

Solubility of Alkyl Benzoates III: Hydrogen Bonding and Solubility—A Theoretical Approach

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Abstract □ The theoretical aspects of the solubility features of a series of alkyl *p*-hydroxybenzoates (parabens), singly or as a combination (benzylparaben with each of the alkyl parabens in a homologous series ranging from methyl to *n*-butyl), were evaluated. The involvement of hydrogen bonding was considered. Both IR and NMR spectrometry were employed for analyses. The interrelation of molecular symmetry, solubility, and entropy was discussed.

Keyphrases □ Parabens, solubility—theoretical aspects □ Alkyl *p*-hydroxybenzoates—solubility, hydrogen bonding, theoretical aspects □ Solubility, alkyl *p*-hydroxybenzoates—theoretical aspects □ IR spectrophotometry—analysis □ NMR spectroscopy—analysis

The experimental results of previous communications (1, 2) on the solubility features of esters of *p*-hydroxybenzoic acid (parabens) revealed that the dielectric constant is a necessary, but not the only, property of a solvent accounting for its solubility. This became particularly obvious when the solubility of a homologous series of alkyl parabens (methyl, ethyl, *n*-propyl, and *n*-butyl) together with benzylparaben and methyl *p*-methoxybenzoate were determined separately and compared with the solubility values obtained when a combination of two of these parabens was used (each alkyl paraben was combined with benzylparaben and then dissolved). In the latter case, the solubility of both parabens increased considerably. Using 60% polyethylene glycol in water (PEG-H₂O) as a solvent in these experiments, the solubility data for benzylparaben in various concentrations of alkyl parabens were compared with the dielectric constant values of various concentrations of alkyl parabens. The results (2) were indicative of the involvement of a contributory factor, other than the dielectric constant of the solvent or solution, to solubility.

The mutual solubilizing potential observed as a result of combining two parabens was envisaged to be due to the participation of hydrogen bonding. Accordingly, several experiments were designed to determine the validity and the theoretical aspects of the proposed postulate. The theoretical consideration possesses the merit of applicability in a number of solubility problems confronting pharmaceutical scientists.

EXPERIMENTAL

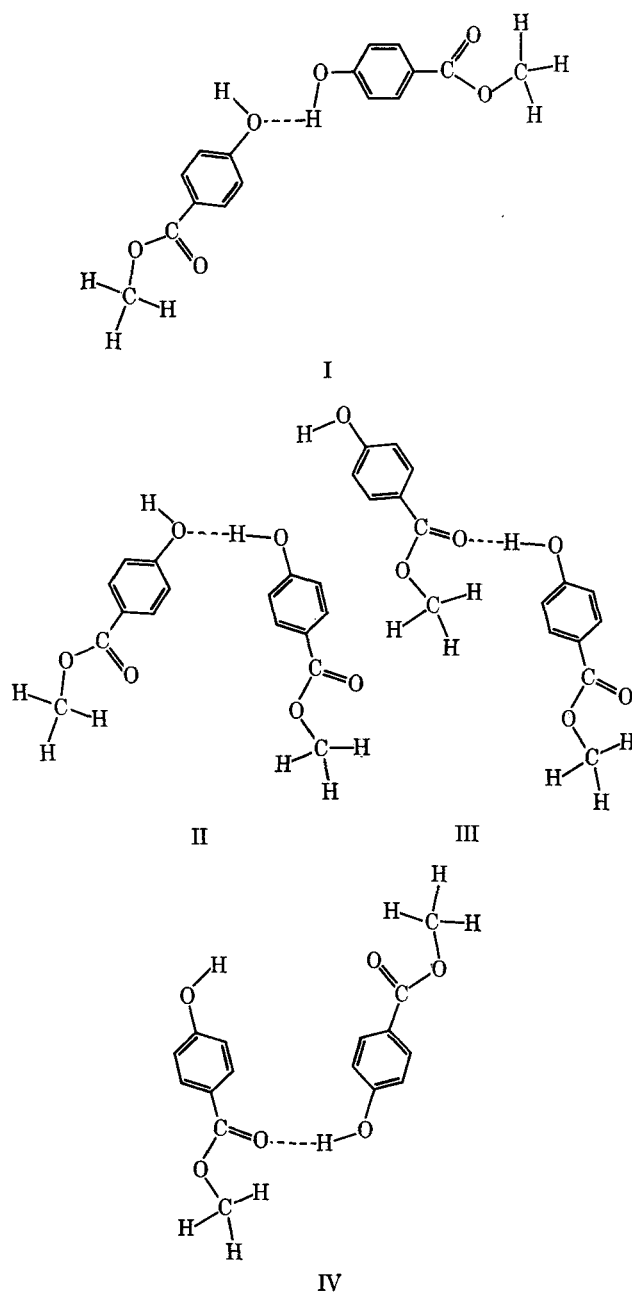
The solvents and solutions were prepared according to the previously reported method (1). The solutions were prepared in 60% PEG-H₂O, except for IR experiments where a spectral quality chloroform was employed. The IR spectra were determined using a Beckman IR-8 spectrophotometer. The NMR spectra were determined using a Varian Associate A-60 spectrophotometer.

