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SOLUBILITY OF VARIOUS SULFONAMIDES IN N-ALKANOLS

I. EFFECT OF POLARITY AND TEMPERATURE

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ABSTRACT

The solubilities of several sulfonamides were studied at three temperatures over a wide spectrum of polarity of normal alcohols. The sulfonamides chosen for study were sulfasoxazole, sulfadimethoxine, sulfasomidine and sulfadiazine and their solubility behavior in various alcohols such as methanol through 1-decanol at 25°, 30° and 37°.

Solubility in alcohols was found to increase with temperature and the rank order of solubility at any temperature was found to be in the general order of sulfasoxizole, sulfadimethoxine, sulfasomidine and sulfadiazine. Solubility was found to be highest in

methanol and diminished with increasing chain length of the alcohol.

The solubility magnitude for several of the sulfonamides gave an interesting reversal in 1-decanol and all the results obtained are discussed further in this communication.

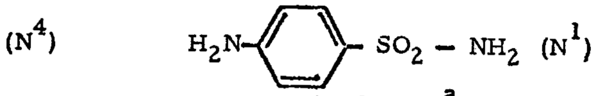
INTRODUCTION

The present study is an investigation of the solubility of four chemically different sulfonamides in a series of normal alcohols. The solubilities were determined at three temperatures which were experimentally varied over a narrow range, 25°, 30° and 37°.

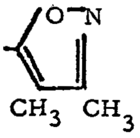
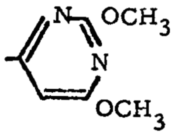
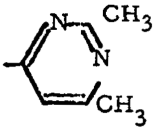
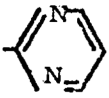
The sulfonamides chosen may all be generally classified as antibacterial agents; however, their structural differences result in varying physical-chemical properties. Table I shows the structure of the parent moiety, sulfanilamide, and the positional substituents for the substances under study (1). It is noteworthy that the N^4 substituent is a primary amine in all cases whereas the N^1 substituents vary from a pyrimidine to an oxazole. Unlike other useful drugs such as the barbiturates or esters of para-hydroxybenzoic acid, these particular sulfonamides do not follow a homologous series. Thus, magnitudes of solubility for each solute in a particular solvent must be viewed only in

TABLE I

STRUCTURES OF SULFONAMIDES



Sulfanilamide[a]

Sulfonamide[a]	N^1 Substitutions	N^4
Sulfisoxazole		H_2N
Sulfadimethoxine		H_2N
Sulfisomidine		H_2N
Sulfadiazine		H_2N

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[a] C. Wilson and O. Gisvold. *Textbook of Organic and Pharmaceutical Chemistry*, 4th ed. J. B. Lippencott, Philadelphia, 1962, p. 254.

terms of relative substituent effects; there can be no regular comparative effect such as increasing chain length.

Several appropriate physical-chemical properties of each sulfonamide are presented in Table II (2-4). The structural difference of each drug is reflected by the different melting points, molecular weights, and ionization constants. The two ionization

TABLE II

PHYSICAL-CHEMICAL PROPERTIES OF SULFONAMIDES USED IN THIS STUDY

Sulfonamide	[a]pK2	[a]pK1	[a]pKi (isoelectric)	Molecular Weight	[b]Melting Point (°C)
Sulfisoxazole	1.55	5.1	3.3	267	192-195
Sulfadimethoxine	2.02	6.7	4.4	310	[c]197-202
Sulfisomidine	2.36	7.5	4.9	278	243
Sulfadiazine	2.00	6.48	4.2	250	252-256

[a] T. Koizumi, T. Arita and K. Kakemi, <u>Chem. Pharm. Bull.</u>, <u>12</u>, 413 (1964).

[b] <u>Remington's Practice of Pharmacy</u>, 12th ed., Mack Publishing Co., Easton, Penna., 1961.

