Solubility of Parabens in Alcohols

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Abstract ☐ The solubilities of methyl, ethyl, propyl, and butyl parabens have been determined in a series of normal alcohols. This pure solvent scan indicated a dielectric requirement of about 14 for the subject compounds. Another dielectric requirement may be postulated to exist at a value of about 30. There is seen to be good parallelism in the magnitude of solubility of these compounds in various 1-alkanols indicating interactions of a similar nature in the dissolution process.

Keyphrases ☐ Parabens solubility—alcohols ☐ 1-Alkanols, carbon number—paraben solubility ☐ Dielectric constants, 1-alkanols—paraben solubility ☐ UV spectrophotometry—analysis

The parabens, while important preservatives in pharmaceutical systems, are also a simple, homologous series of aromatic esters. Previous studies of these *n*-alkyl derivatives have shown rather minor changes in solubility in syrup vehicles (1) and a solubility parameter value of about 11 in pure alcohols (2). This latter study reported by Restaino and Martin was essentially a pure solvent scan in which the solubility of the parabens was determined in a series of pure alcohols. The solubility parameter values for these compounds showed good consistency, with virtually no difference or discrimination as a function of the polarity of this series of solutes. This study broadens the spectrum of the solvents used, including methanol, ethanol, and decanol in addition to those used previously (2). The data that were obtained were treated from a dielectric constant approach which predicts one solubility maximum at a dielectric constant value of about 14 and predicts another maximum (DR = dielectric requirement) at a value of about 30. Treatment of Martin's data (2) by a dielectric constant approach partially substantiates the validity of this method.

EXPERIMENTAL

Reagents—The reagents used were methanol and 1-propanol[1]; 1-pentanol, 1-hexanol, and 1-octanol[2]; 1-butanol[3]; 1-decanol[4]; and ethanol sealed absolute.[5] The parabens used were methyl paraben, ethyl paraben, propyl paraben, and butyl paraben.[6]

Procedure—Solubilities were determined by either a spectrophotometric or gravimetric determination. A constant-temperature bath set at 25 ± 0.1° containing screw-capped bottles with the appropriate paraben in excess and solvent were rotated for 24 hr. Samples were withdrawn through a pledget of glass wool into a pipet, which was wiped clean and allowed to drain into either a tared weighing bottle or a volumetric flask. Samples were dried to
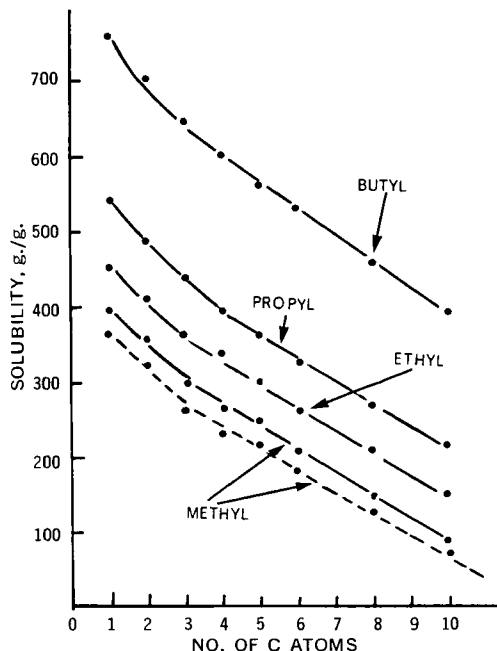

Figure 1—*A plot of the solubility of the parabens noted in mg./g. of saturated solution at 25° versus the number of carbon atoms in the n-alcohols studied. Dashed line, as above for methyl paraben in the mg./ml. convention.*

constant weight in an oven or/and appropriately diluted for spectrophotometric analysis at 255 mμ. Solubilities were determined from final dried weights or from absorbance and previously ascertained Beers' law plots determined on a spectrophotometer.[7] Each paraben was determined in each alcohol at least in triplicate and average results are reported. Densities were determined by weighing the withdrawn sample previous to drying.

