Solubility of Polar Organic Solutes in Nonaqueous Systems: Role of Specific Interactions

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Abstract □ The changes in solubility of several polar organic solutes when polar organic solvents are added to a relatively inert solvent such as isooctane were determined. The relative changes in solubility predicted from regular solution theory using solubility parameters often did not agree with the observed results. However, the solubilities could be rationalized mathematically by assuming the formation of specific solute–solvent complexes. Agreement of the thermodynamic data reported here with such models provides further evidence that specific interactions, when they occur, are more important than the bulk properties of the pure components in determining drug solubilities in nonaqueous systems. Specific examples demonstrate the relationship between the solubility and molecular structure of the solute and solvent. For example, solubility can be related to the hydrogen-donating and hydrogen-accepting abilities of the solute and solvent. Steric factors also appear to play a role in solubility, while structural modifications in a solute or solvent molecule far removed from the interactive functional group have little influence on molar solubility changes with the added polar cosolvent.

Keyphrases □ Solubility—polar organic solutes in nonaqueous systems, role of specific interactions □ Solute–solvent interactions—polar organic solutes in nonaqueous systems, role of specific interactions □ Solvents, nonaqueous—solubility of polar organic solutes, role of specific interactions

The solubility of a drug in a given solvent is an important property in pharmaceutical chemistry. Much work in drug design and drug product formulation stems from a need to achieve higher or lower solubilities to promote drug stability and bioavailability, to obtain controlled release rates, to avoid unpleasant side effects, and to optimize drug delivery to a target site. Consequently, the ability to predict drug solubility from molecular structure would be useful.

Current methods of solubility prediction often rely on the premise that the solubility of a solute in a given solvent is related simply to the bulk properties of the pure components. Such expressions as "polar solutes dissolve in polar solvents" or "like dissolves like" are based on this approach. This assumption also is the basis of a popular predictive method derived from regular solution theory, in which solubility is predicted from the solubility parameters of the pure components (1). Although this approach originally was intended strictly for systems involving only London dispersion forces, its use has been extended to include quite polar solution components in some cases (2, 3).

Recent studies indicated that the relative solubilities of polar solutes in both polar and nonpolar organic solvents often may be unrelated to the bulk properties of the pure components but are highly sensitive to the functional groups of the interacting molecules (4–9). One study suggested that specific intermolecular interactions, when they occur, often are the dominant factors in determining solubility, with corrections based on regular solution theory being unnecessary (4).

In the present study, the relative solubilities of several organic substances in various solvents or cosolvent mixtures were compared with predicted solubilities from regular solution theory and from a model assuming the existence of stoichiometric solvate species. The results indicate that the relative solubilities of polar substances in solvents that interact specifically with the solute are determined largely by these specific interactions.

EXPERIMENTAL

Reagents—Isooctane[1], with a stated purity of ≥99 mole %, was used without further purification. *n*-Butyl ether[2] was purified by slow shaking with an alkaline-saturated potassium permanganate solution followed by repeated washing with distilled water, concentrated sulfuric acid, and water. It was dried with calcium chloride overnight. This liquid then was distilled from sodium, and the middle fraction was collected and stored under nitrogen in an amber glass bottle.

n-Butyl ether[3], with a stated purity of 99%, was used without further purification. *n*-Pentyl ether[4] was treated similarly to *n*-butyl ether. *n*-Butyl *n*-butyrate[5] was shaken with 2 *N* NaOH, washed repeatedly with distilled water, dried over anhydrous magnesium sulfate, and then distilled under reduced pressure. The middle fraction was collected for use. Chloroform[6] was purified by washing with water to remove the ethanol preservative, dried over calcium chloride, and distilled. All solvents were stored over 4-Å molecular sieves[7] to remove possible trace amounts of water.

The solutes selected had relatively low isooctane solubilities and a minimum number of hydrogen donor or acceptor functional groups available for interaction with solvent molecules. Anthracene[3] had a claimed purity of 99.7% and was used without further purification. Anthraquinone[2], *p*-iodophenol[3], and *p*-nitrophenol[8] were recrystallized from chloroform–isooctane. Carbazole[3] and *p*-phenylphenol[3], with an indicated purity of 99+ and 97%, respectively, were recrystallized further from acetone–isooctane. 2,4,6-Triiodophenol[3] was recrystallized from methanol.

