Dielectric Constant Correlations with Solubility and Solubility Parameters

By WILLIAM G. GORMAN and GARY D. HALL

Correlations and lack of correlations of dielectric constants (DEC's) with solubility and solubility parameters are discussed. By restricting various solvent systems to solvents exhibiting similar bonding characteristics, such as by using members of homologous chemical series or by using solvent blends, essentially linear relationships were obtained for plots of log mole fraction of solute *versus* the DEC of the solvent or solvent system. Relationships of this type were demonstrated for (*a*) a nonpolar liquid in a series of polar polyethylene glycols, (*b*) a nonpolar liquid in a series of semipolar polypropylene glycols, (*c*) nonpolar liquids in blends of polar and semipolar solvents, (*d*) polar liquids in blends of nonpolar and semipolar solvents, and (*e*) a solid organic solute in blends of polar solvents. A ternary phase diagram for the system methyl salicylate/isopropanol/water is presented and resolved into a straight line by this procedure. This approach is presented as a means for the quantitative evaluation of solubility in homologous solvent series and solvent blends.

THE CONCEPT of solubility parameters as proposed by Hildebrand (1, 2) appears to have been accepted as one of the basic theories in the area of solubility. However, limitations such as the lack of readily available thermodynamic data, difficulty in readily determining such data, and the limited areas of applicability have prompted continued efforts to secure other solubility relationships.

Paruta *et al.* (3) have reported their observations on correlations of dielectric constants with solubility parameters. From a comparison of a number of solvents, they have proposed that a linear relationship exists between these two values which can be expressed by

$$\delta = 0.22 \, \epsilon + 7.5 \qquad \text{(Eq. 1)}$$

where δ is the solubility parameter, and ϵ is the dielectric constant (DEC). They also have indicated that the best correlation between solubility parameters and dielectric constants was obtained with those solvents which associate primarily through hydrogen bonding, whereas Hildebrand (4) has carefully noted that justification for the theory of solubility parameters rests upon the London dispersion forces and that its use for polar substances is somewhat questionable.

EXPERIMENTAL

If we assume, as claimed by Paruta *et al.*, that DEC's are directly related to solubility parameters, correlations of solubility with the DEC's would be expected to follow a pattern similar to those presented by Hildebrand. For example, Hildebrand (5) has shown that plots of log mole fraction of solute *versus* the square of the difference between the solubility parameters of the solute and of the solvent result in a linear relationship. Assuming that a direct relationship exists between DEC's and solubility parameters, substitution of DEC values for the solubility parameters in these plots would be expected to produce similar type plots. A graph of this type (Fig. 1) was prepared for the solubility of iodine in various nonpolar solvents utilizing data presented by Hildebrand (5) and dielectric constant values as reported in the literature (6, 7). The log mole fraction of solute was plotted *versus* the square of the difference between the DEC's of solute and solvent as well as against the square of the difference between the solubility parameters of solute and solvent in order that a direct comparison could be made of the two relationships. The excellent correlation between solubility and solubility parameters may be observed readily, compared to the rather poor correlation with dielectric constants.

Hildebrand (8) has also shown good correlation for the solubility of gases in various solvents by plotting log mole fraction of solute *versus* the solubility parameter of the solvent. A plot of this type was prepared (Fig. 2) for the solubility of dichlorodifluoromethane[1] in several solvents of varying polarity, again substituting dielectric constants for solubility parameters. The solubility data were obtained from (9, 10), while DEC values consisted of both those reported in the literature (6) and determined experimentally. All experimental DEC values were determined with a Sargent model V oscillometer (11) using the purest commercially available solvents which were dried over calcium chloride prior to use. Although a vague linear trend was apparent, the solubility correlation was again rather poor. This is believed due to a wide variation in the chemical nature of the solvents employed with a resultant variation in their molecular associations. It was noted, however, that those solvents of similar chemical types (*e.g.*, *n*-alkyl alcohols, polyethylene glycols, and polypropylene glycols) showed closer trends toward linearity. This suggested the possibility of demonstrating linear correlations between solubility and dielectric constants by restricting the solvents to similar chemical types, such as homologous series in which similar molecular associations would be contemplated.