RESULTS AND DISCUSSION

In Fig. 1, the solubilities of the parabens noted expressed in mg./g. of solution as a function of the number of carbon atoms of the solvent is shown. Linearity is seen to exist over a certain portion of this figure from about 1-butanol to 1-decanol for the 1-alkanols and the slopes of these lines, *i.e.*, the change in solubility in mg./g. of solution per carbon atom is compiled in Table I. There is also seen to be parallelism for these solubility curves for all the alcohols studied. The solubility profile for methyl paraben is also shown in the mg./ml. convention as a dashed line. These results are reported and plotted in the mg./g. of solution convention in order to compare these results directly with those given by Martin (2). In all cases, the results in this study correlate very well with the values given previously. The average difference in solubility in mg./g. of solution per methylene group is given in Table II considering the methyl paraben to be defined as the base line. The results are plotted in Fig. 2, where the cumulative values are plotted *versus* the number of carbon atoms. It can be seen that the butyl derivative very strongly deviates in a positive sense from linearity. The solubilities of these compounds could be viewed in another manner. In Fig. 3,

[1] Fisher certified, Fisher Scientific Co.
[2] Baker analyzed, J. T. Baker Chemical Co., Phillipsburg, N. J.
[3] Eastman-Kodak No. 50, Eastman-Kodak, Rochester, N. Y.
[4] No. 5189, Matheson, Coleman and Bell, East Rutherford, N. J.
[5] U. S. Industrial Chemical Corp.
[6] Obtained from Matheson, Coleman and Bell.

[7] Cary model 16.

Table I—Summary of Rate of Change of Solubility for Parabens in mg./g. of Solution per Carbon Atom

Paraben Derivative	d(concn.)/C atom
Methyl	30
Ethyl	32
Propyl	30
Butyl	33

the solubility is plotted as the n-alkyl chain of the parabens for each straight-chain alcohol. It can easily be seen that the expected parallelism between each alcohol solvent exists. It is further interesting to note that the solubility is in the order butyl, propyl, ethyl, and methyl in decreasing magnitude in all cases.

In Table III, the experimentally determined values for the solubility of each paraben expressed as mg./g. of solution and mole fraction is given, as well as the density for each system.

In Fig. 4, the solubility expressed as mole fraction for each paraben is plotted *versus* the dielectric constant of the 1-alkanols used in this study. It would seem that a twin-peak array or two dielectric requirements is approximately evidenced for these parabens, having ranges of values of about 13-16 and about 25-32. This latter value is suggested since the mole fraction solubility values are rather

Table II—Summary of Average Difference in Solubility in mg./g. of Solution per Methylene Group for Parabens Studied

Paraben Derivative	mg./g.
Methyl	—
Ethyl	60
Propyl	70
Butyl	200

close to one another for these alcohols and a peak is not absolutely discernable. The first peak at a value of about 14 can be easily seen. The value of the dielectric requirement has been shown previously (3) to have a dependence upon the concentration notation used in plotting the data. In order to view this in a clearer fashion, the solubility of the parabens in mg./g. have been plotted *versus* the dielectric constants of the alcohol solvents in Fig. 5. In this figure, a clearly defined break occurs at a dielectric constant value of 14, and then the solubility is seen to tail off approximately asymptotically to a dielectric constant value of 32. In this study and previous ones (3, 4) a w/v and w/w convention for representing solubility is preferred.
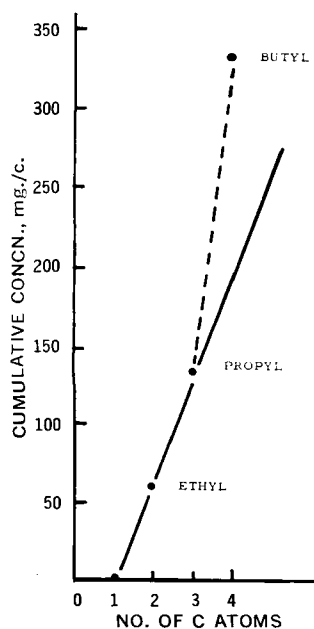

Figure 2—*A plot of the cumulative difference for the solubility of the parabens defining methyl paraben as the base line.*
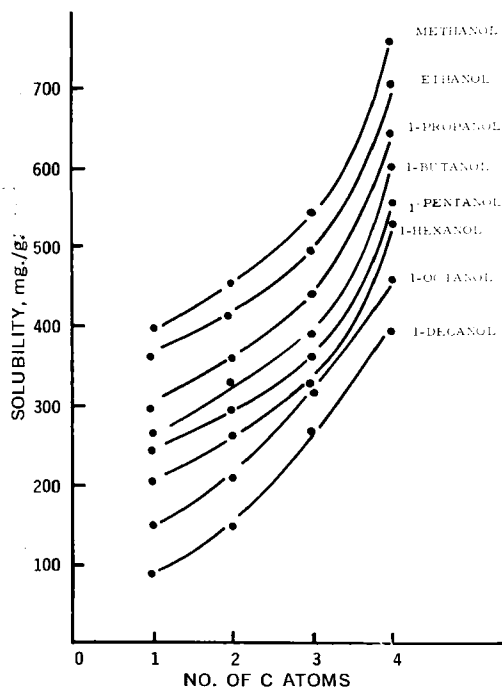

