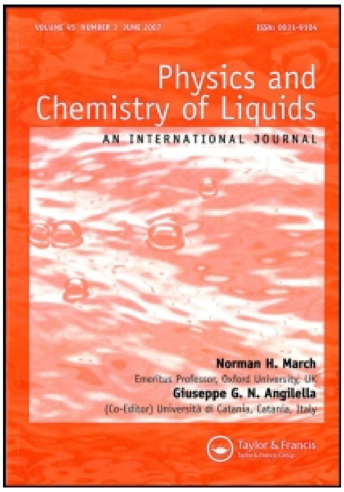

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Solubility in Binary Solvent Systems: Comparison of Predictive Equations Derived from the NIBS Model

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Experimental solubilities are reported for pyrene in binary solvent mixtures containing benzene with *n*-hexane, cyclohexane, *n*-heptane, *n*-octane, cyclooctane and isooctane at 26°C. Results of these measurements, combined with published pyrene and biphenyl solubilities, are used to test predictive expressions derived from the Nearly Ideal Binary Solvent (NIBS) model. The most successful equation in terms of goodness of fit involved a surface fraction average of the excess Gibbs free energy relative to Raoult's law and predicted the experimental solubilities in 17 systems with an average deviation of 2.3% and a maximum deviation of 8.9%. Two expressions approximating weighting factors with molar volumes provided accurate predictions in many systems studied but failed in their ability to predict pyrene solubilities in solvent mixtures containing benzene.

KEY WORDS and PHRASES Binary solvents—predictive expressions for solubility; Solubility—binary solvent systems; Pyrene—solubility in binary solvents; Biphenyl—solubility in binary solvents.

INTRODUCTION

The use of binary solvents for influencing solubility and multiphase partitioning has many potential applications in both the chemical and pharmaceutical industry. Maximum realization of these applications depends, however, on the development of equations that enable *a priori* prediction of solution behavior in mixed solvents from a minimum number of additional observations. Ideally, the ability to predict a

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molecule's solubility and partition coefficients based solely on a consideration of molecular structure is desired, but for more practical applications a less fundamental approach must often suffice.

Study of the solubility process also provides, at a more fundamental level, an understanding of molecular interactions in solution. A convenient approach to elucidating solute–solvent, solvent–solvent and solute–solute interactions for use in predicting solubility behavior is facilitated by an analysis of the solution properties of simpler molecules. The Nearly Ideal Binary Solvent (NIBS) model developed previously[1–10] provides a relatively simple method for estimating the excess partial molar properties of a solute, $\bar{Z}_3^{ex}$, at infinite dilution in a binary solvent (components 1 and 2):

$$\bar{Z}_3^{ex} = f_1^0(\bar{Z}_3^{ex})_1^* + f_2^0(\bar{Z}_3^{ex})_2^* - \Gamma_3(X_1^0\Gamma_1 + X_2^0\Gamma_2)^{-1}\bar{Z}_{12}^{ex} \tag{1}$$

$$f_1^0 = 1 - f_2^0 = X_1^0\Gamma_1/(X_1^0\Gamma_1 + X_2^0\Gamma_2) \tag{2}$$

in terms of a weighted mole fraction average of the properties of the solute in the two pure solvents $(\bar{Z}_3^{ex})_1^*$ and $(\bar{Z}_3^{ex})_2^*$ and a contribution due to the unmixing of the solvent pair by the presence of the solute. Equation 1 (with $\bar{Z}^{ex} = \bar{G}^{ex}$) gives accurate predictions for naphthalene, iodine, *p*-dibromobenzene, benzil, *p*-benzoquinone, benzoic acid and phenylacetic acid solubilities in systems of non-specific interactions when molar volumes are used as weighting factors (Γ_i). Approximation of weighting factors with molecular surface areas enables Eq. 1 to provide accurate predictions for anthracene solubilities in binary solvent mixtures containing benzene.

Continued development of solution models for predicting the properties of a solute in binary solvent systems requires that a large data base be available for assessing the applications and limitations of derived predictive expressions. Currently, only a limited data base exists for crystalline nonelectrolyte solubility in binary solvent systems. For this reason, pyrene solubilities were determined in mixtures containing benzene with *n*-hexane, cyclohexane, *n*-heptane, *n*-octane, cyclooctane and isooctane, which cover up to an eightfold range of mole fraction solubilities. Results of these measurements are compared to the predictions of the NIBS model.

