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SOLUBILITY OF VARIOUS SULFONAMIDES IN N-ALKANOLS II. THERMODYNAMIC PARAMETERS

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ABSTRACT

The solubilities of several useful sulfonamides were studied at three temperatures over a wide spectrum of polarity of normal alcohols. Thermodynamic elements were generated from both literature values and experimental values of solubility as a function of temperature. Although all these sulfonamide solutions were of a dilute nature, the thermodynamic parameters that were obtained gave a set of results of complex nature. It was possible with this approach to determine the values of the mixing functions for enthalpy and entropy, activity coefficients and the excess free energy function. The overall solution

thermodynamics for these solutes is discussed in this communication.

INTRODUCTION

In order to investigate the thermodynamic parameters associated with solubility phenomena, certain theoretical reasoning had to be developed. The following analytical relationships apply to the solubility process and relate thermodynamic functions to measurable quantities.

The solubility process can be shown as follows

$$\text{Solute (solid} \xrightarrow{\Delta H_f} \text{Solute (liquid)} \xrightarrow{\Delta H_m} \text{Solute in Solution}$$

for the non-ideal case where ΔH_f is the heat of fusion and ΔH_m is the heat of mixing. When the heat of mixing has a zero value, then this process obtains for the ideal case. The above deals only with the enthalpy effect and the entropy must also be considered since one deals with the overall process of free energy change. A similar scheme can also be written for the entropy in the solution process as follows

$$\text{Solute (solid)} \xrightarrow{\Delta S_f} \text{Solute (liquid)} \xrightarrow{\Delta S_m} \text{Solute in Solution}$$

when ΔS_f is the entropy of fusion and ΔS_m is a zero value, then this process describes the ideal case.

Other thermodynamic terms can be defined here, ΔH_s, the enthalpy of solution and ΔS_s the entropy of solution. These functions can be set equal to the following

$$\Delta H_s = \Delta H_f + \Delta H_m \qquad \text{Eq. 1}$$

$$\Delta S_s = \Delta S_f + \Delta S_m \qquad \text{Eq. 2}$$

where the terms have been previously defined.

Several other analytical expressions relating to solubility can be given as follows

$$-\log X_2^I = \frac{\Delta H_f (T_m - T)}{2.3\ R\ T_m T} \qquad \text{Eq. 3}$$

$$-\log X_2^A = \frac{\Delta H_f (T_m - T)}{2.3\ R\ T_m T} + \log\ _2 \qquad \text{Eq. 4}$$

where $\log X_2^I$ and $\log X_2^A$ are the ideal and actual mole fraction solubilities, T_m is the melting point of the solute, T, the temperature of the solution and $_2$, the activity coefficient of the solute.

The overall free energy can be given as follows

$$\Delta F^I = -2.3R \log X_2^I \qquad \text{Eq. 5}$$

$$\Delta F^A = -2.3R \log X_2^A \qquad \text{Eq. 6}$$

where ΔF^I and ΔF^A are the ideal and actual free energy of the solubility process for the ideal and non-ideal (actual case).

Obviously, the following relationships can also be stated

$$\Delta F^I = \Delta H_f - T \Delta S_f \qquad \text{Eq. 7}$$

$$\Delta F^E = \Delta H_s - T \Delta S_s \qquad \text{Eq. 8}$$

where ΔF^I, ΔF^E are the ideal free energy and excess free energy respectively. The excess free energy can also be obtained in the following manner.

$$\Delta F^E = \Delta F^A - \Delta F^I \qquad \text{Eq. 9}$$

where ΔF^A is the actual free energy. ΔF^E allows for the activity coefficient rather than the actual mole fraction solubility.

Only one more relationship is necessary to completely define all the parameters utilized in this study, that is the activity coefficient of the solute γ_2 which can be obtained by

$$\gamma_2 = \frac{X_2^I}{X_2^A} \qquad \text{Eq. 10}$$

where these terms have been previously defined.

In order to quantitate the various thermodynamic elements shown above, the actual solubility must be known at several temperatures, the ΔH_f and ΔS_f must also be known, as well as the melting points of the solutes.

For this study actual solubility data was obtained in n-alkanols at three temperatures, the melting points were also determined and were available from the literature. The magni-

tude of the enthalpy of fusion ΔH_f and entropy of fusion ΔS_f were taken from the work of Guillory (1, 2).

When the log mole fraction of actual solubility is plotted versus 1/T, the slope of the line is related to ΔH_s heat of solution and the intercept related to the entropy of solution ΔS_s.

If the heat of fusion and entropy of fusion are also known, then one can obtain the ideal mole fraction solubility as a function of temperature. In this manner, the heat of mixing ΔH_m and the entropy of mixing can be obtained by the difference in the values of the enthalpy and entropy terms (see Eq. 1 & 2).

The log of the mole fraction solubility for the four sulfonamides is plotted versus reciprocal temperature (°K) for each alcohol in Figures 1-4. It can be seen that in all cases linearity is observed, however, parallelism which would imply constancy of the heat of solution is not observed. Further, in several cases, abberent results seemed apparent as in the case of sulfadimethoxine in 1-octanol and 1-decanol, sulfasomidine in 1-decanol, and sulfadiazine in 1-decanol.

The heats of solution ΔH_s and the entropies of solution ΔS_s were obtained from the slopes and intercepts of these lines (Eq. 4) and one given in Tables I-IV. Reasonable values of the heats of solution, about 5-10 Kcal. /mole were obtained,

