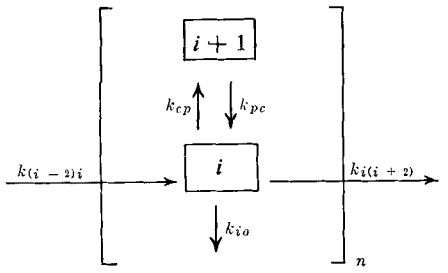

Scheme IV—General model composed of n *individual two-compartment open-model units*

and eigen vectors may be generalized as follows. Where:

$i = 1, 3, 5 \ldots$ $\quad i + 1$ = peripheral compartment
i = central compartment $\quad k_{io} + k_{i(i+2)} = k_{el}$

the general solution of the eigen values would therefore be:

$$a_{j-1} = \frac{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)}) + \sqrt{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)})^2 - 4\,(k_{io} + k_{i(i+2)})\,k_{pc}}}{2} \quad \text{(Eq. A26)}$$

$$a_j = \frac{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)}) - \sqrt{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)})^2 - 4\,(k_{io} + k_{i(i+2)})\,k_{pc}}}{2} \quad \text{(Eq. A27)}$$

Where $j = 3, 4, 5 \ldots i + 3$, the general solution of the eigen vector A_{ij} for the ith central compartment is:

$$A_{ij} = \frac{A_{(i-2)j}\,k_{(i-2)i}\,(k_{pc} - a_j)}{(a_j - k_{cp} - k_{el})\,(a_j - k_{pc}) - k_{cp}k_{pc}} \qquad j = 3,4,5 \cdots j - 2 \quad \text{(Eq. 28)}$$

$$A_{i(j-1)} = \left[-\sum_{j=3}^{j-2} A_{ij} + \frac{(a_{i+3} - k_{pc})}{k_{cp}} \left(-\sum_{j=3}^{j-2} A_{(i+1)j} \right) \right] \times \frac{(k_{pc} - a_{i+2})}{(a_{i+3} - a_{i+2})} \qquad j = i + 2 \quad \text{(Eq. A29)}$$

$$A_{ij} = -\sum_{j=3}^{j-1} A_{ij} \qquad j = i + 3 \quad \text{(Eq. A30)}$$

Therefore, the general solution of the eigen vectors, A_{ij}, for the $_{i+1}$th peripheral compartment is:

$$A_{(i+1)j} = \frac{A_{ij}\,K_{cp}}{k_{pc} - a_j} \qquad j = 3, 4, 5 \cdots i + 3 \quad \text{(Eq. A31)}$$

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Solubility of Alkyl Benzoates I: Effect of Some Alkyl *p*-Hydroxybenzoates (Parabens) on the Solubility of Benzyl *p*-Hydroxybenzoate

F. SHIHAB, W. SHEFFIELD, J. SPROWLS, and J. NEMATOLLAHI

Abstract □ The solubility features of a homologous series of alkyl *p*-hydroxybenzoates (parabens) with alkyl groups, in an ascending order from methyl to *n*-butyl, were investigated together with benzyl paraben and methyl *p*-methoxybenzoate. A phenomenon of mutual solubilizing potential was observed to exist when the solubility of a mixture of an alkyl paraben and benzyl paraben in 60% polyethylene glycol 400–water was examined. The analysis was carried out by means of UV spectrophotometry and NMR spectroscopy. The scope of application of these esters for their antimicrobial properties, for which they are primarily employed in pharmaceutical sciences, is envisaged to be augmented by considering factors influencing solubility.

Keyphrases □ Parabens—mutual solubilizing potential □ Polyethylene glycol–water system—paraben solubility □ UV spectrophotometry—analysis □ NMR spectroscopy—analysis

A gross solubilizing effect of alkyl *p*-hydroxybenzoates (parabens) on benzyl paraben in polyethylene glycol 400–water (designated as PEG–H_2O) mixture was first observed by Sprowls (1). Owing to the interest of pharmaceutical scientists in the physicochemical properties of parabens (2–4), which are employed both as medicinal

Table I—Solubility of Alkyl Parabens in Moles/Liter (M) and in Grams/Liter (G) in PEG–H_2O Ranging from 0 to 100% at 27° (Analyzed by Using UV)

