THERMODYNAMICS OF SULFONAMIDE SOLUTIONS

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DOCTOR OF PHILOSOPHY THESIS

OF

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ABSTRACT

The solubility of four sulfonamides in normal alcohols and in buffered aqueous systems was determined at 25°, 30° and 37° Centigrade. The solubility pathway for a nonelectrolyte solute can be described by a process which follows a two-step sequence:

\[ \text{solid} \xrightarrow{1} \text{liquid} \xrightarrow{2} \text{solute in solution.} \]

This pathway was assumed operative for the solute-solvent systems studied, and was used as a basis for the interpretation of the thermodynamic quantities associated with the dissolution process. Heats of solution and their corresponding entropies were evaluated by semilog plots of mole fraction solute concentration versus reciprocal temperature (degrees Kelvin) and these solubilities were found to increase with increasing temperature. Quantitative determination of the solute concentrations was achieved using spectrophotometric analysis and these data were subjected to statistical evaluation.

Partition coefficient data were determined for a particular sulfonamide, sulfadiazine, in an attempt to assess the value of these quantities. All partitioning data were determined in a
constant temperature environment, and the solute concentration of the equilibrated systems was measured using a spectrophotometric assay. The partition coefficients were found to yield a practical method of determining the ionization constants for poorly soluble weak electrolytes. These data were of limited usefulness, however, with respect to theoretical considerations of solute-solvent interactions.
ACKNOWLEDGEMENT

Acknowledgement is gratefully made to the several members of the faculty of the University of Rhode Island College of Pharmacy for their valuable suggestions and criticisms, and to Doctor Anthony N. Paruta, under whose supervision this work was carried out, for his guidance and for his insistence upon devotion to a goal of scientific excellence.
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INTRODUCTION

Whereas, strictly speaking, thermodynamics deals with the macroscopic properties of systems as such, it is not beyond the limits of extrapolation to cite solutions as molecular systems and thus bring the scrutiny of thermodynamic interpretation to bear upon their behavior. In the present investigation the solubility of four medicinal sulfonamides in normal alcohols and buffered aqueous systems was determined. As nonelectrolyte solutes, these compounds were used as models in a thermodynamic study of the mechanism of molecular interactions, manifested as the solubility phenomenon.
The literature concerning the chemistry and pharmacology of the sulfonamides is abundant; noteworthy reviews include those by Northey (1), Seydel (2) and Struller (3). Bell and Roblin (4) have described a relationship between the chemical structure and the antibacterial activity of these compounds. But of major importance to the present study are sulfonamide solubilities, of which several are cited in the literature (5-12). "The solubility is of interest with respect to toxicologic (crystalluria) and the pharmaceutical (absorption) properties of sulfonamides" (2). Therefore, most of the work published describes aqueous, serum and urine solubilities of the sulfonamides. For example, Bandelin and Malesh (7) were concerned primarily with the solubilities of several sulfonamides in phosphate buffers and in synthetic urine at 37°C. The literature revealed no attempt to use sulfonamide molecules as nonelectrolyte solutes and then to treat the data from a thermodynamic and theoretical point of view. Most of the aqueous solubility studies are concerned with relatively complex systems because of other dissolved constituents, and application of non-electrolyte solubility theory to these existing data would be severely limited.
Since partition coefficients are a measure of the solubility of sulfonamides, these quantities are also of interest to this study. Partition coefficients, like solubilities, are important to the toxicologic and pharmaceutical properties of sulfonamides (2, 3, 13-15).

Koizumi collected data (13) on a number of sulfonamides; however, his biphasic partitioning systems of water and an immiscible organic liquid considered only four relatively nonpolar solvents. Examination of the literature does not give evidence that the partition coefficients of sulfonamides have been determined in biphasic systems where the organic phase is varied, thereby allowing an opportunity to study the relationship between the polarity of the organic liquid and the magnitude of the partition coefficient.
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 physical-chemical processes. Unfortunately, quantification of the magnitudes dealing with this process have not, as yet, been put forth. In addition, a rational explanation of solubility depends largely upon the intuitive ability of the investigator to interpret and explain observed results using the disciplines of thermodynamics and quantum chemistry. J. H. Hildebrand, whose work has contributed significantly to this area based his predictive and interpretive equations on thermodynamic quantities (1). At the same time, the quantum approach has a unique appeal because it establishes a basis for understanding solubility implications at the molecular level.

The development of predictive equations in solubility research has been hampered by a lack of mechanistic understanding. Indeed, the adage that "like dissolves like" is not an oversimplification of the current knowledge, especially with regard to predicting the magnitude of solubility for any given system. Only rarely is it possible to predict solubility expectations with any degree of success. However,
problems will probably be alleviated as more is learned about the structural state of solid and liquid materials. Even now, research continues (2) to explain the structural state of water, the most important liquid known.

Scott and Fenby (3), commenting recently on solubility research, stated "Any complete understanding of mixtures must await the solution of two problems: (a) the quantum mechanical problem of the intermolecular potential energy; and (b) the statistical mechanical problem of the equation of state of a dense fluid. To date, only very approximate treatments (or intractable formalisms) exist, but they suffice to yield much qualitative understanding of liquid solutions. Indeed, at times it has seemed that theories of solutions can be much more successful than one would expect from the approximations about intermolecular potential energy functions and liquid properties or structure upon which they are based; conversely, it follows that the empirical success of solution theories cannot always be adduced as support for the liquid models from which they are derived." From this statement, it would seem that the solubility investigator must either contribute toward the solution of the two problems mentioned or continue to base solubility understanding on approximations. The latter pathway is still more practical and is quite legitimate if the limitations of the approximations are recognized. Indeed, many physical-chemical processes are studied in this manner, because the
exact equations are either too difficult to handle or are unknown; moreover, as Scott and Fenby have observed, the inexact solution can lead to a qualitative understanding.

The first step toward an explanation of solubility is a definition of the solution process. According to Higuchi (4), "The solubility of a substance in a given solvent is usually defined as the concentration of the solute in solution which is in equilibrium with the solute phase." This definition may be expressed as

\[ \text{solute particles} \xleftrightarrow{\frac{k_1}{k_2}} \text{solute particles} \]

\[ (\text{solute phase}) \quad (\text{solution phase}) \]

where \( k_1 = k_2 \times \) concentration of solute in the saturated solution.

The equilibrium constant, \( K \), relating \( k_1 \) and \( k_2 \) is

\[ K = \frac{k_1}{k_2} \]

From equation 1, it will be observed that solubility is a dynamic and reversible condition involving \( k_1 \), the rate of solution, and \( k_2 \), the rate at which the solute is transferred to its original state. The equilibrium constant is a quantitative indication of all prevailing molecular interplays and forces involved in the dissolution process.

If the reaction in equation 1 proceeds to the right, i.e., for solubility to be favored, it is necessary that intermolecular interactions exist between the solute and solvent. The nature and magnitude of these interactions will ultimately determine the magnitude of \( K \). Higuchi (5) confirms that solubility is an interaction process,
stating, "Although, for example, various theories and hypotheses have been proposed in the area of solubility behavior of nonelectrolytes the most pharmaceutically useful approach appears to be that based on the concept that such solutions represent summation of effects arising from interactions of a large number of equilibrium systems."

The interactions involved when a solute is dissolved are quite complex, because they include not only the solvent-solute interactions, but the attractive forces between the solvent-solvent and solute-solute molecules as well. Repulsive forces must also be considered, because there would be molecular annihilation if the molecules were mutually attracted to the extent that interpenetration existed (6). Schueler (7) suggests that the repulsive forces act as an internal barrier to the closeness of molecules, whereas cohesive forces prevent the dissipation of molecules from their present state.

Molecular Forces - Ketelaar (8) has listed several of the most important forces which act between molecules as: (a) dipole-dipole, orientation effect or Keesom force, (b) dipole-induced dipole, induction or Debye force, (c) induced dipole-induced dipole, dispersion effect or London force and (d) hydrogen bonding.

The dipole-dipole or Keesom force occurs between molecules that have permanent dipoles. Interaction exists when the molecules align themselves such that the negative pole of one is attracted to the
positive pole of the next. A negative interaction or repulsion occurs when the arrangement is such that like poles are oriented. Theoretical consideration of the Keesom force (9) suggests that the interaction will decrease with increasing intermolecular distance and with temperature. The distance factor is to the sixth power and its reciprocal relationship with the Keesom interaction indicates that a small change in distance will drastically reduce the magnitude of the attractive force. This means that the intermolecular force will only be considerable when the distance between molecules is relatively small.

Dipole-induced dipole interactions arise because molecules with a permanent dipole have the ability to induce a dipole in a nearby nonpolar molecule. An example of this type of interaction occurs when alcohol, which has a permanent dipole, is mixed with benzene. The apparent importance of this interaction is that it offers an explanation for the miscibility or solubility of molecules with unlike electrical properties. Although Debye forces are related to distance in the same way as Keesom interactions, they are not theoretically related to temperature (9).

Dispersion forces, of considerable importance for molecules that have no permanent dipole moment, are the weak electrostatic forces responsible for the liquid state of many nonpolar molecules. Conceptually, the dispersion force is recognized to be the result of molecules inducing a weak electrostatic attraction not conditioned by
the presence of a permanent dipole. The magnitude of this force, as mentioned above, is sufficient in many cases to maintain the liquid state at room temperature. Like the other interactions, the attraction falls off with distance, but in this case it is not temperature related.

The hydrogen bond or bridge has been given considerable attention recently (5) and may be thought of as a special case of a dipole-dipole interaction because of its electrostatic nature. As the name implies, the bond or attractive force exists between hydrogen and an electronegative atom such as oxygen. Perhaps the best example of hydrogen bonding is between water molecules, where the oxygen has a partial negative charge and hydrogen has a partial positive charge. These unlike charges provide for an electrostatic attraction and hence the hydrogen bond.

Hydrogen bonding in systems of miscible liquids such as water and ethanol has been discussed by Bobtelsky (10), who suggests that the water-alcohol interaction results in a molecular arrangement somewhat akin to a polymer. If one considers this type of arrangement for certain liquids to be reasonable, then it follows that hydrogen bonded liquids are to some extent structured like materials in the solid state. Bailey (11) confirms the opinion that a considerable degree of order does exist in these liquids. He tempers the analogy between liquids and solids, however, by pointing out that the order in the liquid structure
does not extend over any great distance, while an ordered arrangement usually prevails throughout each crystal of a solid crystalline substance. In other words, the ordering associated with hydrogen bonding is a short rather than a long range force. The structuring of water is significant because x-ray investigations have shown that the structure of liquid water is much more like that of ice than of the vapor state. In fact, the liquid state exhibits to a considerable extent the tetrahedral structure found in ice (12). Any structuring which does occur is said to be due to cybotactic groups (which promote hydrogen bonding), composed of microcrystalline aggregates consisting of many molecules within the bulk of otherwise randomly ordered molecules (11).

The hydrogen bond is of special significance with respect to solubility. In systems of pharmaceutical interest, e.g., benzoic acid in ethanol, where both the solute and solvent can form the hydrogen bridge, the magnitude of solubility is certainly expected to be enhanced. On the other hand, a solute which cannot form hydrogen bonds can be expected to be literally "squeezed out" by a structured liquid solvent.

It should not be implied that the interaction for any particular molecular system can be attributed to a single force. Any or all of the forces discussed may be involved, and the magnitude of contribution is unique depending on the properties of the molecules. The cohesive forces of one solvent, water, for example, are the summation of the
Keesom, Debye and London interactions.

Although the interaction forces which prevail in the solution process have been shown to be significant, they are, however, only a part of an explanation of solubility. Higuchi (13) emphasizes that the magnitude of the solute-solvent interactions does not totally determine the solubility, but that solubility is rather a summation of many and various factors involved in equation 1. Moreover, the Hildebrand treatment of nonelectrolyte solubility recognizes the intermolecular interactions as a primary step in the understanding of solubility (1); but the next step in the Hildebrand fabric of development is the selection of Raoult's Law as a standard state on which to base both qualitative and quantitative formulas.

Raoult's Law- Raoult’s Law, with applications to solubility, provides a standard condition and permits interpretation of perturbations from a defined ideal state. The formulas expressing Raoult's Law are (14)

\[ p_a = p_a^0 x_a \quad \text{and} \quad p_b = p_b^0 x_b \]  

(3)

where \( p_a \) and \( p_b \) are the partial vapor pressures of components a and b, \( p_a^0 \) and \( p_b^0 \) are the vapor pressures of components a and b, and \( x \) is the mole fraction concentration of the component. If \( p_a \) and \( p_b \) are entirely additive, the total pressure, \( P \), becomes

\[ P = p_a + p_b \quad \text{or} \quad P = p_a^0 x_a + p_b^0 x_b \]  

(4).
If the system remains strictly additive, the attraction of molecules a and b for each other are the same as the a-a and b-b attractions of the pure species. Thus, equation 4 now becomes fundamental to a definition of IDEAL solution behavior.

Systems which do not adhere to Raoult's Law are known as REAL solutions, and two types of deviations are recognized. When the a-b attractions are greater than the a-a or b-b interactions, the vapor pressure of the solution is less than that predicted by Raoult's Law, and a negative deviation occurs. When the a-b interaction is less than that predicted by Raoult's Law, the vapor pressure is larger than expected, and a positive deviation is said to occur.

The Ideal Solubility Equation - The formula for the ideal solubility of a nonelectrolyte solute, \( X_2 \), is (15)

\[
\ln X_2 = \frac{-H_f}{R} \frac{(T_m - T)}{T \cdot T_m} \quad (5)
\]

where \( X_2 \) is the mole fraction solubility of the solute, \( H_f \) in calories/mole is the heat of fusion of the solute, \( T_m \) is the absolute melting point of the solute and \( T \) is the absolute temperature of the system, and \( R \) is 1.987 calories/degree mole. Equation 5 suggests several interesting facts: a) the solubility of the solute is independent of the solvent, b) a low heat of fusion enhances solubility and c) a low melting point temperature increases solubility. The heat of fusion is a regulating quantity in the equation; its effect on the equation leads to the
melting of the solid solute to a liquid form. By definition (16), the heat of fusion is the heat taken up by one mole of a solid when it melts without temperature change. Therefore, under conditions of ideal solubility, there is no particular distinction between the processes of melting and solution. Bailey (17) points out that the term "melting" might be applied only to a pure substance, whereas "solution" should refer to a multicomponent system; but this distinction, despite its logic, is not usually recognized. More important is the fact that solution as a melting process is a much better foundation for solution theory than are older ideas which thought of the solvent simply as a medium in which the solute could be sufficiently dispersed to approximate the state of a gas.

Equation 5 is also important from a thermodynamic point of view because it implies: a) the molecules of an ideal solution exhibit complete freedom of motion and randomness of distribution in solution, b) there is no change in heat content during the mixing process, and c) the volume of the solute does not change during the mixing process. These implications also mean that Raoult's Law is obeyed with respect to the resultant interactions.

Martin (18) has given quantitative interpretations of the above information. The free energy change for an ideal solution is

\[ F = RT \ln \chi_2 \]

(6)

\(^a\)All thermodynamic functions discussed refer to delta quantities. The delta symbol has been omitted for brevity.
The symbols have been previously defined. Following the argument above, the heat change is zero, so that

\[ F = -TS \]  

(7).

The entropy of mixing, \( S \), of the ideal solution now becomes

\[ S = -\frac{F}{T} = -R \ln X^2 \]  

(8)

and the quantity \(-R \ln X^2\) is known as the entropy of mixing.

The heat of fusion in equation 5 must be constant when the formula is given in this form. This means that the difference between the heat capacities, \( C_p \), of the liquid and solid solute are zero, which is not true for most, if not all, nonelectrolyte solutes. In definitive terms, \( C_p \) is the amount of heat needed to raise the temperature of a system one degree. The correction for \( C_p \), given by Hildebrand (15) is

\[
\ln X^2 = (-H_f/R) \int \frac{(T_m - T)}{T_m T} \, dT + (C_p/R) \times \\
\int \frac{(T_m - T)}{T_m} - (C_p/R) \int \ln(T_m/T) \, dT
\]

(9)

where \( H_f \) is now the heat of fusion of the pure solute at its absolute melting point. Ordinarily equation 5 is used for solubility calculations rather than equation 9 because, first, \( C_p \) for many solutes is not known and, second, the uncorrected form of the formula, perhaps because of a cancelling of errors, offers a very good approximation.

It is important to test equation 5 for a real solute in order to verify the solution process in terms of melting of the solute. From
the data presented by Martin (19), the heat of fusion for naphthalene is 4500 calories per mole and the melting point temperature is 353° Kelvin. The calculated mole fraction at 20° Centigrade is 0.27, a value correlating very well with the data of Scatchard (20), who found that the experimental mole fraction solubility at 20° Centigrade was 0.24 in benzene, 0.23 in toluene and 0.21 in carbon tetrachloride.

The naphthalene calculation gives credence to the theory expressed by equation 5; but there is, unfortunately, a limit to its usefulness. One of the most important contributions to the theory of nonelectrolyte solubility has been proposed by Hildebrand and Scott (21), who investigated the solubility of iodine in many solvent systems (22). They recognized the thermodynamic implications regarding systems that deviated from the ideal and developed a special type of deviation which came to be known as a REGULAR solution.

The Regular Solution Equation - Hildebrand and Scott developed regular solution theory by correcting equation 5 or 9 to account for the deviations from the calculated quantity $X_2$ (15). Their first step was to redefine $X_2$ as $X_{2i}$, i.e., $X_2$ideal. Then, $X_{2i}$ was corrected for deviation from ideal solution behavior by introducing an activity coefficient of the solute, $Z$,

$$X_{2i} = X_2Z$$

(10).

In logarithmic form, equation 10 becomes

$$\log X_{2i} = \log X_2 + \log Z$$

(11).