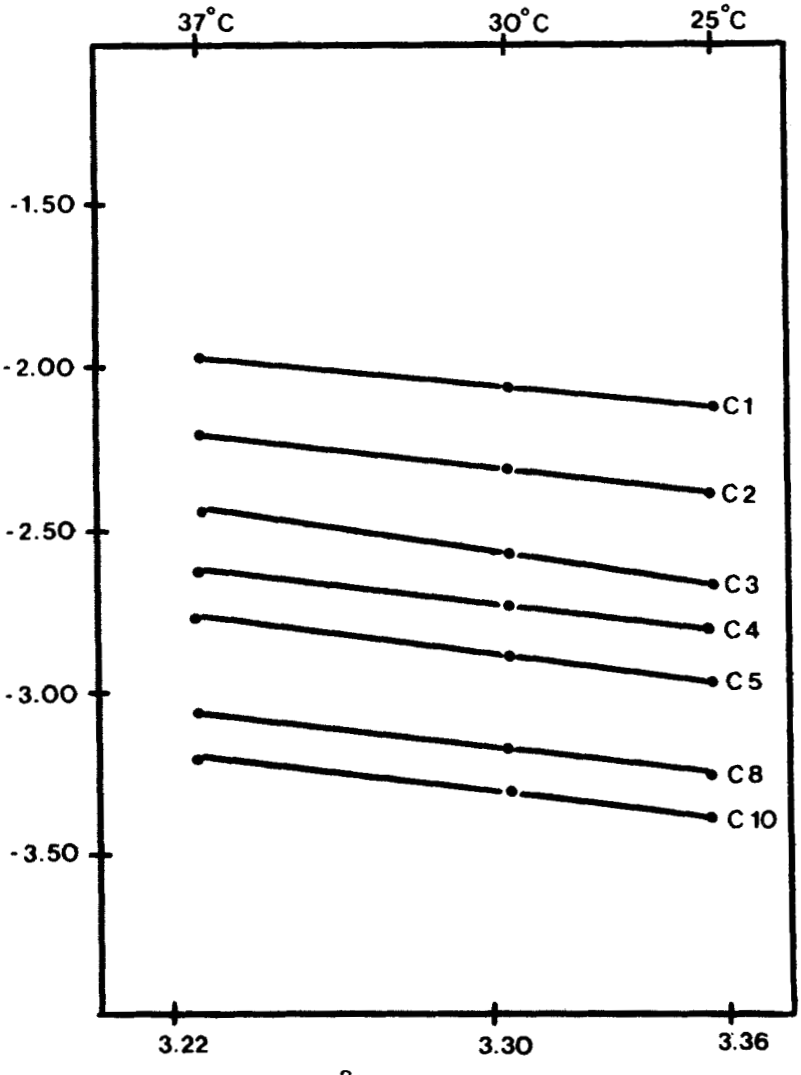

Figure 1 - Log Mole Fraction Solubility of Sulfisoxazole vs. Reciprocal Temperature (Kelvin)

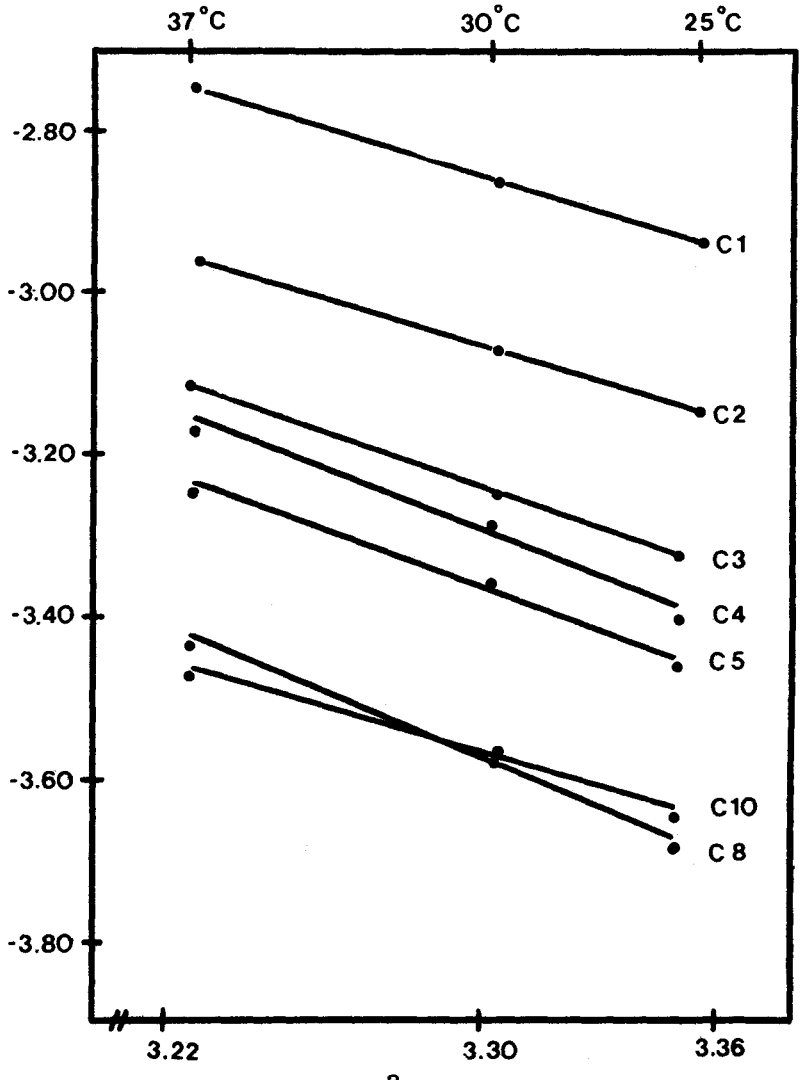

Figure 2 - Log Mole Fraction Solubility of Sulfadimethoxine vs. Reciprocal Temperature (Kelvin)

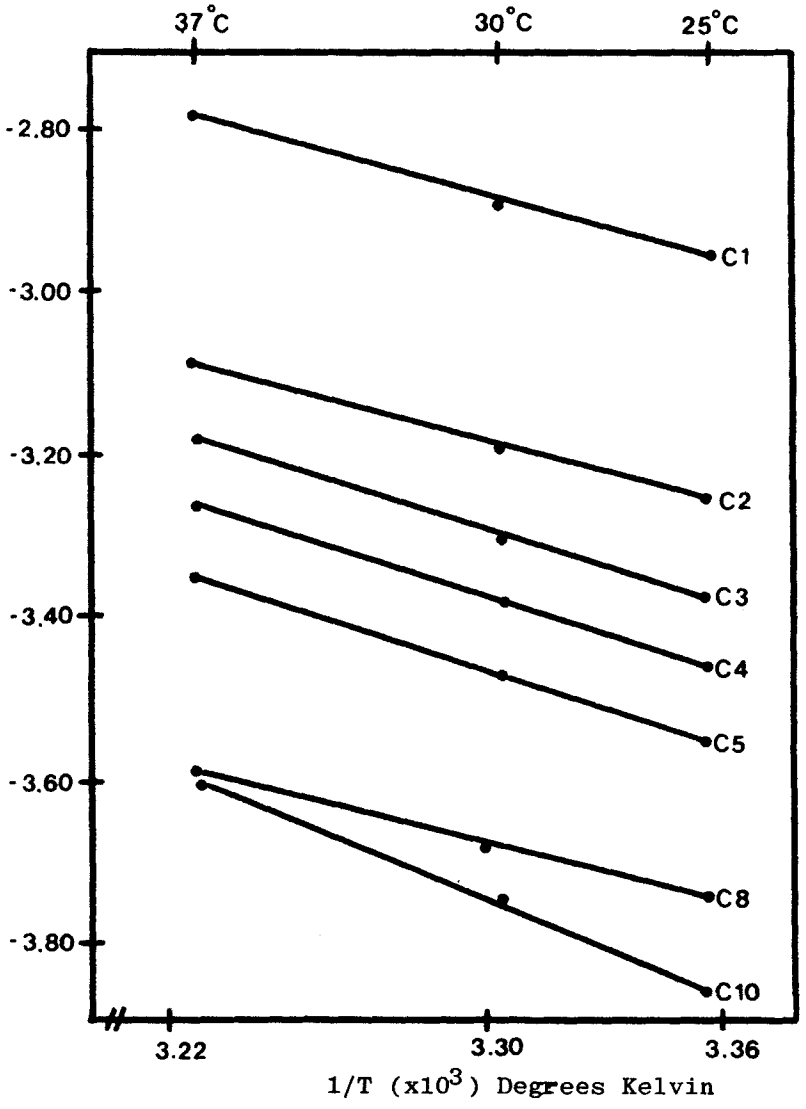

Figure 3 - Log Mole Fraction Solubility of Sulfisomidine vs. Reciprocal Temperature (Kelvin)