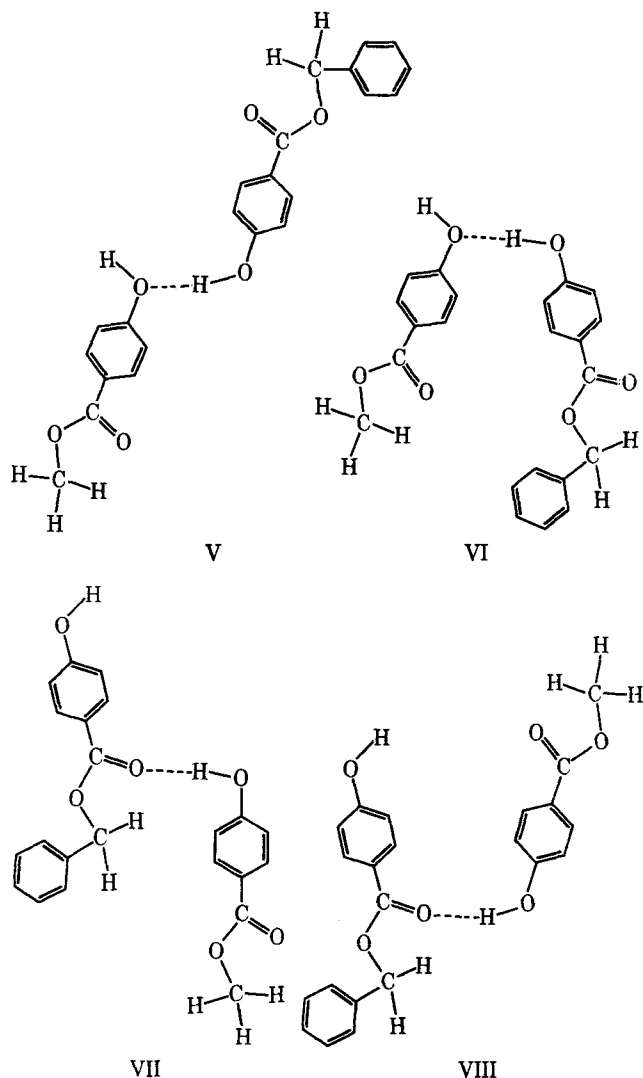
The chloroform solutions for the determination of C=O stretching frequency were injected by means of a hypodermic syringe into liquid cells, pathlengths 0.25 and 0.50. A polystyrene film was used as a standard to make the necessary corrections for the positions of the bands.

RESULTS AND DISCUSSION

The results obtained previously (1) on the solubility features of a mixture of two parabens were indicative of the existence of a mutual solubilizing phenomenon among these esters. The pairs of parabens subjected to this evaluation were benzylparaben with methyl, ethyl, *n*-propyl, *n*-butyl paraben, or methyl *p*-methoxybenzoate.

The theoretical aspects of the solubility enhancement of combined parabens are expressed by considering the fact that a decrease in the dielectric constant of the solvent as a result of dissolving any one of the parabens should induce the solubility of its closely related homolog. The reported data (2) on the dielectric constant





values of various concentrations of paraben solutions and the potential of each of the solutions to effect the solubility of benzylparaben revealed that the dielectric constant was not a major factor in the enhancement of solubility. Both 0.1 *M* of methyl *p*-methoxybenzoate and 0.1 *M* of ethylparaben, prepared separately in 60% PEG-H₂O, possess nearly identical dielectric constants, 43.20 and 43.23, respectively. Their solubilizing potentials on benzylparaben are, however, quite different, 0.4412 *M* of benzylparaben in the former solution and 0.3753 *M* in the latter.