Equation 5 may now be rewritten as

$$- \log X_2 = \left(\frac{H_f}{R}\right) \frac{1}{T_m - T} \log \frac{TmT_m}{TmT} + \log Z$$

(12).
Equation 12 now accounts for deviate behavior, but it is the quantity $Z$ and the concept behind it that emerges as significant. It is logical to assume that, when two species are mixed, deviations under certain boundary conditions are at least partially due to changes in heat content or entropy. As early as 1906, van Laar (23) derived theoretical equations that yielded qualitative agreement only. A much better theory, and one still accepted, was developed by Scatchard (24). Hildebrand and Scott (25) discuss Scatchard's work as it is based on these assumptions: a) the mutual energy of two molecules depends only upon the distance between them and their relative orientation, and not at all on the nature of the other molecules between or around them or on temperature, b) the distribution of the molecules in position and in orientation is random and c) the change in volume on mixing at constant pressure is zero. From these assumptions, Scatchard deduced the energy of mixing for a bicomponent system to be

$$E_m = (X_1V_1 + X_2V_2)(c_{11} + c_{22} - 2c_{12})$$

(13).

With reference to equation 13, $c_{11}$, $c_{22}$ and $c_{12}$ are energetic quantities related to the interactions involved for the pure components $c_{11}$ and $c_{22}$ and the resultant interacted species $c_{12}$. $V$ is the molar volume of the pure solute as a supercooled liquid, defined as the molecular weight divided by its density. The volume fraction term, $\phi$, for species 1 is $V_1/(X_1V_1 + X_2V_2)$; it is the same for species 2.
except \((X_2V_2)\) is the numerator. According to the assumption made by Scatchard, that there is no volume change at constant pressure, the value for \(V\) will remain unchanged after mixing. Scatchard also assumed that

\[ c_{12} = (c_{11}c_{22})^{1/2} \]  

(14).

Under the condition of equation 14, the value for the \(c\) quantities simplifies to

\[ A_{12} = \frac{1}{2} (c_{11})^{1/2} - (c_{22})^{1/2} - \frac{1}{2} \]

(15)

and equation 13 then becomes

\[ E^m = (X_1V_1 + X_2V_2)A_{12} \]

(16).

The manipulations leading to equation 16 are far more than a mere mathematical simplification procedure. The equality in equation 14 is known as the geometric mean assumption and is embodied as part of the regular solution theory. That is, the interactions which result to yield \(c_{12}\) must be related to the component parts of equation 14; otherwise, the solution by definition is not regular.

For a solid nonelectrolyte solute in a solvent, the quantities in equation 16 are related to the change in heat content on mixing, \(H_m\), by

\[ H_m = V_2\nu_1^2 \frac{1}{2} (c_{11})^{1/2} - (c_{22})^{1/2} - \frac{1}{2} \]

(17)

or

\[ H_m = RT \ln Z \]  

(18).

Now, the value for \(Z\) in equation 12 assumes definition and indeed is related to the heat content change when mixing occurs.
One of the most common means of evaluating $c_{11}$ and $c_{22}$ is by

$$c^{1/2} = \sqrt{\frac{(H_v - RT)}{V}} = S.P. \quad (19)$$

where $H_v$ is the heat of vaporization at temperature $T$ and $S.P.$ is the solubility parameter. In this formula, $H_v$ is the energy necessary for one mole of a substance to change from the liquid to vapor state, at its boiling point, and in terms of intermolecular interactions, a substance with a large affinity for itself will have a large $H_v$ value. The molar volume, $V$, in the denominator modifies the heat of vaporization with respect to molecular volume. The quantity $RT$ appears in equation 19 as an approximation of the energy necessary to displace the air against atmospheric pressure during the vaporization process (27).

The value for $(H_v - RT)$ is actually an approximation of a quantity known as the cohesive energy; and the solubility parameter is the square root of the cohesive energy density (26). In regular solution theory, the solubility parameter is a measure of the internal pressure of the pure substance, either solute or solvent, and is useful in predicting the miscibility or solubility of the solute. From a thermodynamic point of view, the solution process will be enhanced as the difference between the internal pressures of the components approaches zero and the enthalpy change is negligible. Schueler (7) devised a relative scale of internal pressures based on naphthalene as 1.00: hexane, representing
a nonpolar liquid, has a value of 0.56, and water on this scale is 4.55. These figures indicate that water has an internal pressure eight times greater than that of hexane; further, water would not be expected to mix with hexane because of the powerful interactions existing in the polar liquid. This may be considered a theoretical justification for the "like dissolves like" concept.

If the activity coefficient, $Z$, is introduced into equation 12, it may then be rewritten in its final and most common form

$$-\ln X_2 = \frac{(H_f/R) \int (T_m - T)/T_m \cdot \int + (V^2 \theta_1^2 / RT)(S.P.1 - S.P. 2)^2}{(20)}$$

where $S.P.1$ and $S.P.2$ are arbitrarily taken as the solubility parameters of the solute and solvent, respectively. When $S.P.1$ and $S.P.2$ are equal, the second term in equation 20 reduces to zero and IDEAL solution behavior is exhibited. However, if the difference between the solubility parameters is not zero, then under the assumption of Scatchard, REGULAR solution behavior is manifest and the deviation from Raoult's Law is a positive one. It should be noticed from equation 20 that the square of the difference between the solubility parameters is always positive; hence, the calculated solubility for a regular solution is less than that calculated for an ideal one.

Of recent interest is the molar volume, $V_2$, which for a regular solution must remain constant. Hence, this quantity becomes an important indicator of regular solution theory.
Glew (28) and Shinoda (29) have studied the molar volumes of iodine in several solvents and shown that \( V_2 \) remains constant under the assumption of regular solution behavior.

Another quantity known as the heat of solution is also helpful in interpreting nonelectrolyte solubility behavior. A discussion of this quantity is presented in the following section.
THE USE OF HEATS OF SOLUTION
AS AN AID IN CHARACTERIZING
NON-ELECTROLYTE SOLUBILITY BEHAVIOR
One of the fundamental relationships in non-electrolyte solubility behavior is that of the temperature effect on the magnitude of solubility. Quantification of this effect is embodied in the heat of solution equation, which takes into account the mole fraction solubility for a solute, temperature and the enthalpy and entropy associated with the process.

An attempt is made to interpret the physical meaning of the enthalpy, i.e., the heat of solution, and its corresponding entropy, as solubility varies with temperature, and to relate these quantities to certain types of non-electrolyte solubility behavior.
INTRODUCTION

The solution process may be viewed as one which occurs in two steps (1):

\[
\begin{array}{ccc}
\text{solid solute} & \xrightarrow{H_f} & \text{liquid solute} \\
\downarrow & & \downarrow \\
\text{solution} & & \text{solution}
\end{array}
\]

As the solid solute proceeds through step one to the liquid state, the enthalpy change is the heat of fusion, \(H_f\). If the solution is "ideal," the enthalpy of the second step is zero. The requirements for an ideal solution are: 1) Raoult's Law is obeyed; 2) there is no volume change at constant pressure; and 3) the magnitude of solubility is essentially independent of the solvent. When a solid solute passes to a liquid state and then into solution, its behavior is said to be "non-ideal" if the enthalpy of the second step is not zero and if the other requirements for an ideal solution are not met. Under conditions where both steps one and two are operative, the total enthalpy for the process is commonly expressed as the heat of solution, \(H_s\), where

\[
H_s = H_f + X \quad (1)
\]

In this solubility pathway, \(X\) reflects the enthalpy involved in the transfer of the solute from the liquid to the solution phase. As the \(X\) term approaches zero, the heat of solution and the heat of fusion approach equality.

\[\text{The heat of solution referred to is also known as the differential heat of solution and is defined as the heat produced per mole of the added solute if a small amount of solute is added to a given solution such that its concentration is not appreciably affected (reference 7).}\]
In quantitative notation, the heat of solution is related to the corresponding standard free energy change, $F^0$, corresponding entropy change, $S$, and temperature (Kelvin), $T$, by (2)

$$F^0 = H_s - TS,$$

(2).

The logarithm of the mole fraction solubility, $X_2$, may also be equated to the standard free energy change, where

$$F^0 = -RT \ln X_2,$$

and $R$ is 1.987 calories/mole degree. Then,

$$F^0 = -RT \ln X_2 = H_s - TS,$$

(4)

and

$$\ln X_2 = -H_s/RT + S/R.$$  

(5)

Therefore, a plot of $\ln X_2$ versus $1/T$ should yield a straight line with a slope of $-H_s/R$ and y-intercept of $S/R$. The slope of the line gives $H_s/R$ directly under the assumption that Henry's Law is obeyed when the concentration of the solute component of the solution is low. Because $H_s$ and $S$ are actually temperature dependent, they remain constant only within constrained temperature limitations (3). Further, the entropy is an extrapolated quantity and only relates to the process as it occurs between $T_1$ and $T_2$.

In addition to its practical use of allowing the calculation of solubilities at different temperatures, equation 5 should assume theoretical importance regarding non-electrolyte behavior.
RESULTS AND DISCUSSION

Hildebrand (4) has classified non-electrolyte solubility behavior. The various classifications together with the enthalpies and entropies of mixing are shown in Table I.

TABLE I
CLASSIFICATION OF SOLUTION BEHAVIOR\textsuperscript{a}

<table>
<thead>
<tr>
<th>Designation</th>
<th>Heat of Mixing\textsuperscript{b} (Enthalpy)</th>
<th>Entropy of Mixing\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athermal, ideal</td>
<td>0</td>
<td>(-R \ln X_2)</td>
</tr>
<tr>
<td>Regular</td>
<td>+</td>
<td>(-R \ln X_2)</td>
</tr>
<tr>
<td>One component</td>
<td>+</td>
<td>(\geq -R \ln X_2)</td>
</tr>
<tr>
<td>associated</td>
<td></td>
<td>(&lt; -R \ln X_2)</td>
</tr>
<tr>
<td>Solvated</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}J. Hildebrand, \textit{Chemical Reviews}, 44, 37 (1949)

\textsuperscript{b}These quantities are distinct from the heat, or enthalpy, of solution and its corresponding entropy.
An ideal solution is one in which the heat of mixing is zero, the entropy of mixing is \(-R \ln X_2\), and Raoult's Law is obeyed. Therefore, the solubility of the non-electrolyte solute is a function of its enthalpy of fusion, \(H_f\), and its melting point temperature, \(T_m\). The equation relating the mole fraction solubility to these quantities is (5)

\[
\ln X_{2i} = -\frac{H_f}{RT} + \frac{H_f}{RT_m}
\]  

Equations 5 and 6 are of the same form so that, if the system is ideal, a plot of \(\ln X_{2i}\) versus \(1/T\) should yield a straight line with a slope of \(-H_f/R\) and a y-intercept of \(H_f/RT_m\). The y-intercept is equivalent to the entropy of fusion, \(S_f\), because of the relationship

\[
S_f = \frac{H_f}{T_m}
\]

for a reversible process. Hildebrand (5) has pointed out that \(H_f\) is constant only over broad temperature ranges, under the assumption that the difference between the molal heat capacities of the liquid and solid solute are zero. Since this is unlikely, \(H_f\) at temperature \(T\) and \(H_f\) at temperature \(T_m\) are not expected to be equal. However, the molal heat capacity quantities are often not known and even if known, they may not be constant with temperature. Thus, equation 6 in its present form will be used for subsequent calculations.
A regular solution differs from an ideal one in that the heat of mixing is positive. This simply means that heat is absorbed when the components are mixed. The equation for this process as given by Martin (6) is

\[-\ln X_2 = \frac{H_f}{RT} \left( \frac{(T_m - T)}{T_m} \right) + \ln Z \quad (8).\]

The term \(Z\) is the activity coefficient of the solute and is related to \(X_{i1}\) and \(X_2\) by

\[X_{2i} = (X_2)(Z) \quad (9).\]

The heat of mixing, \(H_m\), is also related to the activity coefficient for a regular solution, where

\[H_m = RT \ln Z \quad (10).\]

Thus, equation 8 may be rewritten as

\[-\ln X_2 = \frac{H_f}{RT} \left( \frac{(T_m - T)}{T_m} \right) + H_m/RT \quad (11).\]

or

\[-\ln X_2 = (H_f/RT) - (H_f/RTm) + (H_m/RT) \quad (12).\]

Substitution of \(H_f/T_m\) from equation 7 yields

\[\ln X_2 = -\left( \frac{H_f + H_m}{RT} \right) + S_f/R \quad (13).\]

which again has the same general form of equation 5. From equation 13, it will be noted that the enthalpy for a regular solution is the sum of the heat of fusion and the heat of mixing. Therefore, the heat of solution is equal to the heat of fusion plus the heat of mixing and the excess enthalpy term, \(X\), in equation 1 is the heat of mixing.
Comparison of equations 6 and 13 reveals that the entropy for an ideal solution and for a regular one are theoretically equal. Again, however, entropy is an extrapolated quantity and may differ from theoretical values because the actual solubilities are measured at temperatures substantially different from Tm.

The heat of mixing term given in equation 13 is also equal to (6)

\[ H_m = V_2 \theta_1^2 (S.P.1 - S.P.2)^2 \] (14).

where \( V_2 \) is the molar volume of the supercooled liquid solute, \( \theta_1 \) is the volume fraction of the solvent and S.P.1 and S.P.2 are the solubility parameters of the solute and solvent, respectively.

Equation 13 implies a linear relation between \( \ln X_2 \) and \( 1/T \) but there are three factors not readily apparent that may lead to deviations from linearity. First, the volume fraction term, \( \theta \), changes with changing solubility. This should not lead to large discrepancies; however, because the volume fraction is nearly unity for dilute solutions. Second, and more serious, equation 13 does not recognize changes of volume on mixing. To correct for this possibility, the partial molal volume of the solute should be measured. For purposes of this paper, however, equation 13 will not be corrected for volume changes on mixing under the assumption that strict regularity is maintained. Third, the solubility parameters are temperature dependent quantities (6):

\[ S.P. = \sqrt[1/2]{(H_v - RT)/V} \] (15).

where \( H_v \) is the heat of vaporization, and \( V \) is the molar volume of the pure species. If the solubilities are measured over a limited temperature
range, this deviation should not be a serious one.

The third and fourth classifications in Table I are in agreement with the general heat of solution equation (equation 5), but not with the ideal or regular solution expressions. That is, when a system is associated or solvated, the excess enthalpy is not directly related to the heat of mixing through the activity coefficient, and the entropy is quite likely unequal to the entropy of fusion. However, the general form of equation 1 is applicable to relate the heat of solution to the heat of fusion and to the corresponding excess enthalpy. In the case of association, the heat of mixing remains positive as for regular solution; but the entropy of mixing is unequal to \(-R \ln X_2\) and the y-intercept is not necessarily \(S_f/R\). The same is true for solvated systems, except in this case the heat of mixing is negative. For association, the heat of solution is generally larger than that calculated by the regular solution equation. For solvation, the heat of solution is usually smaller than predicted.

From the previous discussion, it can be seen that the heat of solution and the corresponding entropy may be valuable in determining whether the solution is ideal, regular, associated or solvated. Higuchi (7) has pointed out that the heat of solution is a valuable quantity because its magnitude may intuitively suggest information pertaining to the solution process, that is, the interaction between the solute and solvent.
Higuchi's general expression relating solution behavior and the heat of solution is (7)

$$H_s = H_{1,2} - (H_{1,1} + H_{2,2})$$  \hspace{1cm} (16)

where $H_{1,1}$ is the molar heat of vaporization of the solvent, $H_{2,2}$ is the molar heat of vaporization of the solute and $H_{1,2}$ is an energy term involving the magnitude of the interaction between the solute and solvent. Equation 16 shows that a large negative number for $H_s$ means that a relatively small interaction has occurred and that the solubility is limited. According to this scheme, it appears that $H_s$ is generally negative for non-electrolyte solubility systems. Actually, the slope of the line, $H_s/R$, relating $\ln X_2$ and $1/T$ is negative but the enthalpy quantity itself, by convention, is positive if the process is endothermic (8).

A value for $H_s$ which approaches zero suggests high solubilities, or in the case of two liquids such as toluene and benzene, such a value suggests that complete miscibility occurs with no heat produced or absorbed.

Mortimer (9) has recognized and discussed the fact that the heat of solution indicates the relative magnitude of interaction for a non-electrolyte and its adherence or deviation from the ideal solubility equation.

Belleau (10) has pointed out that the free energy change for a particular process is dependent on both the corresponding enthalpy and entropy. Further, the entropy term changes in sign and magnitude to compensate for changes in enthalpy. The heat of solution for non-electrolyte solubility is almost always positive, indicating an endothermic process; and the entropy may be positive or negative. This leads
to two possibilities:

a) enthalpy +, entropy +

b) enthalpy +, entropy -.

In the first case, the enthalpy term predominates at lower temperatures and the mole fraction solubility will be less than one. The second case allows for increasing solubility with increasing temperature, but the standard free energy will always remain a positive value (11).

The entropy term associated with the heat of solution is related to the extent of disorganization in the system and becomes more negative as organization, relative to the initial state, becomes manifest. As suggested previously, the entropy for a regular solution is approximately $S_f$. For solvated systems where solute-solvent interactions are relatively large, the entropy is usually a smaller positive number, indicating a decrease in the number of independent molecules. Associated solutions, however, would be expected to show a reverse trend for the entropy term.

In order to relate the general heat of solution equation (equation 5) to all the classifications in Table I, a hypothetical solute with a heat of fusion of 4600 calories/mole and a melting point of 373° Kelvin was used to plot the curves shown in Figure 1. The heats of solution and y-intercepts for the hypothetical solute are presented in Table II. As predicted from equation 13, a regular solution shows an increased heat of solution and decreased solubility as compared with the ideal system.
It should be noted, however, that the y-intercepts for the ideal and regular solution are equal, while the intercept value for an associated system is a larger positive value. A solvated system, in keeping with increased molecular organization, exhibits a smaller positive intercept, i.e., a smaller entropy. The associated and solvated systems shown in figure 1 were derived arbitrarily, but the values for the heats of solution and corresponding y-intercepts were chosen so as to reflect the general properties of the respective classifications.
Figure 1 - A Plot of $\log_{10} X_2$ Versus $1/T$ (absolute) for a Hypothetical Solute with a Heat of Fusion of 4600 cal./mole and a Melting Point of 373°.
TABLE II

SOLUTION DATA FOR A HYPOTHETICAL SOLUTE WITH A HEAT OF FUSION OF 4600 CAL./MOLE AND A MELTING POINT OF 373° KELVIN

<table>
<thead>
<tr>
<th>Designation</th>
<th>Heat of Solution (cal./mole)</th>
<th>y-intercept (S/2.303R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athermal, ideal</td>
<td>4600</td>
<td>2.68</td>
</tr>
<tr>
<td>Regular</td>
<td>5750</td>
<td>2.68</td>
</tr>
<tr>
<td>One component associated</td>
<td>6500</td>
<td>2.85</td>
</tr>
<tr>
<td>Solvated</td>
<td>3500</td>
<td>2.25</td>
</tr>
</tbody>
</table>
Actual solubility data are more difficult to interpret than those indicated by the curves generated for the hypothetical solute. To test equation 5 against the classifications in Table I, the data given by Mortimer (9) for benzoic acid in various solvents were subjected to analysis. Mortimer's data are reproduced in Table III. The ideal solubilities shown are based on the heat of fusion of 4302 calories/mole and a melting point of 396° Kelvin for benzoic acid as given by Chertkoff and Martin (12). The data in Table III were subjected to a least squares analysis for a plot of \( \log_{10} X_2 \) (\( 2.303 \log_{10} X_2 = \ln X_2 \)) versus \( 1/T \). Table IV shows the resulting information, along with the correlation coefficients, R, for the derived lines. The R values are included because they indicate the degree of linearity for the system under study.