This concept is illustrated in Fig. 3, where solu-

[1] Marketed as Freon 12 by E. I. du Pont de Nemours & Company, Wilmington, Del.
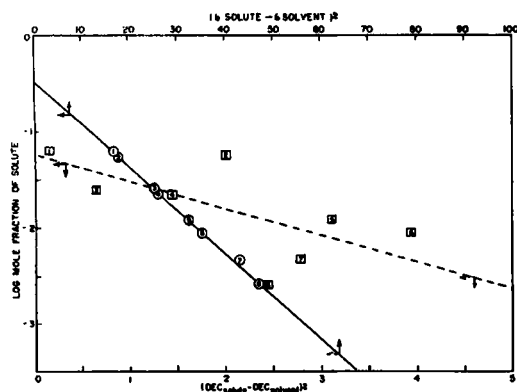
Fig. 1.—Correlation of the solubility of iodine with O, solubility parameters (δ) and □, dielectric constants (DEC's) of various solvents. Key: *1*, CHBr₃; *2*, CS₂; *3*, CHCl₃; *4*, TiCl₄; *5*, CCl₄; *6*, c-C₆H₁₂; *7*, SiCl₄; *8*, CCl₂F-CClF₂.
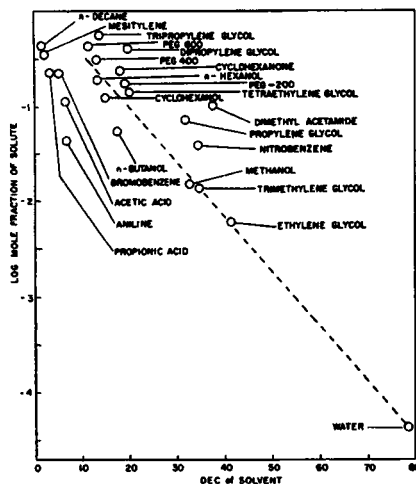

Fig. 2.—Correlations of the solubility of dichlorodifluoromethane with the dielectric constants (DEC's) of various solvents.

bility (10) of solutes dichlorotetrafluoroethane[2] and trichloromonofluoromethane[3] expressed as log mole fractions, were plotted *versus* the experimentally determined DEC's of two homologous series—polypropylene glycols and polyethylene glycols, respectively. In general, good agreement was observed in each case. In addition to showing solubility trends, this graph indicates the probable solubility of these solutes in other glycols of the series. For example, the solubility of dichlorotetrafluoroethane in polypropylene glycol 250 could be estimated from the graph.

If the above assumption is valid, even better agreement might be expected by further restriction of the molecular associations between solute and solvent. It was felt that this might be accomplished through the use of solvent blends. Previous investigations, such as the correlation of solubility with solubility parameters as reported by Chertkoff and Martin (12) and correlations with dielectric constants as reported by Paruta *et al.* (3) and Moore

(13, 14) have been based on solvent blends which qualitatively restrict the molecular associations in the systems.

In order to investigate systems of this type for possible correlations of solubility with the DEC of the solvent system, use was made of liquid ternary phase systems. These systems were selected as they present solubility data covering the full range of miscibility for the mixtures. Figure 4 illustrates such a diagram for the system methyl salicylate/isopropanol/water prepared using experimental data. The log mole fractions of methyl salicylate, calculated from the weight values in Fig. 4, were plotted in Fig. 5 against the dielectric constants of the corresponding water/isopropanol mixtures. Also included in Fig. 5 are the systems chloroform/acetone/water and carbon tetrachloride/ethanol/glycerol utilizing the solubility data of Bonner (15) and McDonald *et al.* (16), respectively. For each system the DEC's of the solvent blends were determined experimentally to compensate for deviation from the theoretical linear values. Linear relationships were realized over most of the solubility range. The possibility of wide correlation in such plots is illustrated, for example, by the curve for carbon tetrachloride/glycerol/ethanol which covers a solute concentration range of 3 to 97% by weight of carbon tetrachloride.
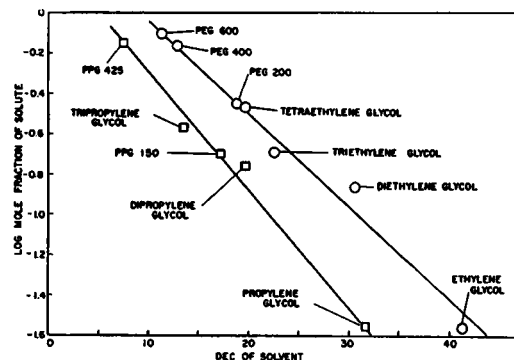
The solubilities of polar solutes in nonpolar-semi-