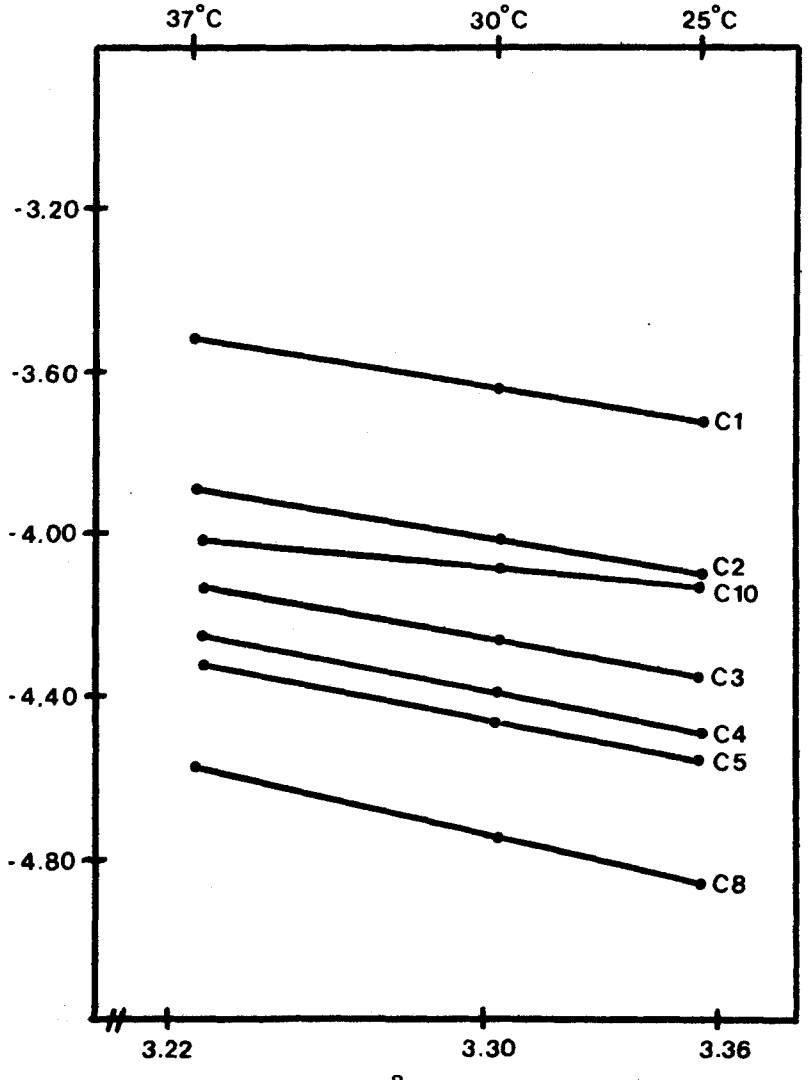

Figure 4 - Log Mole Fraction Solubility of Sulfadiazine vs. Reciprocal Temperature (Kelvin)

TABLE I

HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFISOXAZOLE AS DETERMINED IN A SERIES OF NORMAL ALCOHOLS

Alcohol	Heat of Solution (calories/mole)	Entropies (calories/degree)
Methanol	5.02×10^3	7.12
Ethanol	5.20×10^3	6.58
Propanol	6.58×10^3	9.97
Butanol	6.40×10^3	8.57
Pentanol	6.38×10^3	7.83
Octanol	6.10×10^3	5.64
Decanol	6.04×10^3	4.78

and reasonable values of the entropy of solution were also found and expressed as calories/degree in the Tables given. In the case of sulfasoxazole, the lowest heat of solution occurs in methanol in keeping with the highest solubility determined. The heats of solution in these cases is indicative of the solute-solvent

interactions, whereas the entropy may be considered to be a configurational term associated with the ordering of a system due to solute-solvent interactions. Decreased solubility of sulfasozole in ethanol leads to the expected increase in the enthalpy term. However, the entropies for the methanol and ethanol systems differ by only 0.54 entropy units, indicating that the interaction term, enthalpy, is predominate over the configurational term, entropy, in determining the difference in solubility for sulfasoxazole in these two solvents. From propanol through decanol there appears to be a pattern with regard to enthalpy and entropy; both values decrease with increasing chain length of the alcohol. Even though the solubilities continue to decrease in these solvents, the decrease in enthalpy and in entropy suggests that the sulfasoxazole molecules are not being "squeezed out" and there is a tendency to promote orderliness in the solution phase. A more subtle explanation for the enthalpy term and its corresponding entropy might be found if the effective molecular sizes of the solute and solvent were known. Obviously, the size of the solvent molecules in question varies considerably and the size and/or shape may be very important for a more complete interpretation of the thermodynamic quantities. From the decreasing entropy values, it is apparent that the solute and solvent molecules affect each other so that the number of configura-

tional possibilities are decreased and would seem to be dependent upon steric factors related to molecular size and shape. From a purely thermodynamic point of view, the decreased solubilities of the solute in propanol through decanol occur because of the relative magnitudes of enthalpies and entropies. The magnitude of solubility will be increased when ΔH_s is relatively small and the corresponding entropy is of the same sign and relatively large (3).