R	0%		20%		40%		60%		80%		100%	
	M	G	M	G	M	G	M	G	M	G	M	G
CH_3	0.0165	2.512	0.0601	9.150	0.2675	40.700	1.1410	174.000	2.2199	337.750	2.2594	343.750
C_2H_5	0.0062	1.030	0.0244	4.063	0.1128	18.750	0.8527	141.690	2.0461	340.000	2.1063	350.000
n-C_3H_7	0.0022	0.400	0.0101	1.825	0.0499	9.000	0.6437	116.000	2.0116	362.500	2.0255	365.000
n-C_4H_9	0.0012	0.240	0.0068	1.313	0.0399	7.750	1.0683[a]	207.500	3.1406	610.000	3.1514	612.100
CH_2-Ph	0.0002	0.040	0.0016	0.378	0.0145	3.313	0.3329	76.000	1.5992	365.000	1.9278	440.000

[a] Concentration of butyl paraben at a point just prior to separation into two phases.

agents and for inhibition of the growth of microorganisms in food, cosmetics, and pharmaceutical preparations, extensive research on the solubility property of parabens and their potential to affect the solubility of each other in a given solvent was presumed to be valuable.

Using 60% PEG–H_2O as a solvent, a preliminary observation revealed that, in contrast to the solubility of the individual parabens, combining two parabens enhances the degree of solubility of both esters. This suggested the existence of a mutual solubilizing phenomenon among parabens. After this empirical observation, a few experiments were designed in an effort to characterize some solubility properties and the solubilizing potential of each member of the homologous series of alkyl parabens (methyl, ethyl, n-propyl, and n-butyl) together with benzyl paraben and methyl p-methoxybenzoate.

Three different solubility aspects of parabens were investigated.

First, the solubility of each paraben in the series was determined in various percentages of PEG–H_2O (0–100% PEG). UV spectrophotometry was employed for quantitative measurements. The solubility information obtained, besides its usefulness *per se*, was found valuable for further solubility study, wherein a mixture of two parabens rather than a single paraben was used. Accordingly, for the solubility study of a mixture of two parabens, a solvent containing 60% PEG in H_2O was adopted. In this solvent the solubilizing affect of the parabens on each other was envisaged to be more pronounced; their individual quantitation in the mixture, using NMR (5), could be performed with adequate accuracy.

Second, four pairs of parabens (combination of benzyl paraben with each of the alkyl parabens in the homologous series: methyl, ethyl, n-propyl, and n-butyl paraben) were subjected to solubility evaluation in an effort to examine the solubilizing effect of the parabens constituting the pair on each other (mutual solubilizing potential). The procedure consisted of adding each paraben in the pair to 60% PEG–H_2O until the solids remained in equilibrium with the solution.

Third, the solubility of benzyl paraben was determined in 60% PEG–H_2O solutions of methyl, ethyl, n-propyl, and n-butyl paraben, respectively, prepared in five different concentrations (0.1, 0.2, 0.3, 0.4, and 0.5 M). Due to the limited solubility of methyl p-methoxybenzoate, only the solubilizing effect of 0.1 M of this ester on benzyl paraben was evaluated. The analysis was performed by using NMR.

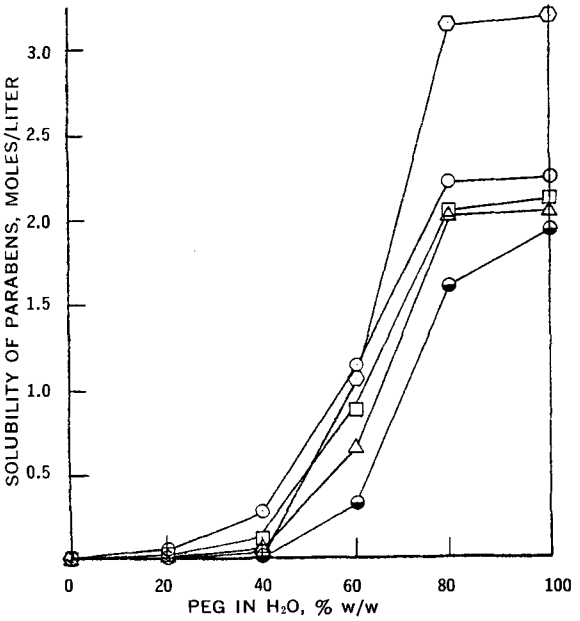


Figure 1—*Solubility of parabens in polyethylene glycol and water mixture of various proportions. Key:* O, *methyl;* □, *ethyl;* △, *n-propyl;* ○, *n-butyl; and* ◒, *benzyl parabens.*

EXPERIMENTAL

All the compounds employed in the experiments were analytical reagents: methyl p-hydroxybenzoate (Lot No. 5266),[1] ethyl p-hydroxybenzoate (Lot No. 5082),[1] n-propyl p-hydroxybenzoate (Lot No. 5294),[1] n-butyl p-hydroxybenzoate (Lot No. 5158),[1] benzyl p-hydroxybenzoate (Lot No. 1167),[1] methyl p-methoxybenzoate (methyl anisate Lot No. 1702),[2] and polyethylene glycol 400 USP YE 889.[3]

The analyses were carried out by using UV spectrophotometry (Beckman DB) and/or NMR spectrometry (Varian Associate A-60) at ambient temperature.

