

Solubility in Binary Solvent Systems I: Specific *versus* Nonspecific Interactions

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Abstract □ Solubilities are reported for benzil in carbon tetrachloride-alkane (isooctane, *n*-octane, cyclooctane) systems at 25° and in similar binary mixtures containing cyclohexane plus alkane. The results of these measurements are compared to solution models previously developed for solubility in systems containing specific solute-solvent interactions and to models for purely nonspecific interactions. A stoichiometric complexation model based primarily on specific solute-solvent interactions requires several equilibrium constants to mathematically describe the experimental solubilities in binary carbon tetrachloride mixtures. However, there was no direct experimental evidence to suggest complexation between benzil and carbon tetrachloride. In comparison, expressions derived from the Nearly Ideal Binary Solvent (NIBS) model for nonspecific interactions predict experimental solubilities with a maximum deviation of 5% and an overall deviation of 1.0%. The success of the NIBS approach for this system is significant because the mole fraction solubility of benzil changes by a factor of 14 in the carbon tetrachloride-isooctane system.

Keyphrases □ Solubility—binary solvent systems, specific *versus* nonspecific interactions □ Solvent systems—binary, specific *versus* nonspecific interactions, solubility □ Solute-solvent interactions—specific *versus* nonspecific, binary systems

A knowledge of the thermodynamic activity of a drug in a given environment is important in drug design and drug product formulation. The development of an effective drug often involves altering its solubility through either structural modifications or complexation. Ideally, the ability to predict solubility based solely on molecular interactions between the dissolved drug and surrounding solvent molecules is desired. For practical applications, a less fundamental approach must often suffice.

BACKGROUND

Studies of solute-solvent interactions generally have focused on integral thermodynamic properties of binary mixtures. Recently, thermodynamic excess properties of a solute at high dilution in binary solvent mixtures (1-5) have been useful in studying the effects of solution nonideality. Equilibrium constants and enthalpies of hydrogen bond formation have been calculated from the heats of solution of proton donors in mixtures containing a proton acceptor and relatively nonpolar solvent (6, 7). GLC studies on a binary liquid phase provide another method for determining the thermodynamic properties of a solute near infinite dilution, and for investigating association complexes between the solute and one of the solvent components (4, 8-12). Experimental solubilities of iodine and stannic iodide in binary solvent mixtures containing benzene were explained through preferential solvational models (13, 14).

The interpretation of solution nonideality generally has followed two dissimilar lines: the "physical" approach originated by van Laar (15) and the "chemical" approach proposed by Dolezalek (16). The physical approach may be described by a random distribution of molecules throughout the entire solution, while the chemical approach may be characterized by a specific geometric orientation of one molecule with respect to an adjacent molecule.

Even in systems known to contain specific interactions, the need to properly account for nonspecific interactions is recognized. Arnett, *et al.* (7) attempted to separate specific and nonspecific interactions with a "pure base" calorimetric method for determining enthalpies of hydrogen bond formation. The sensitivity of the numerical results to the selection of the model compound and the solvent (17) points out the difficulty in separating physical and chemical contributions of solution nonideality.

Bertrand (18) demonstrated that neglecting nonspecific interactions in a chloroform-triethylamine system led to an appreciable error in the enthalpy of complex formation determined with an ideal associated solution model.

Recent solubility determinations of polar organic solutes in binary solvent mixtures containing a polar organic solvent and a nonpolar solvent (such as isooctane) have shown the value of considering nonspecific as well as specific interactions.

For example, do large differences between the solubility of a substance in two pure solvents necessarily indicate complex formation, or can these differences sometimes be just as adequately described with simple mixing models based on nonspecific interactions? One report (19) showed that solubilities of polar nonelectrolytes in polar nonaqueous solvents could not be predicted with the solubility parameter approach of Scatchard and Hildebrand. Another report (20) showed that large differences in the solubilities of polar organic substances could be mathematically described by models that assume stoichiometric solvate species. In many of the systems studied (20), nonspecific interactions were considered unimportant because of the large contributions from specific interactions and the fact that the solubility parameter approach was not adequate.

