Solubilities of Sulfadiazine, Sulfisomidine, and Sulfadimethoxine in Several Normal Alcohols

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Abstract □ The solubilities of sulfadiazine, sulfisomidine, and sulfadimethoxine in several normal alcohols were determined over a limited temperature range. For all solutes, the highest solubility occurred in methanol, a relatively polar solvent. The entropy of solution, as developed by Hildebrand, was used for interpretive purposes. Experimental results showed that in most cases the entropy quantity increased with decreasing solubility for any particular solute. Solutions of sulfonamides in 1-decanol yielded relatively small entropy values when compared with those for the other normal alcohol solvents. It appears that this diminishing entropy correlates with the substitutions on the pyrimidine moiety of the N^1-substituted sulfanilamides.

Keyphrases □ Sulfadiazine—solubility in normal alcohols, function of entropy of solution □ Sulfisomidine—solubility in normal alcohols, function of entropy of solution □ Sulfadimethoxine—solubility in normal alcohols, function of entropy of solution □ Solubility—N^1-substituted sulfanilamides, related to entropy of solution □ Thermodynamics, solution—solubilities of sulfadiazine, sulfisomidine, sulfadimethoxine □ Entropy of solution—correlated with solubilities of N^1-substituted sulfanilamides

The simple interaction at a molecular level between a molecule fixed in a lattice and a randomly moving molecule in the condensed state leads to the phenomenon of solubility. This phenomenon is one of the most challenging and perhaps one of the least understood of all physicochemical processes.

Hildebrand *et al.* (1), whose work has contributed significantly to this area, based their predictive and interpretive equations on thermodynamic quantities. Whereas the Hildebrand framework of development centers about nonpolar systems, the fundamental principles of solution thermodynamics (*e.g.*, entropy of solution) apply to systems that are not strictly nonpolar. Polar and semipolar solutions of pharmaceutical interest were studied by various authors (2–4). However, there remains the need to extend explanations of solubility behavior in polar systems where hydrogen bonding or other complicating factors are present. To investigate such behavior, sulfonamides in selected normal alcohol solvents were chosen to generate data to which basic theoretical functions could be applied in the interpretations of the results.

One fundamental relationship in nonelectrolyte solubility behavior is that of the temperature effect on the magnitude of solubility. This relationship was discussed by Hildebrand (5) and Hildebrand *et al.* (6) and is given by Eq. 1:

$$\Delta\bar{S}_2/R = (\partial \ln X_2/\partial \ln T)_{sat.,P}\,(\partial \ln a_2/\partial \ln X_2)_{P,T} \quad \text{(Eq. 1)}$$

where X_2 is the mole fraction solubility of the solute, a_2 is the activity of the solute[1], and $\Delta\bar{S}_2$ is the entropy of solution. When Raoult's law is obeyed ($a_2 = X_2$) or in the dilute region where Henry's law holds, the quantity $(\partial \ln a_2/\partial \ln X_2)_{P,T}$ approaches unity, allowing Eq. 1 to simplify to:

$$\Delta\bar{S}_2 = R(\partial \ln X_2/\partial \ln T)_{sat.,P} \quad \text{(Eq. 2)}$$

The entropy of solution is of basic theoretical importance and permits interpretations regarding the nature and magnitude of forces involved when the solute molecules interact with those of the solvent phase. This function has proved very useful with respect to regular solution theory (7). Essentially, $\Delta\bar{S}_2$ is a quantity which suggests the ordering of the system resulting from the short-range forces existing between the solute and solvent. Hildebrand (8), commenting on the entropy of solution, stated: "Entropy is the thermodynamic function most closely related to structure, and maximum entropy of mixing indicates that the molecules in the mixture are in a state of maximum disorder." The concept that $\Delta\bar{S}_2$ is a consequence of solute–solvent interactions, *i.e.*, a solution property, is extremely important because it is, in fact, a partial molal quantity. In the present investigation, this thermodynamic function is used to interpret solubility data.