Figure 3—*A plot of the solubility of the parabens at 25° in mg./g. of solution as a function of the number of carbons in each alkyl paraben for each alcohol studied.*

Table III—Summary of the Solubility of the Subject Parabens in n-Alcohols at 25° Expressed in mg./g. and Mole Fraction

| Normal Alcohol	Density	Solubility mg./g.	Solubility m.f.
Methyl Paraben			
Methanol	0.9166	395	0.121
Ethanol	0.8970	360	0.147
Propanol	0.8881	295	0.138
Butanol	0.8894	262	0.146
Pentanol	0.8863	246	0.149
Hexanol	0.8819	205	0.155
Octanol	0.8712	147	0.111
Decanol	0.8658	90	0.088
Ethyl Paraben			
Methanol	0.9256	452	0.135
Ethanol	0.9098	412	0.165
Propanol	0.9081	362	0.176
Butanol	0.9082	340	0.178
Pentanol	0.8911	299	0.185
Hexanol	0.8860	260	0.189
Octanol	0.8791	207	0.156
Decanol	0.8702	148	0.115
Propyl Paraben			
Methanol	0.9318	540	0.172
Ethanol	0.9076	490	0.197
Propanol	0.9112	436	0.198
Butanol	0.9066	394	0.206
Pentanol	0.8994	362	0.212
Hexanol	0.8981	326	0.210
Octanol	0.8809	266	0.200
Decanol	0.8732	217	0.171
Butyl Paraben			
Methanol	0.9896	755	0.336
Ethanol	0.9730	703	0.360
Propanol	0.9719	647	0.355
Butanol	0.9612	601	0.364
Pentanol	0.9547	558	0.363
Hexanol	0.9413	526	0.369
Octanol	0.9346	457	0.331
Decanol	0.9313	392	0.293
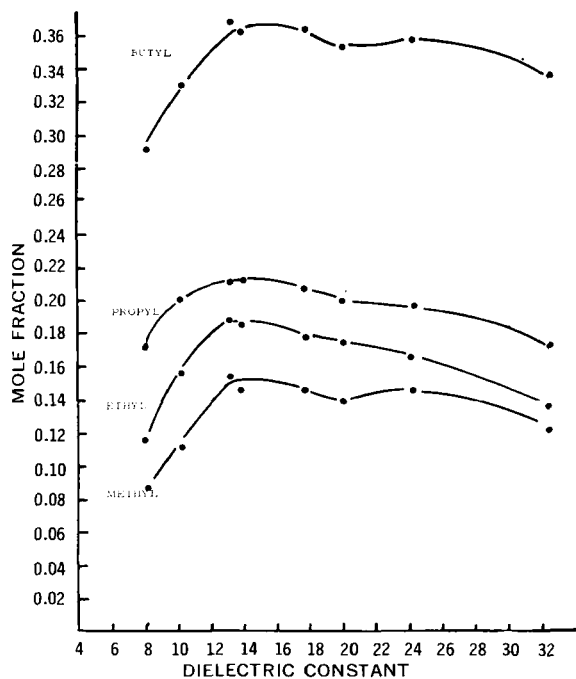
Figure 4—*A plot of the solubility of the parabens noted in the mole fraction notation plotted as a function of the dielectric constant of the individual alcohol solvents.*

If water were considered to be the next solvent of higher polarity in this 1-alkanol series, then the peaking for these parabens or solubility maximum would be about 30 since the water solubility is significantly lower. The insert in Fig. 5 illustrates this point. It should be pointed out that this spectrum of alcohols would seem to predict the existence of at least two dielectric requirements or overlapping cosolvency distribution curves whereas the solubility parameter theory would predict only one maximum.