A zero-parameter equation was developed (3, 5) which predicted solubilities in 35 systems containing naphthalene, stannic iodide, iodine, and benzil as solutes where nonspecific interactions dominate with an average deviation of 2.2% and a maximum deviation of 25%. The maximum deviation occurred in a system (benzil-benzene-cyclohexane) in which complex formation was suggested, and if this system is excluded from calculations, the maximum deviation becomes 6%. The success of the equation is striking because the mole fraction solubility of benzil changes by a factor of 14 in the carbon tetrachloride-*n*-hexane system (5).

The present report describes how nonspecific interactions may contribute significantly to the total nonideality of a solution. Equilibrium constants calculated *via* solvational complexation models may not always represent only specific solute-solvent interactions, but also the failure of the model to properly describe nonspecific interactions. This phenomenon was further examined by measuring additional solubilities for benzil in carbon tetrachloride-alkane (isooctane, *n*-octane, cyclooctane) systems and in similar binary mixtures containing cyclohexane-alkane. These systems were selected primarily because the experimental solubilities of benzil are considerably different in each of the pure solvents. The experimental values in the binary mixtures are interpreted with models for either specific or nonspecific interactions.

EXPERIMENTAL

Reagents—Benzil¹ was recrystallized several times from methanol giving a melting point of 95.0 ± 0.5° [lit. (21) mp 95.2°]. Cyclohexane², *n*-heptane³, *n*-octane⁴, isooctane³, cyclooctane⁴, and carbon tetrachloride⁵ were all stored over molecular sieves⁶ to remove possible trace amounts of water. Binary solvent mixtures were prepared by weight so that compositions could be calculated to 0.0001 mole fraction.

Solubility Determinations—Excess solute and solvent were placed in amber glass bottles and allowed to equilibrate in a constant temperature bath at 25° for several days. Random duplicate samples were allowed to equilibrate for longer periods, but no significant differences in saturation solubility were observed. Aliquots of saturated benzil solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample and then diluted quantitatively with

¹ Eastman.

² Purity ≥99.5 Wt %, Phillips Petroleum Co.

³ Purity ≥99 mol %, Phillips Petroleum Co.

⁴ Gold label grade, Aldrich Chemical Co.

⁵ Spectranalyzed, Fisher Scientific Co.

⁶ Linde, Type 4A.

Table I—Mole Fraction Solubilities of Benzil in Several Binary Solvent Mixtures at 25°

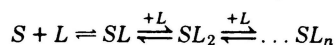
Solvent 1 + Solvent 2	X_1^0	$X_{\text{solute}}^{\text{sat}}$
CCl ₄ + iso-C ₈ H ₁₈	0.0000	0.00587
	0.1676	0.00797
	0.3104	0.01068
	0.4072	0.01360
	0.4096	0.01368
	0.6057	0.02249
	0.6358	0.02463
	0.7246	0.03126
	0.8266	0.04368
	1.0000	0.08082
C ₆ H ₁₂ + iso-C ₈ H ₁₈	0.0000	0.00587
	0.2494	0.00670
	0.3791	0.00724
	0.6180	0.00838
	0.7919	0.00935
	0.8704	0.00980
	1.0000	0.01067
	0.0000	0.00659
C ₆ H ₁₂ + C ₇ H ₁₆	0.0000	0.00659
	0.1893	0.00718
	0.3475	0.00778
	0.5774	0.00874
	0.7763	0.00959
	0.8582	0.01001
	1.0000	0.01067
	0.0000	0.01454
C ₆ H ₁₂ + C ₈ H ₁₆	0.0000	0.01395
	0.2260	0.01354
	0.3330	0.01266
	0.5620	0.01178
	0.7548	0.01133
	0.8566	0.01068
	1.0000	0.01068
	0.0000	0.08082
	0.1081	0.05542
	0.1877	0.04299
n-C ₈ H ₁₆ + CCl ₄	0.2997	0.03077
	0.3750	0.02512
	0.4358	0.02143
	0.5851	0.01535
	0.7129	0.01183
	1.0000	0.00726
	0.0000	0.00726
	0.2468	0.00798
	0.3763	0.00837
	0.5978	0.00911
C ₆ H ₁₂ + n-C ₈ H ₁₈	0.7892	0.00988
	0.8737	0.01019
	1.0000	0.01068
	0.0000	0.08082
	0.1773	0.05762
	0.2575	0.04864
	0.4158	0.03726
	0.5839	0.02768
	0.6524	0.02394
	0.7559	0.02115
1.0000	0.01454	
C ₈ H ₁₆ + CCl ₄	0.0000	0.08082
	0.1773	0.05762
	0.2575	0.04864
	0.4158	0.03726
	0.5839	0.02768
	0.6524	0.02394
	0.7559	0.02115
	1.0000	0.01454

cyclohexane. Concentrations were determined spectrophotometrically⁷ at 390 nm.