Solubility Determination—Solubilities of the solutes were determined in a series of solvents or cosolvent mixtures ranging from 100% isooctane to 100% ether, ester, or chloroform. Isooctane–interactive cosolvent mixtures were prepared by weight. Cosolvent molarities were calculated from the densities of the pure components. A series of vials was prepared, each containing an amount of solid well in excess of its estimated saturation solubility and ~5 ml of one of the described solvents or cosolvent mixtures. The vials were sealed[9] and brought to equilibrium by rotating in a constant-temperature bath at 25° for at least 2 days. Random duplicate samples were allowed to equilibrate for longer periods, but no significant differences in saturation solubility were observed.

The molar concentration of solute in solution was determined spectrophotometrically[10] by filtering[11] a portion of the solution and diluting a known aliquot as required. The filter assemblies, pipets, and other materials used in transferring the original sample were maintained at a temperature equal to the sample equilibration temperature prior to sampling. The solvent used as a diluent in the spectrophotometric de-

[1] Phillips Petroleum Co.
[2] Baker grade, J. T. Baker Chemical Co.
[3] Aldrich Chemical Co.
[4] Pfaltz and Bauer.
[5] Eastman.
[6] Reagent grade, Fisher Scientific Co.
[7] Linde.
[8] Matheson, Coleman and Bell.
[9] Teflon cap liners were used.
[10] Cary 14, 15, 16, or 118 spectrophotometer.
[11] Millipore filters BDWP 01300 or FHLP 01300.

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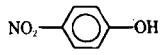
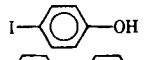
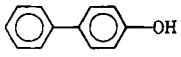
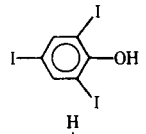
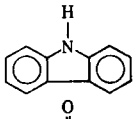
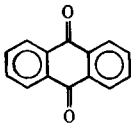
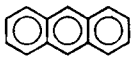
Table I—Molar Solubilities of Various Organic Solutes in Organic Solvents at 25°

Solute	Structure	Isooctane ($\times 10^4$)	Butyl Butyrate	Butyl Ether	Pentyl Ether	Chloroform
p-Nitrophenol		3.3	—	1.27	—	—
p-Iodophenol		150	—	3.39	—	—
p-Phenylphenol		12.4	0.62	0.21	0.12	0.10
2,4,6-Triiodophenol		50	—	0.10	—	—
Carbazole		7.7	0.099	0.029	0.018	0.047
Anthraquinone		2.8	0.0038	—	—	0.044
Anthracene		66	—	0.021	0.016	—

terminations was methanol or methanol containing 0.1 *N* HCl. While the nonphenolic compounds obeyed Beer's law in methanol, the phenols followed Beer's law more closely at low concentrations when the solvent was acidified.

RESULTS AND DISCUSSION

The molar solubilities determined in this study for various organic substances in several organic solvents are listed in Table I. Compounds expected to be strong hydrogen donors (phenols), weak hydrogen donors (chloroform and carbazole), and hydrogen acceptors (ethers, butyl butyrate, and anthraquinone) are included. Table II lists the molar solubility of carbazole in various interactive and inert solvents.

Comparison of Experimental Data with Regular Solution Theory Predictions—The term regular solution as proposed by Hildebrand in 1929 refers to solutions in which the entropy change is the same as for an ideal solution of the same composition but where the heat content increases with mixing (1). Regular solution theory gave rise to the now familiar solubility equation, expressed here in terms of the activity coefficient of the solute, γ_2:

$$\gamma_2 = \exp \frac{V_2\phi_1^2(\delta_1 - \delta_2)^2}{RT} \qquad \text{(Eq. 1)}$$

where δ_1 and δ_2 are the solubility parameters or cohesive energy densities [$\delta = (\Delta E/V)^{1/2}$] of the solute and solvent, respectively (12). Equation 1 involves an important assumption, the geometric mean rule, that frequently has been incorrectly taken for granted. In using solubility parameters, it is assumed that the energy of interaction of unlike molecules is given by the geometric mean of the interaction of like pairs ($\epsilon_{12} = [\epsilon_{11}\epsilon_{22}]^{1/2}$). This assumption is strictly true only for nonpolar molecules interacting *via* London dispersion forces (13). The geometric mean rule should not be presumed to be valid for either polar solutes or solvents.