The thermodynamic functions for sulfadimethoxine are presented in Table II. These data show that the heats of solution increase steadily for methanol through butanol with corresponding decreases in the solubility of sulfadimethoxine. The entropies associated with these solutions also increase with increasing chain length of the alcohol, except for ethanol. The ethanol solution when compared with the methanol solution exhibits an entropy decrease of 0.66 calories/degree. The data for the methanol through propanol systems indicate that the solute is being excluded from the solvent as the solute passes from the liquid solute to the solute in solution. This exclusion is manifested by decreased interactions, larger ΔH_s values, and increased disarray, i.e., larger positive entropy values. With pentanol, there is evidence of increased interactions, but the solubility of the solute does not increase because of the in-

TABLE II

HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFADIMETHOXINE AS DETERMINED IN A SERIES OF NORMAL ALCOHOLS

Alcohol	Heat of Solution (calories/mole)	Entropies (calories/degree)
Methanol	6.43×10^3	8.16
Ethanol	6.52×10^3	7.50
Propanol	7.76×10^3	10.8
Butanol	8.18×10^3	11.9
Pentanol	7.61×10^3	9.72
Octanol	8.48×10^3	11.6
Decanol	6.21×10^3	4.17

fluence of the entropy factor. The enthalpy and entropy values for the octanol solution show an increase over those of the pentanol system; and the increase, as previously explained, is probably due to the decrease in the solute-solvent interactions and the corresponding increase in molecular randomness in the solution phase. The decanol solution is interesting because of the large decrease in the heat of solution and entropy. Although

the solubility of sulfadimethoxine in decanol is much less than its solubility in methanol, there is a large difference in the respective entropy values. The entropy for the decanol solution is almost 4.0 calories/degree lower than that for the methanol solution, and the heat of solution for the decanol system is about 200 calories/mole less than that for the methanol system. Therefore, it appears that when sulfadimethoxine is dissolved in decanol, the molecular interactions are somewhat increased and the randomness of the system is diminished. The smaller entropy term also indicates that steric factors are very important in the decanol-sulfadimethoxine system.

The magnitudes of the heats of solution and the corresponding entropy values for sulfadimethoxine follow the same trend as the thermodynamic data for sulfisomidine. (Table III) Again, the decanol system exhibits a decrease in enthalpy and a very small entropy term of about 0.3 calories/degree. From a structural point of view, it seems that the dimethylpyrimidine group of sulfisomidine is able to interact and "fit" into the solvent structure of decanol much better than the dimethoxypyrimidine group of sulfadimethoxine. This possibility is suggested by the fact that the entropy for sulfisomidine in decanol is about fourteen times less than the entropy value for sulfadimethoxine in the same solvent. In fact, the entropies for all the sulisomidine

TABLE III

HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFISOMIDINE AS DETERMINED IN A SERIES OF NORMAL ALCOHOLS

Alcohol	Heat of Solution (calories/mole)	Entropies (calories/degree)
Methanol	6.05×10^3	6.77
Ethanol	6.07×10^3	5.44
Propanol	6.58×10^3	6.64
Butanol	7.36×10^3	8.86
Pentanol	7.16×10^3	6.73
Octanol	8.81×10^3	11.9
Decanol	5.19×10^3	0.277

solutions, with the exception of octanol and decanol, are smaller than the corresponding entropies for sulfadimethoxine.

The thermodynamic data for sulfadiazine are presented in Table IV and these values follow the trend established for sulfadimethoxine and sulfisomidine solutions. Attention is again drawn to the decanol system where it will be noted that the enthalpy and entropy have decreased by a relatively large magni-

TABLE IV

HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFADIAZINE AS DETERMINED IN A SERIES OF NORMAL ALCOHOLS

Alcohol	Heat of Solution (calories/mole)	Entropies (calories/degree)
Methanol	6.73×10^3	5.58
Ethanol	7.34×10^3	5.79
Propanol	8.28×10^3	7.82
Butanol	8.77×10^3	8.85
Pentanol	8.59×10^3	7.86
Octanol	9.72×10^3	10.4
Decanol	3.80×10^3	-6.18

tude. The negative entropy term for this solution indicates that steric factors play an important role in the solubility mechanism for sulfadiazine and decanol. It is difficult to visualize the possibility of configurational relationship between solute and solvent, but the relatively small enthalpy indicates that the interactions are strong and that they are due, at least in part, to the way in which the solute can "fit" into the solvent structure.

It is also of interest to compare the thermodynamic data for sulfadiazine in decanol with that 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 molecular orderliness in the solution phase. Thus, there appears to be a functional relationship between the N^1 substituent of the sulfomamide molecule and the configurational interpretation of entropy.

The thermodynamic data for sulfadiazine suggest that the solubilities of this solute in decanol should be unusually high. Indeed, within the temperature range studied, the solubility of sulfadiazine in decanol is approximately the same as that of sulfadiazine in ethanol. From a thermodynamic point of view, however, the ethanol system is favored because of the positive enthalpy and entropy values, which will promote increased solubilities, especially at higher temperatures. (37)

In a previous communication (4), the entropy of solution developed by Hildebrand (5) was used to present some interpretive aspects of solution behavior. Prior work by Guillory (1, 2) in an excellent piece of work gave enthalpies and entropies of fusion for various sulonamides including several which we had studied. It was then possible with this data to explore the entire spectrum of thermodynamics elements, given previously, for these solu-

tions. Thus, the work extends the extensive work of Hildebrand (6-8) on solubility phenomena to pharmaceutical solutions possessing polar characteristics and non-ideal behavior. Because of the low solubility of these sulfonamides in the selected alcohols, it could be assumed that these solutions would obey dilute solution behavior. In general, the heat of solution and the entropy of solution can be determined when solubility of a solute as a function of temperature is available (9). If the heat and entropy of fusion are also known, one can also calculate thermodynamic elements such as activity coefficients and excess free energies in order to aid in the interpretation of solubility behavior. The pertinent thermodynamics can be obtained from the equations previously given.

From the previous discussion, the ΔH_s and ΔS_s were given for the various systems and their relative magnitudes discussed. Since this is only part of the thermodynamics initially sought, the following considerations deal with the ΔH_s and ΔS_s obtained from the literature (1, 2) and the calculations of other derived thermodynamic functions.

In Table V, the ΔH_f and ΔS_f are given from the work of Guillory and the ideal mole fraction solubilities calculated for each temperature in this study as well. Solute melting points are also given.

Table V: A Summary of the Fusion Values of Enthalpy and Entropy and the Ideal Mole Fraction Solubilities at the Various Temperatures Utilized and the Melting Points for the Four Sulfonamides Studied.

	ΔH_f cal./mole	ΔS_f cal./deg.	$X_2^I(25)$	$X_2^I(30)$	$X_2^I(37)$	M. P. °C.
Sulfasoxazole	7500	16	.0105	.0127	.0172	192-195
Sulfadimethoxine	7120	14.9	.0116	.0141	.0180	197-202
Sulfasomidine	10810	20.9	.00047	.00063	.00096	243-244
Sulfadiazine	9740	18.3	.00075	.00098	.00142	252-256

As expected from the ideal mole fraction equation, non-electrolytes with lower heats of fusion and lower melting points would be more soluble and this is the case for sulfasoxazole and sulfadimethoxine compared with sulfasomidine and sulfadiazine.