[c] <u>The National Formulary</u>, XIII ed., American Pharmaceutical Association, Washington, D.C., 1970, p. 672

constants for each sulfonamide derive from the ionizable groups at the N^1 and N^4 positions. The pK2 values attributed to the ionization of the N^4 group for the three pyrimidine-substituted sulfonamides are quite close to one another, while that for the oxazole-substituted sulfonamide is about 0.6 pK units less than the average of the others, a four fold difference. On the other hand, the pK1, which derives from the N^1 substitution, varies by almost one hundred times (two logarithm units) among the compounds studied. Foernzler and Martin (5) have investigated several fulfonamides using molecular orbital calculations as a measure of the electronic characteristics of the molecule. These authors showed that the electronic characteristics of the molecule. These authors showed that the electronic characteristics of the molecule. These authors showed that the electronic charge was approximately constant at the N^4 position, but varied at the N^1 position. It may be intimated that the electronic characteristics of the sulfonamides are functionally related to the ionization constants.

The solubility of any substance is dependent on the unique interactions that occur between the solute and the solvent. Further, these interactions and their magnitudes will depend both qualitatively and quantitatively on the structure and physical-chemical properties of the solute.

EXPERIMENTAL

Reagents - The solvents used were methanol[1], ethanol[2], 1-propanol[3], 1-butanol[4], 1-pentanol[5], 1-octanal[6], and 1-decanol[7]. Refractive index values and densities were found to be in agreement with literature values. The sulfonamides used were sulfasoxazole[8], sulfadiazine[9], sulfadimethoxine[10], and sulfasomidine[11]. Melting points of all sulfonamides agreed with literature values.

Procedure - The solubilities were determined by a previously reported method (6). Equilibrium was established prior to assay and all temperatures were maintained within ± 0.1° throughout the equilibrium period. Solute concentrations were determined by spectrophotometric assay[12] at predetermined wavelength.

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[1] Spectrograde solvent, Mallinckrodt Chemical Works.

[2] U.S. Industrial Chemicals Co.

[3] Baker Analyzed Reagent, J.T. Baker Chemical Co.

[4] Mallinckrodt Chemical Works.

[5] Fisher Scientific Co.

[6] Fisher Scientific Co.

[7] Matheson, Coleman and Bell

[8] Lot 378067, Courtesy of Hoffman-LaRoche, Inc.

[9] Lot WO2235, Courtesy of Eli Lilly and Co.

[10] Lot 203027, Courtesy of Hoffman-LaRoche, Inc.

[11] Lot E2498, Courtesy of Ciba Pharmaceutical Co.

[12] Cary Model 16 Spectrophotometer

Sulfonamide Solubilities in the Normal Alcohols

The solubilities of the particular sulfonamides in the n-alcohols used are given in Tables III through VI. Notations

Table III: A Summary of the Solubility of Sulfasoxazole Expressed in mg. /ml. and Mole Fraction in N-Alkanols at the Noted Temperatures

Alcohol	Solubility mg. /ml.	 mole fraction x 10^3	Temp.
Methanol	49.4	7.52	25°
Methanol	56.0	8.57	30°
Methanol	67.9	10.4	37°
Ethanol	19.1	4.18	25°
Ethanol	22.6	4.99	30°
Ethanol	26.6	5.90	37°
1-Propanol	7.95	2.23	25°
1-Propanol	9.53	2.69	30°
1-Propanol	12.2	3.44	37°
1-Butanol	4.31	1.48	25°
1-Butanol	5.30	1.83	30°
1-Butanol	6.53	2.26	37°
1-Pentanol	2.61	1.06	25°
1-Pentanol	3.20	1.30	30°
1-Pentanol	3.95	1.62	37°
1-Octanol	.94	.55	25°
1-Octanol	1.17	.69	30°
1-Octanol	1.40	.83	37°
1-Decanol	.57	.41	25°
1-Decanol	.68	.49	30°
1-Decanol	.85	.61	37°

Table IV: A Summary of the Solubility of Sulfadimethoxine Expressed in mg. /ml. and Mole Fraction in N-Alkanols at the Noted Temperatures

Alcohol	Solubility		Temp.
	mg. /ml.	mole fraction x 10^4	
Methanol	8.84	11.6	25°
Methanol	10.5	13.9	30°
Methanol	13.4	17.7	37°
Ethanol	3.78	7.14	25°
Ethanol	4.52	8.58	30°
Ethanol	5.74	11.0	37°
1-Propanol	1.95	4.71	25°
1-Propanol	2.32	5.63	30°
1-Propanol	3.20	7.79	37°
1-Butanol	1.31	3.89	25°
1-Butanol	1.77	5.26	30°
1-Butanol	2.25	6.70	37°
1-Pentanol	.98	3.41	25°
1-Pentanol	1.26	4.41	30°
1-Pentanol	1.60	5.65	37°
1-Octanol	.40	2.04	25°
1-Octanol	.54	2.78	30°
1-Octanol	.70	3.59	37°
1-Decanol	.36	2.24	25°
1-Decanol	.44	2.69	30°
1-Decanol	.54	3.37	37°

both in mg. /ml. and mole fraction concentration are given at the various temperatures used in this study.