The failure of simple one-component solubility parameter theory in systems of polar or interactive components has been recognized (14). However, since this approach still is widely used and recommended, several additional examples may illustrate the inadequacy of regular solution theory for predicting the solubilities of substances considered in this study.

The solubility parameters for various solvents are listed in Table II along with the molar solubility of carbazole in those solvents. The solubility parameter of carbazole is estimated as ~10, and its molar volume is ~150 cm^3. By comparing the solubility parameters of the hydrocarbon solvents in Table II, the solubility of carbazole predicted from regular solution theory should be five times higher in hexadecane and cyclohexane than in isooctane. The actual solubilities are relatively constant in these hydrocarbon solvents, which is intuitively satisfying considering the chemical similarity of these solvent molecules. Also, previous studies showed that the molar solubilities of several other polar solutes are relatively independent of the alkane reference solvent chosen (4, 5). Although molar volume corrections may be a factor, these errors apparently are compensated for by using molarity as the concentration unit. In addition, recent work suggested that even for systems involving components of markedly different molal volumes, the assumption of ideal entropy of mixing gives more satisfactory agreement with observed results than do theories considering molal volume differences (15).

From a comparison of solubility parameters in Table II, the solubility of carbazole in some hydrocarbon solvents should be roughly equal to or higher than its solubility in ethyl ether (δ = 7.4), butyl ether (δ = 7.5), pentyl ether (δ = 7.9), and butyl butyrate (δ = 8.0). However, the observed solubilities are 20–100 times higher in the hydrogen-accepting solvents than in the relatively inert alkane solvents, a result that cannot be accounted for by regular solution theory but is readily explainable from a consideration of the specific interactions occurring.

In general, one would predict from regular solution theory that, for all solutes in this study, the order of solubility should be chloroform > butyl butyrate > ethers ≃ hydrocarbons. These predictions obviously are not confirmed in Table II or by the relevant data for phenylphenol in Table I. Only for anthraquinone (and perhaps anthracene) is the solubility highest in chloroform, which also would be predicted from the knowledge that anthraquinone is a hydrogen acceptor and chloroform is a weak hydrogen donor.

In some instances, it may be possible to rationalize a particular change in solubility between two solvents using solubility parameters, even though the molecules involved would be expected to interact through hydrogen bonding. For example, the ratio of the solubility of anthraquinone in chloroform to its solubility in isooctane is 77 (using mole fractions) and is consistent with a solubility parameter of ~11.8, assuming

Table II—Molar Solubility of Carbazole at 25° in Several Solvents with Various Solubility Parameters (δ)

Solvent	δ	Solubility, *M*
Isooctane	6.9[a]	1.1×10^{-3} [a]
n-Hexane	7.3[a]	1.3×10^{-3} [a]
n-Heptane	7.4[a]	1.6×10^{-3} [a]
Ethyl ether	7.4[a]	1.25×10^{-1} [a]
Butyl ether	7.6[b]	2.9×10^{-2} [c]
Decane	7.8[a]	1.5×10^{-3} [a]
Dodecane	7.9[a]	1.4×10^{-3} [a]
Pentyl ether	7.9[d]	1.8×10^{-2} [c]
Butyl butyrate	8.0	1.0×10^{-1} [c]
Hexadecane	8.0[a]	1.7×10^{-3} [a]
Chloroform	9.2[a]	4.5×10^{-2} [a]

[a] From Ref. 4. [b] Calculated from heat of vaporization (Ref. 10). [c] Data from this study. [d] Estimated from Ref. 11.

