Solubility of Benzoic Acid and Related Compounds in a Series of *n*-Alkanols

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The solubility of benzoic acid and esters of *p*-hydroxybenzoic acid were determined in a series of *n*-alkanols, and Hildebrand's solubility parameters were assigned to these compounds. The experimental results were compared with the theoretical solubility calculated from the Hildebrand equation for regular solutions. Fair agreement was found for methyl and ethyl *p*-hydroxybenzoic acid, but propyl and butyl *p*-hydroxybenzoic acid and benzoic acid agreed less favorably. Hildebrand's equation appears most applicable to solvents whose solubility parameters are quite similar to those of the solutes; it is strictly applicable to nonpolar rather than polar systems.

THERE IS scarcely anything more important for a practicing chemist than a knowledge of solubilities, but unfortunately he finds it more difficult to predict the solubility of a substance in a given solvent than to predict almost any other property. An attempt to remove this difficulty was made by Hildebrand and Scott (1) who developed equations restricted to nonpolar solvents. Negoro, *et al.* (2), have applied the Hildebrand treatment to pharmaceutical solutions. Chertkoff and Martin (3) showed that Hildebrand's equation for regular solutions is applicable to some polar systems where the polarity of solvent and solute are not significantly different from one another. This observation together with Burrell's (4, 5) series of articles entitled "solubility parameters" and Mortimer's (6, 7) adaptation of Hildebrand's idea of internal pressure encouraged further investigations of the Hildebrand-Scott equation in polar solvents.

Therefore, this investigation was undertaken to determine the solubility of benzoic acid and the esters of *p*-hydroxybenzoic acid in a series of *n*-alkanols at 25° and to compare these with the solubility predicted by Hildebrand's equation.

A regular solution, one in which heat is absorbed on mixing but no entropy change occurs, was assumed to apply for the solutions studied. A modified form of Hildebrand and Scott's (1) equation was used and applied to the systems studied. The equation is

$$\log x_2 = \frac{-\Delta H^f_m \ (T_m - T)}{4.575 \ (T_m T)}$$
$$- \frac{V_2}{4.575 \ T} \ (\delta_1 - \delta_2)^2 \ \phi_1{}^2 \quad \text{(Eq. 1)}$$

where x_2 is the mole fraction solubility of solute, ΔH^f_m is the heat of fusion of the solute at its melting point, T_m is the absolute melting temperature of the solute, T is the absolute temperature of the solution studied, δ_1 and δ_2 are the solubility parameters of solvent and solute, respectively, ϕ_1 is the volume fraction of solvent, and V_2 is the molar volume of the supercooled solute.

The solubility parameter is defined by Hildebrand and Scott (8) as the square root of the internal pressure of the substance. It is a measure of polarity so that the more polar a substance, the greater is its solubility parameter. The solubility parameters of the solvents are known and are listed in Table I. The parameters, the heats of fusion, and the molar volumes of the solutes must be determined before Hildebrand's equation can be applied.

EXPERIMENTAL

Reagents.—Normal propyl alcohol, Fisher certified reagent grade (b.p. 96.9 to 97.2°); *n*-amyl alcohol, Fisher certified reagent grade (b.p. 136.2 to 138.1°); and *n*-butyl alcohol, Fisher certified reagent grade (b.p. 116.6 to 117.8°) were used without further purification. Normal hexyl alcohol, Eastman Organic Chemicals (b.p. 156.5 to 157.5°) and *n*-octyl alcohol, Eastman Organic Chemicals (b.p. 194–195°) were redistilled.

A purified grade of Parasepts (esters of *p*-hydroxybenzoic acid), methyl, ethyl, propyl, and butyl obtained from Heyden Newport Chemical Corp. were recrystallized from chloroform until a sharp melting point was obtained. Benzoic acid, Fisher reagent, was also recrystallized from chloroform.

Procedure.—A slight excess of solid was added to approximately 40 ml. of a solvent contained in a screw-top bottle. A closure was made with aluminum foil, the top fixed tightly over the foil, and the

TABLE I.—SOLUBILITY PARAMETERS OF SOLVENTS AT 25° C.[a]

Solvent	Parameter
n-Propanol	11.9
n-Butanol	11.4
n-Pentanol	10.9
n-Hexanol	10.7
n-Octanol	10.3

[a] Taken from (9).

whole sealed with several turns of electrical tape. The bottles were shaken in a constant temperature bath (Wilkens-Anderson Lo-Temp bath) at the desired temperature ±0.05° for 48 hours. The equilibrated solutions were then removed, filtered, and samples taken.