From the data in Table IV, it appears that benzoic acid in acetic acid behaves as a nearly regular solution. The y-intercept for this system is almost equal to that for the ideal solution, indicating that the larger heat of solution value is likely due to the additive term in equation 13. If this is true, the following equality should obtain:

\[
H_m = RT \ln \left( \frac{X_{21}}{X_2} \right) = H_s - H_f \quad (17)
\]

At 20° C., \( RT \ln \left( \frac{X_{21}}{X_2} \right) \) is equal to approximately 373 calories/mole and \( (H_s - H_f) \) is 473 calories/mole. The lack of complete equality is due to the difference between the y-intercepts for the ideal solution and benzoic acid-acetic acid solution.
TABLE III

\textsuperscript{a} SOLUBILITY OF BENZOIC ACID IN VARIOUS SOLVENTS

(SOLUBILITIES GIVEN IN TERMS
OF
MOLE FRACTION OF THE SOLUTE)

<table>
<thead>
<tr>
<th>Temperature (Centigrade)</th>
<th>Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ideal</td>
</tr>
<tr>
<td>20'</td>
<td>.148</td>
</tr>
<tr>
<td>40</td>
<td>.237</td>
</tr>
<tr>
<td>60</td>
<td>.358</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Heat of Solution (cal./mole)</th>
<th>y-intercept ( (S/2.303R) )</th>
<th>( ^a R ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>4300</td>
<td>2.36</td>
<td>-1.0000</td>
</tr>
<tr>
<td>Acetone</td>
<td>2748</td>
<td>1.36</td>
<td>-0.9977</td>
</tr>
<tr>
<td>Benzene</td>
<td>6578</td>
<td>3.69</td>
<td>-1.0000</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>4773</td>
<td>2.43</td>
<td>-0.9907</td>
</tr>
</tbody>
</table>

\(^a\)A value for \( R \) of unity indicates perfect linearity between the independent and dependent variables.
This difference, 0.07, can be added to equation 17 modifying the heat of mixing in this case to

\[ H_m = RT \frac{\ln (X_{z1}/X_2)}{0.07} = 466 \text{ calories/mole} \]  

(18).

This modification brings the heat of mixing value into agreement with the \(( H_s - H_f )\) value of 473 calories per mole. Further, this calculation shows that deviations from regularity are extremely sensitive to small differences; in fact, the equation may be more sensitive than the experimental procedures. Feldman and Gibaldi (13) have pointed out that differences between enthalpy terms are also very sensitive to slight changes in \( \ln (X_{z1}/X_2) \). The sensitivity of the thermodynamic quantities in question does not, however, invalidate their usefulness in approximating the characteristics of solution behavior.

For benzoic acid dissolved in benzene, the larger heat of solution value, as well as a larger y-intercept, suggest association of one component. This is very likely the case: Glasstone (14), in his discussion of colligative properties, has pointed out that benzoic acid forms double molecules in benzene. The data in Table IV for benzoic acid in acetone indicates a solvated system. Solvation occurs with increased interactions between solute and solvent. Reference to equation 5 shows that lower heats of solution favor increased solubility, which is the case for benzoic acid in acetone. Mortimer (9) also included this solute-solvent system and noted that it shows the properties of solvation. Important also for this system is the much smaller y-intercept, suggesting increased orderliness in the solution phase.
Although the data in Table IV for benzoic acid systems correlate very well with solution behavior based on interpretations of theoretical equations, such may not always be the case. It is noteworthy that Hildebrand (4), in his discussion of the various classifications in Table I, states, "This represents a classification of the main essential factors rather than of the solutions themselves, because scarcely any actual solution can be said to behave solely in any of the several ways designated by such terms as ideal or regular." Even though Hildebrand's classification system may not be entirely adequate, his approach to solubility interpretation remains a valid one. Lindstrom (15) has emphasized that "it would be of immeasurable aid if explanations of observed solubility were possible in terms of purely basic theoretical concepts."

In summary, the heats of solution and their attendant y-intercept values are most useful in interpreting non-electrolyte behavior even in the presence of certain complicating factors. Moreover, they are thermodynamic quantities which aid in characterizing the type(s) of solution behavior occurring in a particular system.
References for Heat of Solution Discussion


Limitations of Regular Solution Theory - When the solubility of a solute in several solvents or solvent blends is determined and the mole fraction solubility is plotted versus the solubility parameter of the solvent, a peak in the curve is often observed (30, 31). The peak is usually interpreted to mean that the differences between the solubility parameters of the solute and solvent are zero at this maximum and ideal solubility behavior is extant. This graphic peak also offers a means of evaluating the solubility parameter of the solute, provided the solubility parameter of the solvent is known. However, both of these interpretations may be unwarranted, even if the solubility calculated by equation 20 correlates well with experimental results. For example, benzoic acid in several solvents has been studied (30) and the results interpreted on the basis of regular solution theory. Such interpretations may not be justified unless the investigator can remain within the boundary conditions stated by Scatchard. In other words, the geometric mean assumption must not be violated, and the volume change must be zero at constant pressure. Therefore, if solubility mechanisms are to be interpreted correctly, it is imperative that the investigator measure not only the magnitudes of solubility, but also other thermodynamic quantities such as molar volume and heats of solution in order to promote a better mechanistic (theoretical) understanding.

A major limitation of the Hildebrand theory at present is that no activity coefficient has been developed which satisfies conditions where
the geometric mean assumption is not followed. Pharmaceutical or biological systems where hydrogen bonding may occur are in most cases specifically outside the regular solution realm. Hildebrand and Scott (32) warn their readers that "Since the justification for the geometric mean law and solubility theory rests upon the London theory of dispersion forces, the use of solubility parameters for polar substances is somewhat questionable." Their admonitions are certainly true, but Raoult's Law and the ideal solubility equation remain as a foundation for all nonelectrolyte solubility theory. The regular solution theory, even if not universally applicable to all systems that are nonideal, remains as a stepping-off point for further development.

Paruta recognized the implications of the Hildebrand approach but chose a different development for solubility interpretations. His published results of the solubility of many solutes of pharmaceutical interest make use of the dielectric constant as an interpretive quantity (33-35).
Dielectric Constant and Solubility - The equation for the dielectric constant, D.C., is given by Smyth in its general form (36) as

\[ P = P_1 + P_2 \]  \hspace{1cm} (21)

where \( P \) is the total molar polarization, \( P_1 \) is the induced polarization and \( P_2 \) is the orientation polarization. \( P \) is also related to the dielectric constant by

\[ P = \sqrt{(D.C. - 1)/(D.C. + 2)} \sqrt[3]{V} \]  \hspace{1cm} (22)

and \( V \) is the molar volume, as before. The induced polarization is a measure of the temporary electric moment which can be induced in each molecule. \( P_1 \) is related to the induced polarizability, \( \alpha \), by

\[ P_1 = \frac{4}{3}(3.1416)(\alpha)N \]  \hspace{1cm} (23)

Another commonly used definition of \( P_1 \) is

\[ P_1 = \sqrt{(n^2 - 1)/(n^2 + 2)} \sqrt[3]{V} \]  \hspace{1cm} (24)

where \( n \) is the refractive index taken at extremely long wavelengths. The value of \( P_2 \) is dependent on the permanent dipole of the molecule and on temperature, thus:

\[ P_2 = \frac{4}{3}(3.1416)(N)(u^2/3kT) \]  \hspace{1cm} (25)

where \( N \) in equations 23 and 25 is Avogadro's number. In equation 25, \( u \) is the dipole moment, \( k \) is the Boltzmann constant and \( T \) is absolute temperature.
For molecules having no permanent dipole, $P_2$ is zero and $P$ is essentially temperature independent. The effect of $P_2$, even for molecules with a permanent dipole is diminished with increasing temperature. From these equations, it is apparent that the induced and permanent dipoles are important molecular quantities because they quantify what is known as the POLARITY of the molecule. The molecule is said to be nonpolar when $P_2$ is zero, and semipolar or polar when $P$ is the summation of both $P_1$ and $P_2$. The values for the dielectric constant increase with increasing polarity as shown by Table I (37).
TABLE I

DIELECTRIC CONSTANTS OF SOME LIQUIDS
AT 20° CENTIGRADE

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Dielectric Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>80.4</td>
</tr>
<tr>
<td>Methyl Alcohol</td>
<td>33.7</td>
</tr>
<tr>
<td>Ethyl Alcohol</td>
<td>25.7</td>
</tr>
<tr>
<td>Acetone</td>
<td>21.4</td>
</tr>
<tr>
<td>Amyl Alcohol</td>
<td>15.8</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.8</td>
</tr>
<tr>
<td>Toluene</td>
<td>2.4</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.3</td>
</tr>
<tr>
<td>Dioxane</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Taken from A. N. Martin, Physical Pharmacy, Lea and Febiger, Philadelphia, 1960, p. 116.*
The solubility parameters of the liquids in Table I also reflect the polarity spectrum; and an apparently linear relationship between the solubility parameters and dielectric constants has been established (38), as expressed by the equation

\[ S. P. = 0.22(D. C.) + 7.5 \]  

(26)

where 0.22 is the slope and 7.5 the y intercept. The equation was calculated from a plot of the solubility parameters of twenty-five pure solvents versus their corresponding dielectric constants; it is most applicable for semipolar and polar liquids. Paruta (38) notes, "Fortuitously, these are the solvents of pharmaceutical importance."

Aside from the practical application of calculating solubility parameters from dielectric constants or vice versa, the equation may have some theoretical importance. The y intercept of 7.5 is a typical solubility parameter for many nonpolar liquids which have no permanent dipole and are maintained in the liquid state by dispersion forces only. Dielectric constants for nonpolar solvents are small, approximately 2.0, and make very little contribution to the calculated solubility parameter. As the polarity scale is ascended, the dielectric constant becomes very significant and may be thought of as an adjusting polarity parameter contributing to the overall cohesive energy density. In other words, 0.22(D.C.) is the relative contribution of the electrostatic forces, (Keesom, Debye and hydrogen bonding) and 7.5 is the relative
contribution of the dispersion forces.

A difficulty concerning equation 21 is that the calculated total molar polarization, \( P \), for very polar liquids does not correlate well with the experimental values. This problem was investigated by Onsager (39) who offered an equation to modify \( P^2 \). However, his equation, because of approximations, was not entirely satisfactory; and theoretical investigation by Kirkwood (40) led to an equation which is much more acceptable. Kirkwood derived a parameter, \( g \), which also modifies \( P^2 \). The quantity \( g \) takes into account the hindered molecular orientation produced by neighboring molecules where association through hydrogen bonding occurs. This factor is greater than one for hydrogen bonded liquids and reduces to unity for nonpolar liquids. The Kirkwood equation in terms of \( P \) is (41)

\[
P = \frac{\sqrt{(D.C. - 1)(2D.C. + 1)/(9D.C.)}}{\sqrt{V}}
\]

(27).

When the dielectric constant is much greater than one, as is the case for water, the limiting form of equation 27 becomes

\[
P = (0.22)(D.C.)(V)
\]

(28).

It is interesting that the value 0.22 is the same as that for the slope of the Paruta equation. At present, 0.22 remains merely as an apparent link between the dielectric constant and the solubility parameter; no absolute theoretical justification can be attached. The importance of establishing a theoretical tie becomes apparent, however, when one
considers that the activity coefficient for regular solutions could possibly be modified to correct for polarity effects in the solution process.

Paruta applied the dielectric constant concept to solubility by plotting the solubility of the solute, usually in mg./ml. units, versus the dielectric constant of the solvent. Peak(s) generally occur when the data are plotted in this manner, and the dielectric constant which corresponds to the observed peak have been termed the dielectric requirement or DR (38). In another paper (42), Lordi stated, "At constant temperature, this requirement should be independent of the actual nature of the solvents in the blend and dependent only upon the nature of the drug." Paruta has since modified this statement because the DR does in fact appear to be dependent on the solvent as well as the drug solute (34). The peaks which appear are also dependent upon the concentration units chosen to express the solubility of the solute (43). In other words, a peak may be shifted if mole fraction rather than mg./ml. is chosen to express solubility.

The DR concept, even if limited to certain systems, is interesting because it relates the polarity of the solute molecule to the polarity of the solvent, demonstrating in itself an indication of the type of interactions present. For example, if the DR for a particular solute occurs at about 25, it is reasonable to expect that the solute-solvent interaction is at least in part due to hydrogen bonding since the solvent-
solvent interactions in this dielectric area are generally of this same type.

The DR concept is of further interest because for certain systems, more than one peak appears (33), despite regular solution theory which predicts only one peak. The exact importance of a multipeak system is not clear, but the implication is that the magnitude and type of interaction involved are modified or changed depending on the dielectric constant of the solvent system.

At present, it appears that the usefulness of the dielectric requirement has leveled off, and further development of this concept awaits the theoretical link between the dielectric constant and the solubility parameter.

**Summary** - Implied in the previous discussion of solubility theory is the fact that certain properties of matter, such as a) the heat of fusion, b) the heat of vaporization, c) molar volume, d) melting point, e) index of refraction and f) dielectric constant, influence the solution process and yield strong evidence of solution mechanisms. Quantitative limitations which exist are not as serious as they would seem to be, for as Hildebrand has noted (44) "The theory is qualitatively very serviceable." Indeed, if he is to develop solubility theory further, the investigator must interest himself with theoretical understanding rather than with quantitative prediction.
THEORETICAL CONSIDERATION OF PARTITION COEFFICIENTS

Nernst's law, as given by Davies and Hallam (1), indicates that a solute added to a system of two immiscible phases, 1 and 2, will partition itself at equilibrium in a constant ratio corresponding to the respective concentrations, C1 and C2, in the two phases:

\[
\frac{C_1}{C_2} = \text{constant}
\]

Equation 1 shows that the dissolved solute will distribute itself under conditions of constant temperature so that the concentration, C, in phase 1 and 2 is constant at equilibrium and is independent of the original concentration of the solute.

Usually, the two phases used in partition systems are water and an immiscible, oily liquid. Therefore, the partition coefficient is very simply a quantitative indication of the lipophilic nature of the solute. The actual magnitude of the partition coefficient is governed by the intermolecular interactions of the solute with the partitioning liquids.

Several authors have used partition coefficients to determine ionization constants of weak electrolytes and bacteriostatic properties of chemical species (2, 3). Since sulfonamides may be classified as weak electrolytes having two ionizable groups, the partition
coefficient may be used to determine the pKa values of sulfadiazine.

The partition coefficient has also proved useful as an aid in determining transport mechanisms of drug molecules through lipid barriers (4-6).

Glasstone (7) has noted that $C_1$ and $C_2$ of equation 1 should more accurately be the activities of the solute. He further said that, in order to meet this dependency, the original concentration must be kept very small. Another condition is that the solute must exist as a monomer in the oil phase and as an unionized species in the aqueous phase.

Equation 1 may be rewritten in another form as

$$\frac{C_o}{C_w} = \frac{C_o}{U} = T.C.,$$  

(2)

where $C_o$ and $C_w$ are the concentrations of the solute in the oil and water phases respectively at equilibrium. $T.C.$, the true partition coefficient, signifies that all the boundary conditions including concentration, polymerization and ionization have been met. It will be observed from equation 2 that the concentration in the water phase in this case is the concentration of the unionized form of the solute, $U$. The concentration units of $C_o$ and $C_w$, as recommended by Glasstone, should be in terms of mole fractions, but at low concentrations they may be moles/liter (7). Units
which are proportional to moles/liter, such as spectrophotometric absorbances, are also acceptable (3).

When the solute is partially ionized in the aqueous phase but acts as a monomer in the oil phase, the concentration in the water phase may be expressed as

$$C_w = U + I$$

(3)

where $U$ and $I$ are the concentrations of the unionized and ionized species respectively. These conditions give rise to the apparent partition coefficient, A. P. C., which may be defined by

$$\frac{C_o}{C_w} = \frac{C_o}{(U + I)} = A. P. C.$$  

(4)

The concentrations of $U$ and $I$ for a weak acid are related to the ionization constant, $K_a$, (8) by

$$K_a = \frac{\overline{I}(H^+)}{(U)\overline{I}/(U)}$$

(5)

where $H^+$ is the hydrogen-ion concentration, permitting the derivation of a relationship between the distribution coefficient and the ionization constant (3) and the solution for $I$:

$$I = \frac{\overline{I}(Ka)(U)\overline{I}/(H^+)}$$

(6)

Substitution of this equality into equation 4 gives

$$A. P. C. = \frac{(Co)\overline{I}(U) + ((Ka)(U))/(H^+)\overline{I}}$$

(7)

which may be rearranged to

$$A. P. C. = \frac{\overline{I}(Co)(H^+)\overline{I}/(U)(Ka + H^+)\overline{I}}$$

(8)
The concentration of the solute in the oil phase, Co, may be cleared from equation 8 by substituting T. P. C. from equation 2 which gives

\[ \text{A. P. C.} = \frac{\text{T. P. C.} \cdot (H^+)}{(\text{Ka} + H^+)} \]  

(9).