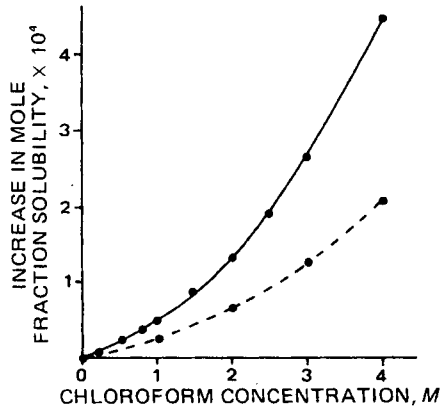


Figure 1—*Solubility of anthraquinone* versus *molarity of chloroform* (●) *in isooctane at 25°. The solid line was calculated from the equilibrium constants in Table III. The dashed line represents predicted solubilities using solubility parameters described from solubility data in the pure solvents.*

a molar volume of 150 cm^3 for anthraquinone. A further test of this solubility parameter is to determine whether the theory can reliably predict solubilities between these two solvent extremes, that is, in mixed solvents. From regular solution theory, the solubility parameter of a mixed solvent is the weighted average (based on volume fractions) of the solubility parameters of the pure components (1):

$$\delta = \phi_1\delta_1 + \phi_2\delta_2 \qquad \text{(Eq. 2)}$$

With Eq. 2, the predicted solubility values for anthraquinone in chloroform–isooctane cosolvent mixtures can be represented by the dashed line in Fig. 1. In comparison to the experimental points, the predicted solubilities increase much too gradually at low chloroform concentrations, illustrating the failure of the solubility parameter approach to predict the shape of the solubility profile for this example.

The inadequacy of the simple one-component solubility parameter approach has led to many more or less empirical multicomponent solubility parameters to incorporate the effects of specific interactions (13, 16). Although such attempts generally lack a firm theoretical foundation, they demonstrate that specific interactions are of great importance in many cases.

Specific Interactions and Solubility—Much early criticism of the specific interaction theory was based on the difficulty in proving the existence of "species" from thermodynamic data alone (1). However, a wealth of spectroscopic data now documents the formation of stoichiometric species through hydrogen-bonding interactions. Abundant evidence, based on IR frequency shifts (17), ^{1}H-NMR data (18, 19), and ^{13}C-NMR studies (20), supports the existence of molecular complexes between various hydrogen donors [including phenols (21) and chloroform (22)] and hydrogen acceptors [even for such a weak hydrogen acceptor as benzene (23)].

It would be unreasonable to assume that hydrogen-bonding interactions are not an important contribution to the solubilities of interest in the present study, based on the available spectroscopic data. Additional features supporting the contention that specific interactions such as hydrogen bonding are reflected in the solubility data reported here will be discussed later.

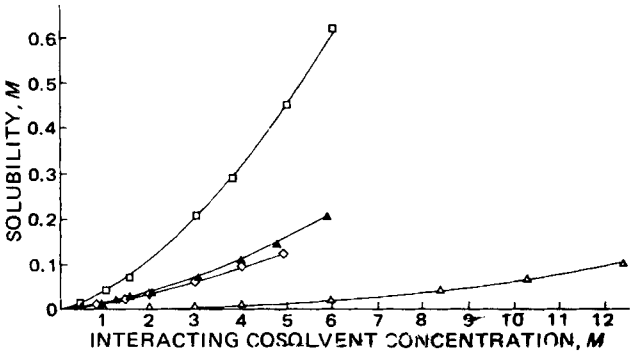


Figure 2—*Solubility of* p-*phenylphenol* versus *molarity of various interacting cosolvents in isooctane at 25°. The lines represent the calculated solubilities based on the equilibrium constants in Table III. Key:* □, *butyl butyrate;* ▲, *butyl ether;* ◇, *pentyl ether; and* △, *chloroform. The final point in each case represents the solubility in the pure cosolvent.*