In Table VI, the mole fraction solubility of sulfasoxazole, the solute with the greatest solubility, is given with respect to the actual mole fraction solubility and the activity coefficient of the solute. Included in this table are the mole fraction values and activity coefficients for the solvents at the various temperatures as well. It can easily be seen that both the mole fraction and activity coefficients are quite close to unity. In subsequent tables, only the mole fraction solubility and activity coefficients for the other solutes will be given since the solvent mole fraction

Table VI: A Summary of the Mole Fraction Solubilities and Activity Coefficients of the Sulfasoxazole-alcohol Systems where X_2^I (25° 30°, 37°) = .0105; .0127; .0172

	X_2^A	γ_2	X_1^A	γ_1	T
Methanol	.00752	1.37	.99248	1.00651	25
	.00857	1.48	.99143	.99583	30
	.01040	1.62	.98960	.99312	37
Ethanol	.00418	2.46	.99582	1.0031	25
	.00499	2.52	.99501	.99225	30
	.00590	2.85	.99410	.98863	37
1-Propanol	.00223	4.62	.99777	1.00118	25
	.00269	4.70	.99631	.99095	30
	.00344	4.87	.99656	1.00239	37
1-Butanol	.00148	6.96	.99852	1.00043	25
	.00183	6.94	.99817	.98911	30
	.00226	7.70	.99774	1.00120	37
1-Pentanol	.00106	9.74	.99894	.98834	25
	.00130	9.77	.99870	.98407	30
	.00162	10.30	.99838	.98439	37
1-Octanol	.00055	18.7	.99945	.99949	25
	.00070	18.2	.99930	.98799	30
	.00083	20.2	.99917	.98361	37
1-Decanol	.00041	25.2	.99959	.99935	25
	.00049	26.0	.99951	.98778	30
	.00061	27.5	.99939	.98339	37

and activity coefficient would, at lower solubilities for the solutes, be closer to unity than even sulfasoxazole.

In Tables VII-IX, the values of the actual mole fraction solubilities and activity coefficients at the three temperatures are given for sulfadimethoxine, sulfasomidine and sulfadiazine.

Table VII: A Summary of the Mole Fraction Solubilities and Activity Coefficients of the Solute in the Sulfadimethoxine-Alcohol Systems, where X_2^1 (25, 30, 37°) = .0116; .0142; .0180

	X_2^A	γ_2	Temp.
Methanol	.00116	10.0	25
	.00136	10.1	30
	.00177	10.2	37
Ethanol	.00071	16.2	25
	.00082	16.3	30
	.00110	16.4	37
1-Propanol	.00047	25.0	25
	.00056	25.2	30
	.00078	22.4	37
1-Butanol	.00039	30.0	25
	.00053	26.6	30
	.00067	27.0	37
1-Pentanol	.00034	34.0	25
	.00044	32.0	30
	.00057	32.0	37
1-Octanol	.00020	57.0	25
	.00028	50.5	30
	.00036	50.0	37
1-Decanol	.00022	52.0	25
	.00027	52.0	30
	.00034	53.3	37

In all the cases of the reported mole fraction solubilities, it is observed that these values are very small fractions; the highest mole fraction solubility occuring for sulfasoxazole in methanol, that value being about .01 and implies dilute solution

Table VIII: A Summary of the Mole Fraction Solubilities and the Activity Coefficient of the Solute in the Sulfasomidine-alcohol Systems where X_2^I (25°, 30°, 37°) = .00047; .00063; .00096

	X_2^A	γ_2	T
Methanol	.001120	.42	25
	.001270	.50	30
	.001650	.60	37
Ethanol	.000553	.84	25
	.000638	.98	30
	.000820	1.21	37
1-Propanol	.000423	1.12	25
	.000489	1.29	30
	.000648	1.53	37
1-Butanol	.000344	1.37	25
	.000417	1.50	30
	.000556	1.79	37
1-Pentanol	.000284	1.81	25
	.000343	1.83	30
	.000454	2.18	37
1-Octanol	.000136	3.50	25
	.000183	3.42	30
	.000244	4.10	37
1-Decanol	.000180	2.64	25
	.000204	3.08	30
	.000253	3.94	37

behavior. Interestingly, the activity coefficients calculated varied over a tremendous range of fractional values to values of about 54. For those cases where the activity coefficient was

Table IX: A Summary of the Mole Fraction Solubilities and the Activity Coefficient of the Solute in the Sulfadiazine-alcohol Systems where X_2^I (25°, 30°, 37°) = .00075; .00098;.00142

	X_2^A	γ_2	T
Methanol	.000193	3.9	25
	.000229	4.3	30
	.000299	4.7	37
Ethanol	.000077	9.7	25
	.000094	10.5	30
	.000124	11.4	37
1-Propanol	.000043	17.1	25
	.000049	18.0	30
	.000065	19.1	37
1-Butanol	.000032	23.6	25
	.000041	24.0	30
	.000057	25.0	37
1-Pentanol	.000026	28.5	25
	.000033	29.7	30
	.000046	30.6	37
1-Octanol	.000014	53.0	25
	.000018	55.8	30
	.000027	53.5	37
1-Decanol	.000074	10.4	25
	.000081	12.2	30
	.000095	14.6	37

greater than unity, the actual mole fraction solubility was a smaller value than the ideal mole fraction solubility. Only for sulfasomidine were fractional values obtained and these were

limited in this case in methanol at the three temperatures and ethanol at the first two temperatures. For these cases, the actual mole fraction solubility was greater than the ideal mole fraction solubility. The activity coefficients were also seen to increase, with the chain length of the alcohol up to 1-decanol for sulfasoxazole, and up to 1-pentanol with the other three solutes and an interesting reversal in activity coefficients in 1-octanol and 1-decanol. There was also found to be an increase in these activity coefficients with temperature which indicates that the increased solubility observed with temperature, while linear, was not in direct proportion to the increases in the calculated ideal mole fraction solubilities. This is to be expected, since the entropies of solution from log m.f. versus 1/T were generally not parallel to one another. With reference to the activity coefficient term in Eq. 4, since it is related to the cohesive energy density difference between solute and solvent, would when these differences are large lead to a large deviational term of the activity coefficient as has been evidenced in these systems.

