

were -3.24 integrator units for niacinamide and +4.70 integrator units for niacin. These data indicate that the procedure is amenable to use of a single-point standard.

The accuracy and precision of the proposed chromatographic procedure were investigated by analysis of laboratory-prepared samples (Table II), and results were compared with those of the USP procedure (4). In each case, the precision of the HPLC procedure was greater than that of the currently official procedure, and this result may be attributed to the less complicated sample workup required by the former. However, the two methods compared quite favorably in terms of the determination of the combined quantity of niacin and niacinamide.

Data regarding the suitability of the proposed procedure in the analysis of commercial multivitamin preparations are presented in Table III. Standard deviations of the HPLC procedure were again lower. Furthermore, niacinamide content, as determined by the proposed procedure, was less in each case. However, when the sum of niacinamide and niacin content was compared with that determined by the USP procedure, results were again comparable. Niacin was found in each sample examined, in quantities as high as 14.2% of the labeled niacinamide concentration.

This type of analysis is very attractive in terms of analysis time, since a trained technician can readily process 10 samples/hr with a minimum of active involvement. Column stability under these conditions of minimum sample preparation was a subject of concern initially. However, over 300 preparations have been processed with no change in the chromatographic characteristics of the system. This stability may be attributed in part to the small quantities of sample injected into the chromatographic system and in part to the daily flushing recommended by the column supplier.

In summary, the reversed-phase, ion-pairing approach to the simultaneous analysis of niacin and niacinamide appears to result in an accurate and precise procedure. These features, in combination with the simple sample preparation and short analysis time, should make the procedure attractive to pharmaceutical analysts. The ap-

plication of this approach to the other water-soluble vitamins is currently under investigation.

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# Solubility Profiles and Thermodynamics of Parabens in Aliphatic Alcohols

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**Abstract** □ The solubility of a series of compounds was determined in a wide polarity spectrum of normal aliphatic alcohols over a limited temperature range. The solutes chosen were the methyl through *n*-butyl *p*-hydroxybenzoates, several of these being useful preservatives. Solubility profiles were determined for these compounds, and the effect of temperature upon their solubility behavior was investigated. The solubility of the solutes is expressed in several concentration notations; mole fraction plots showed a variable twin peak array as a function of the dielectric constant for the solutes studied. Since heats of fusion were available and data were generated as a function of temperature, thermodynamic parameters for these systems could be calculated. The re-

lationship of these parameters to multiple solubility peak array is discussed.

**Keyphrases** □ Parabens, alkyl—solubility and thermodynamics in aliphatic alcohols, effect of temperature □ Solubility—alkylparabens in aliphatic alcohols, effect of temperature □ Thermodynamics—alkylparabens in aliphatic alcohols, effect of temperature □ Alcohols, aliphatic—solvents for series of alkylparabens, effect of temperature □ Structure—activity relationships—alkylparabens, solubility and thermodynamics in aliphatic alcohols □ Antifungal agents—alkylparabens, solubility and thermodynamics in aliphatic alcohols

The effect of temperature upon the solubility of four normal alkyl *p*-hydroxybenzoates (parabens) was determined over a wide polarity spectrum of aliphatic alcohols from methanol to 1-decanol. The effect of decreasing polarity with an increase in size for the first four *n*-alkyl members for this ester series was also considered.

Previous solubility work (1-5) considered several of these compounds at ambient temperatures. It was believed

that the extension of this work in pure solvents over a temperature range and polarity range would be instructive. Additionally, since several of these solutes gave multiple peak solubility isotherms, it was useful to determine if solubility was linear as a function of temperature. The temperature range used was 25-40° in four steps; the polarity range *via* dielectric constants was from 32 for methanol to eight for 1-decanol at 25°, utilizing seven in-

Table I—Experimentally Determined Methylparaben Solubility Values

Solvent	25°		30°		35°		40°	
	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g
Methanol	0.121	395.0	0.139	433.0	0.162	479.0	0.178	508.0
Ethanol	0.147	360.0	0.156	379.0	0.174	410.0	0.201	454.0
1-Propanol	0.138	295.0	0.152	309.0	0.180	355.0	0.199	383.0
1-Butanol	0.146	262.0	0.154	272.0	0.172	298.0	0.191	326.0
1-Hexanol	0.155	205.0	0.166	212.0	0.186	253.0	0.205	262.0
1-Octanol	0.111	147.0	0.151	172.0	0.166	188.0	0.172	195.0
1-Decanol	0.088	88.0	0.109	103.0	0.128	122.0	0.144	139.0

Table II—Experimentally Determined Ethylparaben Solubility Values

Solvent	25°		30°		35°		40°	
	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g
Methanol	0.135	452.0	0.157	490.0	0.185	541.0	0.208	576.0
Ethanol	0.165	412.0	0.184	449.0	0.218	501.0	0.220	505.0
1-Propanol	0.176	362.0	0.188	388.0	0.216	429.0	0.229	447.0
1-Butanol	0.178	340.0	0.183	335.0	0.210	373.0	0.234	407.0
1-Hexanol	0.189	260.0	0.195	282.0	0.212	305.0	0.228	325.0
1-Octanol	0.156	207.0	0.183	222.0	0.204	246.0	0.226	271.0
1-Decanol	0.115	148.0	0.175	182.0	0.192	200.0	0.215	223.0

dividual solvents. The Hildebrand solubility parameter (6) was applied previously (2, 3) in a study of benzoic acid and alkyl esters of *p*-hydroxybenzoic acid; these solutes also were studied in binary mixtures (4, 5, 7) consisting of dioxane–water and ethanol–water.