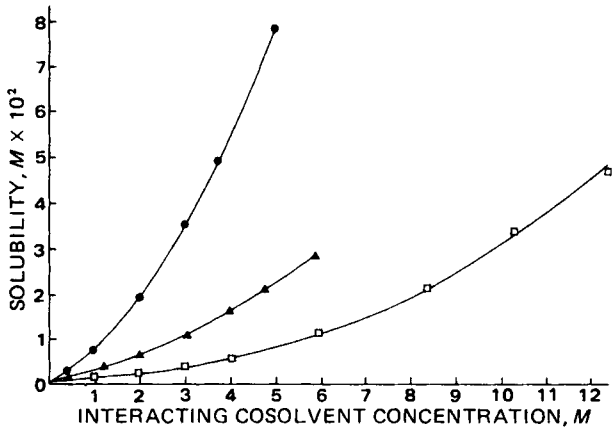


Figure 3—*Solubility of carbazole* versus *molarity of various interacting cosolvents in isooctane at 25°. The lines represent the calculated solubilities based on the equilibrium constants in Table III. Key:* ●, *butyl butyrate;* ▲, *butyl ether; and* □, *chloroform. The final point in each case represents the solubility in the pure cosolvent.*

Mathematical Treatment of Solubility Data in Terms of Solute–Solvent Species Formation—Typical diagrams of solubility *versus* molarity of the interactive cosolvent are shown in Figs. 2 and 3 for *p*-phenylphenol and carbazole in the presence of various complexing agents. A plot of the solubility of anthraquinone *versus* chloroform molarity was shown in Fig. 1. The solubility curves generally are parabolic. These curves can be fitted mathematically using a model that assumes solvate species formation.

Solubility in Unassociated Solvents—It is assumed that the following equilibria hold between the solute, S, and the complexing agents or interacting cosolvents, L:

$$S + L \rightleftharpoons SL \overset{+L}{\rightleftharpoons} SL_2 \overset{+L}{\rightleftharpoons} \ldots SL_n$$

Scheme I

Each reaction is defined by an equilibrium constant for formation of the complex:

$$K_{1:1} = \frac{[SL]}{[S_0][L_f]} \qquad \text{(Eq. 3)}$$

$$K_{1:n} = \frac{[SL_n]}{[SL_{n-1}][L_f]} \qquad \text{(Eq. 4)}$$

where the concentrations are expressed as molarities; S_0 is the saturation solubility of solute in isooctane, which is assumed to represent the free solute concentration in the cosolvent mixtures; and L_f is the free (uncomplexed) ligand. It also is assumed that a single solute molecule is present in each complex, but the mathematical form of the resulting equation is not changed by allowing more than one solute per complex. Throughout this discussion, it is assumed that the activity coefficients of all species are one where the standard state in every case is a 1 M solution of solute behaving as if it were completely surrounded by isooctane solvent. The total solubility of solute in any system can be expressed as:

$$S_T = [S_0] + K_{1:1}[S_0][L_f] + K_{1:2}K_{1:1}[S_0][L_f]^2 + \ldots \qquad \text{(Eq. 5)}$$

and L_T, the total complexing agent added, is:

$$L_T = [L_f] + K_{1:1}[S_0][L_f] + 2K_{1:2}K_{1:1}[S_0][L_f]^2 + \ldots \qquad \text{(Eq. 6)}$$

The total concentration of interactive cosolvent, L_T, is equal to L_f in the absence of solute. This relationship is true only when the extent of self-association of cosolvent is negligible, and it cannot be assumed for alcohol cosolvents.

As is evident from Eq. 5, the shape of the plots of solubility *versus* cosolvent added should be concave upward in unassociated solvents, in agreement with the data in Figs. 1–3.

Estimation of Equilibrium Constants—If S_0, the solubility of the solute in isooctane, is very low, the amount of ligand in complexes is small

Table III—Solvate Equilibrium Constants (Liters per Mole) of Various Solutes with Polar Solvents at 25°

Solute	Butyl Ether			Pentyl Ether			Butyl Butyrate			Chloroform			
	$K_{1:1}$	$K_{1:2}$	$\sigma\%$[a]	$K_{1:1}$	$K_{1:2}$	$\sigma\%$	$K_{1:1}$	$K_{1:2}$	$\sigma\%$	$K_{1:1}$	$K_{1:2}$	$K_{1:3}$	$\sigma\%$
p-Nitrophenol	102.5	0.56	2.2[b]	—	—	—	—	—	—	—	—	—	—
p-Iodophenol	26.0	—	0.5[c]	—	—	—	—	—	—	—	—	—	—
p-Phenylphenol	8.9	0.42	2.7	8.3	0.27	2.1	21.2	0.78	3.3	0.73	0.25	0.15	2.8
Carbazole	2.5	0.25	1.1	1.9	0.23	1.9	6.5	0.44	3.3	0.68	0.30	0.06	4.3
2,4,6-Triiodophenol	1.1	0.33	1.4	—	—	—	—	—	—	—	—	—	—
Anthraquinone	—	—	—	—	—	—	—	—	—	0.96	0.39	0.15	2.5