Experimental solubilities of benzil in several binary solvent mixtures are given in Table I. The measurements were reproducible to within 1.5%.

THEORETICAL

Stoichiometric Complexation Model—Stoichiometric complexation models have been used frequently to quantitatively explain enhanced solubilities of a polar organic solute in binary mixtures containing an inert hydrocarbon and a polar cosolvent. The basic model assumes complexation between the solute, *S*, and an interacting cosolvent, *L* (19,20):



Scheme I

Each reaction is described by an appropriate equilibrium constant with concentrations expressed in molarities:

⁷ Cary 118.

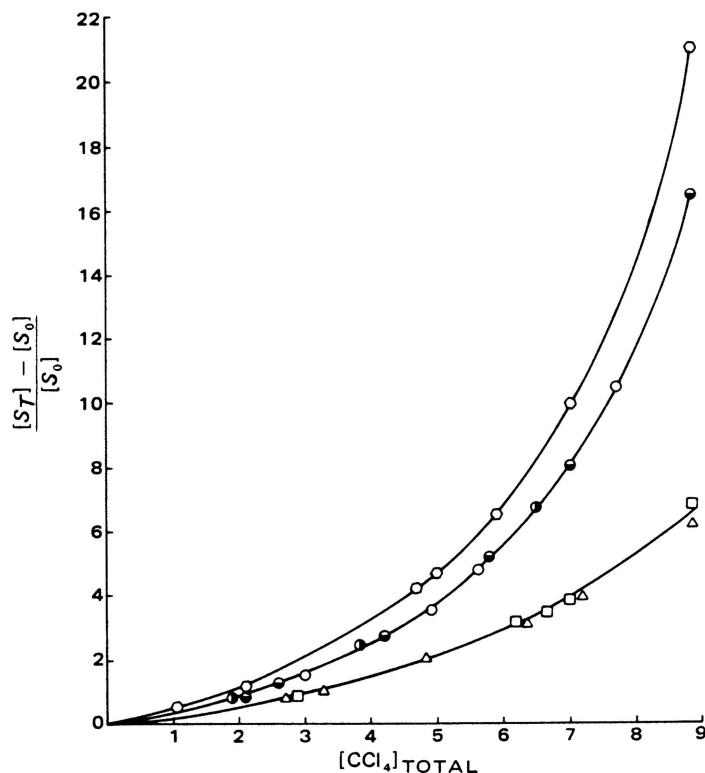


Figure 1—Graphical determination of $K_{1:1}$ from plots of fractional change in solubility versus carbon tetrachloride molarity for benzil in several binary solvents consisting of carbon tetrachloride and \circ , n-octane; \bullet , n-heptane; \circ , n-hexane; Δ , cyclohexane; and \square , cyclooctane. Solubilities in solvent mixtures containing cyclohexane, n-hexane, and n-heptane are from Ref. 5. The basic model requires additional solute-solvent complexes to explain curvature from the linearity. (See Eqs. 5 and 6).

$$K_{1:1} = \frac{[SL]}{[S_0][L]_f} \quad (\text{Eq. 1})$$

$$K_{1:n} = \frac{[SL_n]}{[SL_{n-1}][L]_f} \quad (\text{Eq. 2})$$

where $[S_0]$ is the saturation solubility of solute in pure inert hydrocarbon (assumed to represent the free solute concentration in binary mixtures as well) and $[L]_f$ is the free (uncomplexed) ligand.