Finally, equation 9 may be inverted and simplified to

\[ \frac{1}{\text{A. P. C.}} = \frac{(\text{Ka})}{\text{T. P. C.}} \cdot (H^+) + \frac{1}{\text{T. P. C.}} \]  

(10).

Equation 10 predicts that a plot of \( \frac{1}{\text{A. P. C.}} \) versus \( \frac{1}{H^+} \) should yield a straight line with a slope of \( \frac{\text{Ka}}{\text{T. P. C.}} \) and a y-intercept of \( \frac{1}{\text{T. P. C.}} \). The log form of equation 10 is

\[ \text{pH} = \text{pKa} + \log \frac{\text{T. P. C.}}{\text{A. P. C.}} - 1 \]  

(11).

Thus, when the ratio of the T. P. C. and A. P. C. is two, the pH is equal to the pKa. It will be noted that equation 10 is of the same general form as that of the Henderson-Hasselbalch formula (1).

Garrett and Woods (3) have given a slightly different form to equation 10:

\[ \frac{(\text{Ka} + H^+)}{(\text{Cw})} = \frac{\text{T. P. C.} + 1}{\text{Cw}} \cdot (H^+) + \frac{\text{Ka}}{\text{Cw}} \]  

(12).

The quantity C in this equation is the original concentration of the solute in the aqueous phase and assumes equal volumes of both phases:

\[ C = C_0 + C_w \]  

(13).

Equations 10 and 12 are equally useful, but equation 10 has the added advantage that a previous knowledge of the ionization constant is not necessary in order to calculate the T. P. C.
A formula analogous to equation 10 may also be derived for the relationship of the ionization constant and the partition coefficient of a weak base, given the condition that the solute acts as a monomer in the oil phase. Equations 2-4 remain the same, but the ionization of a weak base, \( K_b \), is

\[
K_b = \frac{\int (OH^-)(U)\,dJ/(U)}{\int (K_b)(U)\,dJ/(OH^-)} \tag{14}
\]

The apparent partition coefficient then is

\[
A\cdot P\cdot C. = \frac{(Co)}{\int U + ((Kb)(U))/(OH^-)\,dJ} \tag{15}
\]

which may be rewritten as

\[
\frac{Co}{U} = T\cdot P\cdot C. = A\cdot P\cdot C. + \frac{\int (A\cdot P\cdot C.)(K_b)\,dJ/(OH^-)}{A\cdot P\cdot C.} \tag{16}
\]

Clearing terms in equation 16 gives

\[
\frac{K_b}{OH^-} = \frac{\int (T\cdot P\cdot C.)-(A\cdot P\cdot C.)\,dJ/(A\cdot P\cdot C.)}{A\cdot P\cdot C.} \tag{17}
\]

where \( OH^- \) in equations 14-17 is the hydroxyl-ion concentration.

The hydroxyl and hydrogen-ion concentrations are related to the dissociation constant of water, \( K_w \), by

\[
K_w = (OH^-)(H^+) \text{ or } OH^- = K_w/H^+ \tag{18}
\]

Thus, equation 17 may be solved using this relationship to yield

\[
K_b = \frac{(K_w)/(H^+)}{\int (T\cdot P\cdot C.)-(A\cdot P\cdot C.)\,dJ/(A\cdot P\cdot C.)} \tag{19}
\]

The dissociation constant of water is also related to the \( K_a \) and \( K_b \) by

\[
K_w = (K_a)(K_b) \tag{20}
\]

and equation 20 becomes

\[
(H^+) = (K_a)\frac{\int (T\cdot P\cdot C.)-(A\cdot P\cdot C.)\,dJ/(A\cdot P\cdot C.)}{(A\cdot P\cdot C.)} \tag{21}
\]
In linear form, equation 21 may be expressed as

\[
(1/A \cdot P \cdot C.) = (H^+)/(T \cdot P \cdot C.) \cdot (K_a) + (1/T \cdot P \cdot C.)
\]  

(22).

The logarithmic form of equation 22 is

\[
\text{pH} = \text{pK}_2 - \log(T \cdot P \cdot C./A \cdot P \cdot C.) - 1
\]

(23).

If the chemical species exhibits the characteristics of both a weak acid and a weak base, it is said to be amphoteric. The relationship between the negative logarithm of their respective ionization constants is

\[
\text{pH}_i = (\text{pK}_1 + \text{pK}_2)/2
\]

(24)

where pH is the isoelectric pH.

The term isoelectric pH is commonly used in amino acid chemistry in conjunction with the word zwitterion. Considerable confusion results from common usage of the terms zwitterion and amphoteric. Albert (11) noted that a substance may be amphoteric but not necessarily zwitterionic, using as an example, the ionization characteristics of m-aminophenol, an ordinary amphoteric substance, and glycine, which is zwitterionic. Meta-aminophenol has two pK values (11), 4.2 and 9.9; and the calculated pH is approximately 7.0, at which hydrogen-ion concentration neither group is ionized. Glycine also has two pK values, but differs from m-aminophenol in that the majority of molecules of both groups are ionized at the isoelectric pH; that is, glycine may be thought of as a dipolar species.
Substances such as sulfonamides exist in the unionized form at pH with respect to both the basic and acidic functions and are not generally thought to be zwitterionic (12).

The equations thus far developed are valid under the assumptions that: (a) the solute species is a monomer in the oil phase; (b) concentrations of the solute approximate activities; (c) the temperature of the system remains constant; (d) the oil and water phases are immiscible; and (e) the oil and water phases are of equal volume. Garrett (3) discusses the modifications necessary for unequal phase volumes, while Davies and Hallam (1) have derived the equations for polymers in the oil phase.

Krebs and Speakman have given formulas similar to equations 11 and 23 for the relationship between the ionization constant, aqueous solubility, and pH of the solvent (13). For a weak acid the equation is

\[ \text{pH} = \text{pK}_a + \log \frac{1}{(S/S^0)} - 1 \]

and for a base

\[ \text{pH} = (\text{pK}_w - \text{pK}_b) - \log \frac{1}{(S/S^0)} - 1 \]

where \( S \) is the molar concentration of the unionized and ionized species and \( S^0 \) is the molar concentration of the unionized form. Both \( S \) and \( S^0 \) are the saturation solubilities at a given temperature and pH. These equations are misleading because they seem to imply a
direct relationship between aqueous solubility and the partition
coefficient. This is actually not the case because it is the ratios
of the solubilities or partition coefficients that are related to the
pH and pK values. In other words, knowledge of the T. P. C. and
A. P. C. does not give access to the molar concentrations of S and S°.

Glasstone has given an equation which does directly relate
solubilities and partition coefficients under certain conditions (7).
When an excess of solute is added to a biphasic system of two
immiscible solvents, the solute will distribute itself at equilibrium
as a constant, K, by the distribution law,

\[ \frac{c_1}{c_2} = K \]  

(27)

where \( c \) is the saturation concentration in the respective phases. If
the saturation solubilities are determined in each phase separately,
the constant is given by

\[ \frac{s_1}{s_2} = K \]  

(28)

The constant, \( K \), in each case should be equal if the saturation
solubilities, \( s \), in equation 28 are small. This does not mean,
however, that \( K \) determined by equation 27 or 28 is equal to the
T. P. C. or A. P. C., since the latter quantities are valid only under
the condition that concentrations approximate activities. Using
solubility terminology, this means that the T. P. C. and A. P. C.
approach ideal solution behavior while \( K \), except in unusual cases,
represents nonideal solution behavior in either one or both phases.

Hansch (14), who developed equations relating the partition coefficients and aqueous solubilities of organic liquids, cited limitations on his formulas in that they ignore nonideal solution behavior. Thus, equations 27 and 28 are the only quantitative statements yielding this relationship.
Materials

Equipment - Items of equipment used for the study included:

6406 - H. Thomas Hoover Melting Point Apparatus

Leeds and Northrup pH Meter, Model 7401

Sargent Chemical Oscillometer, Model V

Cary Model 16 Spectrophotometer

Tecam Tempunit

Mettler Balance, Type H6T

Abbe-3L Refractometer

Swinny Hypodermic Adapter, Cat. No. XX 30 012 00


3 E. H. Sargent and Company, Chicago, Illinois

4 Cary Instruments, Monrovia, California


7 Bausch and Lomb Optical Company, Rochester, N.Y.

8 Millipore Filter Corporation, Bedford, Mass.
Materials (continued)

Chemicals - The chemicals used for the study were as follows:

Sulfadiazine, Lot W02235
Sulfisoxazole, Lot 378067
Sulfadimethoxine, Lot 203027
Sulfisomidine, Lot E2498
Methyl Alcohol Anhydrous, Spectrophotometric Grade
Solvent, Lot VMN
Absolute Ethyl Alcohol, U.S.P.-N.F., Reagent Quality
1-Propanol, "Baker Analyzed" Reagent, Lot 35592
Normal Butyl Alcohol, Analytical Reagent, Lot TDY

1 Supplied Through the Courtesy of Eli Lilly and Company
2 Supplied Through the Courtesy of Hoffmann-LaRoche, Inc.
3 Supplied Through the Courtesy of Hoffmann-LaRoche, Inc.
4 Supplied Through the Courtesy of Ciba Pharmaceutical Co.
5 Mallinckrodt Chemical Works
6 U. S. Industrial Chemicals Company
7 J. T. Baker Chemical Company
8 Mallinckrodt Chemical Works
Materials (continued)

Chemicals (continued)

Normal Amyl Alcohol, Certified, Lot 776291

1-Octanol, ORtm, Lot 22

Decyl Alcohol, Lot 17

Certified Acetone, 99 Mol % Pure, Lot 792702

Certified Benzene, 99 Mol % Pure (Thiophene Free), Lot 793869

Sodium Phosphate Dibasic Heptahydrate, Analytical Reagent, Lot WTKL

Sodium Acetate, Baker Analyzed Reagent, Lot 32649

Potassium Chloride, U.S.P., Lot 8678

Sodium Hydroxide, Lot W183J

1Fisher Scientific Company

2Mallinckrodt Chemical Works

3Matheson, Coleman and Bell

4Fisher Scientific Company

5Fisher Scientific Company

6Mallinckrodt Chemical Works

7J. T. Baker Chemical Company

8J. T. Baker Chemical Company

9Allied Chemicals
Materials (continued)

Chemicals (continued)

Glacial Acetic Acid, A.C.S. Reagent, Lot Y167

Hydrochloric Acid, C.P. Reagent, Lot E108262

\[1^{1}\text{Allied Chemical}

\[2^{2}\text{Allied Chemical} \]
Purity of Alcohols Used for Solubility and/or Partition Coefficient

Studies - In order to verify the purity of the alcohols, refractive index, density and dielectric constant measurements were made.

Refractive Index - All measurements were made with the Abbe-3L Refractometer at 25°C. The accuracy of the instrument was checked using 99 mol % free benzene for which an experimental value of 1.4983 was recorded. The literature value listed is 1.4979 (1). Refractive index values for the various alcohols tested are presented in Table I.

Density - The density of the alcohols was determined using the plummet method. A plummet was weighed in air, weighed again while submerged in distilled water, and weighed a third time while submerged in the test liquid. In order to relate the density of the test liquid to the experimental values, the formula given in the literature (2) is

\[ D = \frac{\bar{\Delta}(w^2/w^1)d}{d_{air}} - d_{air} \frac{\bar{\Delta}(w^2/w^1)d}{1} \quad (1) \]

where \( w^2 \) is weight of the plummet in air minus its weight in the test liquid, \( w^1 \) is weight of the plummet in air minus its weight in water, \( d \) is density of water at temperature \( t \), and \( d_{air} \) is the density of air at temperature \( t \). The density of air is included in the formula to correct for the buoyancy effect of air on the plummet. The plummet was suspended from the weighing mechanism of a Mettler H6T balance and weighed in air. Distilled water and the test alcohols were placed in vials, supported by a stand directly below the suspended plummet.
TABLE I
REFRACTIVE INDEX VALUES
FOR
VARIOUS ALCOHOLS AT 25° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Experimental Value</th>
<th>Literature Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>1.3288</td>
<td>1.3266&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1.3640</td>
<td>1.3594&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Propanol</td>
<td>1.3840</td>
<td>1.3835&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Butanol</td>
<td>1.4025</td>
<td>1.3992&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Pentanol</td>
<td>1.4098</td>
<td>1.4080&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Octanol</td>
<td>1.4320</td>
<td>1.4275&lt;sup&gt;a&lt;/sup&gt;(25°)</td>
</tr>
<tr>
<td>Decanol</td>
<td>1.4410</td>
<td>1.4366&lt;sup&gt;b&lt;/sup&gt;(20°)</td>
</tr>
</tbody>
</table>


The plummet was weighed in each test liquid, suspended such that it did not touch the sides of the vial, and was submerged to an equal depth in each liquid. Prior to each weight determination, the liquids were placed in a temperature bath and brought to 25°C. The experimental and literature density values are shown in Table II.

Dielectric Constant - The dielectric constant was chosen as a purity index for the alcohols because it is sensitive to water contamination, an especially important consideration with methanol, ethanol, and propanol, which are very hygroscopic. Further, it is manifest that any water present as a contaminant would strongly influence the solution properties of the alcohol.

All measurements were made using a Model V Sargent Chemical Oscillometer. The instrument was warmed for at least twenty-four hours prior to use. The sample holder, a glass cell with a ground glass top, was washed, rinsed with distilled water, dried in an oven, and stored in a dessicator for twenty-four hours prior to use. When readings were taken, the glass cell and cell holder were maintained thermostatically at a temperature of $30^\circ \pm 1^\circ$C. in a container free from air currents.
TABLE II
DENSITY VALUES
FOR
VARIOUS ALCOHOLS AT 25° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Experimental Value</th>
<th>Literature Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>0.7862</td>
<td>0.7868&lt;sup&gt;a&lt;/sup&gt; (25°)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.7850</td>
<td>0.7851&lt;sup&gt;a&lt;/sup&gt; (25°)</td>
</tr>
<tr>
<td>Propanol</td>
<td>0.7996</td>
<td>0.7995&lt;sup&gt;a&lt;/sup&gt; (25°)</td>
</tr>
<tr>
<td>Butanol</td>
<td>0.8053</td>
<td>0.8021&lt;sup&gt;a&lt;/sup&gt; (30°)</td>
</tr>
<tr>
<td>Pentanol</td>
<td>0.8102</td>
<td>0.8076&lt;sup&gt;a&lt;/sup&gt; (30°)</td>
</tr>
<tr>
<td>Octanol</td>
<td>0.8219</td>
<td>0.8221&lt;sup&gt;a&lt;/sup&gt; (25°)</td>
</tr>
<tr>
<td>Decanol</td>
<td>0.8264</td>
<td>0.8287&lt;sup&gt;b&lt;/sup&gt; (20°)</td>
</tr>
</tbody>
</table>


The clean dry cell was placed in the cell holder, and after a sufficient length of time for the cell to reach thermal equilibrium, a zero adjustment of the instrument was made. After the test liquid was placed in the cell, the cell and liquid were allowed to reach the required temperature before a reading was taken. Since lack of thermal equilibrium could be detected by needle drift from the instrument readout, readings were taken only after a nondrift condition was established. To increase the reproducibility of the readings, the cell was filled to the same level for each measurement and placed in the cell holder in the same position.

The oscillometer does not yield a direct reading of dielectric constant and is a relative method. Therefore, it is necessary to standardize the instrument with liquids of known dielectric constant. The expression relating instrument readings to dielectric constant as given by Sherrick, Dawe, Karr and Ewan (3) is

\[ S = \frac{A (K - 1)}{1 + BK} \]  

(2)

where \( S \) is the readout value, \( K \) is the dielectric constant of the standard liquid and \( A \) and \( B \) are constants. Mixtures of acetone and benzene and of acetone and distilled water were used to generate values of \( S \). Certified benzene and acetone, 99 mol % pure, were used in all cases. The dielectric constants and temperature coefficients for the standard liquids mentioned above are given in the literature (3).
After several values of $S$ were determined from liquids of known dielectric constant, the constants $A$ and $B$ from equation 2 were calculated. With $A$ and $B$ known, values of $S$ for the alcohols were determined and used to calculate the respective dielectric constants from equation 2.

The dielectric constants which were experimentally determined are shown in Table III with their corresponding literature values. The literature values taken from Maryott and Smith (4) were usually given at $25^\circ C$. Temperature coefficients were given for each alcohol, however, and values at $25^\circ$ were converted to those at $30^\circ C$ by

$$\log_{10} K_2 = \log_{10} K_1 - a(t_2 - t_1) \quad (3)$$

where $K_1$ is the dielectric constant at $25^\circ$, $K_2$ is the calculated dielectric constant at $30^\circ$, $t_2$ is $30^\circ$ and $t_1$ is $25^\circ$. The value $a$ is the temperature coefficient given by Maryott and Smith (4), and equation 3 is the expression given by these authors for the relationship of dielectric constant to temperature.
**TABLE III**

**DIELECTRIC CONSTANT VALUES FOR VARIOUS ALCOHOLS AT 30° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Experimental Value</th>
<th>Literature Value (30°)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>30.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Ethanol</td>
<td>22.7</td>
<td>23.6</td>
</tr>
<tr>
<td>Propanol</td>
<td>19.0</td>
<td>19.4</td>
</tr>
<tr>
<td>Butanol</td>
<td>16.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Pentanol</td>
<td>13.6</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Although methanol and ethanol were observed to deviate most from the literature values, the actual error was less than 4% in both cases. More important is the fact that the experimental values were less than those cited in the literature. Since water, if present in appreciable quantities, would have raised the dielectric constants for the alcohols considerably, elevated values would have suggested aqueous contamination. The validity of using the dielectric constant as an indication of water in the alcohols is substantiated by the work of West, Senise and Burkhalter (5) who used oscillometry to determine water content in several alcohols. These authors determined for ethyl alcohol that a 1% by weight water contamination could be detected to \( \pm 0.05\% \) in terms of percentage of water by weight.