MATERIALS AND METHODS

Pyrene (Aldrich 99%) was recrystallized three times from absolute ethanol, giving a melting point of 151.1 ± 0.5°C (literature values are

151.3[11] and 149–150°C[12]). Cyclohexane (Aldrich HPLC grade), benzene (Aldrich HPLC grade), *n*-hexane (Aldrich 99%), *n*-heptane (Aldrich Gold Label), *n*-octane (Aldrich Gold Label), cyclooctane (Aldrich Gold Label) and isooctane (Fisher 99%) 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 pyrene and solvent were placed in amber glass bottles and allowed to equilibrate in a constant temperature bath at 26.0 ± 0.1°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 pyrene solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample, and diluted quantitatively with methanol. Concentrations were determined spectrophotometrically at 372 nm on a Bausch and Lomb Spectronic 2000. Experimental solubilities of pyrene in several binary solvent mixtures are given in Table I. Experimental results at each composition represent the average of 4 to 8 determinations with a maximum deviation of about 1.5%.

RESULTS AND DISCUSSION

The general NIBS expressions for predicting solubilities in systems on non-specific interactions depend on different models of solution ideality and weighting factor approximations:

$$RT\ln(a_3^{\text{solid}}/X_3^{\text{sat}}) = (1 - X_3^{\text{sat}})^2[X_1^0(\bar{G}_3^{\text{ex}})_1^* + X_2^0(\bar{G}_3^{\text{ex}})_2^* - \bar{G}_{12}^{\text{ex}}] \quad \text{(XX)}$$

$$\begin{aligned} RT\ln(a_3^{\text{solid}}/X_3^{\text{sat}}) = (1 - \phi_3^{\text{sat}})^2[&\phi_1^0(\bar{G}_3^{\text{ex}})_1^* + \phi_2^0(\bar{G}_3^{\text{ex}})_2^* \\ &- V_3(X_1^0V_1 + X_2^0V_2)^{-1}\bar{G}_{12}^{\text{ex}}] \quad \text{(XV)} \end{aligned}$$

$$\begin{aligned} RT\ln(a_3^{\text{solid}}/X_3^{\text{sat}}) = (1 - \theta_3^{\text{sat}})^2[&\theta_1^0(\bar{G}_3^{\text{ex}})_1^* + \theta_2^0(\bar{G}_3^{\text{ex}})_2^* \\ &- A_3(X_1^0A_1 + X_2^0A_2)^{-1}\bar{G}_{12}^{\text{ex}}] \quad \text{(XA)} \end{aligned}$$

$$\begin{aligned} &RT\left[\ln(a_3^{\text{solid}}/\phi_3^{\text{sat}}) - (1 - \phi_3^{\text{sat}})\left(1 - \frac{V_3}{X_1^0V_1 + X_2^0V_2}\right)\right] \\ &= (1 - \phi_3^{\text{sat}})^2[\phi_1^0(\bar{G}_3^{\text{fh}})_1^* + \phi_2^0(\bar{G}_3^{\text{fh}})_2^* - V_3(X_1^0V_1 + X_2^0V_2)^{-1}\bar{G}_{12}^{\text{fh}}] \quad \text{(VV)} \end{aligned}$$

$$\begin{aligned} &RT\left[\ln(a_3^{\text{solid}}/\phi_3^{\text{sat}}) - (1 - \phi_3^{\text{sat}})\left(1 - \frac{V_3}{X_1^0V_1 + X_2^0V_2}\right)\right] \\ &= (1 - \theta_3^{\text{sat}})^2[\theta_1^0(\bar{G}_3^{\text{fh}})_1^* + \theta_2^0(\bar{G}_3^{\text{fh}})_2^* - A_3(X_1^0A_1 + X_2^0A_2)^{-1}\bar{G}_{12}^{\text{fh}}] \quad \text{(VA)} \end{aligned}$$

TABLE I

Solubility of pyrene in several binary solvents at 26.0°C.

Solvent (1) + Solvent (2)	X_1^0	X_3^{sat}
Benzene + *n*-Hexane	0.0000	0.00852
	0.2833	0.01676
	0.4977	0.02756
	0.6008	0.03389
	0.6824	0.03961
	0.8451	0.05107
	1.0000	0.06316
Benzene + Cyclohexane	0.0000	0.01089
	0.2504	0.02058
	0.4420	0.03118
	0.5524	0.03680
	0.6525	0.04289
	0.8196	0.05243
	1.0000	0.06316
Benzene + *n*-Heptane	0.0000	0.01101
	0.3091	0.02049
	0.5277	0.03102
	0.6219	0.03702
	0.7213	0.04352
	0.8627	0.05280
	1.0000	0.06316
Benzene + *n*-Octane	0.0000	0.01379
	0.3288	0.02455
	0.5434	0.03398
	0.6549	0.04006
	0.7355	0.04428
	0.8729	0.05432
	1.0000	0.06316
Benzene + Cyclooctane	0.0000	0.01956
	0.2969	0.03236
	0.5031	0.04327
	0.6026	0.04898
	0.6982	0.05371
	0.8517	0.05993
	1.0000	0.06316
Benzene + Isooctane	0.0000	0.00721
	0.3021	0.01373
	0.5482	0.02446
	0.6520	0.03165
	0.7444	0.03854
	0.8799	0.05160
	1.0000	0.06316