Fig. 3.—Solubility of chlorinated fluorinated hydrocarbons in homologous series of polyethylene glycols. Key: O, trichloromonofluoromethane; □, dichlorotetrafluoroethane.

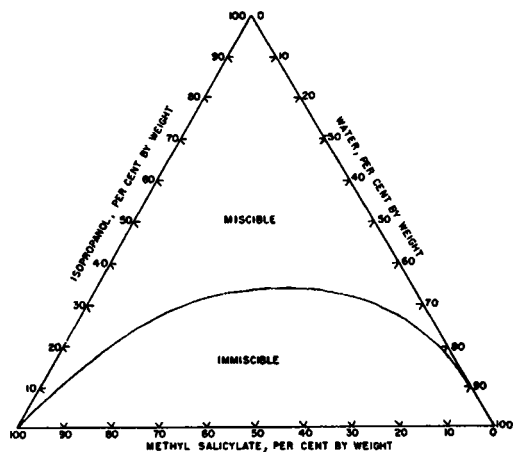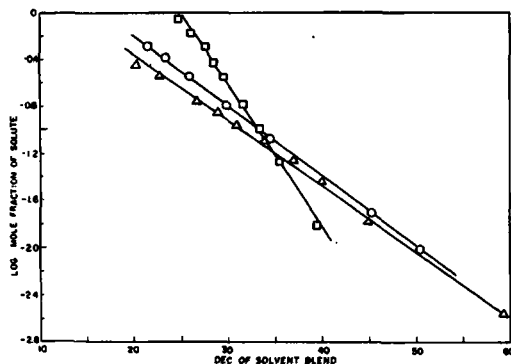Fig. 4.—Ternary phase diagram of the system methyl salicylate/isopropanol/water.

Fig. 5.—Solubility of various nonpolar solutes in polar solvent blends. Key: □, carbon tetrachloride in ethanol-glycerol; O, methyl salicylate in isopropanol-water; △, chloroform in acetone-water.

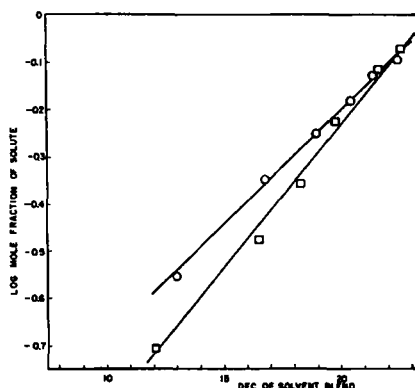Fig. 6.—Solubility of polar solute in nonpolar/semipolar solvent blends. Key: O, water in ethanol-dichlorodifluoromethane; □, water in hexylene glycol-carbon tetrachloride.

polar solvent blends are presented in Fig. 6. The solubility of water in mixtures of dichlorodifluoromethane/ethanol (10) and of carbon tetrachloride/hexylene glycol (17) was expressed again in terms of log mole fraction of solute *versus* DEC of the solvent blend. DEC values of the carbon tetrachloride/hexylene glycol mixtures were determined experimentally, while the values of dichlorodifluoromethane/ethanol mixtures were estimated because of their high volatility at room temperature. A straight line relationship was obtained over most of the miscibility range.