Melting Points of Pure Sulfonamides - The melting points of the sulfonamides were determined using the Melting Point Apparatus. The experimental and corresponding literature values are presented in Table IV.
<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>Experimental Value</th>
<th>Literature Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadiazine</td>
<td>251-253° C</td>
<td>252-256° C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td>242-245° C</td>
<td>243° C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>194-198° C</td>
<td>192-195° C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>202-206° C</td>
<td>197-202° C&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


Assay Procedure for the Quantitative Determination of Sulfonamides

A spectrophotometric assay using a Cary Model 16 Spectrophotometer, was developed for the quantitative determination of the sulfonamides. The procedure was based on establishing the wavelength at which maximum absorbance occurs and then evaluating a quantitative relationship between absorbance and concentration. The mathematical expression for this relationship, in its general form, as given by Martin (6) is

\[ Y = MX + B \] (4)

where \( Y \) is the instrument readout, in this case absorbance, and \( X \) is the solution concentration in mcg./ml.. The constants \( M \) and \( B \) are the slope and \( y \) intercept respectively; \( B \) is generally very close to zero. Because the dependent and independent variables are linearly related as manifest by the form of the equation, \( M \) and \( B \) were evaluated by the method of least squares. A computer program was written for the method of least squares (Appendix I) based on the equations given by Yamane (7). Each sulfonamide was dissolved in 95% ethanol and placed in standard silica cuvettes with a 1.00 cm. lightpath. The maximum wavelengths and values of \( M \) and \( B \) for each sulfonamide are shown in Table V.
<table>
<thead>
<tr>
<th>Sulfonamide (solvent-95% ethanol)</th>
<th>Maximum Wavelength (millimicrons)</th>
<th>M</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadiazine</td>
<td>270</td>
<td>$8.091 \times 10^{-2}$</td>
<td>$-1.973 \times 10^{-3}$</td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td>273</td>
<td>$7.190 \times 10^{-2}$</td>
<td>$6.100 \times 10^{-4}$</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>272</td>
<td>$6.932 \times 10^{-2}$</td>
<td>$-4.985 \times 10^{-3}$</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>273</td>
<td>$6.723 \times 10^{-2}$</td>
<td>$5.800 \times 10^{-3}$</td>
</tr>
</tbody>
</table>
Procedure for Solubility Studies - The determination of the solubility of the sulfonamides in several solvents was based essentially on the procedure given by Martin (6). A slight excess of solute was placed in a glass vial and a quantity of solvent added. The vials, sealed by means of plastic caps with teflon liners, were placed on a rotating device in a temperature-controlled water bath for a period of twenty-four hours, a time found sufficient to reach equilibrium. The temperature, maintained by a Tecam Tempunit, was observed to vary not more than ± 0.1°C. at each of three temperature settings: 25, 30 and 37°C. An excess of solute was always present during the rotation period.

After the samples had come to equilibrium, the rotating device was stopped in order to allow the excess solute to settle in the vials to whatever extent the viscosity of the solvent permitted. All samples were kept in the temperature bath until just prior to assay.

For assay, a sample vial was removed from the bath; the contents were immediately filtered, using a hypodermic syringe fitted with a Swinny adaptor, into a second vial; and a portion of the filtrate was removed by pipette to a volumetric flask. Suitable dilutions with 95% ethanol were prepared, and the concentration of solute was determined by the spectrophotometric assay previously described. Samples were read against a blank of 95% ethanol. The hypodermic syringes, Swinny adaptors, pipettes and transfer vials were prewarmed in an oven prior to use.
Densities of the saturated solutions were determined using either the plummet method previously described or an alternate gravimetric method. The gravimetric procedure involved pipetting a known quantity of the solution into a tared vial. The vial containing the solution was then weighed, and the weight of solution was determined by difference.

Hydrogen-ion concentrations of aqueous solutions were determined using the Leeds Northrup pH meter. Because pH is a temperature dependent measurement, the pH meter temperature control setting was placed at a temperature corresponding to the temperature at which the solubility determination was made. The pH meter was standardized using a buffer which was also prewarmed to the desired temperature.

In order to determine if degradation of the solute occurred or if polymorphic species were produced during the solution process, pooled mixtures of the solute were air dried and melting point determinations made using the 6406 - H. Thomas Hoover Melting Point Apparatus. In no case, were the melting points outside the melting point range found for the pure sulfonamide.

Each solubility determination was the result of a triplicate run and aberrant values which could not be explained on the basis of experimental error were redetermined. The reproducibility of the
method was checked by running single samples at one temperature and comparing the results with the average of the triplicate run at the same temperature. These single values were found to be within ±5% of the average value. The average values and their respective standard deviations were determined using the general equation for the standard deviation given by Martin (6) which is

\[ \text{Std. Dev.} = \sqrt{\frac{\sum (X_i - \bar{X})^2}{N-1}} \]  

where \( X_i \) is a single determination, \( \bar{X} \) is the average of the determinations and \( N \) is the number of determinations.

Procedure for Partition Coefficient Studies - The samples used for determining the partition coefficients consisted of equal volumes of an aqueous buffered layer in which the drug was dissolved and a non-miscible alcoholic layer. The concentration of the sulfonamide initially in the aqueous layer was approximately \( 10^{-3} \) or \( 10^{-4} \) molar and the ionic strength of the buffer maintained at \( 0.053 \) to \( 0.057 \). All alcohols were presaturated with distilled water prior to use as partitioning agents. The samples were placed in pyrex containers of about 50 ml capacity with round rather than flat bottoms to minimize turbulence during the partitioning process. The containers were sealed with teflon lined plastic caps.

Subsequent to preparation, the samples were secured on a rocking device; the device was placed in a constant temperature environment maintained at \( \pm 1^\circ C \) of the desired temperature setting, and the
samples were rocked at a constant frequency of about one cycle per minute until equilibrium was reached. A period of 24 hours was found satisfactory for equilibrium. The rocking device, similar to that described by Doluisio and Swintosky (8), had the distinct advantage that, during each cycle, the sample vials moved from a horizontal to a vertical position and back again, producing a turbulence much less than that produced when the samples rotated through a 360° degree cycle.

Sample containers removed from the rocker at specified intervals were immediately put in a water bath maintained at a temperature corresponding to that of the rocking period. After the samples had stood in the water bath, they were visually examined to determine if emulsification had occurred; however, on standing, the samples reverted to biphasic systems leaving no apparent disturbance at the interface.

Just prior to assay, the samples were removed from the bath; and the alcohol layer was removed carefully with the aid of a suction device and saved if necessary for assay.

A portion of the remaining aqueous phase was rapidly removed for pH measurement, using a Leeds Northrup pH meter. A special housing was constructed to allow the sample to remain at constant temperature during the pH determination. In addition, the temperature control device on the pH meter was adjusted to correspond to the temperature of the partitioning period. Further, the electrodes were allowed to remain in the aqueous sample for 3-5 minutes, a period of
time that proved sufficient for a constant readout.

Another portion of the aqueous or alcoholic phase was used for spectrophotometric analysis with a Cary Model 16 spectrophotometer. The sample was suitably diluted and read against a blank of the same dilution. The blank was prepared and treated in exactly the same manner as the sample except that it contained no sulfonamide. All readings were made at a predetermined wavelength.

The initial concentration of the sulfonamide in the aqueous phase was determined spectrophotometrically using the same stock solution as that used to prepare the aqueous portion of the sample. The aliquot of stock solution used for assay purposes was subjected to the same temperature and rocking conditions as the sample.

The stock solution discussed above was observed after the rocking period to determine whether any colored by-products of a degradation reaction had occurred. No discoloration was observed for any samples. Sulfadiazine stock solutions kept at room temperature for several days were observed to turn slightly yellow and for this reason all such solutions were prepared fresh and the unused portion was discarded.

Partition coefficient values at each pH level were the average of at least three runs and were subjected to the same statistical analysis as described for the solubility determinations.
VI
RESULTS AND DISCUSSION

The present study is an investigation of the solubility of four chemically different sulfonamides in a series of normal alcohols and in buffered aqueous systems. The solubilities were determined as a function of temperature which was experimentally varied over a narrow range.

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. 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 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. The structural difference of each drug is
**TABLE I**

**STRUCTURES OF SULFONAMIDES**

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>(N^1) Substitutions</th>
<th>(N^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfadiazone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(H_2N\)

---

\(N^4\) \(H_2N\) - \(SO_2\) - \(NH_2\) (\(N^1\))

---

TABLE II

PHYSICAL-CHEMICAL PROPERTIES OF SULFONAMIDES
USED IN THIS STUDY

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>( a_{pK2} )</th>
<th>( a_{pK1} )</th>
<th>( a_{pK1} ) (isolectric)</th>
<th>Molecular Weight</th>
<th>( b_{Melting} ) Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>1.55</td>
<td>5.1</td>
<td>3.3</td>
<td>267</td>
<td>192-195</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>2.02</td>
<td>6.7</td>
<td>4.4</td>
<td>310</td>
<td>c197-202</td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td>2.36</td>
<td>7.5</td>
<td>4.9</td>
<td>278</td>
<td>243</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>2.00</td>
<td>6.48</td>
<td>4.2</td>
<td>250</td>
<td>252-256</td>
</tr>
</tbody>
</table>


reflected by the different melting points, molecular weights, and ionization constants. The two ionization constants for each sulfonamide derive from the ionizable groups at the N⁴ and N¹ positions. The pK₂ values attributed to the ionization of the N⁴ 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 N¹ substitution, varies by almost one hundred times (two logarithm units) among the compounds studied.

Foernzler and Martin (1) have investigated several sulfonamides using molecular orbital calculations as a measure of the electronic characteristics of the molecule. These authors showed that the electronic charge was approximately constant at the N⁴ position, but varied at the N¹ position. It may be intimated that the electronic characteristics of the sulfonamides are functionally related to the ionization constants. Therefore, there is at least qualitative agreement between the molecular orbital calculations and the experimentally determined 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. Because of the complexity of these interactions, it was not intended that solubilities studied would be amenable to calculation by an
**a priori** theoretical argument. Rather, the data from this study were interpreted using established theory. This approach allows for a mechanistic understanding of the solubility process, based on the use of established theoretical concepts, without constraining the investigator to a pathway dependent entirely upon development of advanced theory.
Sulfonamide Solubilities in the Normal Alcohols-

The solubilities of the particular sulfonamides in the n-alcohols used are given in Tables III through XIV. Notations both in mg./ml. and mole fraction concentration are given to make the data more useful, the former to the pharmacist and the latter to the physical scientist.

As expected, the data in these tables show that the solubility of the sulfonamides in each normal alcohol increased with increasing temperature. To facilitate the interpretation of these data, graphs (figures 1-4) were constructed using the mole fraction solubility data versus the chain length of the normal alcohols. In these plots, the following symbols are used to identify each alcohol: 1) C1 = methanol, 2) C2 = ethanol, 3) C3 = propanol, 4) C4 = butanol, 5) C5 = pentanol, 6) C8 = octanol, and 7) C10 = decanol.

Figure 1 is the plot of the solubility data for the mole fraction solubilities of sulfisoxazole in the normal alcohols. It 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 solubilities are shown in figure 2. With respect to the temperature effect these curves display the same
**TABLE III**

**SOLUBILITY OF SULFISOXAZOLE IN SEVERAL NORMAL ALCOHOLS AT 25° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$4.94 \times 10^1$</td>
<td>$3.40 \times 10^{-1}$</td>
<td>$7.52 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$1.91 \times 10^1$</td>
<td>$2.34 \times 10^{-1}$</td>
<td>$4.18 \times 10^{-3}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$7.95 \times 10^0$</td>
<td>$1.31 \times 10^{-1}$</td>
<td>$2.23 \times 10^{-3}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$4.31 \times 10^0$</td>
<td>$5.41 \times 10^{-2}$</td>
<td>$1.48 \times 10^{-3}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$2.61 \times 10^0$</td>
<td>$9.57 \times 10^{-3}$</td>
<td>$1.06 \times 10^{-3}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$9.38 \times 10^{-1}$</td>
<td>$1.25 \times 10^{-2}$</td>
<td>$5.55 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$5.72 \times 10^{-1}$</td>
<td>$7.84 \times 10^{-3}$</td>
<td>$4.09 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
TABLE IV

SOLUBILITY OF SULFISOXAZOLE
IN
SEVERAL NORMAL ALCOHOLS
AT
30° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>5.60 x 10^1</td>
<td>1.04 x 10^0</td>
<td>8.57 x 10^-3</td>
</tr>
<tr>
<td>Ethanol</td>
<td>2.26 x 10^1</td>
<td>1.31 x 10^-1</td>
<td>4.99 x 10^-3</td>
</tr>
<tr>
<td>Propanol</td>
<td>9.53 x 10^0</td>
<td>1.79 x 10^-1</td>
<td>2.69 x 10^-3</td>
</tr>
<tr>
<td>Butanol</td>
<td>5.30 x 10^0</td>
<td>4.96 x 10^-2</td>
<td>1.83 x 10^-3</td>
</tr>
<tr>
<td>Pentanol</td>
<td>3.20 x 10^0</td>
<td>1.66 x 10^-2</td>
<td>1.30 x 10^-3</td>
</tr>
<tr>
<td>Octanol</td>
<td>1.17 x 10^0</td>
<td>1.31 x 10^-2</td>
<td>6.96 x 10^-4</td>
</tr>
<tr>
<td>Decanol</td>
<td>6.79 x 10^-1</td>
<td>1.05 x 10^-2</td>
<td>4.87 x 10^-4</td>
</tr>
</tbody>
</table>
TABLE V

SOLUBILITY OF SULFISOXAZOLE
IN
SEVERAL NORMAL ALCOHOLS
AT
37° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$6.79 \times 10^1$</td>
<td>$2.38 \times 10^{-1}$</td>
<td>$1.04 \times 10^{-2}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$2.66 \times 10^1$</td>
<td>$2.39 \times 10^{-1}$</td>
<td>$5.90 \times 10^{-3}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$1.22 \times 10^1$</td>
<td>$2.52 \times 10^{-1}$</td>
<td>$3.44 \times 10^{-3}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$6.53 \times 10^0$</td>
<td>$3.10 \times 10^{-2}$</td>
<td>$2.26 \times 10^{-3}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$3.95 \times 10^0$</td>
<td>$1.99 \times 10^{-2}$</td>
<td>$1.62 \times 10^{-3}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$1.40 \times 10^0$</td>
<td>$1.21 \times 10^{-2}$</td>
<td>$8.33 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$8.45 \times 10^{-1}$</td>
<td>$1.12 \times 10^{-2}$</td>
<td>$6.08 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
### TABLE VI

**SOLUBILITY OF SULFADIMETHOXINE IN SEVERAL NORMAL ALCOHOLS AT 25° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>8.84 x 10⁰</td>
<td>4.62 x 10⁻²</td>
<td>1.16 x 10⁻³</td>
</tr>
<tr>
<td>Ethanol</td>
<td>3.78 x 10⁰</td>
<td>4.44 x 10⁻²</td>
<td>7.14 x 10⁻⁴</td>
</tr>
<tr>
<td>Propanol</td>
<td>1.95 x 10⁰</td>
<td>1.64 x 10⁻²</td>
<td>4.71 x 10⁻⁴</td>
</tr>
<tr>
<td>Butanol</td>
<td>1.31 x 10⁰</td>
<td>1.38 x 10⁻²</td>
<td>3.89 x 10⁻⁴</td>
</tr>
<tr>
<td>Pentanol</td>
<td>9.75 x 10⁻¹</td>
<td>6.00 x 10⁻³</td>
<td>3.41 x 10⁻⁴</td>
</tr>
<tr>
<td>Octanol</td>
<td>4.01 x 10⁻¹</td>
<td>2.63 x 10⁻³</td>
<td>2.04 x 10⁻⁴</td>
</tr>
<tr>
<td>Decanol</td>
<td>3.64 x 10⁻¹</td>
<td>4.91 x 10⁻³</td>
<td>2.24 x 10⁻⁴</td>
</tr>
</tbody>
</table>
TABLE VII

SOLUBILITY OF SULFADIMETHOXINE
IN
SEVERAL NORMAL ALCOHOLS
AT
30° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$1.05 \times 10^1$</td>
<td>$1.21 \times 10^{-2}$</td>
<td>$1.39 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$4.52 \times 10^0$</td>
<td>$1.74 \times 10^{-2}$</td>
<td>$8.58 \times 10^{-4}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$2.32 \times 10^0$</td>
<td>$3.77 \times 10^{-3}$</td>
<td>$5.63 \times 10^{-4}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.77 \times 10^0$</td>
<td>$5.60 \times 10^{-2}$</td>
<td>$5.26 \times 10^{-4}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$1.26 \times 10^0$</td>
<td>$2.18 \times 10^{-3}$</td>
<td>$4.41 \times 10^{-4}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$5.43 \times 10^{-1}$</td>
<td>$2.10 \times 10^{-2}$</td>
<td>$2.78 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$4.35 \times 10^{-1}$</td>
<td>$1.03 \times 10^{-2}$</td>
<td>$2.69 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
TABLE VIII

SOLUBILITY OF SULFADIMETHOXINE
IN
SEVERAL NORMAL ALCOHOLS
AT
37° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$1.34 \times 10^1$</td>
<td>$8.68 \times 10^{-2}$</td>
<td>$1.77 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$5.74 \times 10^0$</td>
<td>$3.93 \times 10^{-2}$</td>
<td>$1.10 \times 10^{-3}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$3.20 \times 10^0$</td>
<td>$2.11 \times 10^{-2}$</td>
<td>$7.79 \times 10^{-4}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$2.25 \times 10^0$</td>
<td>$3.69 \times 10^{-3}$</td>
<td>$6.70 \times 10^{-4}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$1.60 \times 10^0$</td>
<td>$1.58 \times 10^{-2}$</td>
<td>$5.65 \times 10^{-4}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$6.99 \times 10^{-1}$</td>
<td>$1.18 \times 10^{-2}$</td>
<td>$3.59 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$5.44 \times 10^{-1}$</td>
<td>$4.50 \times 10^{-3}$</td>
<td>$3.37 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
TABLE IX