In the solution containing two different esters, the formation of dimers from two nonidentical molecules is more probable than from identical molecules. This argument is based on the fact that dimers I and II, as shown by the structural formulas, both possess elements of symmetry, whereas V and VI do not. The symmetry number, σ , which represents the number of equivalent orientations a molecule can assume as a result of rotation around an axis, enters into entropies of molecules. The contribution of entropy due to symmetry is $-R \ln \sigma$. Dimers I and II (transoid and cisoid, assuming both dimers are flat on the paper) thus possess an entropy value 2.76 cal./deg. mole lower than their counterparts V and VI.

In the case of hydrogen bonding between the C=O group of the ester and the phenolic OH, formation of dimeric species such as III and VII is not probable due to the proximity of the alkyl group and phenyl hydrogens. This can be visualized easily by observing the molecular models of these compounds. In the cisoid configurations (IV and VIII), the dimer VIII, because of possessing an entropy value 1.38 cal./deg. mole more than IV, will be the predominant dimeric species of such type. Thus, a solution containing two differ-

ent parabens will consist of a high ratio of dimers comprised of two nonidentical moieties to dimers with identical moieties.

The hydrogen bonding between the C=O, HO, or the HO, HO does not necessarily require that both esters exist in the same plane. The coplanarity, however, is favored by considering the existence of orbital overlap in hydrogen bonding and the fact that overlap is most effective with orbitals having axes on a common plane. Nevertheless, assuming that some dimers are formed from monomers on two different planes, there seems to be a greater steric hindrance for dimers constructed *via* the C=O, OH than *via* the two phenolic OH's. Even if this relatively high probability of formation of the latter type of dimer is disregarded and only dimers having their monomers on a common plane are envisioned, dimers of types V and VI ought to predominate over VIII. This is because the entropy value of V and VI is 1.36 cal./deg. mole larger than the entropy value of VIII, a reasoning based on the analogy with two diastereoisomers, such as *cis*-1,3- and *trans*-1,3-dimethylcyclohexane, of which the *trans*, due to existing in *dl*-forms, contains an entropy value of $R \ln 2$ larger than *cis* (3). Another factor which may not favor the predominant existence of VIII is the requirement of a high energy of activation for the formation of this relatively rigid molecule.

The monomeric species of the esters that are in equilibrium with dimers will therefore originate to a larger extent from V and VI. An abundance of monomeric species or dimers of types V and VI in the solution of a mixture of two parabens *versus* the solution of a single paraben was shown by determining separately the IR spectra of 0.1 and 0.05 *M* methylparaben and benzylparaben and a 0.1 *M* solution of a mixture of these two parabens. The carbonyl stretching frequencies of 0.1 and 0.05 *M* of the solution of a single paraben (either methylparaben or benzylparaben) were at 1690 and 1703 cm^{-1} , respectively. The band for 0.1 *M* of the mixture of the two was at 1698 cm^{-1} . The presence of dimer V or VI may not be solely responsible for this shift. As the reported data, based on NMR spectrometry, indicate (1), in comparison with the individual solubility of benzylparaben and methylparaben, dissolving a mixture of these two increases solubility from 0.3 to 0.6 and 1.1 to 1.3 *M*, respectively. Such difference in solubility enhancement, therefore, cannot be attributed only to the abundance of V and VI but rather to the presence of more monomeric species.

The effect of dilution on the OH stretching frequency of the paraben solutions could not be investigated easily because of the limitation of the instrument. The regions between 3400 and 3600 cm^{-1} is quite condensed, and a variation of about 20 or 30 cm^{-1} due to twofold dilution cannot be detected readily. The NMR spectrometry for the OH resonance peak position as a function of dilution was explored. The OH proton peak positions for the solutions of single parabens and the mixture of parabens were found to be: 0.1 *M* methylparaben, δ 6.12; 0.1 *M* benzylparaben, δ 6.08; and 0.1 *M* of the mixture of the two, δ 6.10 (exactly at midpoint). In spite of these NMR data, the postulate relating solubility enhancement to a high proportion of monomers V and VI still holds correct. The occurrence of hydrogen bonds between relatively acidic phenolic protons and relatively electronegative Cl of chloroform prevents observing a shift in the position of OH, by using either IR or NMR, whereas the C=O stretching frequency is not affected by such bonding.

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