Table V: A Summary of the Solubility of Sulfasomidine Expressed in mg. /ml. and Mole Fraction in N-Alkanols at the Noted Temperatures

	Solubility		
Alcohol	mg. /ml.	mole fraction x 10^4	Temp.
Methanol	7.64	11.2	25°
Methanol	8.67	12.7	30°
Methanol	11.2	16.5	37°
Ethanol	2.63	5.53	25°
Ethanol	3.02	6.38	30°
Ethanol	3.86	8.20	37°
1-Propanol	1.57	4.23	25°
1-Propanol	1.81	4.89	30°
1-Propanol	2.39	6.48	37°
1-Butanol	1.04	3.44	25°
1-Butanol	1.26	4.17	30°
1-Butanol	1.67	5.56	37°
1-Pentanol	.73	2.84	25°
1-Pentanol	.88	3.43	30°
1-Pentanol	1.16	4.54	37°
1-Octanol	.24	1.36	25°
1-Octanol	.32	1.83	30°
1-Octanol	.43	2.44	37°
1-Decanol	.26	1.80	25°
1-Decanol	.30	2.04	30°
1-Decanol	.37	2.53	37°

As expected, the data in these tables show that the solubility of the sulfonamides in each normal alcohol increased with increasing temperature.

Table VI: A Summary of the Solubility of Sulfadiazine Expressed in mg. /ml. and Mole Fraction in N-Alkanols at the Noted Temperatures

Alcohol	Solubility mg. /ml.	Solubility mole fraction x 10^5	Temp.
Methanol	1.18	19.3	25°
Methanol	1.40	22.9	30°
Methanol	1.82	29.9	37°
Ethanol	.33	7.68	25°
Ethanol	.40	9.36	30°
Ethanol	.53	12.4	37°
1-Propanol	.14	4.32	25°
1-Propanol	.18	5.45	30°
1-Propanol	.25	7.44	37°
1-Butanol	.087	3.18	25°
1-Butanol	.111	4.09	30°
1-Butanol	.153	5.66	37°
1-Pentanol	.061	2.63	25°
1-Pentanol	.076	3.31	30°
1-Pentanol	.106	4.61	37°
1-Octanol	.022	1.41	25°
1-Octanol	.028	1.76	30°
1-Octanol	.042	2.65	37°
1-Decanol	.097	7.4	25°
1-Decanol	.105	8.04	30°
1-Decanol	.123	9.47	37°

Figure 1 is the plot of the solubility data for the mole fraction solubilities of sulfasoxazole in the normal alcohols. It