EXPERIMENTAL

Reagents—The solvents used were methanol[2], ethanol[3], 1-propanol[4], 1-butanol[5], 1-pentanol[6], 1-octanol[5], and 1-decanol[7]. Refractive index values and densities were found to be in agreement with literature values.

The sulfonamides used were sulfadiazine[8], sulfadimethoxine[9], and sulfisomidine[10]. Melting points of all sulfonamides agreed with literature values.

Procedure—The solubilities were determined by a previously reported method (9). Equilibrium was established prior to assay, and all temperatures were maintained within ±0.1° throughout the equilibration period. Solute concentrations were determined by spectrophotometric assay[11] at predetermined wavelengths.

RESULTS

Mole fraction solubilities and entropies of solution for the various sulfonamides in the normal alcohol solvents are presented in Tables I–III. The entropy quantities were calculated from slopes of the solubility curves, $\log_{10} X_2$ *versus* $\log_{10} T$, according to the relationship:

$$\Delta\bar{S}_2 = R(d \log_{10} X_2/d \log_{10} T)_{sat.,P} \quad \text{(Eq. 3)}$$

[1] The activity of the solute in solution, a_2, refers to the same standard state, the pure liquid, as the activity of the solid, a_2^s (*Reference 1*, p. 23).

[2] Spectrophotometric grade solvent, Mallinckrodt Chemical Works.
[3] U. S. Industrial Chemicals Co.
[4] Baker Analyzed Reagent, J. T. Baker Chemical Co.
[5] Mallinckrodt Chemical Works.
[6] Fisher Scientific Co.
[7] Matheson, Coleman & Bell.
[8] Lot WO2235, courtesy of Eli Lilly and Co.
[9] Lot 203027, courtesy of Hoffmann-La Roche, Inc.
[10] Lot E2498, courtesy of Ciba Pharmaceutical Co.
[11] Cary model 16 spectrophotometer.

Table I—Solubility and Thermodynamic Data for Sulfadimethoxine

Solvent	Mole Fraction Solubility ($\times 10^4$) 25°	30°	37°	$\Delta\bar{S}_2$, e.u.
Methanol	11.6	13.9	17.7	21.3
Ethanol	7.14	8.58	11.0	21.8
1-Propanol	4.71	5.63	7.79	25.5
1-Butanol	3.89	5.26	6.70	27.0
1-Pentanol	3.41	4.41	5.65	25.2
1-Octanol	2.04	2.78	3.59	28.1
1-Decanol	2.24	2.69	3.37	20.5

Table II—Solubility and Thermodynamic Data for Sulfisomidine

Solvent	Mole Fraction Solubility ($\times 10^4$) 25°	30°	37°	$\Delta\bar{S}_2$, e.u.
Methanol	11.2	12.7	16.5	19.7
Ethanol	5.53	6.38	8.20	20.0
1-Propanol	4.23	4.89	6.48	21.7
1-Butanol	3.44	4.17	5.56	24.2
1-Pentanol	2.84	3.43	4.54	23.7
1-Octanol	1.36	1.83	2.44	29.2
1-Decanol	1.80	2.04	2.53	17.2

The limited solubility of the solutes in the study placed the solutions within the range of dilute solution behavior such that it could be safely assumed that $(\partial \ln a_2/\partial \ln X_2)_{P,T}$ approaches unity. The limited temperature range over which the solubilities were determined allows the assumption that $\Delta\bar{S}_2$ is independent of temperature.

DISCUSSION

The structural differences of sulfadiazine (2-sulfanilamidopyrimidine), sulfisomidine (4-sulfanilamido-2,6-dimethylpyrimidine), and sulfadimethoxine (4-sulfanilamido-2,6-dimethoxypyrimidine) result in varying physicochemical properties which influence the magnitudes of observed solubilities. Although each solute is a pyrimidine-substituted sulfanilamide, the change in the N^1-substituent does not follow a homologous series. Thus, magnitudes of solubility for each solute in a particular solvent must be viewed only in terms of relative substituent effects; there can be no regular comparative effect such as increasing chain length.

