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Solubilities in binary solvent systems II. The importance of non-specific interactions

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Summary

Solubilities have been determined at 25°C for *p*-benzoquinone in binary mixtures of cyclohexane with *n*-heptane, cyclooctane and isooctane, in mixtures of *n*-heptane with *n*-dodecane, and in binary mixtures of carbon tetrachloride with *n*-heptane and *n*-octane. The Nearly Ideal Binary Solvent (NIBS) model predicts these solubilities with a maximum deviation of 5% and an overall standard deviation of 1.6%. The NIBS model correctly predicts maxima for the mole fraction solubility of *p*-benzoquinone in both cyclohexane + *n*-heptane and cyclohexane + isooctane mixtures. The success of this simple model, based entirely on non-specific interactions, is significant considering the solubility of *p*-benzoquinone changes by a factor of 6 in the two binary solvent mixtures containing carbon tetrachloride. Solution models that attribute all solubility enhancement to the formation of stoichiometric complexes require several equilibrium constants to mathematically describe the 6-fold range of *p*-benzoquinone solubilities in these two solvent mixtures.

Introduction

The relationship between the molecular structure of a drug molecule and its physical and biological behavior is of paramount importance in designing improved drugs and drug delivery systems. The design of an effective drug involves delivery of the drug to the target site, optimizing the release rate from a pharmaceutical

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formulation, controlling the rate of transport through physiological barriers, and favorably altering the drug's solubility through either complexation or structural modifications. All of the above properties are related directly to the thermodynamic activity of the drug in the phases involved. Naturally, one of the major goals of research in the area of pharmaceutical chemistry has been the development of models which enable a priori predictions of solution behavior.

The interpretation of solution non-ideality basically has followed two dissimilar lines: the "physical" approach originated by van Laar (1910) and the "chemical" approach proposed by Dolezalek (1908). The physical approach may be described in terms of a random distribution of molecules throughout the entire solution while the chemical approach may be characterized in terms of 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 non-specific interactions has been recognized. Arnett et al. (1970) with their "pure base" calorimetric method for determining enthalpies of hydrogen bond formation attempted to separate specific and non-specific interactions, but the sensitivity of the numerical results to the selection of "model" compound and inert solvent (Duer and Bertrand, 1970) raises important doubts regarding the overall effectiveness of this particular method. Salija et al. (1977) used a somewhat similar rationale in their comparison of enthalpies of transfer of alkenes and the corresponding alkenes from the vapor state to methanol, dimethylformamide, benzene and cyclohexane, with the more exothermic values for the alkenes in methanol and dimethylformamide attributed to dipole-induced dipole interactions between the solvent and the polarizable π-bond. Bertrand (1975) demonstrated that neglect of non-specific interactions in the chloroform and triethylamine system can lead to an appreciable error in the enthalpy of complex formation determined with the ideal associated solution model. Fenby et al. (1977) presented a similar analysis of the diethyl ether + chloroform system.

Many of the remaining methods for estimating complex formation constants can be classified as solubility methods. That is, the increase in solubility of a solute at constant fugacity in a complexing-inert solvent mixture, relative to the solubility in pure inert solvent, is generally attributed to the formation of molecular complexes. This primary assumption is common to several thermodynamic methods, such as the partition of solutes between two immiscible liquid phases, the measurement of infinite dilution gas–liquid chromatographic partition coefficients and the increase in solubility of solids. The techniques for calculating formation constants are essentially identical for all solubility methods, as are the difficulties in properly assessing what portion of solubility enhancement is due to non-specific interactions.

In the first paper of this series (Acree and Rytting, in press) we reported experimental solubilities for benzil in binary solvent mixtures containing carbon tetrachloride, in which the mole fraction solubility covers a 14-fold range. The results of these measurements were compared to solution models developed previously for solubility in systems containing specific solute–solvent interactions and to models of purely non-specific interactions. A stoichiometric complexation model based entirely on specific interactions (non-specific interactions ignored) required several equilibrium constants to describe the experimental results, while the simple

Nearly Ideal Binary Solvent (NIBS) model based on non-specific interactions described adequately the observed solubilities without introducing a single equilibrium constant.