Equations XX, XV and XA are based on Raoult's law while Eqs VV and VA are based on the Flory–Huggins model. In the above expressions V_i is the molar volume of a pure liquid, A_i is the molecular surface area, X_i denotes mole fraction, ϕ_i is volume fraction, θ_i is surface fraction, $\bar{G}_{12}^{\text{ex}}$ refers to the molar excess Gibbs free energy of the binary solvent relative to Raoult's law, and

$$\bar{G}_{12}^{\text{fh}} = \bar{G}_{12}^{\text{ex}} + RT[\ln(X_1^0 V_1 + X_2^0 V_2) - X_1^0 \ln V_1 - X_2^0 \ln V_2]$$

Numerical values of $\bar{G}_{12}^{\text{ex}}$ can be found in the chemical literature for many common binary systems. For example, the thermodynamic excess properties of several hundred binary systems have been listed by Gmehling, *et al.*[13] The superscript (0) indicates that the solvent composition is calculated as if the solute were not present. The activity of the solid solute (a_3^{solid}), relative to the supercooled liquid, can be calculated from

$$\ln a_3^{\text{solid}} = -\frac{\Delta H_3^{\text{fus}}(T_m - T)}{RTT_m} + \frac{\Delta C_p(T_m - T)}{RT} - (\Delta C_p/R)\ln(T_m/T)$$

the molar heat of fusion (ΔH_3^{fus}) at the normal melting point (T_m) and the differences between the molar heat capacities of the liquid and solid.

The predictive ability of the five equations are compared in Table II for systems for which solubility data and the excess free energy of the binary solvent are available at or near the same temperature. Each system reports solubility data in both pure solvents and 5 binary mixtures covering the entire range of solvent composition. Surface areas of the individual molecules were taken from tabulated values presented in previous reports.[14–17] In all cases, the surface areas exclude solvent molecules which may be located within the solvation sphere surrounding the solute molecule. Table III lists numerical values of the surface areas and molar volumes used in the NIBS predictions.

Equation XA, based on surface areas as weighting factors for the excess Gibbs free energy relative to Raoult's Law, is found to be the most generally predictive expression with an overall average (RMS) deviation of 2.3 % and a maximum error for a single data point of 8.9 %. Large deviations noted in the benzene + *n*-heptane system may be attributed, in part, to uncertainties in published $\bar{G}_{12}^{\text{ex}}$ values. As shown in Table II, deviations between predicted and experimental pyrene solubilities depend to a large extent on which literature source is used for the benzene + *n*-heptane solvent properties. This leads to two sets of predicted pyrene solubilities that differ from each other by as much as 6 %. Discrepancies in the reported values of $\bar{G}_{12}^{\text{ex}}$ were not noted for the remaining 13 binary solvent systems. The primary advantage of Eq. XA

TABLE II

Comparison of predictive equations for the solubilities of biphenyl and pyrene in various binary solvent mixtures.

Solvent System	Data Ref.	RMS Deviations[a] (%) for the Predictive Equations					$\bar{G}^{ex}_{12}$ Ref.
		(XX)	(XV)	(VV)	(XA)	(VA)	
Solute = Biphenyl							
Cyclohexane + *n*-Hexane	24	+1.5	+0.5	+0.5	+1.4	+1.5	26
Cyclohexane + *n*-Heptane	24	+2.2	0.4	0.6	+1.0	+1.1	27
Cyclohexane + *n*-Octane	24	+2.7	0.6	0.6	+0.9	+1.1	28
Cyclohexane + Carbon tetrachloride	24	0.7	+0.7	+0.7	+1.6	+1.6	29
Carbon tetrachloride + *n*-Hexane	24	+2.8	0.7	0.7	+4.3	+4.3	30
Carbon tetrachloride + *n*-Heptane	24	+4.8	0.6	+0.6	+3.3	+3.3	31
Solute = Pyrene							
Cyclohexane + *n*-Hexane	25	−2.9	−2.5	−2.4	−1.6	−1.4	26
Cyclohexane + *n*-Heptane	25	−2.3	−1.4	−1.0	−0.8	0.4	27
Cyclohexane + *n*-Octane	25	−3.8	−1.2	0.7	0.8	0.4	28
Cyclohexane + Cyclooctane	25	−4.3	−1.1	−0.9	−1.0	−0.7	32
Cyclohexane + Isooctane	25	+2.0	−1.6	−1.1	0.5	+1.0	33
Benzene + *n*-Hexane	*	1.1	−8.0	−7.5	2.0	2.1	34
Benzene + Cyclohexane	*	−10.0	−9.2	−9.1	−4.2	−4.2	29
Benzene + *n*-Heptane	*	+5.9	−5.6	−4.5	+2.1	+2.8	35
Benzene + *n*-Heptane	*	+3.6	−9.3	−8.4	2.8	2.3	36
Benzene + *n*-Octane	*	+5.7	−9.7	−8.6	−4.0	−2.8	35
Benzene + Cyclooctane	*	−7.2	−12.0	−11.3	−7.6	−7.1	37
Benzene + Isooctane	*	+10.3	−13.4	−12.2	0.8	+1.5	38