The solvents were prepared by mixing accurately weighed quantities of polyethylene glycol 400 and water. The percentages are expressed on a weight-to-weight basis.

The molar solution of each paraben was prepared by weighing accurately a precalculated quantity of the desired paraben in a volumetric flask and then dissolving the solid in 60% PEG–H_2O by gentle shaking.

The solubility of each paraben was determined by adding the compound beyond its saturation point to the solvent and shaking the mixture in a constant-temperature water bath (27.0 ± 0.1°) for 24 hr.

The solubility of benzyl paraben in the 0.1, 0.2, 0.3, 0.4, and 0.5 M solutions of each of the methyl, ethyl, n-propyl, and n-butyl paraben and in the 0.1 M of methyl p-methoxybenzoate was determined by

[1] Supplied by Matheson Coleman & Bell.
[2] Supplied by Eastman Organic Chemicals.
[3] Supplied by City Chemical Corp.

Table II—Quantitative Analysis of Each Phase Formed as a Result of Dissolving Butyl Paraben in 60% PEG–H_2O

	% w/v	% w/w
Upper Phase		
Butyl paraben	1.25	1.21
PEG	43.39	42.13
Water	58.36	56.66
Lower Phase		
Butyl paraben	54.31	51.94
PEG	40.53	38.66
Water	9.72	9.40

adding solid benzyl paraben, beyond its saturation point, to the solution and shaking the flask in a constant-temperature water bath (27.0 ± 0.1°) for 24 hr. The analysis of the solutions was carried out by using NMR spectrometry.

For determining the solubilizing effect of one paraben on the other, benzyl paraben and one of the alkyl parabens were added alternately and portionwise into 60% PEG–H_2O until a noticeable quantity of each paraben remained undissolved.

The samples for analysis were obtained by withdrawing the solution with a pipet on whose tip had been tied one layer of Whatman No. 1 filter paper for the purpose of ensuring the exclusion of of solid particles.

If NMR was to be used for the analysis, the samples were instilled into an NMR tube as such. For UV analysis, a known volume of the sample was diluted further with 50% ethanol using volumetric flasks. The absorbance values were recorded at $\lambda = 256$ mμ.

RESULTS AND DISCUSSION

Table I and Fig. 1 depict the results of experiments on the solubility of parabens in various proportions of PEG–H_2O. Probably due to a decrease in the polarity of the solvent, the solubility of parabens increases as a function of increase in the proportion of PEG to H_2O. In the homologous series of parabens employed in these experiments on a mole-to-mole basis up to a concentration of 40% PEG–H_2O, the solubility of each member was found to be slightly lower than its next lower homolog. If molar concentrations were converted to weight percentage, a reverse trend was observed for butyl paraben in 60% and for all the others in 80% PEG–H_2O and 100% PEG.

A sharp increase in the solubility of butyl paraben beyond 60% PEG–H_2O is probably due to the lipophilic nature of the butyl chain.

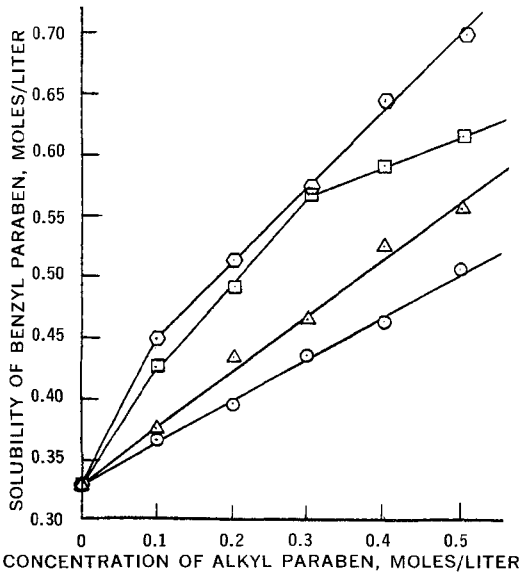


Figure 2—*Solubility of benzyl paraben in 60% PEG–H_2O solutions of a homologous series of alkyl parabens in concentrations ranging from 0.1 to 0.5* M. *Key:* O, *methyl;* △, *ethyl;* □, n-*propyl; and* ○, n-*butyl.*