SOLUBILITY OF SULFISOMIDINE IN SEVERAL NORMAL ALCOHOLS AT 25° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg. /ml.)</th>
<th>Standard Deviation (mg. /ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$7.64 \times 10^0$</td>
<td>$8.08 \times 10^{-2}$</td>
<td>$1.12 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$2.63 \times 10^0$</td>
<td>$1.33 \times 10^{-2}$</td>
<td>$5.53 \times 10^{-4}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$1.57 \times 10^0$</td>
<td>$4.03 \times 10^{-2}$</td>
<td>$4.23 \times 10^{-4}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.04 \times 10^0$</td>
<td>$1.00 \times 10^{-2}$</td>
<td>$3.44 \times 10^{-4}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$7.28 \times 10^{-1}$</td>
<td>$3.85 \times 10^{-3}$</td>
<td>$2.84 \times 10^{-4}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$2.40 \times 10^{-1}$</td>
<td>$4.83 \times 10^{-3}$</td>
<td>$1.36 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$2.63 \times 10^{-1}$</td>
<td>$1.26 \times 10^{-3}$</td>
<td>$1.80 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
## TABLE X

**SOLUBILITY OF SULFISOMIDINE IN SEVERAL NORMAL ALCOHOLS AT 30° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$8.67 \times 10^0$</td>
<td>$5.74 \times 10^{-2}$</td>
<td>$1.27 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$3.02 \times 10^0$</td>
<td>$3.91 \times 10^{-3}$</td>
<td>$6.38 \times 10^{-4}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$1.81 \times 10^0$</td>
<td>$2.85 \times 10^{-2}$</td>
<td>$4.89 \times 10^{-4}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.26 \times 10^0$</td>
<td>$8.84 \times 10^{-3}$</td>
<td>$4.17 \times 10^{-4}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$8.75 \times 10^{-1}$</td>
<td>$6.22 \times 10^{-3}$</td>
<td>$3.43 \times 10^{-4}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$3.20 \times 10^{-1}$</td>
<td>$4.21 \times 10^{-3}$</td>
<td>$1.83 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$2.97 \times 10^{-1}$</td>
<td>$1.60 \times 10^{-3}$</td>
<td>$2.04 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
TABLE XI
SOLUBILITY OF SULFISOMIDINE
IN SEVERAL NORMAL ALCOHOLS
AT 37° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$1.12 \times 10^1$</td>
<td>$1.23 \times 10^{-1}$</td>
<td>$1.65 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$3.86 \times 10^0$</td>
<td>$8.21 \times 10^{-2}$</td>
<td>$8.20 \times 10^{-4}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$2.39 \times 10^0$</td>
<td>$1.75 \times 10^{-2}$</td>
<td>$6.48 \times 10^{-4}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.67 \times 10^0$</td>
<td>$2.53 \times 10^{-2}$</td>
<td>$5.56 \times 10^{-4}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$1.16 \times 10^0$</td>
<td>$3.97 \times 10^{-3}$</td>
<td>$4.54 \times 10^{-4}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$4.25 \times 10^{-1}$</td>
<td>$1.32 \times 10^{-3}$</td>
<td>$2.44 \times 10^{-4}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$3.66 \times 10^{-1}$</td>
<td>$6.32 \times 10^{-3}$</td>
<td>$2.53 \times 10^{-4}$</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Solubility (mg./ml.)</td>
<td>Standard Deviation (mg./ml.)</td>
<td>Solubility (mole fraction)</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Methanol</td>
<td>$1.18 \times 10^0$</td>
<td>$7.33 \times 10^{-3}$</td>
<td>$1.93 \times 10^{-4}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$3.28 \times 10^{-1}$</td>
<td>$1.42 \times 10^{-3}$</td>
<td>$7.68 \times 10^{-5}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$1.44 \times 10^{-1}$</td>
<td>$2.35 \times 10^{-4}$</td>
<td>$4.32 \times 10^{-5}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$8.67 \times 10^{-2}$</td>
<td>$3.23 \times 10^{-4}$</td>
<td>$3.18 \times 10^{-5}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$6.06 \times 10^{-2}$</td>
<td>$9.49 \times 10^{-4}$</td>
<td>$2.63 \times 10^{-5}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$2.23 \times 10^{-2}$</td>
<td>$5.52 \times 10^{-4}$</td>
<td>$1.41 \times 10^{-5}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$9.69 \times 10^{-2}$</td>
<td>$1.79 \times 10^{-3}$</td>
<td>$7.40 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
### TABLE XIII

**SOLUBILITY OF SULFADIAZINE IN SEVERAL NORMAL ALCOHOLS AT 30° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$1.40 \times 10^0$</td>
<td>$9.27 \times 10^{-3}$</td>
<td>$2.29 \times 10^{-4}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$3.98 \times 10^{-1}$</td>
<td>$2.53 \times 10^{-3}$</td>
<td>$9.36 \times 10^{-5}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$1.81 \times 10^{-1}$</td>
<td>$1.73 \times 10^{-3}$</td>
<td>$5.45 \times 10^{-5}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.11 \times 10^{-1}$</td>
<td>$1.53 \times 10^{-3}$</td>
<td>$4.09 \times 10^{-5}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$7.61 \times 10^{-2}$</td>
<td>$4.61 \times 10^{-4}$</td>
<td>$3.31 \times 10^{-5}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$2.77 \times 10^{-2}$</td>
<td>$1.42 \times 10^{-2}$</td>
<td>$1.76 \times 10^{-5}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$1.05 \times 10^{-1}$</td>
<td>$4.04 \times 10^{-3}$</td>
<td>$8.04 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
# TABLE XIV

**SOLUBILITY OF SULFADIAZINE IN SEVERAL NORMAL ALCOHOLS AT 37° CENTIGRADE**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$1.82 \times 10^0$</td>
<td>$1.39 \times 10^{-2}$</td>
<td>$2.99 \times 10^{-4}$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$5.25 \times 10^{-1}$</td>
<td>$6.23 \times 10^{-3}$</td>
<td>$1.24 \times 10^{-4}$</td>
</tr>
<tr>
<td>Propanol</td>
<td>$2.46 \times 10^{-1}$</td>
<td>$1.41 \times 10^{-3}$</td>
<td>$7.44 \times 10^{-5}$</td>
</tr>
<tr>
<td>Butanol</td>
<td>$1.53 \times 10^{-1}$</td>
<td>$2.15 \times 10^{-3}$</td>
<td>$5.66 \times 10^{-5}$</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$1.06 \times 10^{-1}$</td>
<td>$2.33 \times 10^{-3}$</td>
<td>$4.61 \times 10^{-5}$</td>
</tr>
<tr>
<td>Octanol</td>
<td>$4.15 \times 10^{-2}$</td>
<td>$1.09 \times 10^{-3}$</td>
<td>$2.65 \times 10^{-5}$</td>
</tr>
<tr>
<td>Decanol</td>
<td>$1.23 \times 10^{-1}$</td>
<td>$1.76 \times 10^{-3}$</td>
<td>$9.47 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
Figure 1- Mole Fraction Solubility of Sulfisoxazole Versus Carbon Number of Normal Alcohols.
Figure 2- Mole Fraction Solubility of Sulfadimethoxine Versus Carbon Number of Normal Alcohols.
Figure 3 - Mole Fraction Solubility of Sulfisomidine Versus Carbon Number of Normal Alcohols.
Figure 4- Mole Fraction Solubility of Sulfadiazine Versus Carbon Number of Normal Alcohols.
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 VI 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 (2) 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 solubilities of a particular solute are measured in a series of solvents, the molecular weight of the solute remains constant but the 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 sulfisomidine and sulfadiazine respectively. These plots exhibit the same trends observed in figures 1 and 2. The maximum solubilities for sulfisomidine occur in methanol, and the solubilities decrease consistently up to octanol. From octanol to decanol the mole fraction solubilities for both sulfisomidine 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 involving a multiplicity of factors. Thermodynamic investigation of solution behavior, discussed elsewhere, would be a basic consideration.

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 XV show the relative solubilities for each solute at 25°C. Since of all the sulfonamides the highest solubilities in all the alcohol solvents occurred with sulfisoxazole, this solute was
TABLE XV

SOLUBILITY RATIOS\textsuperscript{a}

AT

25\textdegree CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>(R) Sulfa-soxazole</th>
<th>(R) Sulfadimethoxine</th>
<th>(R) Sulfo-somidine</th>
<th>(R) Sulfa-diazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>1.0</td>
<td>0.15</td>
<td>0.15</td>
<td>0.026</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1.0</td>
<td>0.17</td>
<td>0.13</td>
<td>0.018</td>
</tr>
<tr>
<td>Propanol</td>
<td>1.0</td>
<td>0.21</td>
<td>0.19</td>
<td>0.019</td>
</tr>
<tr>
<td>Butanol</td>
<td>1.0</td>
<td>0.26</td>
<td>0.23</td>
<td>0.022</td>
</tr>
<tr>
<td>Pentanol</td>
<td>1.0</td>
<td>0.32</td>
<td>0.27</td>
<td>0.025</td>
</tr>
<tr>
<td>Octanol</td>
<td>1.0</td>
<td>0.37</td>
<td>0.25</td>
<td>0.025</td>
</tr>
<tr>
<td>Decanol</td>
<td>1.0</td>
<td>0.55</td>
<td>0.44</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Solubility ratio = R = (mole fraction solubility sulfonamide/mole fraction solubility sulfa-soxazole)
chosen as a basis for comparison. The solubility ratios, \( R \), were calculated by dividing the mole fraction solubility of sulfisoxazole into the mole fraction solubility of the sulfonamide in question; therefore, the ratios for sulfisoxazole 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 sulfisoxazole. Table XV shows that the sulfadimethoxine and sulfisomidine solubilities in methanol are smaller than the mole fraction solubility of sulfisoxazole 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 sulfisoxazole solubility in decanol. In relative terms, decanol appears to be a much better solvent for sulfadimethoxine and sulfisomidine than methanol. The solubility ratios for sulfadiazine in methanol through octanol show that sulfadiazine, when compared with sulfisoxazole, is extremely insoluble. In fact, the average sulfadiazine solubilities in methanol through octanol are about 2.5 percent that of the sulfisoxazole solubilities. In decanol, however, the sulfadiazine solubility increases to eighteen percent of the sulfisoxazole 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 sulfonamides 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 sulfisoxazole 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 sulfisomidine 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 sulfisomidine, 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.
Polarity Aspects of Nonelectrolyte Solubility-

Several authors (3-6) have recognized the dependence of observed solubility upon the relationship between the polarity of the solute and solvent. Paruta (5) used solvent polarity as a parameter to explain changing solubility for a solute dissolved in a series of related solvents. He plotted the values for the solubilities of a particular solute versus the dielectric constants of the solvents to generate a curve which suggested that the solubilities change in a manner consistent with changing solvent polarity. These changes were interpreted as indications of solute-solvent interactions which are apparently related to the polarity of the system.

Solubility parameters and dielectric constants are the values most commonly used to describe the polarity spectrum and the values for the normal alcohols used in this investigation are shown in Table XVI. These data show that both polarity indicators decrease as the carbon chain length of the alcohol increases; however, the solubility parameter scale is much more compressed than the dielectric scale.

Gordon and Scott (7) have observed that regular solution theory should apply to three-component systems with no further assumptions than those involved in the two-component case. Therefore, it is anticipated that, if the relative polarity of the solute lies between the polarities of two pure liquids, the solubility of the solute will be greater
## TABLE XVI

SOLUBILITY PARAMETERS AND DIELECTRIC CONSTANTS

OF THE NORMAL ALCOHOLS

AT 25° CENTIGRADE

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Solubility<strong>a</strong> Parameter</th>
<th>Dielectric<strong>c</strong> Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>14.5</td>
<td>32.6</td>
</tr>
<tr>
<td>Ethanol</td>
<td>12.7</td>
<td>24.3</td>
</tr>
<tr>
<td>Propanol</td>
<td>11.9</td>
<td>20.1</td>
</tr>
<tr>
<td>Butanol</td>
<td>11.4</td>
<td>17.1</td>
</tr>
<tr>
<td>Pentanol</td>
<td>10.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Octanol</td>
<td>10.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Decanol</td>
<td>9.3<strong>b</strong></td>
<td>8.1 (20°)</td>
</tr>
</tbody>
</table>


**b**Calculated from- solubility parameter = dielectric constant \( \times 0.22 + 7.5 \)

in certain binary liquid blends than in either pure liquid. In order to test the possibility that sulfonamide solubilities may be maximized in certain solvent blends, sulfadiazine was dissolved in dioxane/water mixtures, and these data are summarized in Table XVII. Figure 5 is a plot of mole fraction solubility versus dielectric constant of the solvent; it reveals that a maximum solubility occurs in a solvent mixture with a dielectric constant of about 6. The increased solubility is a manifestation of the simple theory that "like dissolves like". It must be recognized, however, that mixtures of solvents do not necessarily lead to a hypothetical "single solvent" with polarity properties that represent an average of the individual pure liquids. Rather, cosolvent systems must be considered to be complex in nature and, any solute-solvent interactions which lead to increased solubility are correspondingly complex. The solubility maximum in figure 5 demonstrates that regular solution theory is qualitatively accurate, and solute-solvent interactions may be enhanced by altering the polarity characteristics of the solvent system.

Solubility-polarity profiles for the solubilities of the sulfonamides determined in normal alcohols are shown in figures 6-9. In the case of sulfisoxazole, which has a dimethylisoxazole substituent at the N₁ position, the curve is smooth, with solubility values rising to a peak in pure methanol. For the other three sulfonamides, which have pyrimidine
# Table XVII

## Solubility of Sulfadiazine in Dioxane/Water Mixtures

### at 25° Centigrade

<table>
<thead>
<tr>
<th>Percent Water (w/w)</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47.5</td>
<td>5.45</td>
<td>$9.50 \times 10^{-2}$</td>
<td>$6.61 \times 10^{-4}$</td>
</tr>
<tr>
<td>42.5</td>
<td>5.53</td>
<td>$1.51 \times 10^{-1}$</td>
<td>$7.17 \times 10^{-4}$</td>
</tr>
<tr>
<td>37.5</td>
<td>6.55</td>
<td>$9.48 \times 10^{-2}$</td>
<td>$9.15 \times 10^{-4}$</td>
</tr>
<tr>
<td>32.5</td>
<td>8.18</td>
<td>$4.70 \times 10^{-1}$</td>
<td>$1.24 \times 10^{-3}$</td>
</tr>
<tr>
<td>30.0</td>
<td>8.58</td>
<td>$1.57 \times 10^{-1}$</td>
<td>$1.36 \times 10^{-3}$</td>
</tr>
<tr>
<td>25.0</td>
<td>8.91</td>
<td>$8.16 \times 10^{-2}$</td>
<td>$1.56 \times 10^{-3}$</td>
</tr>
<tr>
<td>20.0</td>
<td>9.75</td>
<td>$2.35 \times 10^{-1}$</td>
<td>$1.90 \times 10^{-3}$</td>
</tr>
<tr>
<td>15.0</td>
<td>9.79</td>
<td>$1.55 \times 10^{-1}$</td>
<td>$2.13 \times 10^{-3}$</td>
</tr>
<tr>
<td>10.0</td>
<td>9.71</td>
<td>$1.37 \times 10^{-1}$</td>
<td>$2.41 \times 10^{-3}$</td>
</tr>
<tr>
<td>0.0</td>
<td>2.94</td>
<td>$8.72 \times 10^{-2}$</td>
<td>$1.01 \times 10^{-3}$</td>
</tr>
</tbody>
</table>
Figure 5- Mole Fraction Solubility of Sulfadiazine in Dioxane/Water Mixtures at 25°C Versus Dielectric Constant (lower axis) and Percent Water (upper axis).
Figure 6 - Mole Fraction Solubility of Sulfadiazine at 25°C Versus Dielectric Constants of Normal Alcohols.
Figure 7 - Mole Fraction Solubility of Sulfadimethoxine at 25°C Versus Dielectric Constants of Normal Alcohols.
Figure 8 - Mole Fraction Solubility of Sulfisomidine at 25°C Versus Dielectric Constants of Normal Alcohols.
Figure 9- Mole Fraction Solubility of Sulfisoxazole at 25°C Versus Dielectric Constants of Normal Alcohols.
substituents at the N\textsuperscript{1} position, the profiles are similar in nature. The solubility minima occur in the area of a dielectric constant of about 10, and peak solubilities occur in methanol. Examination of these curves does not yield any significant quantitative correlation between mole fraction solubility and solvent polarity. Qualitatively, however, it is clear that the dielectric constant, \textit{i.e.}, the polarity, of the solvent is related, at least in part, to the changes in observed solubilities as the pure solvent systems are varied.
Melting Point of the Solute and Nonelectrolyte Solubility -

The general equation relating mole fraction solubility for a nonelectrolyte solute to its melting point is

\[ -\ln X_2 = \frac{(H_f/R)}{T_m-T} \frac{1}{T_mT} \]

where \( X_2 \) is the mole fraction solubility, \( H_f \) is the heat of fusion (calories/mole), \( T_m \) is the melting point of the pure solute and \( T \) is the temperature at which the process takes place. The equation indicates that, as the melting point of a nonelectrolyte solute increases, the mole fraction solubility decreases. Hildebrand (8) has demonstrated that this data trend does exist for three related dinitrobenzenes dissolved in the same solvent at 50°C. In Table XVIII the melting points of the sulfonamides used in the present study are listed together with the mole fraction solubilities of the four solutes in methanol at 25°C. These data confirm the expectation suggested by the equation, since the solubilities do decrease with increasing melting point.

The data in Table XVIII show, however, that a relatively large change in 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°C, but the solubilities for these solutes are nearly equal. On the other hand, only a ten degree difference exists between sulfisomidine and sulfadiazine, yet sulfisomidine is nearly six times more soluble. These findings suggest that factors, such as the heats of fusion and the chemical structures of the solutes, also influence the magnitudes of observed solubilities.
**TABLE XVIII**

**SOLUBILITIES OF SULFONAMIDES IN METHANOL AT 25°C COMPARED WITH MELTING POINTS OF PURE SOLUTES**

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>Solubility (mole fraction)</th>
<th>Average Melting Point (degrees C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>$7.52 \times 10^{-3}$</td>
<td>193</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>$1.16 \times 10^{-3}$</td>
<td>200</td>
</tr>
<tr>
<td>Sulfinomidine</td>
<td>$1.12 \times 10^{-3}$</td>
<td>243</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>$1.93 \times 10^{-4}$</td>
<td>253</td>
</tr>
</tbody>
</table>
Thermodynamic Evaluation of Nonelectrolyte Solubility Data

The relationship between temperature and mole fraction solubility is given by

\[
\log_{10} x_2 = -\frac{H_s}{(2.303RT)} + \frac{S}{(2.303R)} \tag{1}
\]

where \(H_s\) is the heat of solution and \(S\) is the corresponding entropy.