Table III—Solubility and Thermodynamic Data for Sulfadiazine

Solvent	Mole Fraction Solubility ($\times 10^5$) 25°	30°	37°	$\Delta\bar{S}_2$, e.u.
Methanol	19.3	22.9	29.9	22.1
Ethanol	7.68	9.36	12.4	24.2
1-Propanol	4.32	5.45	7.44	27.4
1-Butanol	3.18	4.09	5.66	29.0
1-Pentanol	2.63	3.31	4.61	28.3
1-Octanol	1.41	1.76	2.65	31.8
1-Decanol	7.40	8.04	9.47	12.5

The maximum solubility for sulfadimethoxine (Table I) occurs in methanol, and at 30 and 37° the solubilities decrease consistently up to 1-decanol. The 25° data for this solute show an increase in solubility in 1-decanol over that in 1-octanol. Tables II and III show the solubility data for sulfisomidine and sulfadiazine, respectively. Again, the maximum solubilities are found in methanol and diminish up to 1-octanol at all temperatures. From 1-octanol to 1-decanol, the mole fraction solubilities for both sulfisomidine and sulfadiazine increase; in fact, the solubility of sulfadiazine in 1-decanol at 25° is approximately the same as its solubility in ethanol. The reason for the increase in solubility in 1-decanol is not apparent, and a thermodynamic investigation of solution behavior must be taken into consideration.

Comparison of the solubility data for each solute points to the influence of the substitutions on the pyrimidine group. The substitutions for sulfadimethoxine and sulfisomidine at the N^1-position are both pyrimidines: dimethoxypyrimidine and dimethylpyrimidine, respectively. As expected, because of the chemical similarities of the two molecules, the solubilities for both solutes are very close in all solvents at each temperature level. The solubility of sulfadimethoxine is slightly greater than that of sulfisomidine, and this

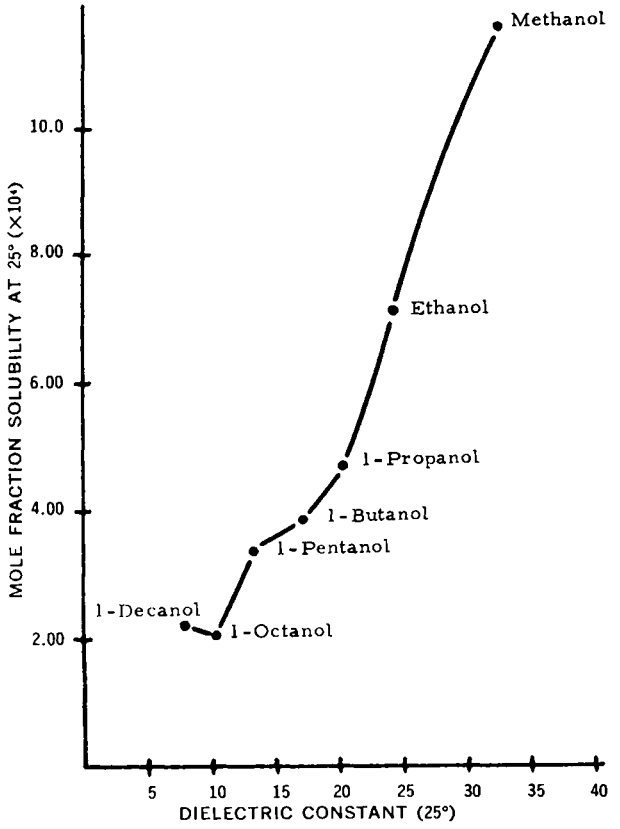

Figure 1- *Mole fraction solubility of sulfadimethoxine at 25°* versus *dielectric constants of normal alcohols.*