In Tables X-XIII, the thermodynamic elements of heat of solution, heat of fusion and heats of mixing for each solute in each alcohol is presented. The entropies of fusion, solution and mixing are also shown in the second three columns and the

Table X: A Summary of the Thermodynamic Elements Obtained for Sulfasoxazole-alcohol Systems Used in this Study

Sulfasoxazole

	Enthalpy (cal./mole)			Entropy (cal./deg.)			Free Energy (cal./mole)		
Carbon #	Fusion	Solution	Mixing	Fusion	Solution	Mixing	Ideal	Actual	Excess
1	7500	5020	-2480	160	7.1	-8.9	2636	2856	220
2	"	5200	-2300	"	6.6	-9.4	"	3200	564
3	"	6580	- 920	"	10.0	-6.0	"	3550	914
4	"	6400	-1100	"	8.6	-7.4	"	3795	1159
5	"	6380	-1020	"	7.8	-8.8	"	4000	1364
8	"	6100	-1400	"	5.6	-10.4	"	4386	1750
10	"	6040	-1460	"	4.8	-11.2	"	4625	1989

Table XI: A Summary of the Thermodynamic Elements Obtained for the Sulfadimethoxine-Systems Used in this Study

Sulfadimethoxine

	Enthalpy (cal./mole)			Entropy (cal./deg.)			Free Energy (cal./mole)		
Carbon #	Fusion	Solution	Mixing	Fusion	Solution	Mixing	Ideal	Actual	Excess
1	7120	6430	-690	14.9	8.2	-6.7	2590	3950	1360
2	"	6520	-600	"	7.5	-7.4	"	4240	1650
3	"	7760	+640	"	10.8	-4.1	"	4477	1887
4	"	8180	+1060	"	11.9	-3.0	"	4562	1972
5	"	7610	+490	"	9.7	-5.2	"	4655	2065
8	"	8480	+1360	"	11.6	-3.3	"	4954	2364
10	"	6210	-910	"	4.2	-10.7	"	4943	2353

Table XII: A Summary of the Thermodynamic Elements Obtained for the Sulfasomidine-alcohol Systems Used in this Study

Solfasomidine

	Enthalpy (cal./mole)			Entropy (cal./deg.)			Free Energy (cal./mole)		
Carbon #	Fusion	Solution	Mixing	Fusion	Solution	Mixing	Ideal	Actual	Excess
1	10810	6050	-4860	20.9	6.8	-14.1	4446	3992	-454
2	"	6070	-4740	"	5.4	-15.5	"	4416	- 30
3	"	6580	-4230	"	6.6	-13.3	"	4561	+115
4	"	7360	-3450	"	8.9	-12.0	"	4667	+221
5	"	7160	-3650	"	6.7	-14.2	"	5114	+668
8	"	8810	-2000	"	11.9	- 9.0	"	5193	+747
10	"	5190	-5620	"	0.3	-20.6	"	5105	+659

Table XIII: A Summary of the Thermodynamic Elements Obtained for the Sulfadiazine-alcohol Systems Used in this Study

Sulfadiazine

	Enthalpy (cal./mole)			Entropy (cal./deg.)			Free Energy (cal./mole)		
Carbon #	Fusion	Solution	Mixing	Fusion	Solution	Mixing	Ideal	Actual	Excess
1	9740	6730	-3010	18.3	5.6	-12.7	4177	5035	+ 857
2	"	7340	-2400	"	5.8	-12.5	"	5589	+1412
3	"	8280	-1460	"	7.8	-10.5	"	5903	+1762
4	"	8770	- 970	"	8.9	- 9.4	"	6080	+1902
5	"	8590	-1150	"	7.9	-10.4	"	6201	+2024
8	"	9720	- 20	"	10.4	- 7.9	"	6558	+2381
10	"	3800	-5940	"	-6.2	-24.2	"	5679	+1502

ideal, actual and excess free energy functions in the final three columns.

Obviously, the enthalpy of fusion, entropy of fusion and ideal free energies are constant values derived from the literature. In all cases, reasonable values of the thermodynamic element were observed. The heats of mixing in almost all cases were negative in value indicating an energy requirement for solubility or relatively low solubility. In the case of sulfadimethoxine, the heats of mixing in 1-propanol, 1-butanol, 1-pentanol and 1-octanol were positive to a moderate quantitative degree but overall is moderated or offset by relatively lower entropy of mixing values with respect to the entropy values of the other solutes in these alcohols.

The excess free energies were, in general, small positive values indicative of the non-ideal nature of the solubility even at these very low mole fraction solubilities. The excess free energy for sulfasomidine in methanol and ethanol were small negative values which indicates activities of fractional values or less than unity.

These thermodynamic elements can be visualized by various plots and are illustrated in Figures 5-8. In these figures, the heat of mixing, entropy of mixing and the free energy of mixing are shown for the four sulfonamides as a function of the carbon