This particular model assumes only a single solute molecule is present in each complex, but the mathematical form of the resulting equations is not significantly altered by additional solute molecules per complex. The total solubility of solute in any system, $[S_T]$, can be expressed as:

$$[S_T] = [S_0] + K_{1:1}[S_0][L]_f + K_{1:1}K_{1:2}[S_0][L]_f^2 + \dots \quad (\text{Eq. 3})$$

The total concentration of complexing agent, $[L_T]$, is:

$$[L_T] = [L]_f + K_{1:1}[S_0][L]_f + 2K_{1:1}K_{1:2}[S_0][L]_f^2 + \dots \quad (\text{Eq. 4})$$

In the absence of solute, the total concentration of interactive cosolvent $[L_T]$ is equal to $[L]_f$ only if the extent of self-association is negligible. Furthermore, the mathematical form of Eq. 3 predicts that plots of solubility versus cosolvent concentration should be concave upward in solvents incapable of self-association.

If only 1:1 complexes are present, Eqs. 3 and 4 can be combined to give:

$$\text{fractional change in solubility} = \frac{[S_T] - [S_0]}{[S_0]} = \frac{K_{1:1}}{1 + K_{1:1}[S_0]} [L_T] \quad (\text{Eq. 5})$$

A plot of the fractional change in solubility versus ligand added gives a straight line. Graphical methods are cumbersome for higher order complexes, and a first approximation often assumes the amount of ligand in complexes is small; $[L_T] = [L]_f$. This additional stipulation enables Eq. 3 to be rewritten as:

$$\frac{[S_T] - [S_0]}{[S_0][L_T]} = K_{1:1} + K_{1:1}K_{1:2}[L_T] \quad (\text{Eq. 6})$$

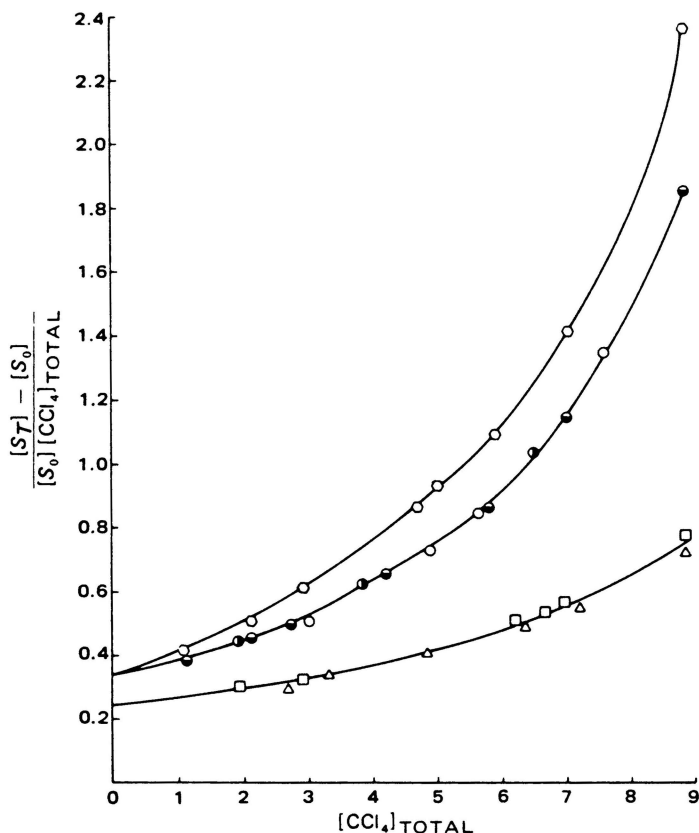


Figure 2—Determination of $K_{1:1}$ and $K_{1:2}$ for the interaction of benzil with carbon tetrachloride in several binary solvents at 25°. (See Eq. 6). The binary mixtures contained O, carbon tetrachloride and *n*-octane; ●, *n*-heptane; ●, *n*-hexane; ○, isooctane; △, cyclohexane; and □, cyclooctane.

$K_{1:2}$ is calculated from the slope of the linear portion of $([S_T] - [S_0])/[S_0][L_T]$ versus $[L_T]$ and $K_{1:1}$ is determined from the intercept. Applying Eqs. 5 and 6 to systems not involving complexation should theoretically give equilibrium constants of zero. Thus, the model might be expected to distinguish between complexing and noncomplexing systems through the relative magnitudes of calculated equilibrium constants. However, non-negligible K values can be obtained in systems where complexation does not occur.