[a] The $\sigma\%$ value is the square root of the sum of the squares of the percent deviation between the calculated and observed solubilities divided by the degrees of freedom. [b] Fit of data below 0.1 *M*. [c] Fit of data in 1:1 region only.

and $[L_T] \simeq [L_f]$. Also, at low concentrations of L, only 1:1 complexes are important, and a plot of the fractional change in solubility *versus* ligand added gives a straight line at low cosolvent concentrations with a slope of $K_{1:1}$:

$$\text{fractional change in solubility} = \frac{[S_T] - [S_0]}{[S_0]} = K_{1:1}[L_T] \qquad \text{(Eq. 7)}$$

Such plots are shown in Fig. 4 for several substances in butyl ether. At higher cosolvent molarities, two-parameter equations containing terms for 1:1 and 1:2 complexes were needed to describe the data adequately. Only two parameters were necessary to describe completely the entire solubility curve in all solvents except chloroform, where three parameters often were required (Table III).

Graphical methods are quite cumbersome when an appreciable amount of the added cosolvent exists in complexed form, because L_T then does not equal the free ligand concentration. Therefore, a computer program using the simplex method of least squares (24, 25) was written to solve Eqs. 5 and 6 simultaneously, optimizing the variables $K_{1:1}$, $K_{1:2}$, and $K_{1:3}$. The sum of squares of the percent deviation of the experimental solubilities from the calculated solubilities was minimized to give equal weight to each point. The computer-calculated complexation constants for those instances where specific interactions can reasonably be assumed are listed in Table III. Constants determined graphically (Fig. 4) usually were within 10% of the computer-optimized values.

Choices of Most Important Factors in Predicting Solubility—Nonaqueous systems of pharmaceutical interest generally involve polar solutes in polar, interactive solvents. Therefore, predictive relationships between solubility and one or more independent variables that express the interactive tendencies of the molecules involved would be valuable. It was shown in the preceding discussion that solubility parameters, which reflect bulk properties of the pure components, often are not related to the observed relative solubilities. However, specific solvation models can readily account for the solubility behavior.

By first determining the solubilities in an alkane solvent, an estimate of factors that are not related to specific interactions in solution is obtained. Differences in alkane solubilities largely reflect differences in solute crystalline energies, although dispersion interactions between the solute and solvent also may vary with molecular structure. In interactive solvents, the specific interaction component, which is of primary interest here, is reflected by the change in solubility from that in isooctane.

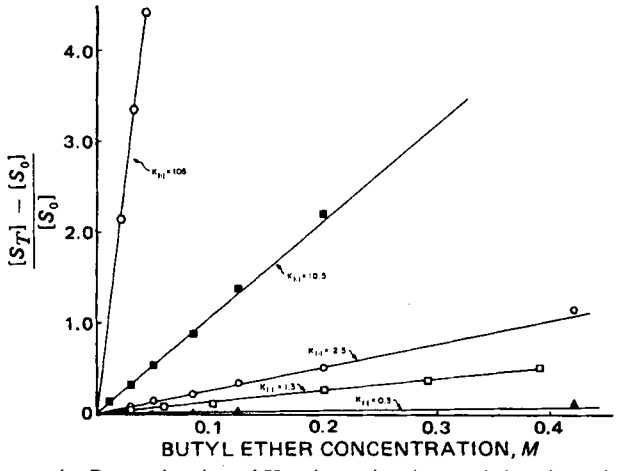


Figure 4—*Determination of* $K_{1:1}$ *from the slopes of the plots of the fractional change in solubility* versus *butyl ether molarity in isooctane at 25° (see Eq. 7). Key:* ○, p-*nitrophenol;* ■, p-*phenylphenol;* ○, *carbazole;* □, *2,4,6-triiodophenol; and* ▲, *anthracene.*