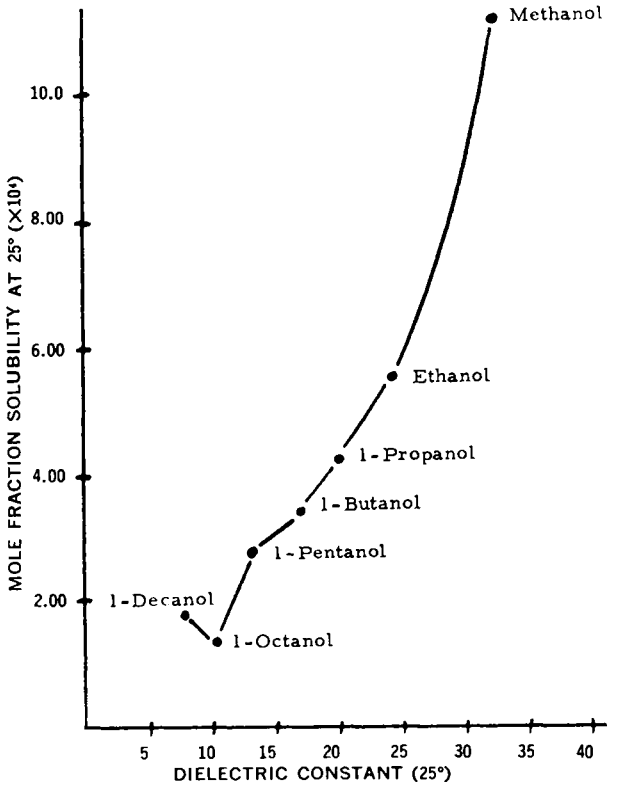

Figure 2—*Mole fraction solubility of sulfisomidine at 25°* versus *dielectric constants of normal alcohols.*

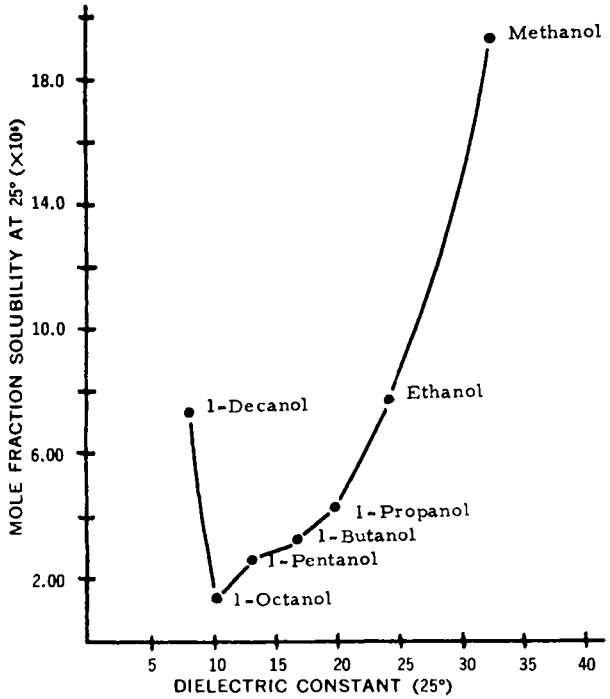

Figure 3—*Mole fraction solubility of sulfadiazine at 25° versus dielectric constants of normal alcohols.*

difference is 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 an unsubstituted pyrimidine group for the N^1-substituent. These data indicate that for the solutes studied, the addition of methyl or methoxy groups to the pyrimidine substituent favors higher solubilities in normal alcohol solvents.

The polarity of the solvent system for any particular solute was shown to be a useful parameter for interpreting solubility data (2–4). Solubility–polarity profiles for the solubilities of the sulfonamides determined in normal alcohols are shown in Figs. 1–3. For all solutes, the profiles are very similar, with solubility minima occurring in the area of a dielectric constant of about 10 and peak solubilities occurring in methanol. Examination of the curves does not yield any significant quantitative correlation between mole fraction solubility and the dielectric constant of the solvent. In particular, the dielectric constant does not yield any information suggesting the reason for the increased solubilities in 1-decanol. Qualitatively, however, it is clear that the dielectric constant, *i.e.*, polarity, of the solvent is related, at least in part, to the change in observed solubilities as the pure solvent systems are varied.