In view of the success of the above correlations for liquid systems, possible extension of the concept to include the solubility of solids was considered. Figure 7 illustrates the solubility of secobarbital in water/ethanol, water/glycerol, and water/propylene glycol mixtures based on the solubility data presented by Udani and Autian (18). Essentially linear relationships were again obtained for each blend. It will be noted, however, that the extent of solubility not only varies with the dielectric constant of each solvent mixture, but also varies from one solvent mixture to another, although the bonding characteristics of each blend are somewhat similar. This suggests that the solubility of a given solute is not only affected by the DEC of the solvent system, but also varies with the particular solvent system employed. Therefore, although the desired

solubility of a solute is achieved in a solvent blend at a given DEC, it does not indicate that the same degree of solubility can be expected for a different solvent blend even at the same DEC. In their study on the solubility of benzoic acid in mixed solvents, Chertkoff and Martin (12) also had similar variations when using solubility parameters.

SUMMARY AND CONCLUSIONS

Although a general linear relationship was reported to exist between dielectric constants (DEC's) and solubility parameters, serious discrepancies were noted when such correlations were extended to solubility data. However, by limiting the solvent system or systems to those exhibiting similar bonding characteristics, such as found in a chemical series, essentially linear relationships were demonstrated by plots of log mole fraction of solute *versus* the dielectric constant of the solvent system. Similar solvent restrictions by the use of solvent blends were investigated. Ternary phase diagrams of such systems were resolved into straight lines when plotted in this manner. Extension of this procedure to include solid solutes was also presented. A typical pharmaceutical solubility system consisting of secobarbital in a series of solvent blends was investigated. Although generally linear relationships were obtained, a common line for all the solvent blends was not observed, indicating that solubility varies with the solvent system employed as well as with its DEC.

It is felt that the above correlations are not strictly linear, but are essentially so over a large enough portion of the curve to make the relationship useful. Deviations from linearity may appear, for example, when extremely high concentrations of solute are present. For this reason the best approximations of solubility are obtained by interpolation between determined points rather than by extrapolation.

The solubility of polar solutes in less polar solvents (Fig. 6) resulted in lines with positive slopes while negative slopes were obtained for the solubility of nonpolar solutes in solvents of higher polarity (Figs. 5 and 7). It is, therefore, probable that a solute with polarity intermediate to that of the solvents would result in a curve which peaks at a certain DEC value. Systems such as those studied by Chertkoff and Martin may be in this category.
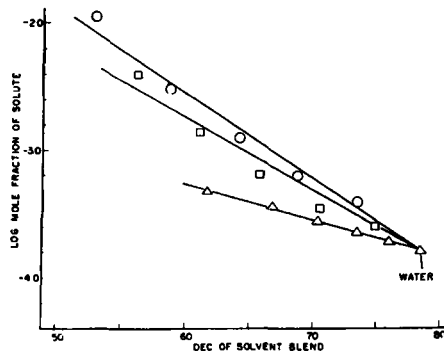
In the preparation of solubility graphs such as de-

Fig. 7.—Solubility of secobarbital in aqueous solvent blends. Key: O, secobarbital in ethanol-water; □, secobarbital in propylene glycol-water; △, secobarbital in glycerol-water.

scribed in this paper, the solute mole fractions can be calculated readily and the DEC's of the solvent systems can be determined experimentally, accurately and quickly. The resulting graphs may be used for estimating the quantitative solubility of a solute in a solvent of a homologous series, for estimating the quantitative solubility of a solute in a solvent blend, for estimating the composition of a solvent blend required to dissolve a given amount of solute, for evaluating the efficiency of various solvents as coupling agents or ingredients of solvent blends, and for predicting the probable solvency properties of related solvents.

Thus, the use of dielectric constants presents an intriguing approach for the determination and correlation of solubility phenomenon.