A rather striking dichotomy appeared in contemporary work on solubility behavior (8–14). The excellent theoretical approach undertaken by Hildebrand and coworkers (15–22), referred to as the “solubility parameter” theory, certainly has much to offer in terms of the interpretation of solubility phenomena. Extension of this theory to systems of some pharmaceutical interest was undertaken by other investigators (23, 24). Work over the last decade has shown that a dielectric constant (dielectric requirement) approach has some validity. The Hildebrand approach only accounts for a monotonic isotherm or a single solubility maximum. This approach assumes a neat and smooth variation of molecular interactions such that an analytical solution can be formulated to approximate real behavior. A symmetrical isotherm can be expected from this theory and is quite reasonable, because the summed interactions are at a mathematical condition of constant differences.

Hildebrand, continuing elegant work in this area (18), was instrumental in shifting the thrust of past work from a dielectric constant approach to a more fundamental and theoretical thermodynamic approach. It now appears that the multiple solubility peak arrays observed for various solutes qualitatively resides in the nature of the systems and quantitatively resides in the values or magnitudes of the thermodynamic functions resulting from each individual system.

Therefore, this study deals with the thermodynamic parameters for various solutes in a series of normal aliphatic alcohols. Since heats of fusion were available (16), a theoretical ideal mole fraction solubility could be determined and compared with the actual mole fraction solubility. In this manner, the activity coefficients could be determined. The solubility of these solutes as a function of temperature would allow for the experimental deter-

mination of enthalpies and entropies of solution. A thermodynamic scheme for the interpretation of solubility behavior is presented. Excess free energy functions were calculated and utilized as a basis for multipeak solubility isotherms.

## EXPERIMENTAL

**Equipment**—The following were used: a melting-point apparatus<sup>1</sup>, a pH meter<sup>2</sup>, a chemical oscillator<sup>3</sup>, a spectrophotometer<sup>4</sup>, a temperature controller<sup>5</sup>, and a refractometer<sup>6</sup>.

**Materials**—The chemicals utilized were ethyl *p*-hydroxybenzoate (ethylparaben) and propyl *p*-hydroxybenzoate<sup>7</sup> (propylparaben); methanol<sup>8</sup>, spectrograde; butyl *p*-hydroxybenzoate<sup>9</sup> (butylparaben); 1-propanol<sup>10</sup>; ethanol<sup>11</sup>, absolute reagent quality; 1-butanol<sup>12</sup>, analytical reagent; 1-hexanol and 1-octanol<sup>13</sup>; 1-decanol<sup>14</sup>; certified acetone<sup>15</sup>, 99 mole % pure; certified benzene<sup>16</sup>, 99 mole % pure; hydrochloric acid<sup>17</sup>, certified pure reagent; and potassium chloride<sup>18</sup> USP. The purity of the alcohols was established by refractive indexes and dielectric constant measurements. Melting points were determined and were within 1° of literature values.

**Method**—Solubility was determined by the method described previously (1). The solubility of each solute was determined at least eight times for each solvent, and average values were taken. The experimental variation in solubility was about 2.5% in replicate samples for these solutes.

## RESULTS AND DISCUSSION

The solubility of a series of solutes was determined in a chemically related series of solvents at various temperatures over 25–40° (Tables I–IV).

<sup>1</sup> Hoover 6406, A. H. Thomas Co., Philadelphia, Pa.

<sup>2</sup> Model 7401, Leeds and Northrup, Philadelphia, Pa.

<sup>3</sup> Model 5, E. H. Sargent and Co., Chicago, Ill.

<sup>4</sup> Cary model 16, Cary Instruments, Monrovia, Calif.

<sup>5</sup> Temptrol 150 tempunit, Precision Scientific Co., Chicago, Ill.

<sup>6</sup> Abbe 3L, Bausch & Lomb Optical Co., Rochester, N.Y.

<sup>7</sup> Lots EX 665 and PX 1910, respectively, Matheson, Coleman and Bell.

<sup>8</sup> Lot VMN, Mallinckrodt Chemical Works.

<sup>9</sup> U.S. Industrial Chemicals Co.

<sup>10</sup> Lot 35592, J. T. Baker Chemical Co.

<sup>11</sup> J. T. Baker Chemical Co.

<sup>12</sup> Lot TDY, Mallinckrodt Chemical Works.

<sup>13</sup> Lots 020251 and 22, respectively, Mallinckrodt Chemical Works.

<sup>14</sup> Lot 16, Matheson, Coleman and Bell.

<sup>15</sup> Lot 792902, Fisher Scientific Co.

<sup>16</sup> Lot 793869, Fisher Scientific Co.