The analysis was done gravimetrically and spectrophotometrically on a Beckman model DU spectrophotometer at a predetermined wavelength.

The densities of the saturated solutions were determined with calibrated pycnometers.

RESULTS

An attempt was first made to assign Hildebrand's "solubility parameter" to the compounds studied. Since the solubility parameters (δ values) of the solvents were known, a plot of mole fraction solubility *versus* δ value of the solvents showed a maximum solubility which is assumed to correspond approximately to the δ parameter of the solute (see Figs. 1 and 2). The fact that the δ value of the solvent at maximum solubility yields the δ value of the solute has been discussed in an earlier paper (3). The parameters for the solutes ranged from 10.9 to 11.3 at 25°. The value of 11.2 determined for benzoic acid by this method is in agreement with the value, 11.3, reported by Chertkoff and Martin (3). The δ values are in doubt in most cases by about ±0.1. The δ value for butyl parasept is particularly difficult to establish because of the absence of a sharp maximum, as seen in Fig. 2. Other techniques must be used, one of which will be presented in a later report, for determining satisfactory δ values when the solubility data fails to produce a sharply defined maximum.

The heats of fusion for the esters of p-hydroxybenzoic acid were determined using Walden's method (10). He observed that $\Delta H_f = T_m K$, where ΔH_f is the heat of fusion, T_m is the melting point of the solid, and K is a constant. Walden found that K had a value of about 13.5 for many organic compounds. Mortimer (11), however, showed how K varied, depending upon the class of compounds. With this in mind, the heats of fusion for the esters of p-hydroxybenzoic acid were determined from a K obtained from the heat of fusion of benzoic acid (12). The constant K was determined as: ΔH_f of benzoic

Fig. 2.—Determination of the solubility parameter of butyl p-hydroxybenzoate at 25°C.

acid $= 4302$ cal./mole, T_m of benzoic acid $= 395.16$, and $K = 4302/395.16 = 10.89$. If one assumes that the entropy of fusion and subsequently the crystal packing for each compound used were similar, then the heats of fusion can be calculated using the constant, $K = 10.89$. These were then labeled "apparent" heats of fusion and can be found in Table II.

TABLE II.—APPARENT HEATS OF FUSION

Ester	M.p., °C.	$\Delta H_f'$
Methyl	126.5	4352
Ethyl	116.5	4243
Propyl	96.5	4026
Butyl	70.0	3737

To substantiate the use of $K = 10.89$, other compounds with similar structures were sought, *i.e.*, compounds with approximately the same substituent groups, corresponding in size, shape, and electronegativity to the hydroxyl group in the *para* position of benzoic acid. The only compound found for comparison was p-aminobenzoic acid. Using the K calculated, the heat of fusion for this compound was determined to be 5027 cal./mole. This value was in agreement with that reported in the literature (13).

Since the molar volume of the supercooled solid required in Hildebrand's equation is extremely difficult to obtain, it became necessary to use the "apparent molar volumes." These values were obtained (14) from knowledge of the densities and weights of solution, the density of solvent, and from the weight of solute. The apparent molar volume of benzoic acid thus determined was 101 ml./mole. This value was in agreement with the molar volume of the supercooled benzoic acid as reported in the literature (3). Accordingly, the apparent molar volumes of the parasepts should be in fair agreement with the molar volume. The apparent molar volumes of the compounds are reported in Table III.

TABLE III.—APPARENT MOLAR VOLUMES AT 25° C. (ml./mole)

Compd.	$V_2{}^a$
Methyl p-hydroxybenzoate	121
Ethyl p-hydroxybenzoate	140
Propyl p-hydroxybenzoate	158
Butyl p-hydroxybenzoate	176
Benzoic acid	101

a The values reported are the average of several values obtained from the various solvents used.