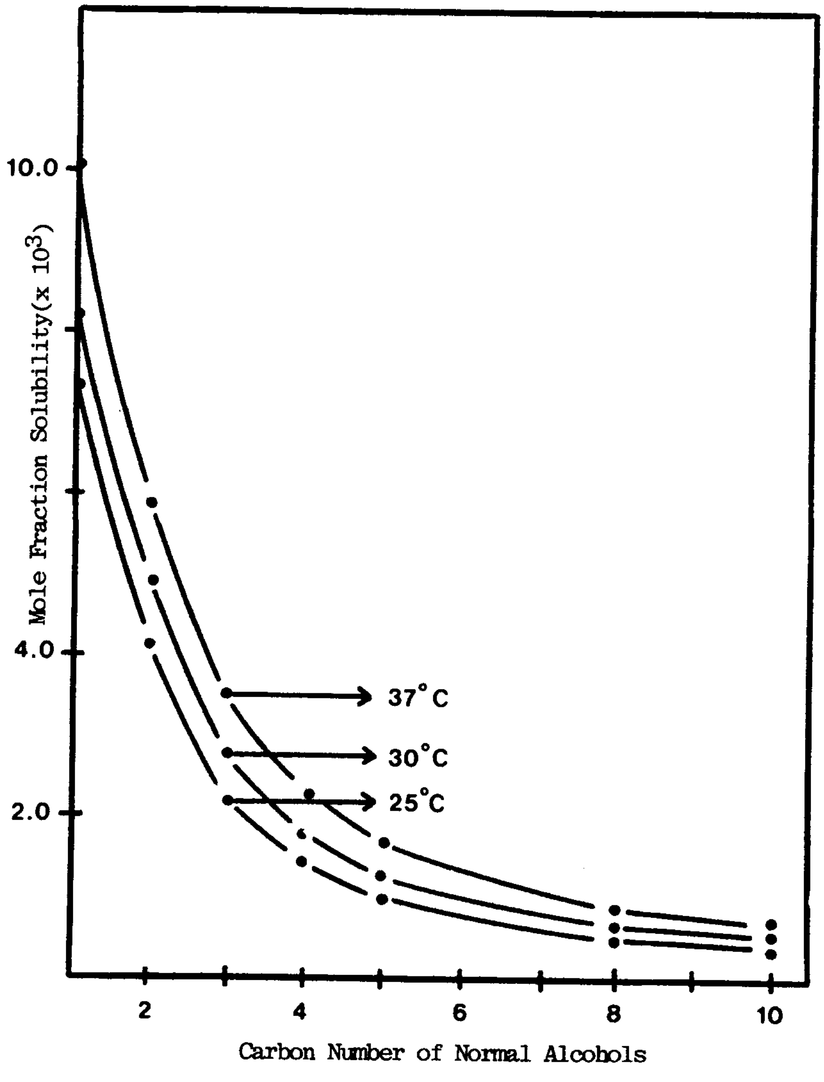

Figure 1 - Mole Fraction Solubility of Sulfisoxazole <u>Versus</u> Carbon Number of Normal Alcohols.

shows that the solubilities decrease consistently with increasing chain length of the alcohols, and the maximum solubility occurs in methanol. The three curves in figure 1 for each temperature are parallel which indicates that the same solubility mechanism is operative throughout the temperature range studied.

Data for sulfadimethoxine solubilites are shown in figure 2. With respect to the temperature effect these curves display the same characteristics as those in figure 1; however, in figure 2 the mole fraction solubility for the drug at 25 °C is slightly higher in decanol than in octanol.

Table IV shows that up to octanol the sulfadimethoxine solubilities in terms of mole fraction decrease consistently with increasing chain length of the alcohol but from octanol to decanol, the trend is reversed. On the other hand, the mg. /ml. solubilities decrease consistently with increasing chain length of the alcohol, and there is no reversal of trend between octanol and decanol. It appears that solubilities in a series of solvents may vary according to which concentration units are chosen. Paruta (7) has shown that the interpretation of solubility data depends greatly upon units chosen to express concentration, and in the present case, there are two reasons why the mole fraction data do not follow the same trend as the mg. /ml. data. First, the mole fraction solubility is dependent upon the mg. /ml. concentration of the solute component and upon the molecular weights of both the solute and the solvent. Second, when the