<sup>17</sup> Lot E108262, Allied Chemical, General Chemical Division.

<sup>18</sup> Lot 8678, J. T. Baker Chemical Co.

**Table III—Experimentally Determined Propylparaben Solubility Values**

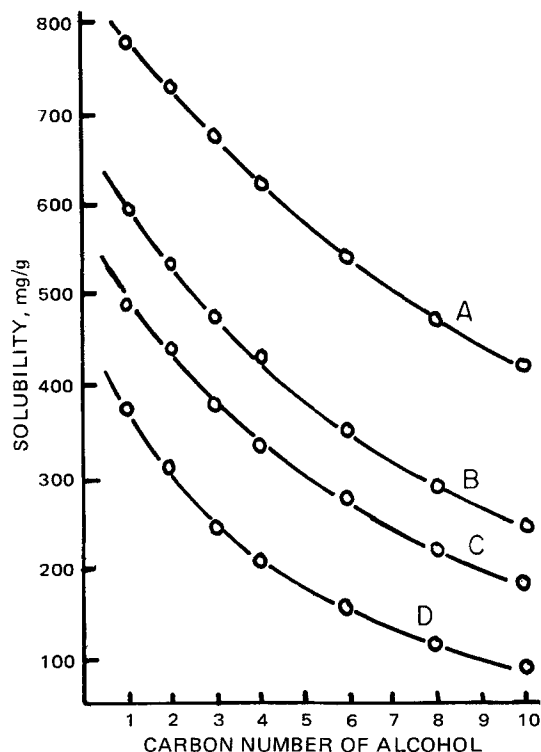
Solvent	25°		30°		35°		40°	
	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g
Methanol	0.172	540.0	0.207	595.0	0.240	639.0	0.276	682.0
Ethanol	0.197	490.0	0.228	535.0	0.296	621.0	0.298	624.0
1-Propanol	0.198	436.0	0.236	478.0	0.273	527.0	0.298	557.0
1-Butanol	0.206	394.0	0.245	441.0	0.278	484.0	0.316	528.0
1-Hexanol	0.210	326.0	0.256	362.0	0.285	412.0	0.303	434.0
1-Octanol	0.200	266.0	0.228	290.0	0.271	339.0	0.298	370.0
1-Decanol	0.171	217.0	0.225	248.0	0.264	290.0	0.285	312.0

**Table IV—Experimentally Determined Butylparaben Solubility Values**

Solvent	25°		30°		35°		40°	
	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g	Mole Fraction	mg/g
Methanol	0.336	755.0	0.369	779.0	0.457	834.0	0.491	854.0
Ethanol	0.360	703.0	0.395	734.0	0.437	766.0	0.500	807.0
1-Propanol	0.355	647.0	0.402	682.0	0.458	729.0	0.502	763.0
1-Butanol	0.364	601.0	0.388	625.0	0.439	672.0	0.501	725.0
1-Hexanol	0.369	526.0	0.395	552.0	0.444	603.0	0.507	661.0
1-Octanol	0.331	457.0	0.379	476.0	0.440	539.0	0.497	595.0
1-Decanol	0.293	392.0	0.371	421.0	0.427	477.0	0.491	542.0

In Fig. 1, the solubility of the solutes is plotted as milligrams per gram of solution *versus* the carbon number in the aliphatic alcohol solvent series used. Typical nonlinear curves were generated in all cases; for each solute, the highest solubility occurred in methanol and decreased in value to 1-decanol. The order of solubility was the butyl ester > propyl ester > ethyl ester > methyl ester.

In Fig. 2, the solubility of the methyl *p*-hydroxybenzoate (methylparaben) as a typical solute is plotted in milligrams per gram of solution as a function of the temperature. The solubility increased linearly over the experimental temperature range utilized.



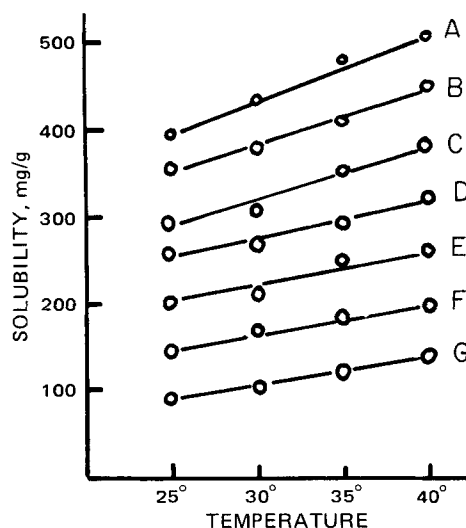
**Figure 1**—Solubility of the noted substances in milligrams per gram of solution as a function of the carbon number of the alcohol used. Curve A = butyl *p*-hydroxybenzoate, curve B = propyl *p*-hydroxybenzoate, curve C = ethyl *p*-hydroxybenzoate, and curve D = methyl *p*-hydroxybenzoate.

In Fig. 3, the solubility of methylparaben in milligrams per gram of solution is plotted as a function of the carbon number of the alcohol solvent at each of four temperatures. Nonlinear curves were observed with the typical incremental response of increased solubility with temperature.