Knowing the heats of fusion, the solubility parameter, and the molar volumes of the solids, one can now use Hildebrand's equation to calculate the predicted solubilities. Equation 1 was used for all calculations; the results appear in Table IV.
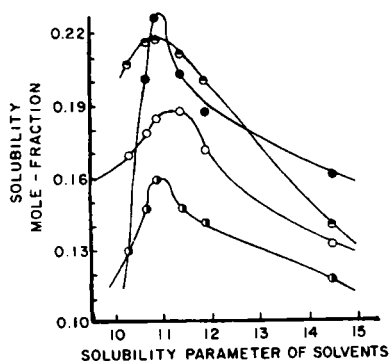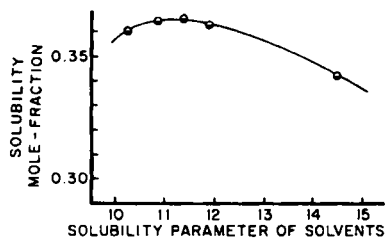
Fig. 1.—Determination of the solubility parameter of benzoic acid and esters of p-hydroxybenzoic acid at 25°C. Key: ◑, methyl p-hydroxybenzoate; ○, ethyl p-hydroxybenzoate; ◕, propyl p-hydroxybenzoate; ◔, butyl p-hydroxybenzoate; ●, benzoic acid.

TABLE IV.—SOLUBILITY DATA AT 25° C.

Solvent	Density	Gm./Gm. s.s.	Mole Fraction Observed	Calcd.
		Methyl *p*-Hydroxybenzoate		
n-Propanol	0.9221	0.2951	0.141	0.140
n-Butanol	0.8885	0.2622	0.147	0.152
n-Pentanol	0.8891	0.2458	0.159	0.155
n-Hexanol	0.8811	0.2052	0.147	0.153
n-Octanol	0.8672	0.1473	0.129	0.143
		Ethyl *p*-Hydroxybenzoate		
n-Propanol	0.9079	0.3626	0.171	0.175
n-Butanol	0.9071	0.3398	0.187	0.185
n-Pentanol	0.8961	0.2987	0.184	0.184
n-Hexanol	0.8888	0.2604	0.178	0.179
n-Octanol	0.8780	0.2065	0.170	0.162
		Propyl *p*-Hydroxybenzoate		
n-Propanol	0.9204	0.4363	0.205	0.244
n-Butanol	0.9146	0.3940	0.211	0.263
n-Pentanol	0.9059	0.3623	0.217	0.269
n-Hexanol	0.8992	0.3265	0.216	0.267
n-Octanol	0.8869	0.2655	0.207	0.255
		Butyl *p*-Hydroxybenzoate		
n-Propanol	0.9724	0.6466	0.361	0.423
n-Butanol	0.9592	0.6005	0.365	0.434
n-Pentanol	0.9527	0.5579	0.364	0.437
n-Hexanol	0.9467	0.5292	0.371	0.435
n-Octanol	0.9291	0.4565	0.360	0.418
		Benzoic Acid		
n-Propanol	0.8986	0.3182	0.187	0.159
n-Butanol	0.8963	0.2960	0.203	0.167
n-Pentanol	0.9007	0.2885	0.226	0.166
n-Hexanol	0.8786	0.2311	0.201	0.163
n-Octanol	0.8708	0.1219	0.129	0.150

The volume fraction of the solvent, ϕ_1, was generally assumed to be 1 as a first approximation. Then using the x_2 calculated, a new ϕ_1 was obtained. This process of iteration was used until x_2 became constant, as described by Chertkoff and Martin (3).

DISCUSSION

The results in Table IV show good agreement between the observed solubility and that calculated from Hildebrand's equation for the methyl and ethyl esters of *p*-hydroxybenzoic acid, but the agreement for the propyl and butyl esters of *p*-hydroxybenzoic acid and benzoic acid were not so good. It must be noted that the calculation involves the use of one point from the experimental curves (the maximum) for obtaining the δ value of the drug. Therefore, the theoretical or predicted solubilities are not completely independent of the experimental values, except in the case of benzoic acid.

The Hildebrand equation also may be used for predicting the solubility of a compound in mixtures of solvents where the δ values of the two solvents are not too different from one another and the δ value of the mixed solvent system is not too far removed from the value of the solute. This can be shown from the data obtained for the solubility of benzoic acid (δ = 11.2) in a solvent mixture of *n*-octanol (δ = 10.3) and *n*-propanol (δ = 11.9). The parameter of the solvent mixture is calculated to be 11.1. If we assume the molar volumes of the solvents to be additive, then the molar volume of the mixture will be 117 ml./mole. Substituting the necessary values in Eq. 1, the predicted mole fraction solu-

bility for benzoic acid is 0.168. The observed mole fraction solubility was 0.164. Therefore, the per cent deviation from the predicted value is 2.4.