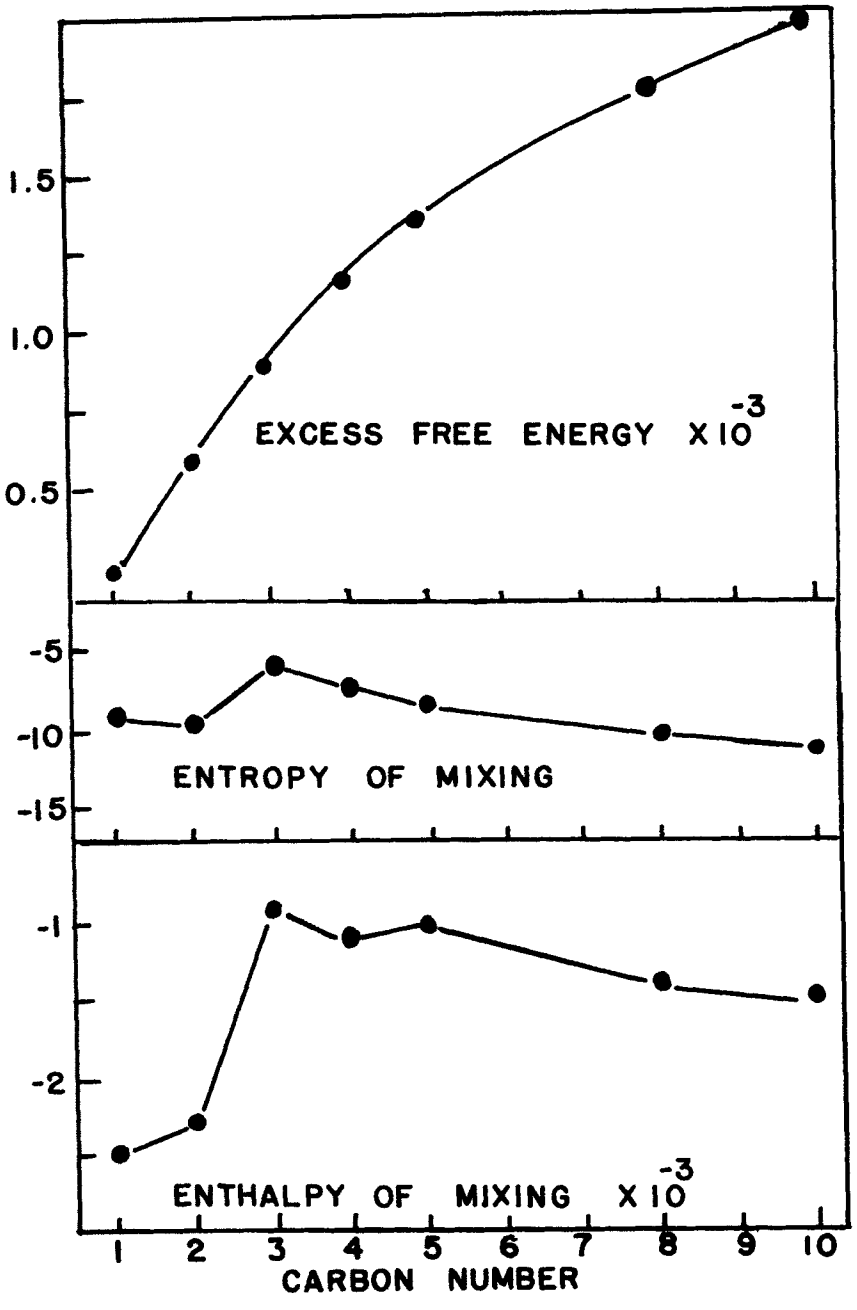

Figure 5-Thermodynamic Functions for Sulfaxazole vs. Carbon Number of Alcohols

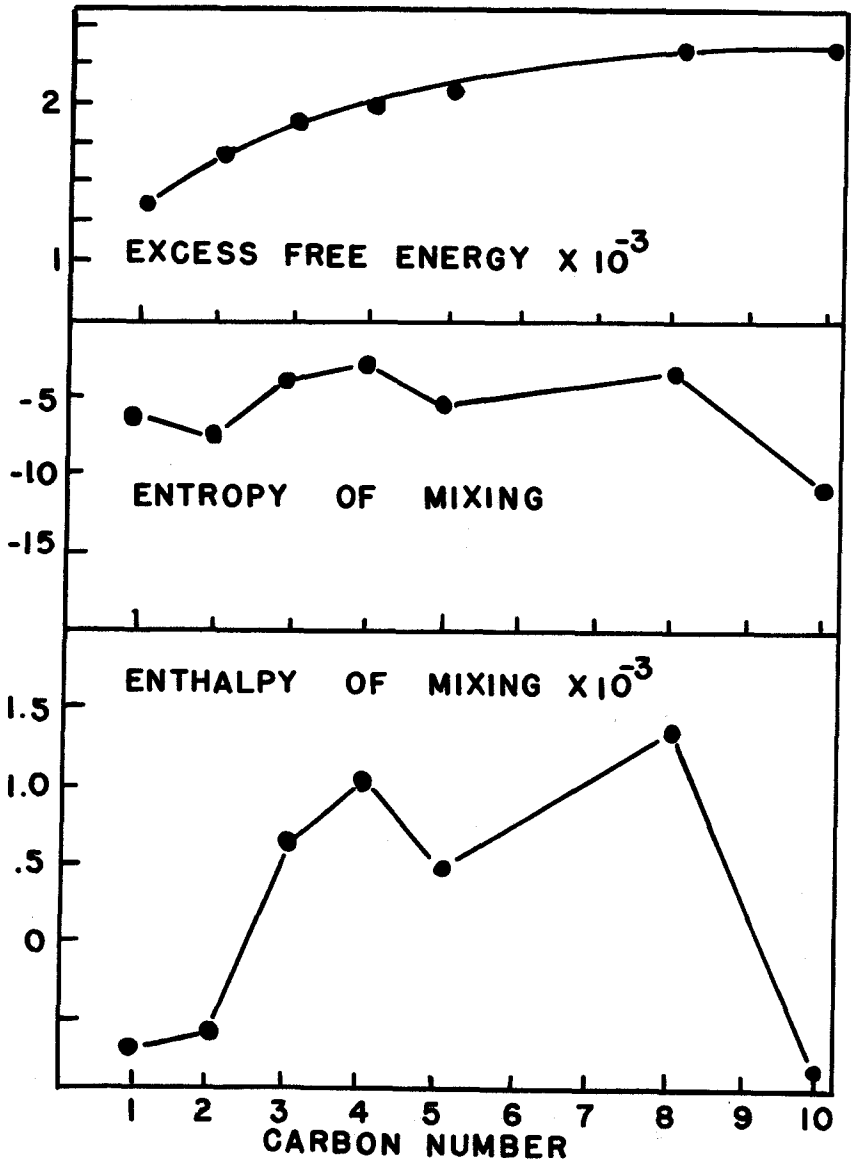

Figure 6-Thermodynamic Functions for Sulfadimethoxine vs. Carbon Number of Alcohols