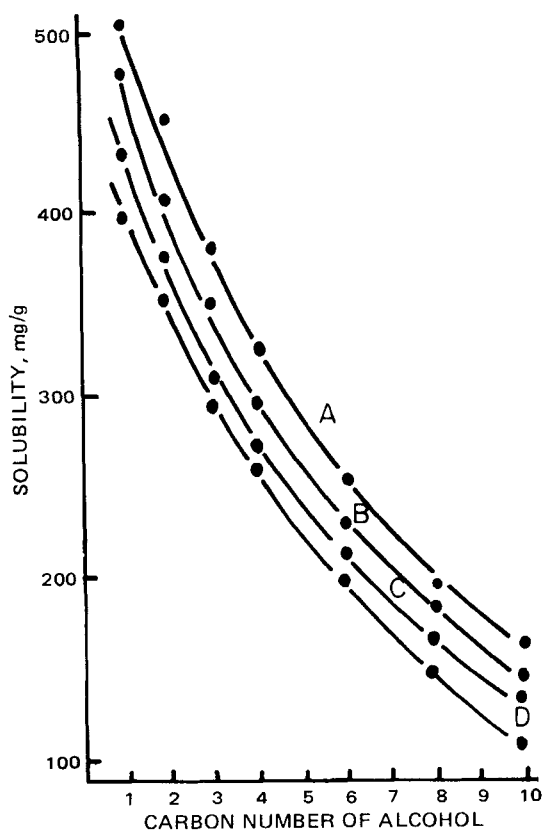
In Fig. 4, the mole fraction solubility is plotted as a function of the dielectric constant of the solvents. For each compound, a twin peak array is observed possessing values of dielectric constants of about 10–13 and 19–22, as previously reported (1).

In Fig. 5, the mole fraction solubility profiles of methylparaben are plotted as a function of the dielectric constant of the alcohols at various temperatures. The dielectric constants vary and decrease over the 15° range of temperature used; however, these variations are about two to three units lower at 40° than at 25°. These solubility profiles are fairly consistent over this temperature range; each profile indicates a binary peak array, with the dielectric constant of maximum solubility showing fair consistency. The first maxima are found at a dielectric constant range of about 12–13.5, whereas the second maxima are found at 21–24.

It is felt that where the solubility maxima occur, these magnitudes of

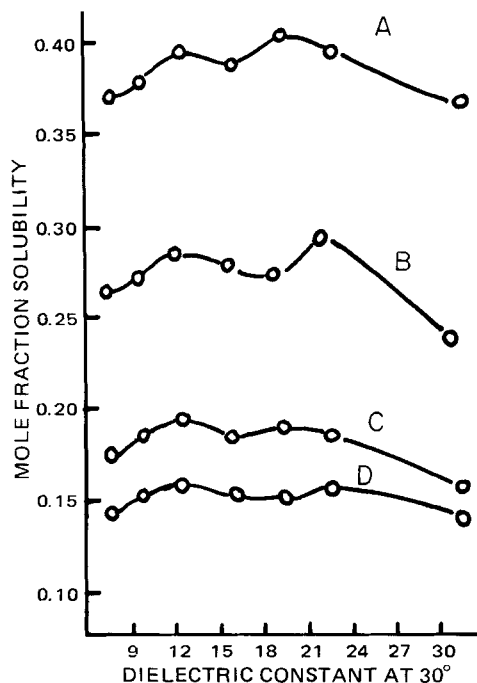


**Figure 2**—Solubility of methyl *p*-hydroxybenzoate in the noted alcohol solvents as a function of temperature. Curve A = methanol, curve B = ethanol, curve C = 1-propanol, curve D = 1-butanol, curve E = 1-hexanol, curve F = 1-octanol, and curve G = 1-decanol.

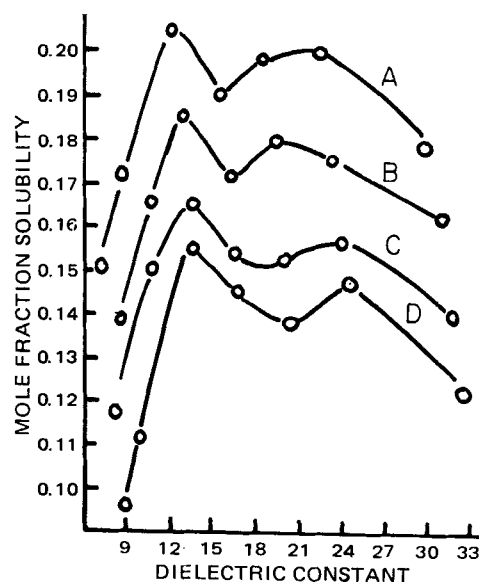


**Figure 3**—Solubility of methyl *p*-hydroxybenzoate at various temperatures as a function of the carbon number of the alcohol solvents used. Curve A = 40°, curve B = 35°, curve C = 30°, and curve D = 25°.