While the fact that these systems can be fit with solvation models does not prove conclusively that the solubility changes are due largely to specific interactions, the $K_{1:1}$ values obtained from the solubility data are consistent with what is expected from a consideration of the relative hydrogen-donating and hydrogen-accepting abilities of the respective molecules (8). A brief comparison of the solubility data in Table I provides a qualitative indication of the importance of hydrogen bonding in determining relative solubilities. The solubility of the strong hydrogen donor *p*-nitrophenol increases by almost 4000-fold in going from isooctane to the hydrogen-acceptor solvent butyl ether. The solubility of the weaker hydrogen donor carbazole increases by ~38 times in going from isooctane to butyl ether; anthracene, which has no donatable hydrogens, differs by a factor of only three in the two solvents.

These large differences cannot be accounted for by solubility parameters since the solubility parameter of butyl ether is quite similar to that of isooctane. However, they are quite consistent with specific interaction theory.

It also is instructive to compare the butyl ether–isooctane solubility ratios for *p*-nitro-, *p*-iodo-, and *p*-phenylphenols, which are 3850, 226, and 169, respectively. These phenols are listed in order of decreasing acidity and also decreasing hydrogen-donating ability based on literature data (8).

Empirical correlations of equilibrium data based on linear free energy relationships were applied previously in hydrogen-bonded systems (8, 26), usually taking the form of the Hammett equation (27, 28), $\log (K/K_0) = \rho\sigma$, where K and K_0 are the equilibrium constants of a substituted and an unsubstituted solute species, respectively; ρ reflects the sensitivity of the reaction to solute substituent changes; and σ represents the Hammett substituent constant. Higuchi *et al.* (8) derived a similar equation, $\log (K/K_0) = h_d h_a$, and calculated h_d and h_a values for donors and acceptors in nonpolar solvents, where h_d is a measure of the effect of change in the hydrogen donor on hydrogen bonding and h_a measures the influence of the acceptor on the interaction.

Figure 5 is a plot of $\log K_{1:1}$ derived from the solubility data of the *para*-substituted phenols in butyl ether *versus* the Hammett σ_p substituent constant obtained from the effect of these *para*-substituents on the ionization of benzoic acids in water[12] (29). Because the ionization

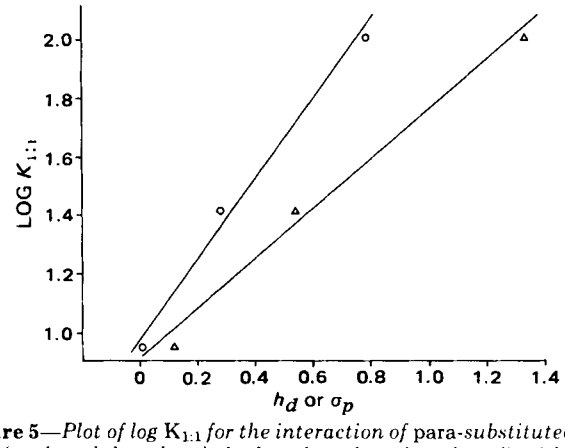


Figure 5—*Plot of log* $K_{1:1}$ *for the interaction of* para-*substituted phenols* (p-*phenylphenol,* p-*iodophenol, and* p-*nitrophenol) with butyl ether in isooctane at 25°* versus *the Hammett* σ_p *substituent* (●) *constant and* versus *Higuchi* h_d *values* (△).

[12] Resonance effects are less important in hydrogen bonding than in Brönsted acidity and basicity, so poor correlations of hydrogen bonding with acidity are obtained with σ^- values, which reflect the substituent effect on phenol ionization (14).