[a] RMS Deviations (%) = $(100/N^{1/2})\{\sum^N[\ln(X^{sat}_{calc}/X^{sat}_{exp})]^2\}^{1/2}$; an algebraic sign indicates that all deviations were of the same sign.

TABLE III

Properties used in the NIBS predictions

Component	V_i, ml/mol	A_i, Å^2/mol
Benzene	89.41	109.5
Carbon tetrachloride	97.08	118.7
Cyclohexane	108.76	120.8
n-Hexane	131.51	142.1
n-Heptane	147.48	160.3
n-Octane	163.46	178.4
Cyclooctane	134.88	148.8
Isooctane	166.09	163.1
Biphenyl	149.40	182.0 ($a_3^{\text{solid}} = 0.3844$)
Pyrene	166.50[39]	213.0 ($a_3^{\text{solid}} = 0.1312$)

over expressions based on molar volumes, Eqs XV and VV, is its applicability to pyrene solubilities in solvent mixtures containing benzene. If these systems are excluded from the comparison, Eqs XV and VV are slightly better than equations based on surface areas. This is in agreement with observations from an earlier study on anthracene solubilities in binary solvent mixtures.[8]

Deviations between observed and predicted solubilities for pyrene in mixtures containing benzene are larger than experimental uncertainties. It must be remembered, however, that three measured values are needed for each NIBS prediction. Pyrene solubility in each pure solvent was reproducible to within 1.5% and, except for the bezene + *n*-heptane system, $\bar{G}_{12}^{ex}$ values are believed to be accurate to at least ± 6 cal/mol. Ratios of $\Gamma_3/(X_1^0\Gamma_1 + X_2^0\Gamma_2)$ greater than unity magnify the effect that errors in the unmixing term has on the solubility predictions. A 6 cal/mol error in $\Gamma_3(X_1^0\Gamma_1 + X_2^0\Gamma_2)^{-1}\bar{G}_{12}^{ex}$ corresponds to an error of 1% in the predicted value. Based on these observations, "uncertainties" in the NIBS predictions are estimated to be on the order of 2-3%, which in part explains deviations between observed and predicted values.

An important consequence of this research involves earlier contentions that the failure of Eq. 1 may be taken as an indication of specific solute-solvent or solvent-solvent interactions. While this concept is relatively straightforward in principle, its practical applications are complicated by the various weighting factor approximations and methods for estimating molecular surface areas.[15,18-20] Unlike molar volumes, molecular surface areas cannot be determined experimentally. For example, does the failure of Eqs XV and VV to predict pyrene solubilities in binary solvent mixtures containing benzene indicate specific solute–solvent ($\pi - \pi$) interactions, or does the success of Eq. XA indicate that surface areas provide better approximations of weighting factors in systems containing both a planar solute and solvent molecule.

Unfortunately, comparisons between experimental and predicted solubilities do not indicate clearly whether weighting factors are better approximated with molar volumes or surface areas. From the standpoint of calculational simplicity and the ready availability of molar volumes, Eq. XV is preferred, and some support for this form can be found in its adaptability to the Scatchard–Hildebrand solubility parameter theory.[21,22] Similar support for Eq. XA (and Eq. VA) can be found in correlations of partition coefficients with surface areas and in several semi-empirical expressions developed for predicting aqueous solubilities and liquid–vapor equilibria. However, Eq. VV is also applicable to polymer solutions, and this form often is preferred because it is more directly related to gas–liquid chromatographic partition coefficients and to molarity-based equilibrium constants. Furthermore, Chiou and Manes[23] recently demonstrated that the Flory–Huggins model, on which Eq. VV is based, represented a more realistical description of solution ideality in systems having molecules of moderate size disparity.

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