solubility are approaching ideal solubility values such that the excess free energy values at the maxima are approaching the ideal free energy values. It thus becomes desirable to differentiate "ideal" and "nonideal" solubility with a view of obtaining thermodynamic elements from literature



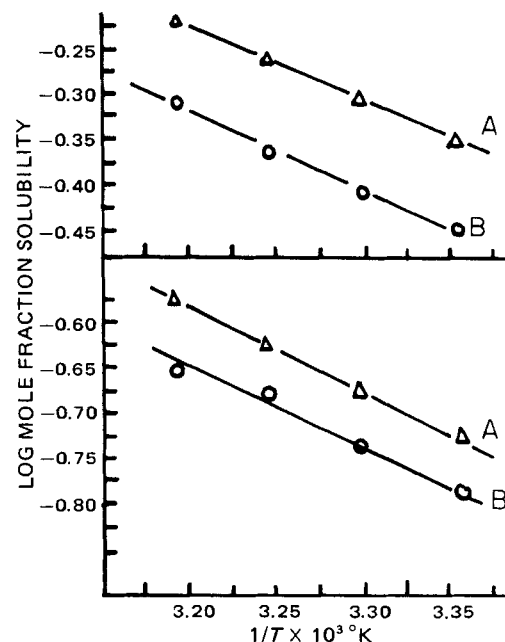
**Figure 4**—Mole fraction solubility of the noted solutes as a function of the dielectric constants at 30° for the alcohol solvents used. Curve A = butyl *p*-hydroxybenzoate, curve B = propyl *p*-hydroxybenzoate, curve C = ethyl *p*-hydroxybenzoate, and curve D = methyl *p*-hydroxybenzoate.



**Figure 5**—Mole fraction solubility of methyl *p*-hydroxybenzoate as a function of the dielectric constants of the alcohol solvents used at four temperatures. Curve A = 40°, curve B = 35°, curve C = 30°, and curve D = 25°.

and experimental data. Thus, ideal solubility can be calculated from  $\Delta F_f$  values once the enthalpy of fusion and entropy of fusion are known. These values can then be compared with those obtained experimentally. Thus, the ratio of the ideal solubility and the actual solubility can be used to determine activity coefficients for both the solute and the solvent. It is well known that the actual solubility is always less than ideal solubility. (The summation of two positive factors leads to a larger negative logarithm or a smaller  $X_2'$  value.) Thus, other determined elements, ideal solubility ( $X_2'$ ) and activity coefficients ( $\gamma_1$  and  $\gamma_2$ ), have been added to the existing list of thermodynamic elements:  $\Delta H_f$ ,  $\Delta H_s$ ,  $\Delta S_f$ , and  $\Delta S_s$ .

In summary, then, solubility can be expressed as a function of the energy change in the following manner:  $F_E$  (excess) =  $F_A$  (actual) -  $F_I$  (ideal) (1); therefore, as the excess energy approaches zero, the nonideal or actual solubility approaches the ideal solubility.



**Figure 6**—Mole fraction solubility for ethyl *p*-hydroxybenzoate (lower figure) and butyl *p*-hydroxybenzoate (upper figure) as a function of reciprocal temperature ( $^{\circ}K$ ). The ideal curves ( $\Delta$ , A) are from heat of fusion data, and the actual curves ( $\circ$ , B) are from experimental data.

**Table V—Literature and Calculated Thermodynamic Elements of the Solutes**

Compound	$\Delta H_f$ , cal/mole <sup>a</sup>	$T_M^a$ , °K	$\Delta S_f$ , cal/deg <sup>b</sup>	$\Delta F_I$ , cal/mole <sup>c</sup>	Ideal Mole Fraction Solubility <sup>d</sup>			
					25°	30°	35°	40°
Methylparaben	4352	398	11.04	1034	0.157	0.178	0.200	0.224
Ethylparaben	4243	388	11.02	926	0.189	0.213	0.239	0.267
Propylparaben	4026	369	10.9	716	0.272	0.304	0.339	0.376
Butylparaben	3737	341	11.02	415	0.450	0.500	0.553	0.610

<sup>a</sup>From Ref. 16. <sup>b</sup>From plot of log ideal mole fraction solubility versus 1/T. <sup>c</sup> $\Delta F$  (ideal) =  $\Delta H_f - T \Delta S_f$ . <sup>d</sup>Calculated values.

**Table VI—Calculated Solute Activity Coefficients**

Temperature	Methanol	Ethanol	1-Propanol	1-Butanol	1-Hexanol	1-Octanol	1-Decanol
Methylparaben							
25°	1.298	1.068	1.138	1.075	1.013	1.415	1.715
30°	1.284	1.141	1.175	1.156	1.072	1.190	1.633
35°	1.238	1.148	1.109	1.167	1.078	1.165	1.562
40°	1.257	1.113	1.126	1.172	1.212	1.305	1.555
Ethylparaben							
25°	1.400	1.146	1.074	1.062	1.000	1.212	1.644
30°	1.361	1.156	1.132	1.163	1.094	1.164	1.221
35°	1.290	1.110	1.106	1.140	1.126	1.173	1.244
40°	1.286	1.212	1.168	1.141	1.170	1.183	1.244
Propylparaben							
25°	1.582	1.381	1.374	1.321	1.295	1.360	1.591
30°	1.466	1.336	1.288	1.242	1.291	1.336	1.353
35°	1.414	1.149	1.241	1.218	1.191	1.253	1.203
40°	1.361	1.262	1.262	1.192	1.240	1.263	1.321
Butylparaben							
25°	1.339	1.250	1.268	1.235	1.220	1.360	1.536
30°	1.354	1.265	1.243	1.290	1.268	1.321	1.347
35°	1.209	1.266	1.208	1.260	1.245	1.256	1.297
40°	1.244	1.220	1.215	1.217	1.204	1.229	1.243