Equation 1 is a special form of a general physical-chemical equation (9), and its usefulness derives from the fact that enthalpy and entropy are basic theoretical quantities. These quantities may be applied to the interpretation of an equilibrium process to determine the change between the initial and final stages. Solubility is a special type of equilibrium wherein the heat of solution and its corresponding entropy are valuable interpretive quantities that suggest both the change in heat content and the randomness of the solution system relative to the solid state.

The enthalpy term in equation 1 is the heat change involved when a solute undergoes a phase change from the solid to the solute in solution. For nonelectrolyte solutions, the enthalpy quantity is usually positive, indicating that the process is endothermic. The entropy term may be positive or negative depending upon the ordered nature of the system relative to the initial state.

Enthalpy and entropy are macroscopic thermodynamic quantities and do not deal directly with molecular behavior. Therefore, their usefulness in solution theory is enhanced if a molecular implication can be ascribed. The enthalpy of solution, \(H_s\), has been given a
qualitative meaning by Higuchi (10) who relates this quantity to the interactions occurring in solution. Higuchi's theory is based on the following relationship

\[ H_s = -H_{1,2} + (H_{1,1} + H_{2,2}) \]  \hspace{1cm} (2)

where \( H_{1,1} \) is the molar heat of vaporization of the solvent, \( H_{2,2} \) is the molar heat of vaporization of the solute, and \( H_{1,2} \) is the energy notation, in calories per mole, of the interaction that has occurred between the solute and solvent. Thus, as \( H_{1,2} \) increases in magnitude, \( H_s \) becomes smaller and there is an indication that at the molecular level the solute-solvent interaction is relatively large. Equation 2 is derived from a model which requires that the solute and solvent molecules be of approximately the same size. Since this requirement will not usually be met, the equation cannot be considered to be quantitative. However, it is of qualitative usefulness and suggests very strongly that \( H_s \) may be regarded as the INTERACTION term.

The entropy term in equation 1 is indicative of the molecular orderliness in the system being analyzed. Butler (11) has noted that "The entropy is a measure of the number of possible configurations of the system having a given energy. When the solute molecule is brought into the field of force of the solvent there may be some restrictions of its possible configurations, which will lower the entropy, and this effect might well be proportional to the energy of interaction of the solute with the solvent. Conversely, the solvent molecules around the solute will be
affected in the same way, and any change of entropy which arises therefrom will appear in the partial entropy of the solute. Thus, in molecular terms the entropy can be regarded as a configurational term which is obviously related to the extent of interactions, the enthalpy of solution, and the magnitude of solubility.

With the molecular interpretations of enthalpy and entropy in mind, it should be possible to develop a general theory or model to explain solubility at the molecular level. The following phase transitions are representative of solubility phenomena:

\[
\begin{align*}
\text{solid} & \xrightarrow{\text{H}_f} \text{liquid} \xrightarrow{\bar{H}_x} \text{solute in solution,} \\
\text{solute} & \xrightarrow{\text{H}_f + \bar{H}_x} \text{solute in solution,}
\end{align*}
\]

The enthalpy and entropy of solution represent the thermodynamic quantities, with respect to the solute, that are involved in the change of the solid solute to a solute in solution. The enthalpy involved in step 1 is the enthalpy of fusion, \(H_f\), and the corresponding entropy is the entropy of fusion, \(S_f\). Of particular interest are the enthalpies and entropies associated with step 2, designed as \(H_x\) and \(S_x\), respectively. The following equations then obtain:

\[
H_s = H_f + H_x
\]  
(3)

and

\[
S = S_f + S_x
\]  
(4)

When \(H_x\) and \(S_x\) are zero, the solute in the solution phase acts essentially as the solute in the liquid phase, and the solubility is independent of the
solvent. An example of this type of behavior is the dissolution of naphthalene in benzene. The implications of this behavior are that the solute-solvent interactions are of the same magnitude as the solute-solute and solvent-solvent interactions.

When $H_x$ is relatively large, there is an indication of correspondingly decreased interactions by virtue of equation 2; and the mole fraction solubility, $X_2$, can be expected to be relatively small. One explanation for this decreased solubility is that the solvent molecules have "squeezed out" the solute molecules and in so doing have brought about a higher level of molecular disarray in the solution phase. The resulting entropy term, $S$, would then be expected to be positive and the solubility process would be essentially entropy-governed, especially at higher temperatures. Conversely, when $H_x$ becomes small, there is an expectation of increased interactions. Under these conditions, however, the solvent molecules no longer "squeezed out" those of the solute, and the solution phase displays increased orderliness, manifested by a small positive or even negative entropy term. This theory is basically consistent with that discussed by Hildebrand (12).

There are obviously other conditions which may be met with regard to the sign and magnitude of $H_x$ and $S_x$, but these two will generally be used as a basis for the explanation of sulfonamide solubility in the normal alcohols studied. Unfortunately, the $H_f$ and $S_f$ quantities for the solute are not available; hence, it is not possible to calculate
Hx and Sx from Hs and S. However, the relative magnitude of Hs and S as well as their sign should serve to interpret the data.

Equation 1 provides a means of calculating the enthalpy of solution and its corresponding entropy and predicts that a plot of log\(_{10} X_2 \text{ versus } 1/T\) should generate a straight line. The slope of the line would be \(-Hs/2.303R\) and the y-intercept \(S/2.303R\). The enthalpy and entropy quantities can then be calculated by

\[-Hs = (\text{slope})(2.303R)\]  \hspace{1cm} (5)

and

\[S = (\text{y-intercept})(2.303R)\]  \hspace{1cm} (6).

Shown in figures 10 through 13 are plots of log\(_{10} X_2 \text{ versus } 1/T\) for the sulfonamides studied. In each of the systems investigated, solubility increased with increasing temperature in the linear manner suggested by equation 1. The temperature range of 25°C to 37°C is shown to be wide enough to exhibit measurable solubility changes.

With the aid of a computer, the values for the enthalpies and entropies of solution were calculated using the method of least squares (Appendix). These data are presented in Tables XIX through XXII.

Table XIX shows that the lowest heat of solution value occurs for sulfisoxazole dissolved in methanol. Since sulfisoxazole displayed the highest solubility in methanol, the magnitude of the enthalpy value is in keeping with equation 2; that is, increased solubility occurs with increased interactions and correspondingly lower Hs values.
Figure 10 - Log Mole Fraction Solubility of Sulfisoxazole Versus Reciprocal Temperature (Kelvin).
Figure 11: Log Mole Fraction Solubility of Sulfadimethoxine Versus Reciprocal Temperature (Kelvin).
Figure 12 - Log Mole Fraction Solubility of Sulfisomidine Versus Reciprocal Temperature (Kelvin).
Figure 13- Log Mole Fraction Solubility of Sulfadiazine Versus Reciprocal Temperature (Kelvin).
<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Heat of Solution (calories/mole)</th>
<th>Entropies (calories/degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$5.02 \times 10^3$</td>
<td>7.12</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$5.20 \times 10^3$</td>
<td>6.58</td>
</tr>
<tr>
<td>Propanol</td>
<td>$6.58 \times 10^3$</td>
<td>9.97</td>
</tr>
<tr>
<td>Butanol</td>
<td>$6.40 \times 10^3$</td>
<td>8.57</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$6.38 \times 10^3$</td>
<td>7.83</td>
</tr>
<tr>
<td>Octanol</td>
<td>$6.10 \times 10^3$</td>
<td>5.64</td>
</tr>
<tr>
<td>Decanol</td>
<td>$6.04 \times 10^3$</td>
<td>4.78</td>
</tr>
</tbody>
</table>
Decreased solubility of this solute 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 sulfisoxazole 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 sulfisoxazole 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 configurational 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 the enthalpies and entropies. The spontaneity of the process will be enhanced when Hs is relatively small and the
corresponding entropy is of the same sign and relatively large (13).

The thermodynamic functions for sulfadimethoxine are presented in Table XX. 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 $H_S$ 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 influence 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
TABLE XX

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

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Heat of Solution (calories/mole)</th>
<th>Entropies (calories/degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$6.43 \times 10^3$</td>
<td>8.16</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$6.52 \times 10^3$</td>
<td>7.50</td>
</tr>
<tr>
<td>Propanol</td>
<td>$7.76 \times 10^3$</td>
<td>10.8</td>
</tr>
<tr>
<td>Butanol</td>
<td>$8.18 \times 10^3$</td>
<td>11.9</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$7.61 \times 10^3$</td>
<td>9.72</td>
</tr>
<tr>
<td>Octanol</td>
<td>$8.48 \times 10^3$</td>
<td>11.6</td>
</tr>
<tr>
<td>Decanol</td>
<td>$6.21 \times 10^3$</td>
<td>4.17</td>
</tr>
</tbody>
</table>
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 sulfisomidine follow the same trend as the thermodynamic data for sulfisomidine. 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 dimethoxy-pyrimidine 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 sulfisomidine solutions, with the exception of octanol, are smaller than the corresponding entropies for sulfadimethoxine.
TABLE XXI
HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFISOMIDINE AS DETERMINED IN A SERIES OF NORMAL ALCOHOLS

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Heat of Solution (calories/mole)</th>
<th>Entropies (calories/degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$6.05 \times 10^3$</td>
<td>6.77</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$6.07 \times 10^3$</td>
<td>5.44</td>
</tr>
<tr>
<td>Propanol</td>
<td>$6.58 \times 10^3$</td>
<td>6.64</td>
</tr>
<tr>
<td>Butanol</td>
<td>$7.36 \times 10^3$</td>
<td>8.86</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$7.16 \times 10^3$</td>
<td>6.73</td>
</tr>
<tr>
<td>Octanol</td>
<td>$8.81 \times 10^3$</td>
<td>11.9</td>
</tr>
<tr>
<td>Decanol</td>
<td>$5.19 \times 10^3$</td>
<td>0.277</td>
</tr>
</tbody>
</table>
The thermodynamic data for sulfadiazine are presented in Table XXII 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 magnitude. 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\textsuperscript{1} substituent of the sulfonamide 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
TABLE XXII

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

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Heat of Solution (calories/mole)</th>
<th>Entropies (calories/degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>$6.73 \times 10^3$</td>
<td>5.58</td>
</tr>
<tr>
<td>Ethanol</td>
<td>$7.34 \times 10^3$</td>
<td>5.79</td>
</tr>
<tr>
<td>Propanol</td>
<td>$8.28 \times 10^3$</td>
<td>7.82</td>
</tr>
<tr>
<td>Butanol</td>
<td>$8.77 \times 10^3$</td>
<td>8.85</td>
</tr>
<tr>
<td>Pentanol</td>
<td>$8.59 \times 10^3$</td>
<td>7.86</td>
</tr>
<tr>
<td>Octanol</td>
<td>$9.72 \times 10^3$</td>
<td>10.4</td>
</tr>
<tr>
<td>Decanol</td>
<td>$3.80 \times 10^3$</td>
<td>-6.18</td>
</tr>
</tbody>
</table>

134
favored because of the positive enthalpy and entropy values, which will promote increased solubilities, especially at higher temperatures (13).
Solubilities of Sulfonamides in Buffered Aqueous Systems -

Solubilities of nonpolar or semipolar nonelectrolytes in water are generally limited. The low magnitude of solubility is attributed to extensive cohesive forces that occur between the solvent molecules themselves which tend to exclude those of the solute phase (14). However, solubility-limiting characteristics of nonelectrolytes are complex and involve polar and nonpolar (hydrophobic) interactions of the solute with water (15, 16). When a semipolar nonelectrolyte containing both a hydrophobic substituent and a polar group that is capable of intermolecular hydrogen bonding is introduced into an aqueous environment, two types of interactions might occur: first, the polar substituent may interact with the water molecules by way of hydrogen bond formation; and second, interaction as a result of Van der Waals forces between water and the hydrophobic portion of the solute may take place.

Investigations have shown that the transfer of a hydrocarbon solute from a nonpolar to a polar (aqueous) system is associated with a negative entropy of solution (16). It has been postulated that the entropy term derives from the Van der Waals interactions with the nonpolar molecule, resulting in a promotion of molecular ordering as the water forms a partial cage around the hydrophobic portion of the solute. The concept of structured water or water "clusters" resulting from hydrophobic-water interactions can be better understood by
considering the model as a dynamic one based on microenvironmental regions in the system.

As might be expected, the hydrogen bond formation is energetically favored over the Van der Waals interaction. Therefore, the aqueous solubilities of nonelectrolytes should increase as a function of increasing hydrogen bonding possibilities. Contribution from Van der Waals interactions are determined by the size and shape of the solute (16) and actually place a limitation on aqueous solubilities because of the large negative entropies and resulting positive free energy changes (15).

Considerable care must be exercised with models that use energetic or entropic quantities to explain nonelectrolyte solubilities in water. The extent to which solubility occurs is the net result of all energetically governed processes, including hydrogen bonding, dipole interactions and Van der Waals forces. Accordingly, actual systems must be viewed as the resultant of numerous effects that cannot be isolated and recognized on a singular basis to give support for any particular model.

In the present study, aqueous solubilities of sulfisoxazole, sulfadimethoxine, sulfisomidine and sulfadiazine were measured at varying temperatures and these data are summarized in Table XXIII. Krebs and Speakman (17) have demonstrated that sulfadiazine dissolved in water shows large changes in solubility as a function of pH. These
authors also presented equations showing that an amphoteric sulfonamide acts essentially as a nonelectrolyte at the isoelectric pH. For this reason, all aqueous systems were appropriately buffered so that ionization of both substituent groups was precluded. The complexity of aqueous systems containing dissolved nonelectrolytes is increased because of the presence of salts included for their buffer effect (18). However, the observed sulfonamide solubilities maintain their instructive integrity in a relative manner by virtue of a constant buffer concentration.

The data in Table XXIV are included to demonstrate the relative solubilities of each solute at a particular temperature. Ratios of mole fraction sulfonamide solubilities divided by the mole fraction sulfisomidine solubility were calculated for this purpose. Table XXIV shows that sulfisomidine has the largest relative solubility of any of the sulfonamides studied. Other authors have noted that this solute has the highest solubility of the available pyrimidine substituted sulfonamides (19). Although sulfadimethoxine and sulfadiazine are pyrimidine substituted sulfonamides, their aqueous solubilities are significantly lower than sulfisomidine.

The data in Table XXIII were further analyzed by calculating heats of solution and their corresponding entropies, using the established relationship between \( \log_{10} \) mole fraction solubility and reciprocal temperatures (Kelvin). These thermodynamic data are
TABLE XXIII

SOLUBILITIES OF SULFONAMIDES IN WATER,a

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>°C</th>
<th>Solubility (mg./ml.)</th>
<th>Standard Deviation (mg./ml.)</th>
<th>Solubility (mole fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>25</td>
<td>$1.40 \times 10^{-1}$</td>
<td>$6.53 \times 10^{-4}$</td>
<td>$9.47 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>$1.77 \times 10^{-1}$</td>
<td>$2.17 \times 10^{-3}$</td>
<td>$1.20 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>$2.43 \times 10^{-1}$</td>
<td>$6.67 \times 10^{-3}$</td>
<td>$1.65 \times 10^{-5}$</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>25</td>
<td>$2.21 \times 10^{-2}$</td>
<td>$2.05 \times 10^{-4}$</td>
<td>$1.28 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>$2.66 \times 10^{-2}$</td>
<td>$7.05 \times 10^{-4}$</td>
<td>$1.55 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>$4.20 \times 10^{-2}$</td>
<td>$8.73 \times 10^{-4}$</td>
<td>$2.45 \times 10^{-6}$</td>
</tr>
<tr>
<td>Sulfisomidine</td>
<td>25</td>
<td>$1.33 \times 10^{0}$</td>
<td>$2.04 \times 10^{-2}$</td>
<td>$8.62 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>$1.56 \times 10^{0}$</td>
<td>$9.57 \times 10^{-3}$</td>
<td>$1.01 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>$1.91 \times 10^{0}$</td>
<td>$2.61 \times 10^{-2}$</td>
<td>$1.24 \times 10^{-4}$</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>25</td>
<td>$6.59 \times 10^{-2}$</td>
<td>$9.53 \times 10^{-4}$</td>
<td>$4.75 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>$8.09 \times 10^{-2}$</td>
<td>$9.44 \times 10^{-4}$</td>
<td>$5.84 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>$1.19 \times 10^{-1}$</td>
<td>$2.57 \times 10^{-3}$</td>
<td>$8.58 \times 10^{-6}$</td>
</tr>
</tbody>
</table>

aSolubilities determined in buffered aqueous systems within ± 0.2 pH units of the isoelectric pH of the sulfonamide. (Salt concentration maintained at 0.1 molar)
### TABLE XXIV

**SOLUBILITY RATIOS\(^a\) FOR SULFONAMIDES**

**DISSOLVED IN WATER AT 25° CENTIGRADE**

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisomidine</td>
<td>1.0</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>0.11</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>0.055</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>0.015</td>
</tr>
</tbody>
</table>

\(^a\)Solubility Ratio = R =

(mole fraction solubility sulfonamide/
mole fraction solubility sulfisomidine)
presented in Table XXV. The enthalpies and entropies for sulfisoxazole, sulfadimethoxine and sulfadiazine are remarkably close in view of the chemical dissimilarity of these solutes. Heats of solution for these three solutes are relatively large and are in keeping with small solute-solvent interactions and diminished solubilities. The large negative entropy for sulfisomidine gives evidence of increased order in the solution phase. Sulfisomidine may possess the ability to interact with the aqueous environment in a manner which promotes a more "structured" solution. One possible explanation lies in the postulated cage of water molecules that surrounds the hydrophobic portion of the solute molecule and results in a large negative entropy (15, 16). The observed solubility for the sulfisomidine molecule is relatively large, however, because the decrease in enthalpy partially compensates for the sign and magnitude of the entropic contribution. As a macroscopic thermodynamic quantity, the negative entropy is a limiting factor with regard to increasing solubilities at much higher temperatures (13).
### TABLE XXV

HEATS OF SOLUTION AND CORRESPONDING ENTROPIES FOR SULFONAMIDES AS DETERMINED IN WATER\(^a\)

<table>
<thead>
<tr>
<th>Sulfonamide</th>
<th>Heat of Solution (calories/mole)</th>
<th>Entropies (calories/degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisomidine</td>
<td>(5.50 \times 10^3)</td>
<td>-5.52</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>(8.44 \times 10^3)</td>
<td>5.33</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>(9.09 \times 10^3)</td>
<td>6.13</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>(1.00 \times 10^4)</td>
<td>6.53</td>
</tr>
</tbody>
</table>

\(^a\) Solubilities determined in buffered aqueous systems within \(\pm 0.2\) pH units of the isoelectric pH of the sulfonamide.
Partition Coefficient Data

Partition coefficients have been used by several authors (20-22) for a variety of investigative purposes. In the present study, the partition coefficients for a particular sulfonamide, sulfadiazine, were determined as a measure of the relative hydrophobic nature of the solute molecule.

