DR at a value of 25, since a small deviation of a given value from a smooth curve could produce a shoulder or peak depending on the magnitude of the deviation. Assuming caffeine and theophylline to be typical, it would seem that DR sensitivity to various concentration notations depends upon the molecular weight of the second component. Since water is the other component common to all these binary mixtures, DR sensitivity to concentration notation would also depend upon the difference in molecular weight of the two components used.

The DR's found for the xanthines in ethyl cellosolve-water mixtures in the various concentration notations used are summarized in Table III.

Since the DR's found for the xanthines were relatively constant, it was felt that these solubility curves might be parallel to one another, indicating proportionality of the magnitude of solubility. Consequently, the ratios of the solubilities in each pure solvent and at the common DR's were taken defining the solubility of theobromine as unity. The solubility of the xanthines in mg./ml. for each pure solvent and at the common DR's and the solubility ratios have been summarized in Table IV. Previous results (2) indicated that the ratios in dioxane-water mixtures were closer to the solubility ratios in pure water, and this was felt to imply the importance of aqueous solvation. Other results (3) for the xanthines in aqueous methanol and aqueous ethanol showed a potentiated effect for caffeine and a linear rise for theophylline in going from the solubility ratios in pure water to pure ethanol and methanol. The solubility ratios in ethyl cellosolve-water mixtures have been calculated and are presented in Fig. 5. In this case, it can be seen that the solubility ratios for theophylline rise approximately linearly going toward pure ethyl cellosolve and are similar to the results observed in alcohol-water mixtures. On the other hand, the solubility ratios for caffeine are close to the ratios in pure water, being similar to the results observed in dioxane-water mixtures. This would indicate that each of the xanthines interacts differently with the second component in terms of the nature of the hydrate/solvate formed.

In order to visualize the above, a composite figure has been prepared in which the solubility of the xanthines in mg./ml. has been plotted versus the dielectric constants of ethyl cellosolve-water mixtures (Fig. 6). Several things can be noted in this

TABLE V.—SUMMARY OF CO-SOLVENCY EFFICIENCY [SOLUBILITY, mg./ml., DR_x/SOLUBILITY, mg./ml., WATER] FOR XANTHINES IN ETHYL CELLOSOLVE-WATER MIXTURES AT COMMON DR'S FOUND

System	DR 30	DR 40	DR 50	DR 60	Substance
Ethyl cellosolve-water	1.63	2.23	2.00	1.67	Caffeine
	3.49	3.25	3.01	1.93	Theophylline
	1.68	2.08	2.04	1.92	Theobromine

TABLE VI.—SUMMARY OF DIFFERENCE OF MAXIMUM CO-SOLVENT EFFICIENCY (DR_{max.}) AND DIELECTRIC CONSTANT OF THE SECOND COMPONENT (ϵ_2) FOR INDIVIDUAL XANTHINES IN ETHYL CELLOSOLVE-WATER AND OTHER MIXTURES^a

Substance	Ethyl Cellosolve DR _{max.} - ϵ_2	DR _{max.} - ϵ_2 ^a
Caffeine	28	22-23
Theophylline	16	17-20
Theobromine	28	24-26

^a Data from Reference 3.

figure. Theophylline shows a strong peak at a DR of 30, whereas both caffeine and theobromine indicate slight shouldering effects. Caffeine at a DR of 42 shows a peak and at a DR of 60 a shoulder in the solubility curve. However, theobromine shows weak peaks at both DR's of about 42 and 60. Variations of this type lead into a consideration of co-solvency efficiency. The co-solvency efficiency is defined as the solubility at a given dielectric requirement relative to the solubility in water for a given solute. In other words, the co-solvency efficiency is the number of times the solubility of a given solute is increased over the solubility in pure water at a given dielectric requirement. This term has been defined previously (3) and it was found that for previous systems studied the dielectric constant of average maximum co-solvency for the xanthines occurred at 21-23 units above the dielectric constant of the second component, ϵ_2 . Furthermore, it was also found that on an individual basis for each xanthine, caffeine fell in the average of 21-23 units while theophylline fell below, *i.e.*, 17-20, and theobromine was above the average, *i.e.*, 24-26. The co-solvency efficiencies have been tabulated and are given in Table V. The values of DR_{max.} - ϵ_2 on an individual basis for each xanthine in ethyl cellosolve-water mixtures have been summarized in Table VI. The values obtained for the previous binary mixtures studied (3) have been included to contrast the xanthines on an individual basis. It can be seen that both caffeine and theobromine deviate from the values found previously, but theophylline is about the same relative to DR_{max.} - ϵ_2 in ethyl cellosolve-water mixtures.

Several things can be noted here; first, the magnitude of solubility of theophylline in pure ethyl cellosolve (Table IV) is higher than the solubility of caffeine. This is the first time that this reverse order has been found in the solvents studied. Normally, the order of solubility is caffeine > theophylline > theobromine. Second, the co-solvency efficiency of the present solvent system toward theophylline is greater than either caffeine or theobromine at the maximum, and this has been noted previously (2, 3) in dioxane-water and alcohol-water mixtures. The solubility ratios (Fig.

5) also indicated a mixed pattern for ethyl cellosolve-water mixtures relative to the patterns found in previous mixtures.

Although there seems to be a generally patternized response for the xanthines in diverse binary mixtures, more studies should be conducted to resolve many of the points brought out in these communications.

Some of the points intended for future study would include the possible dependency of DR's on the nature, type, and dielectric constant span produced by the second or semipolar component.

It may also be judicious to investigate the nature of the xanthine species involved when at common DR's a strong peak or weak shoulder is produced.

SUMMARY

The DR's obtained in this study for the xanthines in ethyl cellosolve-water mixtures showed good correlation with the DR's found in alcohol-water mixtures (3) and dioxane-water mixtures (2) except the former two systems showed a consistent new peak at a DR of about 40. The expected DR at a value of 20 was not found in ethyl cellosolve-water mixtures and this was felt to be due to the closeness of the expected DR to the ϵ_2 (Table II).

The xanthines, at least caffeine and theophylline, showed a high DR sensitivity to concentration notation and this is felt to be due to the high molecular weight of the second component.

The solubility ratios, defining theobromine as unity, showed a pattern for caffeine similar to that found with dioxane-water mixtures, whereas theophylline showed a pattern similar to that found with alcohol-water mixtures but dissimilar to that found in dioxane-water mixtures. The co-solvency efficiency and the DR_{max.} - ϵ_2 showed relative consistency relative to order and magnitude.

In aqueous dioxane and aqueous alcohol (2, 3), the difference DR_{max.} - ϵ_2 was 17-20 units for theophylline, whereas the difference in ethyl cellosolve-water mixtures was about 16 units.

For caffeine and theobromine (2, 3), the range of DR_{max.} - ϵ_2 in the former mixtures was 22-23 and 24-26 units, respectively. In ethyl cellosolve-water mixtures DR_{max.} - ϵ_2 for caffeine and theobromine were about 28 units. The order of DR_{max.} - ϵ_2 in the solvent system studied were found to be theophylline < caffeine < theobromine. The higher maximum co-solvency efficiency for theophylline in all these solvent systems (3) is relatively consistent, the order being theophylline > caffeine > theobromine except in ethanol where theophylline \approx caffeine.

REFERENCES

- (1) Paruta, A. N., Sciarrone, B. J., and Lordi, N. G., *J. Pharm. Sci.*, **53**, 1349(1964).
- (2) *Ibid.*, **54**, 838(1965).
- (3) Paruta, A. N., and Irani, S. A., *ibid.*, **55**, 1055(1966).