In Fig. 6, the solubility data in g./g. of solution for the parabens in 1-alkanols from Martin's paper have been plotted *versus* the dielectric constants for these solvents. It is apparent that a shoulder exists at a dielectric constant value of 14. Calculation of a solubility parameter value from previously presented equation (5) gives a value
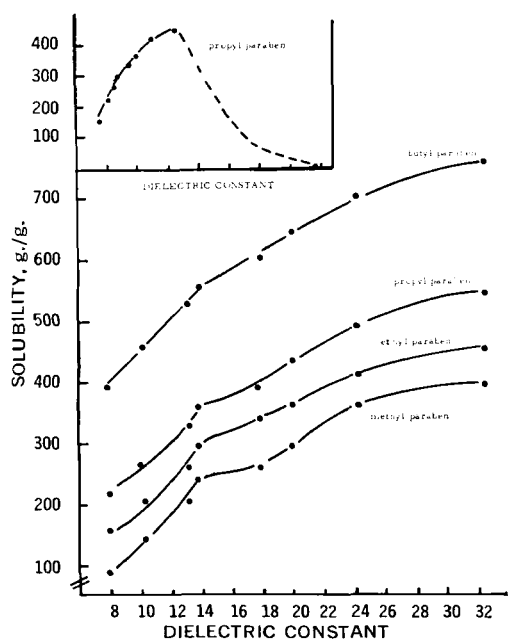

Figure 5—*A plot of the solubility of the parabens noted at 25° in mg./g. of saturated solution versus the dielectric constant of the alcohol solvents studied. For insert, see text.*
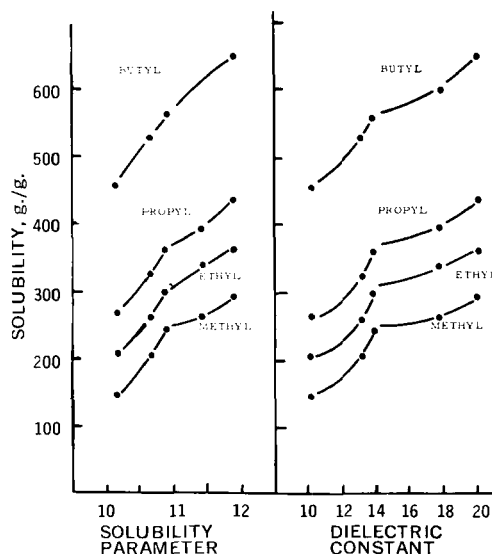
Figure 6—*A plot of the solubility of the parabens noted in g./g. of saturated solution versus either solubility parameter values or respective dielectric constants. Data taken from Martin (2).*

of 10.3. Solubility parameter values are calculated by

$$\delta = 7.5 + 0.2\epsilon \qquad \text{(Eq. 1)}$$

where δ is the solubility parameter and ε is the dielectric constant. Generally, solubility parameter values calculated from dielectric constant values by the use of Eq. 1 are about 0.5 units less than those values determined from energies of vaporization (6). Thus, Martin's range of values of 10.9 to 11.3 should be compared with a value of 10.8 from the foregoing discussion. The solubility parameter value could thus be obtained from a consideration of solubility parameter values themselves or dielectric constants of the pure solvents. The solubility values given by Martin in g./g. saturated solution *versus* the solubility parameters for the solvents studied are also shown in Fig. 6. Again, in this case, these compounds show shouldering in the solubility curve at a parameter value of about 11. It would seem that a plot using dielectric constants shows a sharper break in the solubility curve for butyl paraben and its DR more easily ascertained. Martin (2) mentions the apparent difficulty in obtaining a solubility parameter value for this compound in this series of esters due to the rather broad nature of the solubility curve.

The parabens, at least the first four members of the *n*-alkyl series, show a dielectric requirement value of about 14 in this pure solvent scan and the probable existence of another DR of about 30. The butyl derivative does not seem to show a smooth incremental increase in solubility behavior relative to the other parabens. It is interesting in this regard to note that the *n*-butyl group is the cut-off point relative to the solubility of alcohols in water (7). This aberrant behavior for the butyl derivative being out of place relative to the other parabens has also been noted in other binary solvent systems presently under study.

SUMMARY

Although parallelism was noted in the solubility profiles for these parabens, it is felt that some curvature exists in these lower member alcohols, *i.e.*, methanol and ethanol. The nonlinearity of the solubility curves for these compounds in pure alcohols also seems to logically imply a cut-off on intersection at about four carbons or the *n*-butyl derivative.

The solubility parameter or dielectric constant approach both lead to approximately the same results and the qualitative relationship of these two parameters cannot be denied. The dielectric constant approach may be more rapid, may produce cleaner breaks, and also allows for the observation of a multiplicity of solubility maxima for any compound.

The solubility profiles of the parabens are presently being studied in several binary mixtures in view of these results, and will be the subject of future communications.