The equations relating the partition coefficient and the pK of a weak electrolyte are

\[ \text{pH} = \text{pK}(N^1) + \frac{\text{T. P. C.}}{\text{A. P. C.}} - 1 \]  

(7)

and

\[ \text{pH} = \text{pK}(N^4) - \frac{\text{T. P. C.}}{\text{A. P. C.}} - 1 \]  

(8)

where T. P. C. is the true partition coefficient and A. P. C. is the apparent partition coefficient. The true partition coefficient is the value measured in a system where the aqueous portion of the sample is buffered so as to preclude ionization. Conversely, the apparent partition coefficient is the value measured in a system where the aqueous portion of the sample is buffered so as to allow ionization. The relationship between pK(N^1) and pK(N^4) for a sulfonamide is

\[ \text{pHi} = \frac{(\text{pK}(N^1) + \text{pK}(N^4))}{2} \]  

(9).

In order to test these equations, the hydrogen-ion concentrations of the aqueous portion of several samples were varied, and the partition coefficients measured for water/n-octanol systems. The T. P. C. and A. P. C. values were then used to calculate pHi, pK(N^1) and pK(N^4).
These data are summarized in Table XXVI which shows that the experimental pK values correlate very well with those found in the literature. This agreement indicates that the true partition coefficient value in Table XXVI is an accurate measure of the properties of the solute molecule as they relate to the theoretical equations in question.

The true partition coefficients for sulfadiazine in water/n-alcohol systems are shown in Table XXVII. These data indicate several interesting facts. First, the partition coefficients increase with increasing polarity of the alcohol phase, until a maximum is reached in pentanol. In fact, the value for the pentanol system is about 6.5 times greater than that for the decanol system, an indication that the attraction between the solute molecules and pentanol is much greater than between the solute and water. In other words, pentanol-sulfadiazine interactions exceed those for water-sulfadiazine. The trend of the data, although not the actual magnitudes for the T.P.C. values, is not surprising since sulfadiazine is much more soluble in the alcohols than it is in water. Second, the true partition coefficient for butanol is less than that for pentanol. This shift in the data trend may be misleading because it suggests that sulfadiazine interactions with pentanol are larger than those for sulfadiazine and butanol. The validity of the T.P.C. value becomes questionable when the aqueous and alcohol phases are not immiscible. Butanol is significantly soluble in water (23), and the measured partition coefficient probably does not suggest the properties
TABLE XXVI

PARTITION COEFFICIENT DATA
FOR SULFADIAZINE
IN aWATER/n-OCTANOL SYSTEMS
AT 30°C

<table>
<thead>
<tr>
<th>TRUE PARTITION COEFFICIENT</th>
<th>observed</th>
<th>pK</th>
<th>literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.797</td>
<td>6.41</td>
<td>pK(N₁)</td>
<td>6.45b</td>
</tr>
<tr>
<td></td>
<td>4.26</td>
<td>pH₁</td>
<td>4.28</td>
</tr>
<tr>
<td></td>
<td>2.09</td>
<td>pK(N₄)</td>
<td>2.10</td>
</tr>
</tbody>
</table>

aIonic strength of aqueous portion of sample maintained at 0.05.

TABLE XXVII

PARTITION COEFFICIENT DATA

FOR SULFADIAZINE IN

*a*WATER/n-ALCOHOL SYSTEMS

AT 37°C

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>True Partition coefficient</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butanol</td>
<td>2.39</td>
<td>1.40 x 10⁻¹</td>
</tr>
<tr>
<td>Pentanol</td>
<td>2.61</td>
<td>7.17 x 10⁻²</td>
</tr>
<tr>
<td>Octanol</td>
<td>7.67 x 10⁻¹</td>
<td>5.14 x 10⁻²</td>
</tr>
<tr>
<td>Decanol</td>
<td>4.07 x 10⁻¹</td>
<td>1.46 x 10⁻²</td>
</tr>
</tbody>
</table>

*a*Ionic strength of aqueous portion of sample maintained at 0.05. Aqueous portion of sample maintained within 0.2 pH units of the pHf for sulfadiazine.
normally attributed to it. Therefore, any correlations between the butanol system and the other alcohol systems are of doubtful value. Further, the usefulness of partition coefficients is definitely limited since only immiscible solvent phases yield values of theoretical importance.
VII
SUMMARY

1) The solubilities of four sulfonamides dissolved in a series of n-alcohols diminish as the \( N^1 \) substituent of the parent sulfanilamide is altered. Solutes in decreasing order of mole fraction solubility are:
   1) sulfisoxazole
   2) sulfadimethoxine
   3) sulfisomidine
   4) sulfadiazine.

2) Solubility-polarity profiles show that each sulfonamide has the greatest solubility in methanol, a relatively polar solvent.

3) Solubility data for sulfadiazine dissolved in dioxane-water mixtures show a maximum solubility in a solvent blend with a dielectric constant of about 6.0. This maximum solubility demonstrates qualitative accuracy of regular solution theory as applied to three component systems.

4) The magnitudes of solubility for each sulfonamide dissolved in methanol at 25°C qualitatively follow the trend predicted for solutes with different melting points. Solutes in decreasing order of solubility and increasing order of melting point are:
1) sulfisoxazole
2) sulfadimethoxine
3) sulfisomidine
4) sulfadiazine.

5) Solubilities of the sulfonamides dissolved in n-alcohols increase with increasing temperature. This temperature dependence is indicative of an endothermic process as the solute molecule undergoes a phase transition from the solid solute to the solute in solution.

6) Thermodynamic data for sulfonamides dissolved in n-alcohols indicate that enthalpy and entropy are quantities related to the solute-solvent interactions and associated steric factors. Sulfadiazine dissolved in decanol shows a dramatic increase in solubility and a large decrease in entropy. The increased solubility suggests a relationship with the entropy term and hence, the way in which sulfadiazine-octanol molecules "fit" at the molecular level.

7) The solubilities of the sulfonamides dissolved in aqueous systems buffered at the isoelectric pH are significantly lower than those in the n-alcohol solvents. Solutes in decreasing order of mole fraction solubility are:
1) sulfisomidine
2) sulfisoxazole
3) sulfadiazine
4) sulfadimethoxine.

The enthalpy quantities associated with the sulfisomidine solubilities are much smaller than those for the other sulfonamides. The large negative entropy for sulfisomidine supports the theory regarding hydrophobic interaction with water molecules and increased structuring in the solution phase.

8) Partition coefficient for sulfadiazine in a water/octanol system demonstrates the usefulness of partitioning as a method of determining the pK values for weak electrolytes of limited solubility.

9) Data for sulfadiazine partitioned in water/n-alcohol systems show that the partition coefficients increase with increasing polarity of the alcohol phase. These data demonstrate, however, that partition coefficients are of limited value as indicators of the relative hydrophobic nature of a solute molecule, because the nonaqueous-liquid portion of the partitioning system is restricted to solvents which are immiscible with water. Hence, the polarity spectrum that can be investigated is necessarily limited.
VIII

REFERENCES
A.

References (sulfonamides)


3) T. Struller, Progress in Sulfonamide Research, Department of Clinical Research and Department of Product Development; F. Hoffmann-La Roche and Co., Ltd., Basle.


8) A. Biamonte and G. Schneller, ibid., 41, 341 (1952).


12) E. Northey, op. cit., ref. 1, p. 458.


14) Ibid., 12, 421 (1964).

References for theoretical section concerning solubility


12) F. W. Schueler, *op. cit.*, ref. 7, p. 186.

13) T. Higuchi, *op. cit.*, ref. 4, p. 175.

14) A. N. Martin, *op. cit.*, ref. 6, p. 149.


17) A. E. Bailey, op. cit., ref. 11, p. 46.
18) A. N. Martin, op. cit., ref. 6, p. 361.
19) ibid., ref. 6, p. 361.
26) ibid., ref. 15, p. 167.
27) T. Higuchi, op. cit., ref. 4, p. 163.
34) A. N. Paruta, ibid., 56, 1565 (1967).
37) A. N. Martin, *op. cit.*, ref. 6, p. 116.


References for theoretical section concerning partition coefficients


10) A. Albert and E. P. Serjeant, op. cit., ref. 8, p. 6.

11) ibid., p. 113.


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D.

References (experimental section)


4) A. Maryott and E. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, 1951.


References for results and discussion section


5) A. Paruta, ibid., 56, 1565 (1967).


IX

APPENDIX
A. Computer Program for a Method of Least Squares in FORTRAN IV Language

```fortran
DIMENSION X(20), Y(20), XD(20), YD(20),
1 XDS(20), YDS(20), XY(20), ALF(15)
READ(5, 1) ALF
1 FORMAT(15A4)
READ(5, 2) N, AN
2 FORMAT(2I2, F10.0)
READ(5, 3) P, TEST
3 FORMAT(2I2)
DO 7 I=1, N
READ(5, 4) X(I), Y(I)
4 FORMAT(2F10.0)
7 CONTINUE
IF(TEST) 70, 71, 70
70 IF(P) 150, 60, 150
150 CONTINUE
DO 36 I=1, N
X(I)=10. ** X(I)
36 CONTINUE
IF(P) 199, 300, 300
199 DO 40 I=1, N
Y(I)=1. / Y(I)
40 CONTINUE
GO TO 60
300 DO 50 I=1, N
Y(I)=1. / Y(I)
X(I)=1. / X(I)
50 CONTINUE
GO TO 60
71 DO 55 I=1, N
Y(I)=ALOG10(Y(I))
55 CONTINUE
GO TO 60
60 XSM=0
YSM=0
DO 5 I=1, N
XSM=XSM+X(I)
YSM=YSM+Y(I)
5 CONTINUE
```

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XA=XSM/AN
YA=YSM/AN
XYS=0
XDSS=0
YDSS=0
DO 6 I=1,N
XD(I)=X(I)-XA
YD(I)=Y(I)-YA
XDS(I)=XD(I)**2
YDS(I)=YD(I)**2
XY(I)=XD(I)*YD(I)
XYS=XYS+XY(I)
XDSS=XDSS+XDS(I)
YDSS=YDSS+YDS(I)
6 CONTINUE
SLOPE=XYS/XDSS
R=XYS/SQRT(XDSS*YDSS)
B=YA-(SLOPE*XA)
RATE=SLOPE*2.303
RATE=RATE*(-1.)
TIMH1F=.693/RATE
T90=(2.303/RATE)**(1.954)
IF(TEST)201,202,201
201 IF(P)350,360,375
350 PK=1./B
PKAA=PK*SLOPE
PKA=ALOG10(1./(PKAA))
GO TO 80
375 PK=1./B
PKAA=1./(PK*SLOPE)
PKA=ALOG10(1./(PKAA))
GO TO 81
360 WRITE(6,10)
10 FORMAT(///,T10,'P=0 IS LEAST SQUARES')
GO TO 200
80 WRITE(6,11)
11 FORMAT(///,T10,'P=-1 IS 1/K(PRIME)=KA/K*H+1/K')
GO TO 200
81 WRITE(6,12)
12 FORMAT(///,T10,'P=+1 IS 1/K(PRIME)=H/KA*K+1/K')
GO TO 200
202 WRITE(6,13)
13 FORMAT(///,T10,'TEST=0 IS FIRST ORDER EQUATION')
GO TO 200
200 WRITE(6,14)ALF
14 FORMAT(/, T10, 15A4)
  WRITE(6, 15)XYS
15 FORMAT(/, T10, 'SUM (X-X AVE.)(Y-Y AVE.) IS ', E20.7)
  WRITE(6, 16)XDSS
16 FORMAT(T10, 'SUM (X-X AVE.)**2 IS ', E20.7)
  WRITE(6, 17)XA
17 FORMAT(T10, 'AVE. OF X VALUES IS ', E20.7)
  WRITE(6, 18)YA
18 FORMAT(T10, 'AVE. OF Y VALUES IS ', E20.7)
  WRITE(6, 19)SLOPE
19 FORMAT(T10, 'SLOPE IS ', E20.7)
  WRITE(6, 20)B
20 FORMAT(T10, 'Y INTERCEPT IS ', E20.7)
  WRITE(6, 21)R
21 FORMAT(T10, 'R IS ', F20.4)
  WRITE(6, 22)
22 FORMAT(/, T10, 'THE FOLLOWING ARE X VALUES')
  WRITE(6, 23)(X(I), I=1, N)
23 FORMAT(T10, E20.7)
  WRITE(6, 24)
24 FORMAT(/, T10, 'THE FOLLOWING ARE Y VALUES')
  WRITE(6, 25)(Y(I), I=1, N)
25 FORMAT(T10, E20.7)
  IF( TEST) 141, 140, 141
141 IF(P) 90, 91, 90
  WRITE(6, 26)PK
26 FORMAT(/, T10, 'TRUE PART. COEFF. IS ', E20.7)
  WRITE(6, 27)PKAA
27 FORMAT(/, T10, 'IONIZAT. CONSTANT IS ', E20.7)
  WRITE(6, 28)PKA
28 FORMAT(/, T10, 'PKA IS ', E20.7)
  GO TO 91
140 WRITE(6, 29)RATE
29 FORMAT(/, T10, 'DEGRADATION RATE IS ', E20.7)
  WRITE(6, 30)TIMHLF
30 FORMAT(/, T10, 'TIME 1/2 IS ', E20.7)
  WRITE(6, 31)T90
31 FORMAT(/, T10, 'TIME 90 PERCENT IS ', E20.7)
  GO TO 91
91 CONTINUE
STOP
END
Comments concerning method of least squares

1) Input
   a) ALF is an alphabetic or numerical statement which may be used to identify the data and is not to exceed 60 characters.
   b) N and AN are the number of independent or dependent variables in the data set. N is an integer number (a decimal number with no decimal point) and AN is a floating point number (a decimal number with a decimal point).
   c) P and TEST are integer numbers used to designate the type of operation the method of least squares is to follow.
      1) P=0 and TEST=+1 or -1 is for a linear relationship between the dependent and independent variables on a nonlogarithmic basis.
      2) P=+1 or -1 and TEST=+1 or -1 is for a linear relationship between the partition coefficient and hydrogen-ion concentration. For a weak acid P=-1 and for a weak base P=+1. TEST may be +1 or -1 in either case.
      3) P=0, +1, or -1 and TEST=0 is for a linear relationship between the log of the dependent variable and the independent variable.
   d) X and Y are the independent and dependent variables respectively and are entered as floating point numbers.
      1) X must be entered as pH rather than hydrogen-ion concentration when using the partition coefficient, hydrogen-ion relationship. The Y values must be entered as the actual partition coefficient, not the reciprocal, because reciprocals are taken internally.
      2) Y must be entered as a nonlogarithmic number when using the semilogarithmic operation because logs are taken internally.

2) Output
   a) The statistics of the least squares process, the slope, the y-intercept, the correlation coefficient, the X and Y values, the title which indicates which operation was followed and the ALF statement.
   b) When using the partition coefficient, hydrogen-ion operation, the output includes the true partition coefficient, the ionization constant and its corresponding pK value.
   c) When using the semilogarithmic operation, the output includes the time of 50% reaction, the time of 10% reaction (commonly called t1/2 and t90 respectively) and the degradation rate. These values are included if the user desires to enter kinetic data.
B. Computer Program for Calculation of Partition Coefficients in FORTRAN IV Language

DIMENSION CW(30), CO(30), X(30), K(30), ALF(15)
READ(5, 1) ALF
1 FORMAT(15A4)
READ(5, 2) N
2 FORMAT(I2)
READ(5, 3) CINT
3 FORMAT(F10.0)
DO 20 I = 1, N
READ(5, 4) CW(I)
4 FORMAT(F10.0)
20 CONTINUE
DO 30 I = 1, N
CO(I) = CINT - CW(I)
X(I) = (CO(I)) / (CW(I))
30 CONTINUE
J = 0
DO 40 I = 1, N
J = J + 1
K(I) = J
40 CONTINUE
WRITE(6, 10)
10 FORMAT(///, T10, 'CALCULATION OF PART. COEFF. FROM ABSORB. DATA')
WRITE(6, 11) ALF
11 FORMAT(///, T10, 15A4)
WRITE(6, 12)(K(I), X(I), I = 1, N)
12 FORMAT(T10, 'SAMPLE NO. ', I3, ' PART. COEFF. = ', E20.6)
STOP
END

a To be put on one line when typed into computer
Comments concerning partition coefficient calculation

1) Input
   a) ALF is an alphabetic or numerical statement which may be used to identify the data and is not to exceed 60 characters.
   b) N is the number of pieces in the data set and is entered as an integer number.
   c) CINT is the original concentration of solute prior to the partitioning process.
   d) CW is the concentration of the solute in the aqueous phase subsequent to the partitioning process.

2) Output
   a) The title of the program, the ALF statement, the calculated partition coefficient and its corresponding sample number

3) General Comment
   a) The program was designed to accept CINT and CW as absorbance units taken directly from a spectrophotometric assay. CINT and CW may be entered, however, in any convenient units such as normality or molarity.
   b) The basic stipulation concerning CINT and CW is that the concentration unit chosen be consistent for any data set.