This particular model includes the basic assumption that the free solute concentration $[S_0]$ is independent of solvent composition, an assumption that is not always supported by experimental evidence. Solubilities of iodine in binary mixtures of *n*-hexane–cyclohexane (0.0460–0.00860 *M*), *n*-hexane–carbon tetrachloride (0.0460–0.116 *M*), and *n*-hexane–chloroform (0.0460–0.176 *M*) depend on solvent composition (22). Yet the violet color of iodine in each of the pure solvents indicates the absence of molecular complexes (23). Similar variations are observed for the benzil solubilities in the binary mixtures of saturated hydrocarbons given in Table I.

Examination of the behavior of Eqs. 3 and 4 in isooctane–cyclohexane mixtures, where association with benzil is considered unlikely, reveals that the equations compensate for variations in $[S_0]$ with solvent composition (0.0353–0.0978 *M*) either by adjusting numerical values of $K_{1:n}$ or by assuming additional solute–solvent complexes. The larger the true variation in the concentration of uncomplexed solute, the larger this compensation becomes. Eventually a point can be reached when the equilibrium constants derived from Eqs. 3 and 4 no longer represent specific solute–solvent interactions, but rather the failure of the particular model to properly describe nonspecific interactions.

Figures 1 and 2 show the graphical determination of potential equilibrium constants calculated from Eqs. 5 and 6 for benzil solubilities in binary mixtures containing carbon tetrachloride. The various cosolvents appear to be grouped along three different curves: one for isooctane, a second for the three normal hydrocarbons (*n*-hexane, *n*-heptane, and *n*-octane), and a third curve for the two cyclic hydrocarbons (cyclohexane and cyclooctane). Presumed equilibrium constants calculated in mixtures containing cyclohexane are not identical to values calculated in

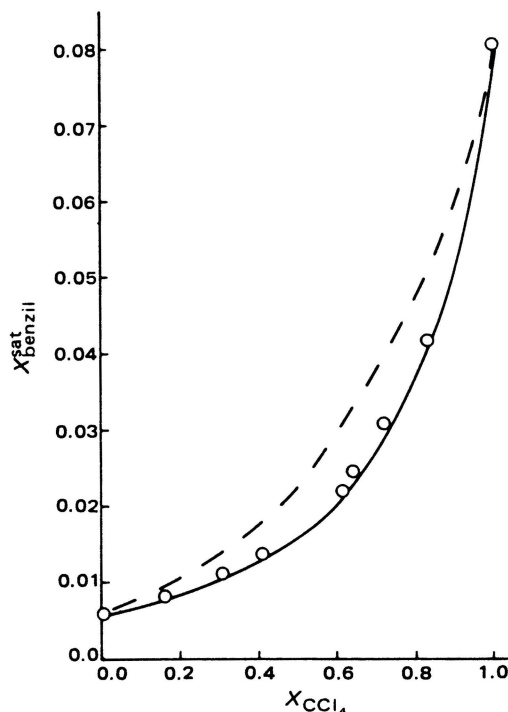


Figure 3—Comparison between experimental solubilities (O) and the NIBS predictions for benzil in binary mixture of carbon tetrachloride and isooctane using Eq. 7 (---), and Eqs. 8 and 9 (—). The free energy of mixing data for the binary solvent ($\Delta\bar{G}_{12}^{ex}$) is taken from Ref. 40.

isooctane mixtures. More importantly, the model requires several constants to represent mathematically the experimental data, and yet there appears to be no experimental evidence suggesting complexation between benzil and carbon tetrachloride.

Dipole moment measurements of benzil in benzene and carbon tetrachloride have been interpreted as evidence for specific interactions of benzil with benzene but not with carbon tetrachloride (24). The GLC retention behavior of carbon tetrachloride and chloroform on a benzil stationary phase has been interpreted (25) in terms of London or simple dispersion forces in the case of carbon tetrachloride and in terms of hydrogen bonding in the case of chloroform. Actual numerical values of the equilibrium constants are not reported to avoid the suggestion that a complex is formed between benzil and carbon tetrachloride. Since the y -intercept in Fig. 2 gives a presumed $K_{1:1}$, $K_{1:1}$ would range from 0.25–0.35 depending on the choice of cosolvent.