Since a major goal of our work continues to be the development of realistic approaches for predicting solubilities in mixed solvents, we are particularly interested in obtaining a thorough understanding of both specific and non-specific interactions. To gain additional insight into the importance of non-specific interactions, we have measured the solubility of *p*-benzoquinone in several binary solvent mixtures containing carbon tetrachloride. During the course of this investigation, the NIBS model was found to predict slight maximum solubilities for *p*-benzoquinone in mixtures of cyclohexane with *n*-heptane and with isooctane. Such "synergic effects" are usually explained by solubility parameter theory in terms of the solubility parameter of the solute being bracketed by the solubility parameters of the two pure solvents (Gordon and Scott, 1952; Buchowski et al., 1979). However, all estimates of the solubility parameter of *p*-benzoquinone are far greater than the values of cyclohexane, *n*-heptane and isooctane. Solubility determinations of *p*-benzoquinone in these binary solvent mixtures will provide an additional test of the NIBS model.

Materials and methods

p-Benzoquinone (Aldrich 98%) was recrystallized several times from petroleum ether, giving a melting point of 115 ± 0.5°C (literature value 115.7°C; Weast, 1970). Cyclohexane (Phillips 99.5 wt.%), *n*-heptane (Phillips 99 mol%), isooctane (Phillips 99 mol%), cyclooctane (Aldrich Gold Label) and *n*-dodecane (Humphrey 99 mol%) were stored over molecular sieves (Type 4A) to remove trace amounts of water. Binary solvent mixtures were prepared by weight so that solvent compositions could be calculated to 0.0001 mole fraction.

Excess solute and solvent were placed in brown bottles and allowed to equilibrate in a constant temperature bath at 25.0°C for several days. Random duplicate samples were allowed to equilibrate for a longer period of time, but no significant difference in the saturation solubility was observed. Aliquots of saturated *p*-benzoquinone solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample, and diluted quantitatively with cyclohexane. Concentrations were determined spectrophotometrically at 285 nM on a Cary 118 spectrophotometer, with the sample cells thermostatted at 25°C to maintain a constant temperature. Experimental solubilities of *p*-benzoquinone in several binary solvent mixtures are given in Table 1. The experimental results at each composition represent the average of 10 determinations with a maximum deviation of 0.3% except for the two carbon tetrachloride + *n*-alkane (*n*-heptane and *n*-octane) systems which had maximum deviations of about 1%.

TABLE 1

SOLUBILITY OF *p*-BENZOQUINONE IN SEVERAL BINARY SOLVENT MIXTURES AT 25.0°C

Solvent (1)+Solvent (2)	X_1^0	X_{solute}^{sat}
n-C_7H_{16}+c-C_6H_{12}	0.0000	0.00652
	0.1682	0.00665
	0.3341	0.00670
	0.4230	0.00673
	0.5284	0.00675
	0.7485	0.00674
	1.0000	0.00664
c-C_8H_{16}+c-C_6H_{12}	0.0000	0.00652
	0.1693	0.00686
	0.2865	0.00697
	0.4465	0.00723
	0.5243	0.00737
	0.7532	0.00769
	1.0000	0.00800
c-C_6H_{12}+i-C_8H_{16}	0.0000	0.00665
	0.2781	0.00668
	0.5081	0.00674
	0.6104	0.00671
	0.7049	0.00669
	0.8682	0.00661
	1.0000	0.00652
n-$C_{12}H_{26}$+*n*-C_7H_{16}	0.0000	0.00664
	0.1380	0.00694
	0.2965	0.00728
	0.3891	0.00747
	0.4936	0.00767
	0.7273	0.00818
	1.0000	0.00872
n-C_8H_{18}+CCl_4	0.0000	0.03437
	0.1676	0.02432
	0.2837	0.01958
	0.3702	0.01694
	0.4766	0.01447
	0.7154	0.01042
	1.0000	0.00749
n-C_7H_{16}+CCl_4	0.0000	0.03437
	0.1894	0.02340
	0.2916	0.01937
	0.3897	0.01640
	0.5243	0.01318
	0.6807	0.01041
	0.7709	0.00901
	1.0000	0.00664