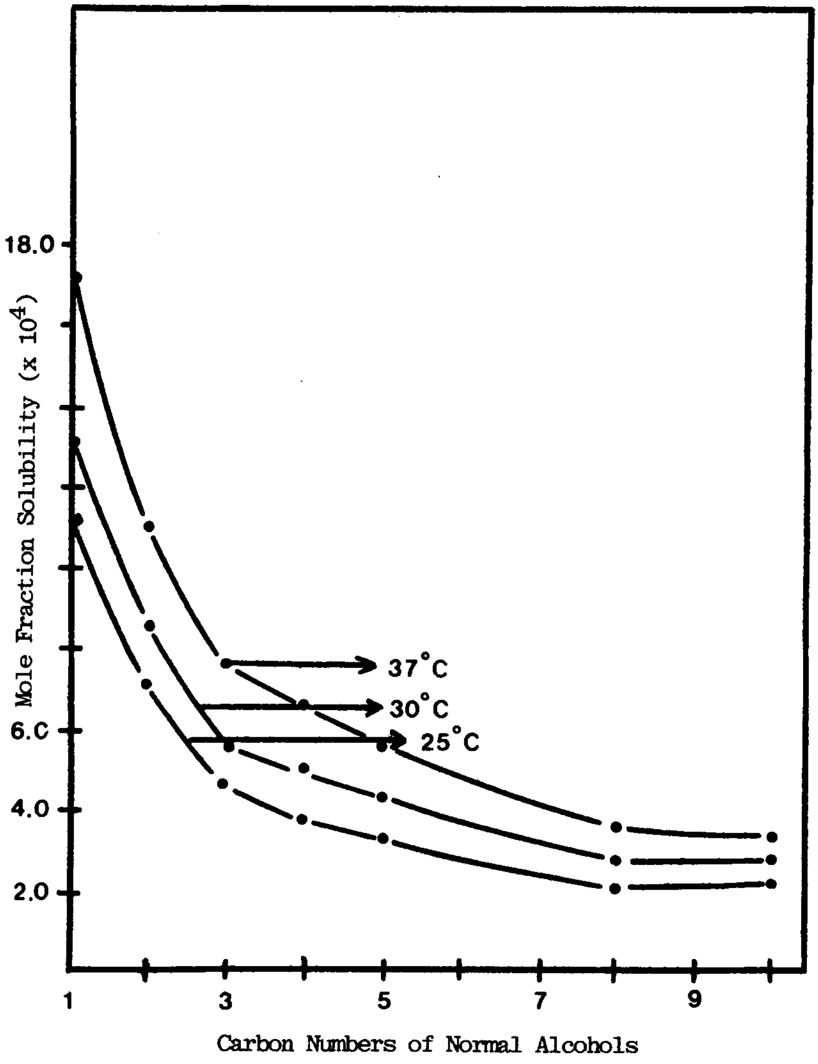

Figure 2 - Mole Fraction Solubility of Sulfadimethoxine
Versus Carbon Number of Normal Alcohols.

solubilities of a particular solute are measured in a series of solvents, the molecular weight of the solute remains constant but molecular weights of the solvents vary. If the mg. /ml. solubilities do not differ greatly from solvent to solvent, then the molecular weights of the solvents may assume unique importance in determining the mole fraction solubility, even reversing the solubilities trend when certain conditions are met. The present case is one in point: the molecular weight of decanol is 1.22 times greater than the molecular weight of octanol and the mg. /ml. solubility of the drug in decanol is about 0.9 times its solubility in octanol. The difference in the data trend has already been cited.

Figures 3 and 4 show the solubility data for sulfasomidine and sulfadiazine respectively. These plots exhibit the same trends observed in figures 1 and 2. The maximum solubilities for sulfasomidine occur in methanol, and the solubilities decrease donsistently up to octanol. From octanol to decanol the mole fraction solubilities for both sulfasomidine and sulfadiazine increase, dramatically so in the case of sulfadiazine. The solubility of sulfadiazine in decanol is approximately the same as its solubility in ethanol, an unusual fact when the polarities of the two solvents are compared. Decanol may be considered a moderately nonpolar molecule with respect to ethanol, and the approximately equivalent solubilities in the two solvents suggest that the solubility of sulfadiazine in decanol is a net effect invol-