The Nearly Ideal Binary Solvent Model—The Nearly Ideal Binary Solvent (NIBS) approach developed by Bertrand *et al.* was shown to provide reasonable estimates for enthalpies of solution (2), GLC partition coefficients (4, 8), and solubilities (3, 5) in systems containing only nonspecific interactions. However, the approach fails for systems with specific solute–solvent or solvent–solvent interactions. The general expressions, derived from the NIBS model, for predicting solubilities in systems of nonspecific interactions depend on two models of solution nonideality:

$$RT \ln(a_3^{\text{solid}}/X_3^{\text{sat}}) = (1 - X_3^{\text{sat}})^2 [X_1^0 (\Delta\bar{G}_3^{\text{ex}})_{X_1^0=1} + X_2^0 (\Delta\bar{G}_3^{\text{ex}})_{X_2^0=1} - (\Delta\bar{G}_{12}^{\text{ex}})] \quad (\text{Eq. 7})$$

$$RT \ln(a_3^{\text{solid}}/X_3^{\text{sat}}) = (1 - \phi_3^{\text{sat}})^2 [\phi_1^0 (\Delta\bar{G}_3^{\text{ex}})_{\phi_1^0=1} + \phi_2^0 (\Delta\bar{G}_3^{\text{ex}})_{\phi_2^0=1} - \bar{V}_3 (X_1^0 \bar{V}_1 + X_2^0 \bar{V}_2)^{-1} (\Delta\bar{G}_{12}^{\text{ex}})] \quad (\text{Eq. 8})$$

$$RT \left[\ln(a_3^{\text{solid}}/\phi_3^{\text{sat}}) - (1 - \phi_3^{\text{sat}}) \left(1 - \frac{\bar{V}_3}{(X_1^0 \bar{V}_1 + X_2^0 \bar{V}_2)} \right) \right] = (1 - \phi_3^{\text{sat}})^2 [\phi_1^0 (\Delta\bar{G}_3^{\text{fn}})_{\phi_1^0=1} + \phi_2^0 (\Delta\bar{G}_3^{\text{fn}})_{\phi_2^0=1} - \bar{V}_3 (X_1^0 \bar{V}_1 + X_2^0 \bar{V}_2)^{-1} (\Delta\bar{G}_{12}^{\text{fn}})] \quad (\text{Eq. 9})$$

Equations 7 and 8 are based on the Regular Solution model (23) and Eq. 9 is based on the Flory–Huggins model (26–30). In these expressions, a_3^{solid} is the activity of the solid solute relative to the pure hypothetical supercooled liquid, X_i is mole fraction, ϕ_i is volume fraction, \bar{V}_i is the molar volume of a pure liquid, and $\Delta\bar{G}_{12}^{\text{ex}}$ is the molar excess Gibbs free

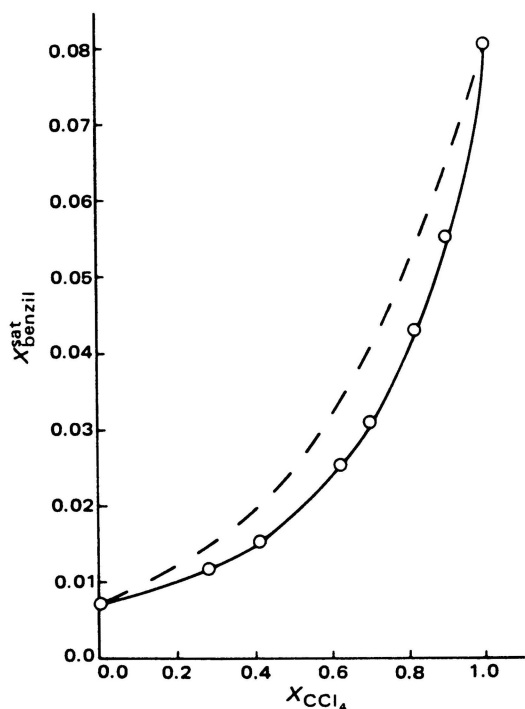


Figure 4—Comparison between the experimental solubilities (O) and the NIBS predictions for benzil in binary mixtures of carbon tetrachloride and n-octane using Eq. 7 (---), and Eqs. 8 and 9 (—). The free energy of mixing for the binary solvent is taken from Ref. 41.

energy of the binary solvent mixture relative to Raoult's law⁸. The superscript (0) denotes the initial binary solvent composition calculated as if the solute were not present. With these equations, solubility data measured in each pure solvent can be used to calculate the excess partial molar Gibbs-free energy of the solute $[(\Delta\bar{G}_3^{\text{ex}})_{X_3^0=1}, (\Delta\bar{G}_3^{\text{h}})_{X_3^0=1}]$. These quantities are then combined with the excess free energy of the binary solvent to predict solubility in mixed solvents using a reiterative process. The quantity $(1 - X_3^{\text{sat}})$ or $(1 - \phi_3^{\text{sat}})$ is taken as unity in the first approximation and convergence is quite rapid unless the solubility is large.