REFERENCES

(1) Hildebrand, J. H., and Scott, R. L., "The Solubility of Nonelectrolytes," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1950.
(2) Hildebrand, J. H., and Scott, R. L., "Regular Solutions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1962.
(3) Paruta, A., Sciarrone, B., and Lordi, N., THIS JOURNAL, 51, 704(1962).
(4) Hildebrand, J. H., and Scott, R. L., *op. cit.*, p. 170.
(5) Hildebrand, J. H., *Am. Scientist*, 51, 2(1963).
(6) Lange, N. A., "Handbook of Chemistry," 10th ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1961.
(7) DuPont's "Freon" Technical Bulletin B-2, E. I. du Pont de Nemours & Company, Wilmington, Del.
(8) Hildebrand, J. H., and Scott, R. L., *op. cit.*, p. 46.
(9) Mellan, I., "Industrial Solvents," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1950.
(10) DuPont's "Freon" Aerosol Report PA-25, E. I du Pont de Nemours & Company, Wilmington, Del.
(11) Sherrick, P. H., Dowe, G. A., Karr, R., and Ewen, E. F., "Manual of Chemical Oscillometry," E. H. Sargent & Co., Chicago, Ill., 1954.
(12) Chertkoff, M. J., and Martin, A. N., THIS JOURNAL, 49, 444(1960).
(13) Moore, W. E., *ibid.*, 47, 855(1958).
(14) *Ibid.*, 51, 391(1962).
(15) Bonner, W. D., *J. Phys. Chem.*, 14, 738(1910).
(16) McDonald, H. J., Kluender, A. F., and Lane, R. W., *J. Phys. Chem.*, 46, 946(1942).
(17) Mellan, I., "Polyhydric Alcohols," Spartan Books, Washington, D. C., 1962, p. 134.
(18) Udani, J. H., and Autian, J., THIS JOURNAL, 49, 376 (1960).

Analogs of Tetrahydrofolic Acid XI

Synthesis and Enzymic Evaluation of p-{[N-(2-Amino-4-hydroxy-6-methyl-5-pyrimidyl)carbamoyl methyl]amino}benzoyl-L-glutamic Acid

By B. R. BAKER and KRISHNA SACHDEV

Condensation of ethyl α-acetamidoacetoacetate (XII) with guanidine carbonate afforded 5-acetamido-2-amino-4-hydroxy-6-methylpyrimidine (X). Acid hydrolysis of X followed by reaction with bromoacetyl bromide gave 2-amino-5-(bromoacetamido)-4-hydroxy-6-methylpyrimidine (XI). Reaction of XI with aniline or p-aminobenzoyl-L-glutamic acid in dimethylsulfoxide resulted in formation of 2-amino-5-(anilinoacetamido)-4-hydroxy-6-methylpyrimidine (XIII) and the title compound (III), respectively. III was a poor inhibitor of both dihydrofolic reductase and 5,10-methylene-tetrahydrofolate dehydrogenase, showing inhibition of about the order obtained with p-aminobenzoyl-L-glutamic acid.

A PYRIMIDYL ANALOG (I) (2–4) of tetrahydrofolic acid has been found to bind to folic reductase five times better than the substrate folic acid (4), to bind to 5,10-methylene-tetrahydrofolate dehydrogenase about one-thirtieth as well as the substrate (1), and to bind to thymidylate synthetase one-sixth as well as the substrate (5); dl-5,10-methylene-tetrahydrofolate was the substrate for the latter two enzymes. In contrast, the analog (II) is only one-eightieth as effective as I as an inhibitor of folic reductase (1), but II binds somewhat better to 5,10-methylene-tetrahydrofolate dehydrogenase than does I (1). It was concluded that the basic p-amino group of

I, R = —CH$_2$CH$_2$CH$_2$—
II, R = —CH$_2$CH$_2$CO—
III, R = —NHCOCH$_2$—
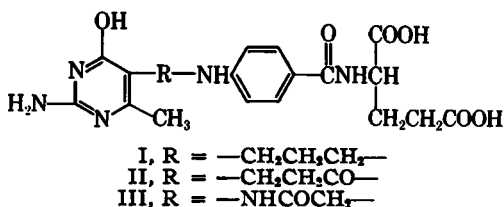
the p-aminobenzoyl-L-glutamate moiety was probably one of the essential groups for binding to folic reductase, but not to 5,10-methylene-tetrahydrofolate dehydrogenase. It was therefore of interest to synthesize III for enzymic evaluation; III has a different bridge between the pyrimidyl and aminobenzoyl moieties, but still retains the basicity of the latter moiety.

A key intermediate in the synthesis of III (see Scheme I) was 2,5-diamino-4-hydroxy-6-methylpyrimidine (IX), a compound described only once in the literature (6). Bromination of 2-amino-4-