**Table VII—Calculated Solvent Activity Coefficients ( $\gamma_1$ )**

Temperature	Methanol	Ethanol	1-Propanol	1-Butanol	1-Hexanol	1-Octanol	1-Decanol
Methylparaben							
25°	0.959	0.988	0.978	0.987	0.998	0.948	0.930
30°	0.966	0.986	0.981	0.984	0.998	0.980	0.922
35°	0.954	0.969	0.976	0.966	0.982	0.959	0.917
40°	0.945	0.972	0.969	0.959	0.964	0.937	0.906
Ethylparaben							
25°	0.938	0.972	0.984	0.987	1.000	0.961	0.917
30°	0.933	0.965	0.970	0.964	0.977	0.963	0.942
35°	0.934	0.973	0.971	0.963	0.966	0.956	0.942
40°	0.925	0.940	0.950	0.957	0.950	0.947	0.934
Propylparaben							
25°	0.879	0.907	0.908	0.917	0.922	0.910	0.878
30°	0.878	0.901	0.911	0.922	0.911	0.901	0.898
35°	0.870	0.939	0.910	0.916	0.924	0.919	0.898
40°	0.862	0.889	0.889	0.912	0.896	0.889	0.872
Butylparaben							
25°	0.813	0.844	0.837	0.850	0.856	0.807	0.764
30°	0.793	0.827	0.837	0.817	0.826	0.805	0.795
35°	0.824	0.794	0.825	0.797	0.804	0.799	0.780
40°	0.766	0.780	0.784	0.782	0.790	0.775	0.766

Table V presents literature values for the heat of fusion,  $\Delta H_f$ , which were applied to calculate ideal mole fraction solubility values. The entropy of fusion,  $\Delta S_f$ , presented can be obtained graphically from a plot of  $\log X_2^i$  versus  $1/T$ . The ideal free energy change and the ideal mole fraction solubilities are also given for the four temperatures.

In Fig. 6, the ideal and actual mole fraction solubility for ethyl- and butylparaben are plotted versus reciprocal temperature. The ideal solubility, as expected, is greater than the actual solubility.

The rational activity coefficients for the solutes in a particular solvent with respect to temperature were calculated in the usual manner (Table VI). The rational activity coefficient for the solvent is given in like manner in Table VII. The error in the activity coefficients due to solubility variation is about  $\pm 0.005$ .

Tables VIII–XI give the thermodynamic elements that were determined graphically or by calculation. The legend for Table VIII applies to all subsequent tables. Inspection of the magnitude of excess free energy

Table VIII—Thermodynamic Elements Determined Graphically or by Calculation for Methylparaben when  $\Delta H_f = 4352^a$ ,  $\Delta S_f = 11.04^b$ , and  $\Delta F_I = 1034^c$

Solvent	$\Delta H_s$ , cal/mole <sup>d</sup>	$\Delta H_m$ , cal/mole <sup>e</sup>	$\Delta S_s$ , cal/deg <sup>d</sup>	$\Delta S_m$ , cal/deg <sup>e</sup>	$\Delta F_A$ , cal/mole <sup>f</sup>	$\Delta F_E$ , cal/mole <sup>g</sup>
Methanol	+4878	+526	12.17	+1.1	+1189	+155
Ethanol	+3894	-458	9.21	-1.8	+1102	+68
1-Propanol	+4714	+362	11.85	+0.8	+1122	+88
1-Butanol	+3384	-968	7.49	-3.5	+1114	+80
1-Hexanol	+2666	-1686	5.19	-5.8	+1093	+59
1-Octanol	+5244	+892	13.36	+2.3	+1194	+160
1-Decanol	+3066	-1566	5.39	-5.6	+1152	+118

<sup>a</sup> From Ref. 16. <sup>b</sup> Obtained from a plot of log ideal mole fraction solubility versus  $1/T$ . <sup>c</sup>  $\Delta F_I = \Delta H_f - T \Delta S_f$ . <sup>d</sup> Obtained from a plot of log mole fraction solubility versus  $1/T$ . <sup>e</sup>  $\Delta H_m = \Delta H_s - \Delta H_f$ ;  $\Delta S_m = \Delta S_s - \Delta S_f$ . <sup>f</sup>  $\Delta F_A = \Delta H_s - T \Delta S_s$ . <sup>g</sup>  $\Delta F_E = \Delta F_A - \Delta F_I$ .