Another consideration of nonelectrolyte solubility behavior is the melting point of the pure solute. The general equation relating mole fraction solubility for a nonelectrolyte solute to its melting point is:

$$-\ln X_2 = (\Delta H_f/R)\,[(Tm - T)/TmT] \qquad \text{(Eq. 4)}$$

where ΔH_f is the heat of fusion (calories/mole), Tm is the melting point of the solute, and T is the temperature at which the process takes place. The equation indicates that as the melting point of the nonelectrolyte solute increases, the mole fraction solubility decreases. In Table IV, the melting points of the sulfonamides used in the present study are listed together with the mole fraction solubilities of the three solutes in methanol at 25°. These data confirm the expectation suggested by the equation, since the solubilities do decrease with increasing melting point.

The data in Table IV show, however, that a relatively high melting point does not necessarily result in a commensurate change in solubility. For example, the difference between the melting points of sulfadimethoxine and sulfisomidine is 43°, but the solubilities for these solutes in methanol are nearly equal. On the other hand, only a 10° difference exists between sulfisomidine and sulfadiazine, yet sulfisomidine is nearly six times more soluble. These findings suggest that other factors, such as the heats of fusion and

Table IV—Solubilities of Sulfonamides in Methanol at 25° Compared with Melting Points of Pure Solutes

Sulfonamide	Solubility (Mole Fraction), $\times 10^4$	Average Melting Point
Sulfadimethoxine	11.6	200°
Sulfisomidine	11.2	243°
Sulfadiazine	1.93	253°

the chemical structures of the solutes, also influence the magnitudes of observed solubilities.

The $\Delta\bar{S}_2$ values for each solution are instructive because they suggest factors regarding the relative number of independent molecules in the systems. For sulfadimethoxine dissolved in the normal alcohol solvents, the entropy values (Table I) increase for methanol through 1-butanol. The increase in entropy indicates increased molecular disorder as the mole fraction solubility data decrease for these solutions. With 1-pentanol, there is evidence of decreased interactions by virtue of the decreasing solubility, but the entropy of solution is about 2 entropy units lower than that of the 1-butanol system. In this case, it seems that the entropic factors associated with the solution process are not the overriding influence with respect to magnitude of solubility. The entropy term of the 1-octanol solutions shows an increase over that of the 1-pentanol system and, as previously mentioned, the increase is commensurate with decreasing solubility. In general, the decreasing solubilities and increasing $\Delta\bar{S}_2$ values bespeak decreased solute–solvent interactions and corresponding increased molecular randomness. This observation is in keeping with the solubility data summarized by Hildebrand *et al.* (10) for violet solutions of iodine.

The solubility data for 1-decanol–sulfadimethoxine show that the solubilities are nearly the same as those for sulfadimethoxine dissolved in 1-octanol. However, the entropy of solution for 1-decanol is the smallest value given in Table I and indicates that the randomness of the system is diminished. A more subtle explanation for the decreased entropy might be found if there were available other parameters governing solution properties, such as the effective shape and/or size[12] of the solute and solvent in solution and the contribution from the entropy of expansion (11). The partial molal volume of the solute is also related to the entropy of solution. In this connection, Shinoda and Hildebrand (12) presented data correlating the partial molal volume for a solute, in various solvents, with $[R(\partial \ln X_2/\partial \ln T)_{sat.,P}]$.