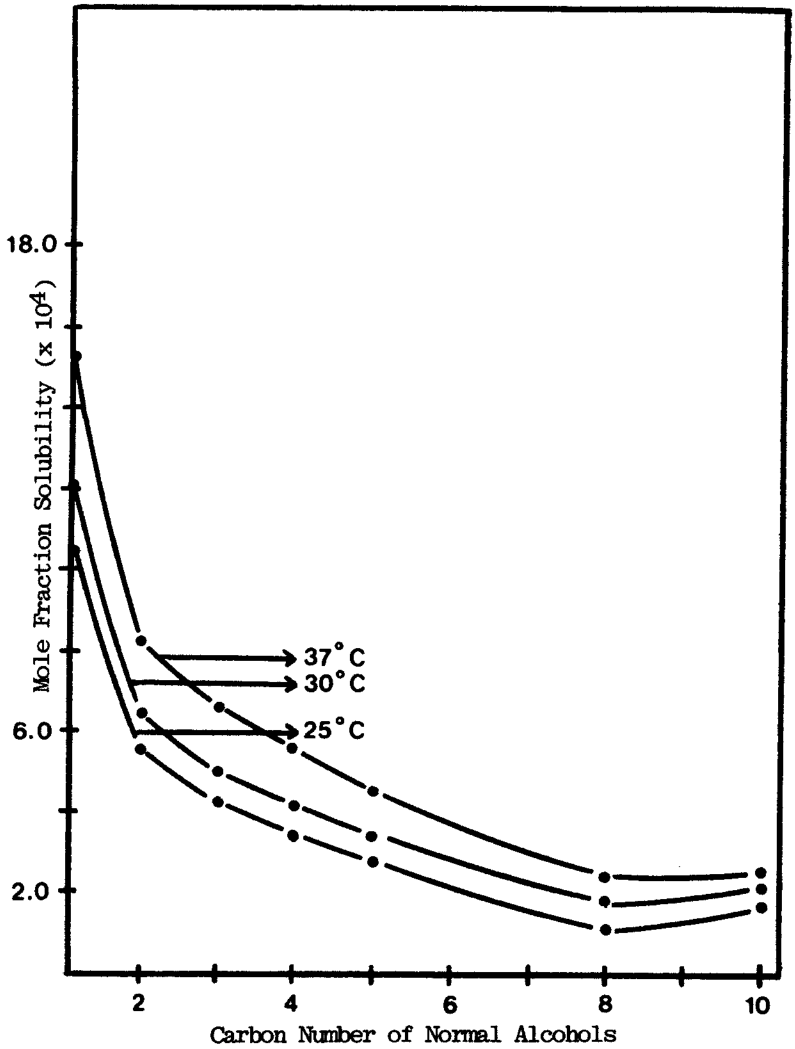

Figure 3 - Mole Fraction Solubility of Sulfisomidine *Versus* Carbon Number of Normal Alcohols.

ving a multiplicity of factors. Thermodynamic investigation of solution behavior, discussed elsewhere, would be a basic consideration.

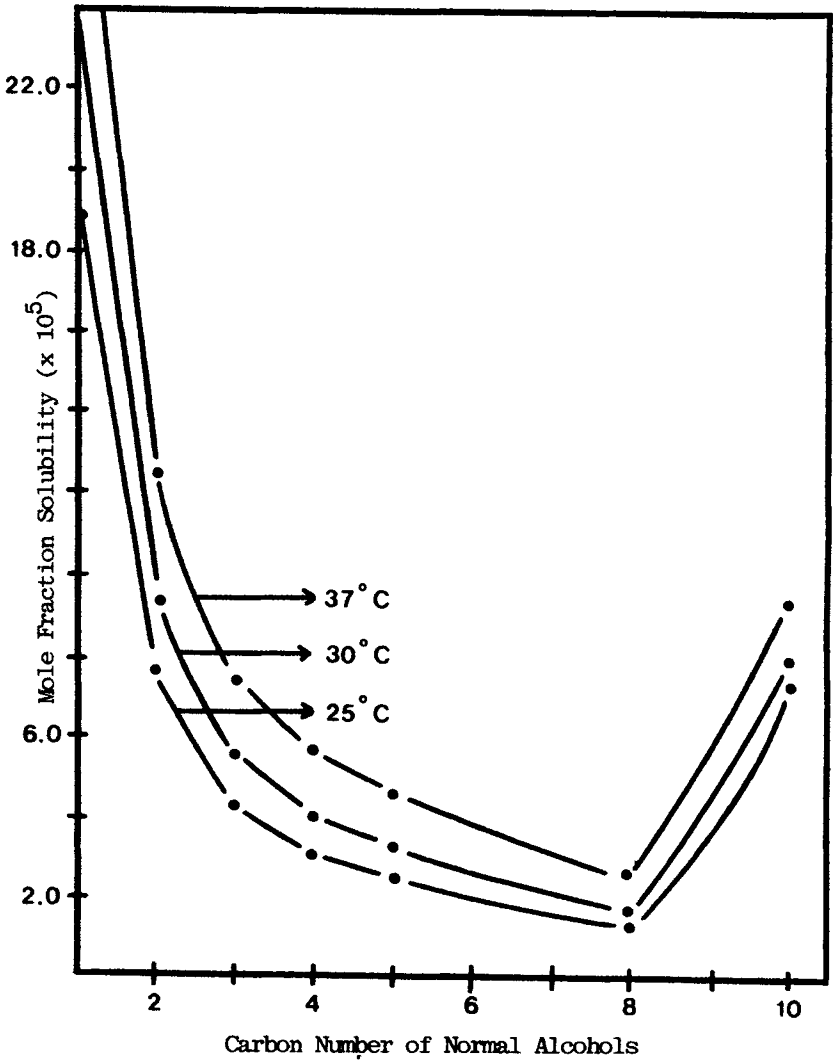

Figure 4 - Mole Fraction Solubility of Sulfadiazine Versus Carbon Number of Normal Alcohols.