If we try to predict the solubility of the same compound in solvents with δ values on either side of that of the solute and with values of the individual solvents differing widely from each other, then we encounter greater differences between predicted and observed solubilities. For example, suppose we wish to predict the solubility of benzoic acid in a mixture of *n*-hexane (δ = 7.3) and ethanol (δ = 13.0[1]) whose value is 11.3. The predicted solubility for this system is 0.228, while the observed solubility is 0.170.[2] The per cent deviation from the predicted value now becomes 25.5.

The results reported here further substantiate the findings of Chertkoff and Martin (3) with respect to predicting the solubility of drugs in various solvents. The Hildebrand δ value seems to be a satisfactory parameter for estimating drug solubilities, and when the δ values of a large number of drugs and solvents are eventually determined and tabulated, presumably it will be a simple matter to choose a satisfactory solvent or solvent mixture for maximum solubility of a given drug. However, the methods and principles suggested here must be checked for other classes of drugs, and a table of values for these compounds must be calculated or determined experimentally. Experimental determination of the solubility in a series of solvents (the alcohols used here should prove satisfactory as hydrogen-bonded sol-
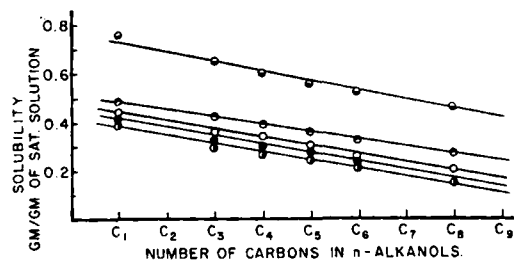
Fig. 3.—Solubility of benzoic acid and esters of *p*-hydroxybenzoic acid at 25°C. in a series of *n*-alkanols.

vents for a large number of drugs) and a plot of the data shown in Figs. 1 and 2 may provide values of satisfactory accuracy. It will be rare that the δ value of a drug can be calculated from the Hildebrand equation since energies of vaporization and molar volumes are not ordinarily available.

When mole fraction solubility was plotted against solvent δ values, a peak was observed in the curves. However, a linear relationship existed between the solubility (in grams of solute per gram of saturated solution) and the number of carbon atoms existing in the solvent. This seems to follow a relationship analogous to Traube's rule (15, 16) as observed from Fig. 3. Besides being linear, the lines for the various esters of *p*-hydroxybenzoic acid appear to be nearly parallel to one another, which leads one to believe that the forces involved in dissolution of the various esters in a series of *n*-alkanols are more or less constant from one solute to the next.

CONCLUSION

The Hildebrand equation appears most applicable to hydrogen-bonding solvents whose solubility parameters are quite similar to those of the solutes; in such cases, it will give a fair estimate of the drug solubility even though the system is a polar one. Optimum solubility may be obtained by using a mixture of solvents having a composite δ value equal to that of the solute, but when using a mixed solvent system, the observed solubility will, in general, be somewhat less than that predicted by the Hildebrand equation.

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Factors Influencing the Properties of Films Used for Tablet Coating I

Effects of Plasticizers on the Water Vapor Transmission of Cellulose Acetate Phthalate Films

By LEON LACHMAN and ARGE DRUBULIS

The water vapor transmission of thin plasticized cellulose acetate phthalate films was studied at 90, 76, and 52 per cent relative humidities. The effect of the plasticizers, triacetin, diacetin, diethyl phthalate, dimethyl phthalate, Citroflex-2, Citroflex-A2, and dibutyl tartrate on this property was determined. In general, a decrease followed by an increase in water vapor transmission was observed with increasing plasticizer concentration. The concentration at which the water vapor transmission is at a minimum appears to be the same for all the plasticizers investigated.

THE USE OF polymeric substances, such as cellulose acetate phthalate, for coating tablets and particles has been widely accepted in recent years. The reports that have appeared in the pharmaceutical literature during this time

have dealt primarily with the development of polymeric substances as film formers (1–6), the formulation of film forming agents for use in tablet and particle coating (7–12), the development of test procedures for film coated tablets (13–15), and the improvement of processes for the application of these agents onto pharmaceutical dosage forms (16–20).

Although work in the above areas has been