REFERENCES

(1) A. N. Paruta, *J. Pharm. Sci.*, **55**, 1208(1966).
(2) F. A. Restaino and A. N. Martin, *ibid.*, **53**, 636(1964).
(3) A. N. Paruta and S. A. Irani, *ibid.*, **55**, 1055(1966).
(4) *Ibid.*, **55**, 1060(1966).
(5) A. N. Paruta, *ibid.*, **53**, 463(1964).
(6) H. Burrell, *Interchem. Rev.*, **14**, 3(1955).
(7) J. Ferguson, *Proc. Roy. Soc. London, Ser. B*, **127**, 387(1939).

Inhibitors of Monoamine Oxidase III: 9-Substituted-β-Carbolines

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Abstract □ A series of 9-alkyl aromatic β-carbolines was synthesized and evaluated as inhibitors of mitrochondrial monoamine oxidase. The possible existence of a hydrophobic or hydrophilic region on the enzyme was explored. Substitution of an electron-withdrawing group such as acetyl on N-9 position reduced the inhibitory activity. This suggested that the increase in the inhibitory activity of 9-methyl-β-carboline was at least partially due to the increase of its electron density by the methyl group, thus making the β-carboline bind better to the enzyme.

Keyphrases □ Monoamine oxidase (MAO) inhibitors—synthesis □ β-Carbolines, 9-substituted—synthesis □ Pharmacological screening—β-carbolines, MAO inhibitors □ IR spectrophotometry—structure □ UV spectrophotometry—structure

From previous work (1), a 35-fold increase in inhibitory activity of tetrahydro-β-carboline was observed when a methyl group was introduced on the indolic nitrogen. This was attributed to either the increase in the binding of the indole nucleus as a result of the electron-donating property of the methyl group or the binding of the methyl group itself hydrophobically to the enzyme, or both. Although the methylation

of the indole nitrogen of the fully aromatic β-carboline (I) did not give such a large increase in the inhibitory activity, the resulting 9-methyl compound (II) was three times more active than the parent compound. It would seem worthwhile to explore the effect of other 9-alkyl groups on the inhibitory activities of aromatic β-carbolines. The hydrophobic region of an enzyme has been demonstrated to be advantageous to the design of inhibitors, because it would contribute to a great extent to the binding of inhibitors to the enzyme (2).

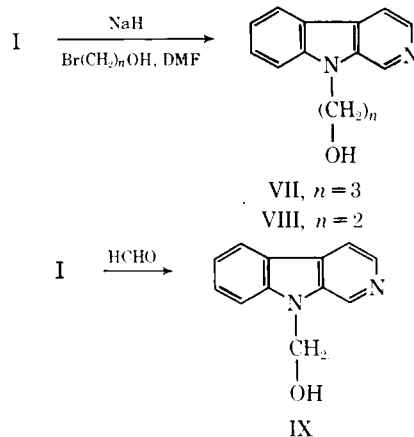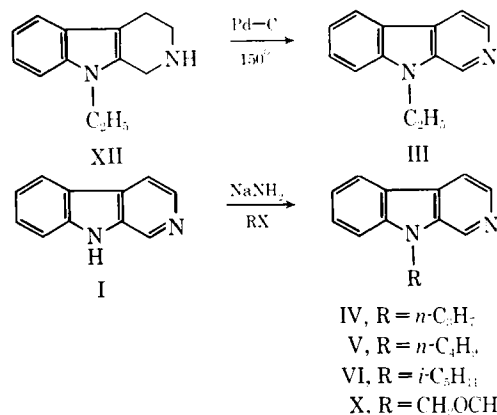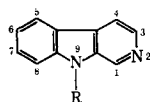Table I showed that the inhibitory activities of 9-

IV, R = n-C₃H₇
V, R = n-C₄H₉
VI, R = i-C₅H₁₁
X, R = CH₂OCH₃

VII, n = 3
VIII, n = 2

IX

Table I—Inhibition of MAO by

Compd	R	I_{50}, mM^a
I	H	0.029[b]
II	CH₃	0.010[b]
III[c]	C₂H₅	0.048
IV[c]	n-C₃H₇	0.15
V[c]	n-C₄H₉	0.14
VI	i-C₅H₁₁	1.8
VII	CH₂CH₂CH₂OH	0.48
VIII	CH₂CH₂OH	0.11
IX[c]	CH₂OH	0.034
X[c]	CH₂OCH₃	0.40
XI	COCH₃	0.15

a Concentration of an inhibitor giving 50% inhibition of the enzyme. *b* Data from *Reference 1*. *c* Hydrochloride salt.