The magnitudes of solubility for each drug solute is of importance since it is indicative of the extent of solute-solvent interactions. The solubility ratios in Table VII show the relative

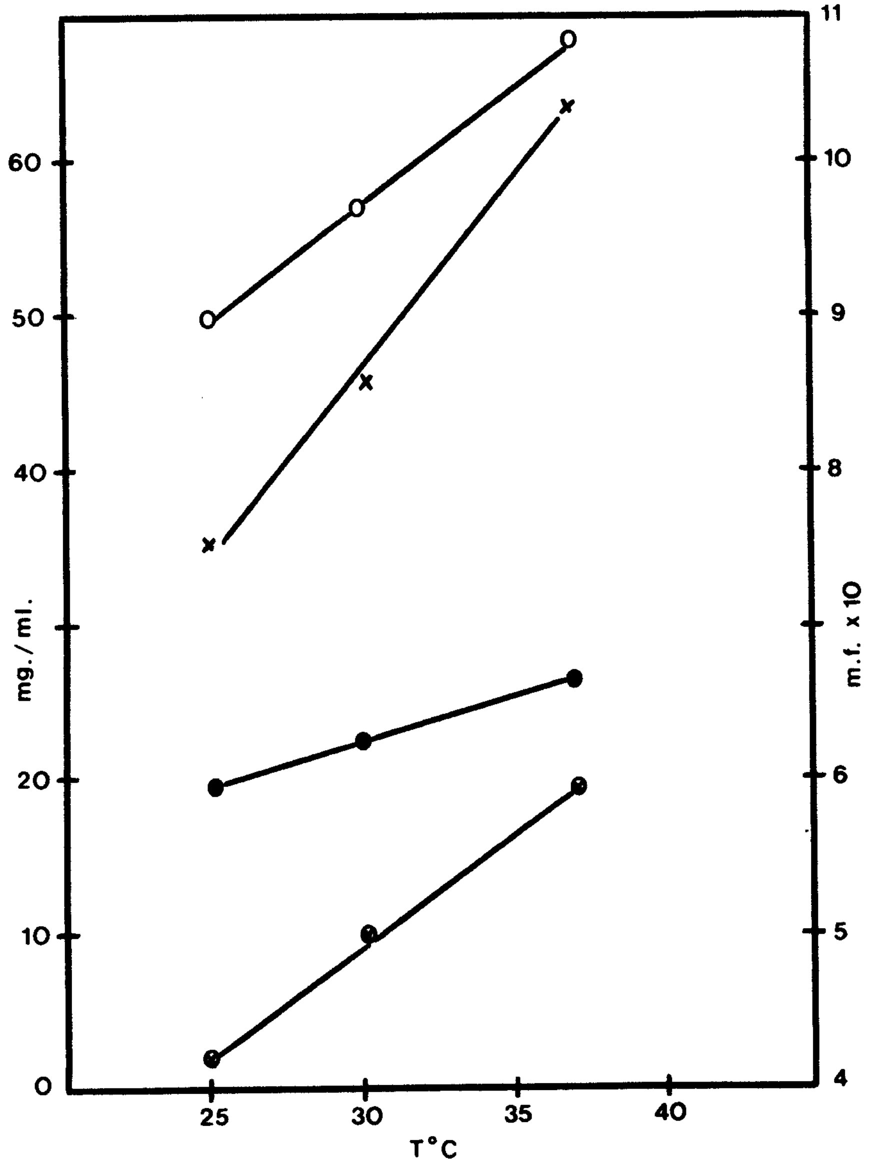

Figure 5 - Solubility of Sulfasoxazole in Both the mg./ml. (O, ●) Mole Fraction Notation (X, ⊗) in Methanol and Ethanol Respectively.