Results and discussion

The Nearly Ideal Binary Solvent (NIBS) approach has been shown to provide reasonable estimates for enthalpies of solution (Burchfield and Bertrand, 1975), gas–liquid chromatographic partition coefficients (Acree and Bertrand, 1979; Acree and Rytting, 1980) and solubilities (Acree and Bertrand, 1977; Acree and Rytting, in press) in systems containing only non-specific interactions, but fails for systems with specific solute–solvent or solvent–solvent interactions. The general NIBS expressions for predicting solubilities in systems of non-specific interactions depend on two different models of solution ideality:

$$RT\ln\left(a_3^{solid}/X_3^{sat}\right)=\left(1-X_3^{sat}\right)^2\left[X_1^0\left(\Delta\overline{G}_3^{ex}\right)^*_{X_1^0=1}+X_2^0\left(\Delta\overline{G}_3^{ex}\right)^*_{X_2^0=1}-\left(\Delta\overline{G}_{12}^{ex}\right)\right]\quad\text{(XX)}$$

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

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

Eqns. XX and XV based on the Regular Solution model and Eqn. VV based on the Flory-Huggins model. In the above 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, $\overline{V}_i$ is the molar volume of pure component i and ΔG_{12}^{ex} is the molar excess Gibbs free-energy of the binary solvent mixture relative to Raoult's Law[1]. The superscript (°) denotes the initial binary solvent composition calculated as if the solute were not present. With these 3 equations, solubility data measured in each of the pure solvents can be used to calculate the excess partial molar Gibbs free-energy of the solute $[(\Delta\overline{G}_3^{ex})^*_{X_i^0=1}$ and $(\Delta\overline{G}_3^{fh})^*_{X_i^0=1}]$. Then these quantities are combined with the excess free-energy of the binary solvent to predict solubility in mixed solvents.

Graphical comparison between experimental and predicted values are shown in Figs. 1 and 2 for *p*-benzoquinone in *n*-heptane + carbon tetrachloride and *n*-octane + carbon tetrachloride mixtures. Properties used in the calculations include a_3^{solid} ($=0.182$) taken from a tabulation presented by Yalkowsky and Valvani (1980), and

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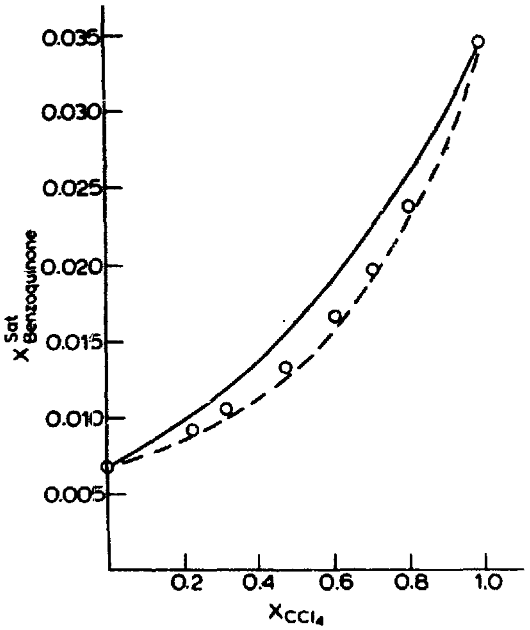
[1] For a binary mixture, the excess molar Gibbs free-energy over the predictions of the Flory-Huggins equation is related to the defined excess free-energy by:

$$\Delta\overline{G}_{12}^{fh}=\Delta\overline{G}_{12}^{ex}+RT\left[\ln\left(X_1^0\overline{V}_1+X_2^0\overline{V}_2\right)-X_1^0\ln\overline{V}_1-X_2^0\ln\overline{V}_2\right]$$



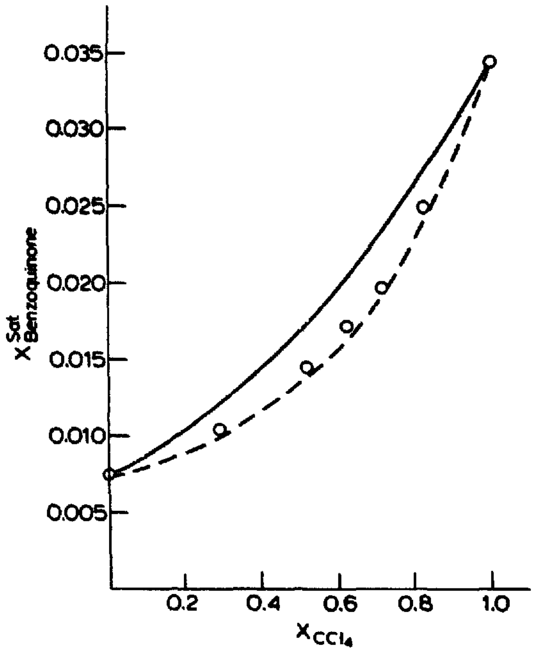


Fig. 1. Comparison between the experimental solubilities (O) and the NIBS predictions using Eqns. XX (————), XV (- - -), or VV (— — —) for *p*-benzoquinone in binary mixtures of carbon tetrachloride and *n*-heptane. The free-energy of mixing for the binary solvent ($\Delta\bar{G}^{ex}_{12}$) was taken from an article by Bissell and Williamson (1975).