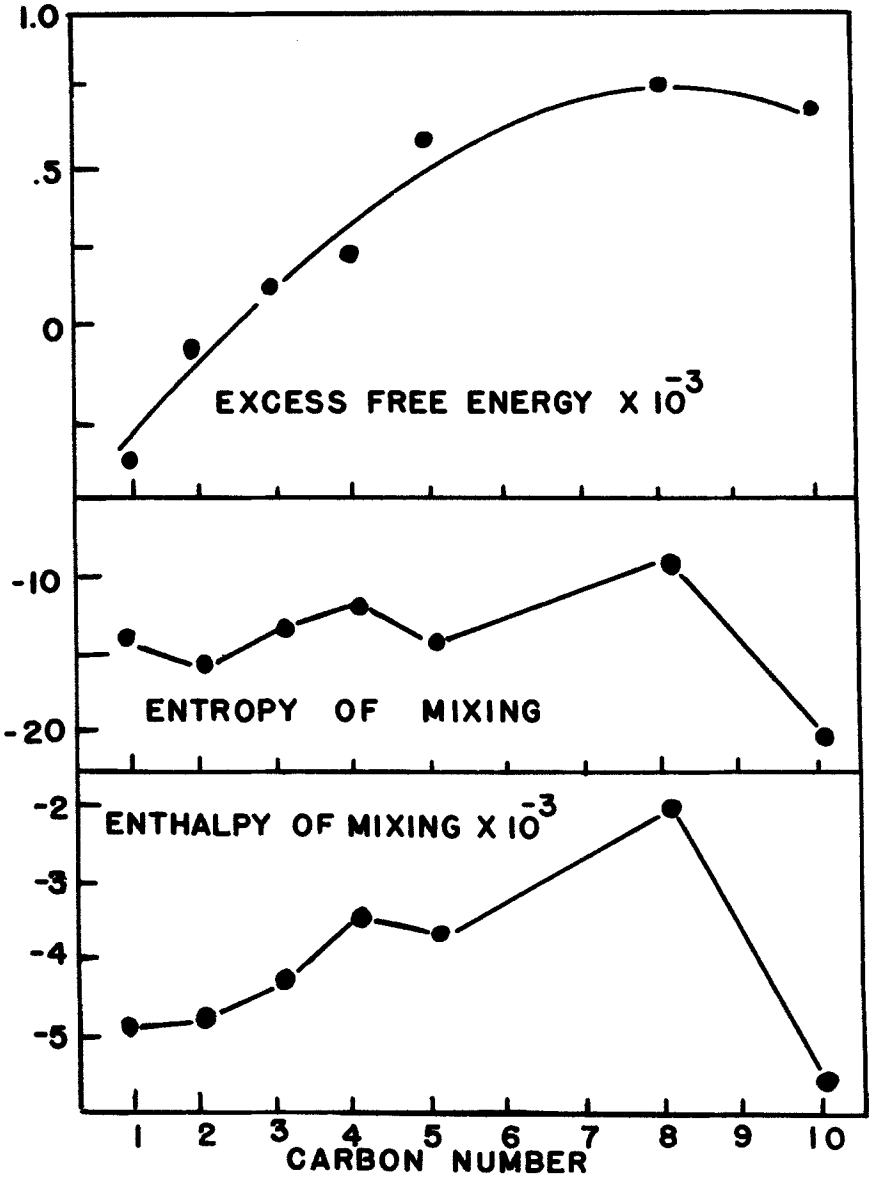

Figure 7-Thermodynamic Functions for Sulfasomidine vs. Carbon Number of Alcohols

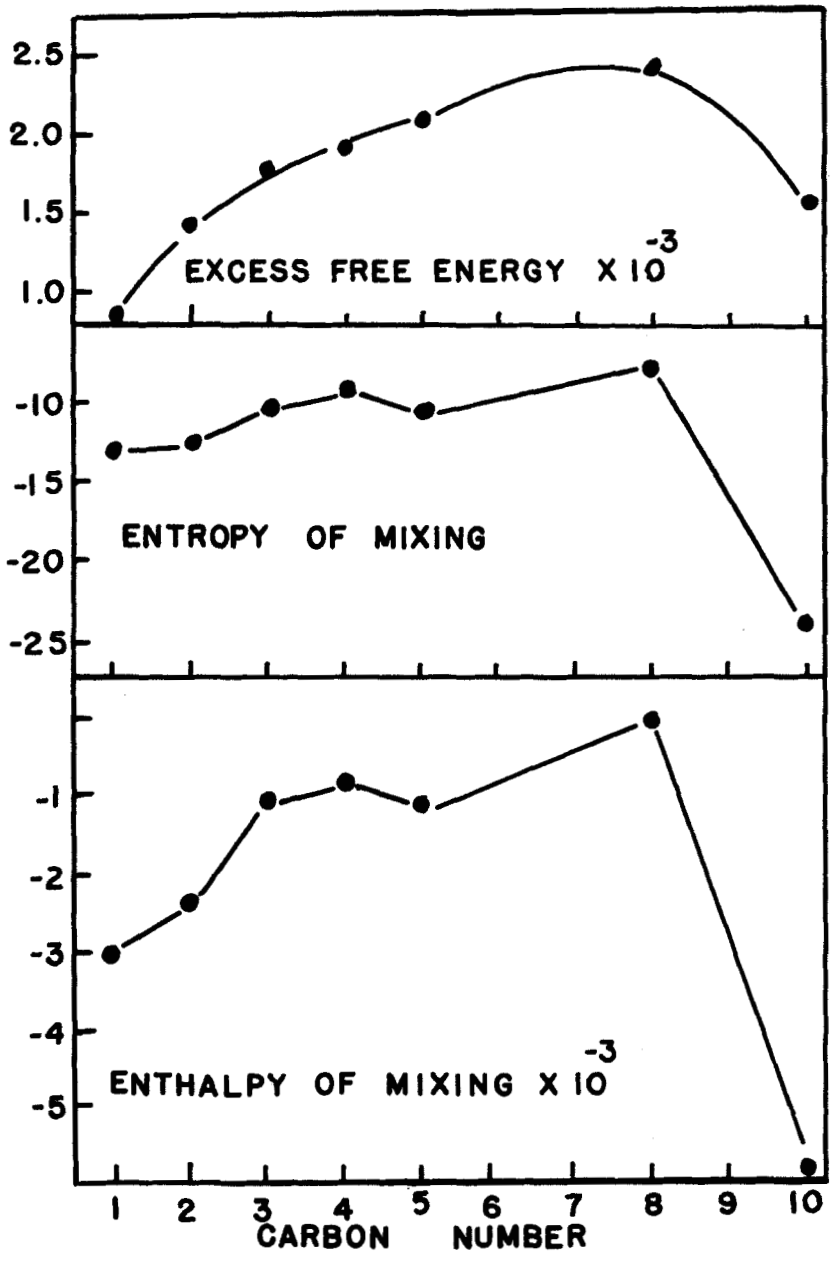

Figure 8-Thermodynamic Functions for Sulfadiazine vs. Carbon Number of Alcohols

number of the linear alkanols used in this study. These "non-ideal" terms give an interesting pattern for these solutes, showing essentially parallelism of the mixing functions and excess free energy values which increase in a smooth fashion with carbon number. The one exception is sulfadiazine in 1-decanol which possesses a value of free energy less than that of 1-octanol. It should be recalled that the solubility of this solute in 1-decanol approximated the solubility in ethanol. The solubility of sulfadimethoxine and sulfasomidine were also similar to or greater than in 1-decanol versus 1-octanol, yet their free energy values are smooth functions.

The general pattern of these free energy curves implies increasing non-ideality as the chain length of the alcohol increases, which is, of course, related to the increasing activity coefficients observed in these solvents.

In summary, the expectation of dilute solution behavior or anticipated "close to ideality" was not observed for these systems. The actual mole fraction solubilities were substantially less than the calculated ideal solubilities. The reciprocal relationship of temperature and log solubility gave straight lines from which enthalpies and entropies could be determined and fusion values from the literature allowed for various thermodynamic elements to be calculated.

It can be stated that solubility behavior and its interpretation, especially semi-polar solutes in semi-polar solvents, must be viewed from the thermodynamic aspects. This suggests that deviations from ideality occur even when dilute solutions are considered.

References

(1) S. S. Yang and J. K. Guillory, J. Pharm. Sci. 61, 26 (1972).

(2) J. K. Guillord, J. Pharm. Sci. 56, 72 (1967).

(3) T. Higuchi, "Solubility" in R. Lyman, "Pharmaceutical Compounding and Dispensing," J. B. Lippincott Co., Philadelphia, 1949, p. 159.

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

(5) J. H. Hildebrand, J. Chem. Phys. 20, 190 (1952).

(6) J. H. Hildebrand, J. M. Prausnitz and R. L. Scott, "Regular and Related Solutions," Van Nostrand Reinhold, New York, NY, 1970, p. 24.

(7) J. H. Hildebrand and R. L. Scott, J. Chem. Phys. 20, 1520 (1952).

(8) J. H. Hildebrand, Science 150, 441 (1965).

(9) K. Shmoda and J. W. Hildebrand, J. Phys. Chem. 61, 789 (1957).