Table III—Solubility and Parabens, in Moles/Liter (*M*) (60% PEG–H_2O and 27°) Determined for Each Paraben Both when Dissolved Individually and as a Combination of Two (NMR Used for Analysis)

Paraben (Single)	Solubility (*M*)	Parabens (Combined)	Solubility (*M*)
Methyl	1.1854	Methyl + Benzyl	1.3195
Benzyl	0.3301		0.6841
Ethyl	0.8346	Ethyl + Benzyl	1.0827
Benzyl	0.3301		0.7934

As indicated in Table I, the solubility of butyl paraben in 60% PEG–H_2O was recorded at the point just prior to its separation into two phases. Beyond this point the addition of more butyl paraben causes a formation of two layers. The constituent of each phase was determined quantitatively by the method described in the *Appendix*. The authors know of no previous explicitly described analysis of the two phases whose formation in alcoholic solvents also has been observed and reported (4). Nor has an unequivocally convincing explanation yet been expressed regarding the physicochemical features of each phase.

Table II depicts the quantity of each component present in each phase; details of the calculations are given in the *Appendix*.

The peaks for water and PEG in the NMR spectrum of the upper phase occur at δ 4.6 and 3.6, respectively. As shown in the calculations, correction has been made for the contribution of two protons to the water peak by the 2 OH's per molecule of PEG. There was no contribution from the phenolic OH of the butyl paraben due to its low concentration in the upper phase (no phenyl proton peak was observed at a spectrum amplitude in which the water and PEG integral values were determined).

For the lower phase, the concentration of butyl paraben was determined by comparing its NMR spectrum with that of a standard, analogous to the previously reported method (5). Similarly, the concentration of PEG was calculated, and then the quantity of H_2O was obtained by the difference (by subtraction from the weight of 1 ml. of the solution).

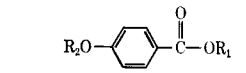
The formation of a two-phase system as a result of dissolving a high quantity of butyl paraben in 60% PEG–H_2O is probably due to the predominant occupation of etheric oxygen of polyethylene glycol by hydrogen bonding with phenolic OH of the paraben. Considering the preferred conformation of polyethylene glycol, such a hydrogen bond will restrict the free rotation of the phenyl group because of interference between phenyl hydrogens *ortho* to OH and methylene hydrogens of PEG. The butyl groups of two butyl parabens hydrogen bonded to two alternate oxygens, as becomes obvious by observing a molecular model,[4] can line up by van der Waals' force and maintain a relatively rigid structure. The net result becomes the formation of a complex, nonpolar enough to be capable of squeezing out water. The water, as it is compelled to form a separate phase, by virtue of hydrogen bonding carries with itself polyethylene glycol molecules which are not bound to butyl paraben.

A similar phase separation was also observed during the determination of mutual solubilizing potential of both benzyl paraben–propyl paraben and benzyl paraben–butyl paraben mixtures. The mechanism of formation of a two-phase system in this case is presumed to be analogous to that postulated for the butyl paraben. However, the benzyl paraben with a bulky nonpolar aralkyl moiety, like its butyl analog, is capable of participating in complex formation. The solubility expression for these two systems henceforth was thought to be meaningless and unsuitable for inclusion in a table. Table III, therefore, includes the experimental results of the mutual solubilizing potential of only two pairs of combinations (methyl paraben–benzyl paraben and ethyl paraben–benzyl paraben).

The solubilizing potential of the alkyl parabens to affect the solubility of benzyl paraben, as depicted in Fig. 2, increases in the ascending order of the alkyl chain of the homologous series and,

[4] The molecular model was constructed by using Dreiding Plastic Stereo model (Rinco Instrument Co., Inc. Greenville, Ill.).