Fig. 2. Comparison between the experimental solubilities (O) and the NIBS predictions using Eqns. XX (————), XV (- - -), or VV (— — —) for *p*-benzoquinone in binary mixtures of carbon tetrachloride and *n*-octane. The excess free-energy of mixing for the binary solvent ($\Delta\bar{G}^{ex}_{12}$) was taken from an article by Jain et al. (1971).

$\bar{V}_3$ (= 82.1 cm^3/mol) estimated from the density of 1,4-cyclohexadiene with 13.0 cm^3/mol subtracted for the two carbonyl groups. For the systems used in this investigation, the NIBS predictions are not very sensitive to the solute's molar volume. A 10% error in estimating $\bar{V}_3$ affects the predicted *p*-benzoquinone solubilities by less than 1%. In general, Eqns. XV and VV are comparable with overall average (RMS) deviations[2] of 1.6% and 1.9%, respectively, and are superior to Eqn. XX which has an average (rms) deviation of 5.1%. These observations are in agreement with earlier findings (Acree and Bertrand, 1977; Acree and Rytting, in press) that Eqn. XX is inferior to the other two predictive expressions for systems in which the molar volumes differ appreciably.

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[2] RMS Deviations (%) $= (100/N^{1/2}) \left\{ \sum_{i=1}^{N} |\ln (X^{sat}_{calc} / X^{sat}_{exp})|^2 \right\}^{1/2}$ and these values are then averaged for the 6 different binary solvent systems.

Conclusion

The success of the NIBS model in predicting the experimental solubilities in binary carbon tetrachloride mixtures suggests that specific solute–solvent interactions between *p*-benzoquinone and carbon tetrachloride are either very weak or are not present in the systems studied as one would expect from the structures of the substances involved. There is a tendency to invoke either specific interaction models or solubility parameter theory when large solubility enhancements are found. Models that attribute all solubility enhancement to the formation of molecular complexes require at least one equilibrium constant to mathematically describe the 5-fold range of solubilities encompassed in the *n*-heptane + carbon tetrachloride system. For example, two equilibrium constants would be required in a model developed by Higuchi and coworkers (Fung and Higuchi, 1971; Anderson et al., 1980) to adequately describe the experimental results as their expression for 1:1 solute–solvent complexes can be expressed as a mole fraction average of the solubilities in the two pure solvents

$$X_3^{sat} = X_1^0 (X_3^{sat})_{X_1^0=1} + X_2^0 (X_3^{sat})_{X_2^0=1} \tag{4}$$

when the experimental solubility is sufficiently small and the excess molar volume of the binary solvent is negligible. Experimental solubilities of *p*-benzoquinone in binary carbon tetrachloride mixtures exhibit considerable deviations from Eqn. 4, with some deviations as large as 50%. Solubility parameter theory cannot account for the maximum observed here as mentioned earlier.

This study also illustrates that the range of solubilities encompassed in a binary solvent mixture does not always provide a clear indication regarding the complexing nature of the system. Comparable solubility ranges are found for iodine solubilities in benzene + cyclohexane (Purkayastha and Walkley, 1972) and in benzene + carbon tetrachloride mixtures (Wood et al., 1957) where complexation is expected to occur since charge transfer complexes between iodine and benzene are well documented in the literature (Benesi and Hildebrand, 1948 and 1949; Mulliken, 1950 and 1952). Nevertheless, large increases in solubility can be accounted for using the NIBS model without invoking complexation equilibria for systems such as *p*-benzoquinone in the several binary mixtures described here provided specific interactions are not anticipated. However, when strong specific interactions are important, models including molecular complexes describe the solubility data well (Fung and Higuchi, 1971; Anderson et al., 1980).

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