TABLE VII

SOLUBILITY RATIOS[a]
AT
25° CENTIGRADE

Alcohol	(R) Sulfasoxazole	(R) Sulfadimethoxine	(R) Sulfasomidine	(R) Sulfadiazine
Methanol	1.0	0.15	0.15	0.026
Ethanol	1.0	0.17	0.13	0.018
Propanol	1.0	0.21	0.19	0.019
Butanol	1.0	0.26	0.23	0.022
Pentanol	1.0	0.32	0.27	0.025
Octanol	1.0	0.37	0.25	0.025
Decanol	1.0	0.55	0.44	0.18

[a] Solubility ratio = R = (mole fraction solubility sulfonamide/mole fraction solubility sulfasoxazole)

solubilities for each solute at 25°C. Since of all the sulfonamides the highest solubilities in all the alcohol solvents occurred with sulfasoxazole, this solute was chosen as a basis for comparison. The solubility ratios, R, were calculated by dividing the mole fraction solubility of sulfasoxazole into the mole fraction solubility of the sulfonamide in question; therefore, the ratios for sulfasoxazole are one and all other values are less than one. Very small values for R indicate that the mole fraction solubility for the sulfonamide is much less than the mole fraction solubility of sulfasoxazole. Table VII shows that the sulfadimethoxine and sulfasomidine solubilities in methanol are smaller than the mole fraction solubility of sulfasoxazole in the same solvent by a factor of 0.15. The solubilities for the same solutes in decanol, however, are only about one-half the sulfasoxazole solubility in decanol. In relative terms, decanol appears to be a much better solvent for sulfadimethoxine and sulfasomidine than methanol. The solubility ratios for sulfadiazine in methanol through octanol show that sulfadiazine, when compared with sulfasoxazole, is extremely insoluble. In fact, the average sulfadiazine solubilities in methanol through octanol are about 2.5 percent that of the sulfasoxazole solubilities. In decanol, however, the sulfadiazine solubility increases to eighteen percent of the sulfasoxazole solubility in the same solvent. This large increase may possibly be due to a steric effect between solute and solvent which promotes increased interactions.

The difference in magnitudes of solubility of the solfonamides in the alcohol series can probably be attributed to changes caused by the N^1 substituents, because each solute species differs structurally only at this position. Reference to Table I shows that the N^1 group for sulfasoxazole is 3, 4-dimethylisoxazole. This group obviously promotes the solubility of this particular sulfonamide molecule to a far greater extent than do the substituents of the other sulfonamides. The substitutions for sulfadimethoxine and sulfasomidine at the N^1 position are both pyrimidines; dimethoxypyrimidine in the case of sulfadimethoxine and dimethylpyrimidine in the case of sulfisomidine. As expected, because of the chemical similarities of the two drugs, the solubilities for both these solutes are very close The solubility of sulfadimethoxine is slightly greater than that of sulfasomidine, and this difference is quite likely due to the methoxy groups which are more polar than the methyl groups. The lowest solubility of the sulfonamides studied was reached with sulfadiazine which has for the N^1 substituent an unsubstituted pyrimidine group. These data indicate that in the pyrimidine series, the addition of the methyl or methoxy groups substantially favors higher solubilities.

The effect of increasing temperature from 25° to 37° increased the solubility in all cases for these solutes in the various solvents. The solubility of sulfasoxazole in methanol and ethanol in both the mg. /ml. and mole fraction notations are shown as a function of temperature. Linearity is observed for the solubility in both notations which held for all the other solutes in each solvent as a function of temperature. It can be seen that for both notations, however, these lines are not parallel to one another. While it can be assumed that the dissolution mechanism is constant, the non-parallelism resides in the fact of variations in the thermodynamic parameters discussed in a companion communication.

References

(1) C. Wilson & O. Gisvold, "Textbook of Organic and Pharmaceutical Chemistry," 4th Ed., J. B. Lippincott Co., Philadelphia, 1962, p. 254.

(2) T. Korzumi, T. Arita & K. Kakemi, Chem. Pharm. Bull. 12, 413 (1964).

(3) Remington's Practice of Pharmacy, 12th Ed., Mack Publishing Co., Easton, Penna., 1961

(4) National Formulary, XIII Ed., American Pharmaceutical Association, Washington, D. C., 1970, p. 672.

(5) E. C. Faernzler & A. Martin, J. Pharm. Sci., 56, 608 (1967).

(6) A. Paruta, J. W. Mauger, R. Gerraughty, J. Pharm. Sci., 61, 94 (1972).

(7) A. Paruta, Am. Jour. of Pharmacy, 138, 137 (1966).