Table IV—Standard Free Energies of Transfer of Solute ($\Delta G°$) from Isooctane to Various Interactive Solvents and the Calculated Hydrogen-Bonding Contribution to the Free Energy from $K_{1:1}$ Values ($\Delta G°_{HB}$)

Solute	Butyl Ether		Pentyl Ether		Butyl Butyrate		Chloroform	
	$\Delta G°$[a]	$\Delta G°_{HB}$[a]	$\Delta G°$[a]	$\Delta G°_{HB}$[a]	$\Delta G°$[a]	$\Delta G°_{HB}$[a]	$\Delta G°$[a]	$\Delta G°_{HB}$[a]
p-Nitrophenol	−4.90	−3.6	—	—	—	—	—	—
p-Iodophenol	−3.2	−2.5	—	—	—	—	—	—
p-Phenylphenol	−3.0	−2.3	−2.7	−2.2	−3.7	−2.8	−2.6	−1.4
Carbazole	−2.1	−1.6	−1.9	−1.4	−2.9	−2.2	−2.4	−1.3
2,4,6-Triiodophenol	−1.8	−1.2	—	—	—	—	—	—
Anthraquinone	—	—	—	—	—	—	−3.0	−1.5

[a] Units are kilocalories per mole.

constants in nonpolar media have not been determined, a direct correlation with acidity under the same solvent conditions is impossible. Figure 5 also shows the plot of the same values of log $K_{1:1}$ *versus* Higuchi's h_d values (8), which were derived from both thermodynamic and spectroscopic data. This correlation clearly suggests that the $K_{1:1}$ values reflect hydrogen-bonding interactions.

Steric effects also come into play in solubility, as demonstrated by the relatively low $K_{1:1}$ and low solubility for 2,4,6-triiodophenol in butyl ether, a hydrogen-accepting solvent (Table III). This effect presumably is due to the steric hindrance to hydrogen bonding by the *ortho*-iodo groups.

While solubility is quite sensitive to the solute and solvent functional group composition, structural alterations that are not in the vicinity of an interacting functional group and do not alter the acidity or basicity of the functional group have little influence on solubility differences in organic solvents. For example, $K_{1:1}$ values for the interaction of carbazole with ethers varying in alkyl chain length are 3.53 M^{-1} for ethyl ether (5), 2.5 M^{-1} for butyl ether, and 1.9 M^{-1} for pentyl ether. Furthermore, $K_{1:1}$ for the interaction of *p*-phenylphenol with butyl ether is 8.9 M^{-1}; with pentyl ether, it is 8.3 M^{-1}. Solubilities in the pure ethers differ by a much larger amount (Table II), due in part to the greater concentration of ether oxygens in pure ethers of shorter chain length.

The $K_{1:2}$ values listed in Table III are very small and relatively insensitive to the molecular structure of the solute or solvent. These constants cannot justifiably be called specific interaction constants. The much smaller magnitudes of $K_{1:2}$ suggest that the 1:1 solute–solvent interactions are saturable, a characteristic of specific interactions. For instance, for the nitrophenol–butyl ether system, $K_{1:1}$ = 102.5 liters/mole and $K_{1:2}$ = 0.56 liter/mole. The strong hydrogen-bonding tendency between these two species does not carry over into the 1:2 interaction since the hydrogen-donating tendency of *p*-nitrophenol is "saturated" in forming the 1:1 complex.

If it is assumed that the $K_{1:1}$ values obtained in dilute solutions of the interactive cosolvents represent specific interactions, one can calculate the contribution of this specific interaction to the overall transfer free energy from isooctane to pure solvent (Table IV). This comparison ignores the likelihood that complexes larger than 1:1 may exist in the pure interactive solvent. For example, 1:2 complexes are expected to be quite important in chloroform solutions of anthraquinone since anthraquinone has two hydrogen-acceptor sites. Therefore, the specific interaction contributions to solubility expressed in Table IV probably are minimum estimates. However, nonspecific contributions to the $K_{1:1}$ values in dilute solution also may be a factor, particularly when the $K_{1:1}$ values are small.

In most cases, the specific interaction contribution to the overall free energy of transfer is the major factor, as is evident from Table IV. The differences may be composed of higher order molecular complexes or nonspecific effects, but these differences generally are small compared to the overall transfer free energy. Clearly, the specific interaction tendency should receive the greatest emphasis in attempts to predict solubility in similar systems.

CONCLUSION

It was shown that solubilities of polar organic substances in polar organic solvents can be rationalized quantitatively by assuming the formation of stoichiometric solvate species. Additional evidence also supports the contention that specific interactions are more important than bulk properties of the pure components in determining relative solubilities.

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