The trend of data for sulfisomidine (Table II) is the same as that for sulfadimethoxine. Again, the 1-decanol system exhibits the smallest entropy value for the normal alcohol solvents studied. In addition, the entropy for sulfisomidine in 1-decanol is about 1.2 times less than the entropy value for sulfadimethoxine in the same solvent. These observations suggest that in 1-decanol the dimethylpyrimidine group of sulfisomidine contributes to a more rigorous configurational dependence than does the dimethoxypyrimidine group of sulfadimethoxine.

In general, the thermodynamic data for sulfadiazine (Table III) are in keeping with those for the other sulfonamide solutes. The 1-decanol data are of interest in this case because of the relatively large solubility values and the small $\Delta\bar{S}_2$ value. The solubility of this solute in 1-decanol is approximately the same as its solubility in ethanol, but the entropy value for the 1-decanol system is only one-half that for the ethanol solution. A question that arises out of this entropy difference and the obviously large difference in the molal volumes of ethanol and 1-decanol was already answered (13): work showed that the entropy of solution is not influenced by the molal volume of the solvent. It may be intimated that the different entropy values point to different solution mechanisms for this solute in ethanol and 1-decanol.

Of further interest is a comparison of the thermodynamic data for sulfadiazine in 1-decanol with those for sulfadimethoxine and sulfisomidine in the same solvent. The deletion of the methoxy or methyl groups from the pyrimidine moiety seems to promote an increase in the molecular orderliness in these systems. Thus, there appears to be a relative relationship between the N^1-substituent of

[12] Configuration, not molecular size, appears to be the function on which $\Delta\bar{S}_2$ is most dependent (11).

the sulfonamide molecule and the configurational interpretation of the entropy of solution.

In summary, the entropy of solution appears to be a function that becomes very instructive in cases of dilute solutions of pharmaceutically useful solutes dissolved in hydrogen-bonding solvents; furthermore, studies at various temperatures yielded suggestions concerning dissolution behavior that could not be found from single-temperature studies. Although the entropy of solution does not directly allow predictions of solubility, its application is in keeping with Lindstrom's (14) statement that: "it would be of immeasurable aid if explanations of observed solubility phenomena were possible in terms of purely basic theoretical concepts."

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DRUG STANDARDS

Assay of Cyclophosphamide

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Abstract □ A GLC procedure was developed for the assay of cyclophosphamide raw materials and cyclophosphamide in formulations. Results obtained by this technique are comparable to those obtained by IR spectroscopy. The GLC procedure offers increased accuracy, reproducibility, and precision. The method is more specific and less time consuming than the IR procedure.

Keyphrases □ Cyclophosphamide—GLC analysis in raw materials and formulations □ GLC—analysis, cyclophosphamide

Cyclophosphamide[1] is a cytotoxic agent related to the nitrogen mustards and valuable in the palliative therapy of certain malignant neoplasms. Cyclophosphamide was first synthesized by Arnold and Boureaux (1) in 1957. Since that time, there have been several attempts to develop methods of assay for this compound. The published methods of analysis are:

A. Analysis based on nitrogen, phosphorus, or chloride content (2).

B. Colorimetric analysis, based on the intensity of a cobalt thiocyanate–cyclophosphamide complex (3) or by means of 4-(*p*-nitrobenzyl)pyridine after hydrolysis (4).

C. Titrimetric analysis, after precipitation of the digested material by quinoline and citric-molybdic acid solution (5).

D. IR spectroscopy (6).

These methods all have in common the disadvantage that they are not specific for the intact cyclophosphamide molecule. Procedures A–C utilize hydrolysis of the molecule before quantitation. Procedures A and C call for digestion with sulfuric and/or nitric acids. Procedure B utilizes an acid hydrolysis before color development.

Of the methods listed, Procedure D has the greatest degree of specificity. The basis for this procedure is the characteristic stretching frequency of the phosphorus–oxygen bond at 9.5 μ. Quantitation is effected by relating the intensity of this absorption band to an internal standard at 4.9 μ. However, the only degradation dis-

[1] Marketed as Cytoxan, Mead Johnson Laboratories.