Graphical comparisons of experimental and calculated values are shown in Figs. 3 and 4 for benzil in isooctane-carbon tetrachloride and in n-octane-carbon tetrachloride mixtures. Properties used in the calculation include: α_3^{solid} (0.224) calculated from the enthalpy of fusion (22.15 cal/g) (21) at the melting point, and V_3 (183 cm³/mole) estimated from the density of the liquid at 102° and the coefficient of thermal expansion for benzophenone calculated over 50–95° (31). In general, Eqs. 8 and 9 are comparable with overall average (rms) deviations of 1.4 and 1.0%, respectively and are superior to Eq. 7 which has an average (rms) deviation of 10.0%.⁹ These observations are in agreement with earlier findings (2–5) that Eq. 7 is inferior to the other two predictive expressions for systems in which the molar volumes differ substantially.

RESULTS AND DISCUSSION

Although experimental solubilities can be described by equations derived from stoichiometric complexation models, the basic assumption that free solute concentration is independent of solvent composition is not always supported by experimental evidence. Solubilities of benzil in binary mixtures of nonpolar solvents such as isooctane-cyclohexane are found to vary with solvent composition. If carbon tetrachloride is included as a nonpolar solvent for benzil, experimental solubilities exhibit a 22-fold range in carbon tetrachloride-isooctane mixtures. Stoichiometric complexation models that attribute all solubility enhancement to the formation of molecular complexes require several equilibrium

⁸ For a binary mixture, the excess molar Gibbs free energy over the predictions of the Flory-Huggins equation is related to the defined excess free energy by: $\Delta\bar{G}_{12}^{\text{ex}} = \Delta\bar{G}_{12}^{\text{FH}} + RT [\ln(X_1^0 V_1 + X_2^0 V_2) - X_1^0 \ln V_1 - X_2^0 \ln V_2]$.

⁹ rms deviations (%) = $(100/N^{1/2}) \{ \sum [\ln(X_{\text{expt}}^{\text{sat}}/X_{\text{pred}}^{\text{sat}})]^2 \}^{1/2}$. These values were averaged for the six different binary solvent systems. The carbon tetrachloride-cyclooctane system was not included in these calculations because the excess Gibbs free energy was unavailable in the literature.

constants to describe benzil solubility in binary mixtures containing carbon tetrachloride.

Much smaller ranges have been observed for iodine solubilities in binary mixtures of n-hexane-benzene (0.046–0.588 M) (32), cyclohexane-benzene (0.083–0.543 M) (14), and carbon tetrachloride-benzene (0.116–0.588 M) (33) where specific solute-solvent interactions are expected to occur. Charge transfer complexes between iodine and benzene are well documented (34–36). Based on these observations, the range of solubilities encompassed in binary solvent mixtures does not always provide a clear indication of the complexing nature of the system. Caution should be exercised in inferring specific complex formation models in the absence of independent physical evidence for complexation, particularly if the model requires several relatively small equilibrium constants to describe the system.

The success of the NIBS approach in predicting the binary solvent effect on solubilities, covering up to a 14-fold range (mole fraction), suggests the possibility that this model may provide a foundation for approximations of the physical interactions even in a system containing chemical interactions such as association between the solute and a complexing solvent. Extensions of the basic NIBS model to systems containing 1:1 solute-solvent complex were shown to provide reasonable correlations of GLC partition coefficients with a mixed liquid phase (4). Through standard thermodynamic relationships, the expression of the NIBS model for a 1:1 solute-solvent complex (Eq. 25 of Ref. 4) can be applied to the solubility of solid substances, without requiring the solubility of the uncomplexed solute to be independent of solvent composition. Similar models have been suggested (37–39) to study the solubility of gases and solids in complexing systems.

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