Table IX—Thermodynamic Elements Determined Graphically or by Calculation for Ethylparaben when  $\Delta H_f = 4243^a$ ,  $\Delta S_f = 11.02^b$ , and  $\Delta F_I = 926^c$

Solvent	$\Delta H_s$ , cal/mole <sup>d</sup>	$\Delta H_m$ , cal/mole <sup>e</sup>	$\Delta S_s$ , cal/deg <sup>d</sup>	$\Delta S_m$ , cal/deg <sup>e</sup>	$\Delta F_A$ , cal/mole <sup>f</sup>	$\Delta F_E$ , cal/mole <sup>g</sup>
Methanol	+5420	+1177	14.20	+3.2	+1115	+189
Ethanol	+3856	-387	9.38	-1.7	+993	+67
1-Propanol	+3428	-815	8.03	-3.0	+1012	+86
1-Butanol	+3545	-698	8.41	-2.6	+995	+69
1-Hexanol	+2415	-1828	4.76	-6.2	+972	+46
1-Octanol	+4514	+271	11.48	+0.5	+1034	+108
1-Decanol	+7346	+3103	20.52	+9.5	+1125	+199

<sup>a</sup> From Ref. 16. <sup>b</sup> Obtained from a plot of log ideal mole fraction solubility versus  $1/T$ . <sup>c</sup>  $\Delta F_I = \Delta H_f - T \Delta S_f$ . <sup>d</sup> Obtained from a plot of log mole fraction solubility versus  $1/T$ . <sup>e</sup>  $\Delta H_m = \Delta H_s - \Delta H_f$ ;  $\Delta S_m = \Delta S_s - \Delta S_f$ . <sup>f</sup>  $\Delta F_A = \Delta H_s - T \Delta S_s$ . <sup>g</sup>  $\Delta F_E = \Delta F_A - \Delta F_I$ .

Table X—Thermodynamic Elements Determined Graphically or by Calculation for Propylparaben when  $\Delta H_f = 4026^a$ ,  $\Delta S_f = 10.86^b$ , and  $\Delta F_I = 716^c$

Solvent	$\Delta H_s$ , cal/mole <sup>d</sup>	$\Delta H_m$ , cal/mole <sup>e</sup>	$\Delta S_s$ , cal/deg <sup>d</sup>	$\Delta S_m$ , cal/deg <sup>e</sup>	$\Delta F_A$ , cal/mole <sup>f</sup>	$\Delta F_E$ , cal/mole <sup>g</sup>
Methanol	+5823	+1797	16.0	+5.1	+958	+242
Ethanol	+5592	+1566	15.6	+5.7	+879	+163
1-Propanol	+5102	+1076	13.9	+3.0	+880	+164
1-Butanol	+5232	+1206	14.4	+3.5	+931	+215
1-Hexanol	+4798	+772	13.0	+2.1	+852	+136
1-Octanol	+5078	+1052	13.8	+2.9	+905	+189
1-Decanol	+6295	+2269	17.7	+6.6	+930	+214

<sup>a</sup> From Ref. 16. <sup>b</sup> Obtained from a plot of log ideal mole fraction solubility versus  $1/T$ . <sup>c</sup>  $\Delta F_I = \Delta H_f - T \Delta S_f$ . <sup>d</sup> Obtained from a plot of log mole fraction solubility versus  $1/T$ . <sup>e</sup>  $\Delta H_m = \Delta H_s - \Delta H_f$ ;  $\Delta S_m = \Delta S_s - \Delta S_f$ . <sup>f</sup>  $\Delta F_A = \Delta H_s - T \Delta S_s$ . <sup>g</sup>  $\Delta F_E = \Delta F_I - \Delta F_A$ .

Table XI—Thermodynamic Elements Determined Graphically or by Calculation for Butylparaben when  $\Delta H_f = 3737^a$ ,  $\Delta S_f = 11.02^b$ , and  $\Delta F_I = 415^c$

Solvent	$\Delta H_s$ , cal/mole <sup>d</sup>	$\Delta H_m$ , cal/mole <sup>e</sup>	$\Delta S_s$ , cal/deg <sup>d</sup>	$\Delta S_m$ , cal/deg <sup>e</sup>	$\Delta F_A$ , cal/mole <sup>f</sup>	$\Delta F_E$ , cal/mole <sup>g</sup>
Methanol	+5005	+1268	14.6	+3.6	579	+164
Ethanol	+4020	+283	11.4	+0.4	548	+138
1-Propanol	+4347	+610	12.5	+1.5	554	+133
1-Butanol	+4017	+280	11.4	+0.4	555	+140
1-Hexanol	+3959	+222	11.3	+0.3	546	+131
1-Octanol	+5077	+1340	14.8	+3.8	581	+166
1-Decanol	+6266	+2529	18.6	+7.6	616	+201

<sup>a</sup> From Ref. 16. <sup>b</sup> Obtained from a plot of log ideal mole fraction solubility versus  $1/T$ . <sup>c</sup>  $\Delta F_I = \Delta H_f - T \Delta S_f$ . <sup>d</sup> Obtained from a plot of log mole fraction solubility versus  $1/T$ . <sup>e</sup>  $\Delta H_m = \Delta H_s - \Delta H_f$ ;  $\Delta S_m = \Delta S_s - \Delta S_f$ . <sup>f</sup>  $\Delta F_A = \Delta H_s - T \Delta S_s$ . <sup>g</sup>  $\Delta F_E = \Delta F_I - \Delta F_A$ .