Table IV—Solubility of Benzyl Paraben in Moles/Liter (M) in the 60% PEG–H_2O Solution of the Alkyl Parabens Ranging from 0.1 to 0.5 M at 27° (Analyzed by Using NMR)



R_1	R_2	0.0 M	0.1 M	0.2 M	0.3 M	0.4 M	0.5 M
CH_3	H	0.3301	0.3654	0.3942	0.4383	0.4627	0.5054
C_2H_5	H	0.3301	0.3753	0.4364	0.4650	0.5252	0.5574
n-C_3H_7	H	0.3301	0.4282	0.4929	0.5689	0.5917	0.6133
n-C_4H_9	H	0.3301	0.4491	0.5178	0.5742	0.6449	0.6952
CH_3	CH_3	0.3301	0.4415				

except for propyl paraben, seems to follow a linear relationship with respect to the concentration of each member in the series. Knowledge of whether or not the odd-number carbon chain of propyl paraben is an influencing factor on causing the curve to bend toward the x-axis requires additional experiments with higher homologs.

The solubilizing effect of methyl p-methoxybenzoate on benzyl paraben, as shown in Table IV, is somewhat similar to butyl paraben. The substitution of a lipophilic group, OCH_3, for OH of methyl paraben apparently enhances the solubilizing potential of the ester.

A theoretical consideration of this and the mutual solubilizing phenomenon in general is under study. The practical aspect of solubility is envisaged to possess application in pharmaceutical preparation and microbiological research and development.

APPENDIX

The following abbreviations are used in the equations: integral peak value = I, apparent = app., molar concentration = M, weight in grams = w, butyl paraben = BuPab, density of solution = d, solution = sln., and standard = st.

The PEG 400 formula is: OH—CH_2—CH_2—(OCH_2—CH_2)$_8$—OH.

Upper Phase—Both UV and NMR were used for analysis.

$$(H_2O)_{app.I} - (PEG)_I \times 1/18 = (H_2O)_I \text{ (correction for 2 OH/mole of PEG)} \quad \text{(Eq. 1)}$$

$$\frac{(PEG)_I}{(H_2O)_I} \times 1/18 = \frac{(PEG)_M}{(H_2O)_M} \text{ (molar ratio)} \quad \text{(Eq. 2)}$$

$$\frac{(PEG)_M}{(H_2O)_M} \times \frac{400}{18} = \frac{(PEG)_w}{(H_2O)_w} \text{ (weight ratio)} \quad \text{(Eq. 3)}$$

Weight of BuPab in g./ml. determined using UV = $(BuPab)_{w/ml.}$. Weight of 1 ml. of solution − $(BuPab)_w$ = $(PEG + H_2O)_{w/ml.}$.

$$\frac{(PEG + H_2O)_{w/ml.} \times (PEG)_w}{(PEG)_w + (H_2O)_w} = (PEG)_{w/ml.} \quad \text{(Eq. 4)}$$

$$\frac{(PEG + H_2O)_{w/ml.} \times (H_2O)_w}{(PEG)_w + (H_2O)_w} = (H_2O)_{w/ml.} \quad \text{(Eq. 5)}$$

$$\frac{(BuPab)_{w/ml.} \times 100}{d} = w\% \text{ BuPab} \quad \text{(Eq. 6)}$$

$$\frac{(PEG)_{w/ml.} \times 100}{d} = w\% \text{ PEG} \quad \text{(Eq. 7)}$$

$$\frac{(H_2O)_{w/ml.} \times 100}{d} = w\% \ H_2O \quad \text{(Eq. 8)}$$

Lower Phase—NMR was used for analysis.

$$\frac{(BuPab)_I \times (BuPab)_{M\cdot st.}}{(BuPab)_{I\cdot st.}} = (BuPab)_M \quad \text{(Eq. 9)}$$

$$\frac{(PEG)_I \times \frac{1}{9} \times (BuPab)_{M\cdot st.}}{(BuPab)_{I\cdot st.}} = (PEG)_M \quad \text{(Eq. 10)}$$

$$\frac{(BuPab)_M \times (BuPab)_{M\cdot w}}{1000} = (BuPab)_{w/ml.} \quad \text{(Eq. 11)}$$

$$\frac{(PEG)_M \times (PEG)_{M\cdot w}}{1000} = (PEG)_{w/ml.} \quad \text{(Eq. 12)}$$

Weight of 1 ml. of solution − $[(BuPab)_w + (PEG)_w]$ = $(H_2O)_{w/ml.}$.

$$\frac{(BuPab)_{w/ml.} \times 100}{d} = w\% \text{ BuPab} \quad \text{(Eq. 13)}$$

$$\frac{(PEG)_{w/ml.} \times 100}{d} = w\% \text{ PEG} \quad \text{(Eq. 14)}$$

$$\frac{(H_2O)_{w/ml.} \times 100}{d} = w\% \ H_2O \quad \text{(Eq. 15)}$$

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