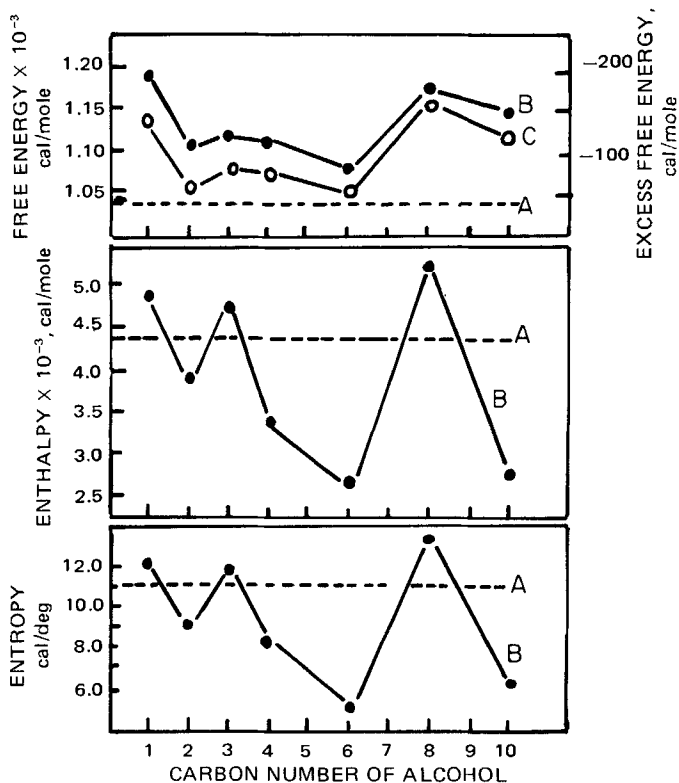
of mixing (11) or  $\Delta F_E$  for each solute shows that the values decrease to minima (approaching ideality) in the ethanol or propanol and hexanol solvents. This finding, of course, supports the concept of a multiple peak array from a thermodynamic point of view. Furthermore, heats of mixing changes were compensated for by entropy gain such that the free energy was reflective of a twin peak solubility array.

The twin peak array observed in the solubility spectrum shown in Fig. 5 is seen throughout the thermodynamic picture of the investigated compounds.

In Fig. 7, the entropy and corresponding enthalpy for methylparaben are plotted versus the carbon number of the alcohol solvent. The paral-

lelism can easily be seen between these elements, leading to the excess free energy minimizing at carbon numbers 2 and 6. Any alteration in  $\Delta H_s$  is also accompanied by a corresponding change in  $\Delta S_s$  such that free energy remains consistent for any given system. Therefore, any increase in  $\Delta H_s$  would be associated with an increase in  $\Delta S_s$  (tending toward greater disorder or randomness).

Since  $\Delta F_I$  is a fixed value for any solute regardless of the solvent, any system in which  $\Delta F_A$  approaches  $\Delta F_I$  will approach the ideal state. Hence, for any particular solute, there may be many combinations of values for  $\Delta H_s$  and  $\Delta S_s$ , depending upon the solvent employed, in which  $\Delta F_A$  may approximate  $\Delta F_I$ . In this study, the solutes dissolved in either



**Figure 7**—Plot for methyl *p*-hydroxybenzoate illustrating the relationship for the entropy (curve A = entropy of fusion and curve B = entropy of solution), enthalpy (curve A = enthalpy of fusion and curve B = enthalpy of solution), and free energy [curve A = ideal free energy, curve B = actual free energy, and curve C = excess free energy (right-hand coordinates)]. Data were taken from Table VIII.

ethanol or 1-propanol and 1-hexanol have their  $\Delta F_A$  values approximating  $\Delta F_I$ . This can be shown by the free energy determinations. However, since the excess free energy terms are based on mole fraction solubility, the emerging trends can be initially perceived by mere inspection of these data.

It has been established that the excess free energy is usually a small value, encompassing a range of 20–200 calories/mole. Since excess free energy is a function of both the mole fraction, which usually ranges from 0.1 to 0.3 for the solute, and the logarithm of the activity coefficient, which usually ranges from  $-0.75$  to  $-0.9$  for the solute and from 0.01 to 0.1 for the solvent, the small numbers obtained are not unexpected.

Thus, total inspection of the thermodynamic functions  $\Delta H_s$ ,  $\Delta S_s$ ,  $\Delta H_m$ , and  $\Delta F_E$  truly reveals a trend for a multipeak solubility array. Any solute that exhibits maxima in various solvents may be approaching ideal solubility at the individual maximum in the particular solubility profile.

The dielectric requirement of one peak is now felt to be related to the thermodynamics of the total system; hence, a multipeak system should signify that ideal solubility is being approximated in those particular solvent–solute systems.

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