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Solubility in binary solvent systems. IV. Prediction of naphthalene solubilities using the UNIFAC group contribution model

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Summary

This work extends the UNIFAC group contribution method of solid–liquid equilibria to binary solvent mixtures, and compares its predictions to experimental solubilities for naphthalene in 16 different solvent mixtures. Deviations between experimental and calculated values are of the order of 10–20% for most solvent systems, and are comparable in magnitude to deviations noted in the pure solvents. The ability of the UNIFAC model to provide reasonable estimates of naphthalene solubilities based only on heat of fusion data and group contribution parameters suggests that the model may be useful in the area of drug design.

Introduction

The ability to predict thermodynamic activity coefficients of drug molecules in any given environment would be of value in considerations of mechanisms of drug delivery. The magnitudes of these coefficients are largely determined by the nature and extent of molecular interactions between the dissolved drug and its surrounding solvent molecules. The various types of interactions present determine to a large extent the macroscopic solubility of the drug.

Earlier attempts (Acree and Bertrand, 1977, 1980; Acree and Rytting, 1982a and b) to correlate the thermochemical properties of a solute as a function of solvent composition have been primarily restricted to testing the applications and limitations

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of the Nearly Ideal Binary Solvent model. While this particular thermodynamic model has been shown to provide very reasonable predictions for the solubility of iodine, naphthalene, *p*-dibromobenzene, benzil, benzoic acid and *p*-benzoquinone in systems containing only non-specific interactions, thefact that the predictive expressions require a priori knowledge of solute solubility in the pure solvents does limit its application to existing drug molecules.

Predictive expressions based on group contribution concepts, on the other hand, appear more suited to the needs of pharmaceutical research as they allow one to estimate the solution behavior of hypothetical drug molecules. The UNIFAC (Universal-functional-group-activity-coefficient) model (Fredenslund et al., 1975, 1977a and b) is a relatively new group contribution approach developed in chemical engineering laboratories for estimating the liquid–vapor characteristics of multicomponent mixtures. The recent success that the UNIFAC model has shown in predicting naphthalene solubilities (Gmehling et al., 1978; Martin et al., 1981) in several pure solvents suggests that this model might be useful in the area of drug design. This study extends the UNIFAC model of solid–liquid equilibria to binary solvent systems, and compares its predictions to experimental solubilities for naphthalene in 16 different solvent mixtures.

Description of predictive method

A solid solute, designated by subscript 3, partly dissolves in a liquid solvent. For the solute, the condition of phase equilibrium is described by

$$f_3^{\mathrm{solid}} = f_3^{\mathrm{liquid}} \tag{1}$$

where f is the fugacity. The fugacity of the solute in the liquid phase can be written as

$$f_3^{\mathrm{liquid}} = X_3 \gamma_3 f_{\mathrm{pure}\,3}^{\mathrm{liquid}} \tag{2}$$

in terms of the mole fraction composition of the solute, X_3, the activity coefficient of the solute, γ_3, and the fugacity of a pure (subcooled) liquid 3 at the system temperature $f_{\mathrm{pure}\,3}^{\mathrm{liquid}}$. The fugacity of the solid phase is expressed as

$$f_3^{\mathrm{solid}} = f_{\mathrm{pure}\,3}^{\mathrm{solid}} \tag{3}$$

assuming that there is no solubility of the solvent component(s) in the solid phase.

As discussed elsewhere (Prausnitz, 1969) we can calculate the fugacity ratio $(f^{\mathrm{solid}}/f^{\mathrm{liquid}})_{\mathrm{pure}}$ from

$$\ln(f^{\mathrm{solid}}/f^{\mathrm{liquid}})_{\mathrm{pure}} = \frac{\Delta\overline{H}^{\mathrm{fus}}}{R \cdot T}\left[\frac{T}{T_m} - 1\right] \tag{4}$$

where there is molar heat of fusion of the solute $\Delta\overline{H}^{fus}$, at its normal melting point, T_m. Eqn. 4 neglects correctional terms proportional to ΔC_p (specific heat differences between the liquid and solid) because the required heat capacity data are rarely available and because these corrections tend to be small in comparison with the uncertainties in the activity coefficients. Combination of Eqns. 2 and 4 provides an estimate of the solubility provided that the activity coefficient, γ_3, is known as a function of solvent composition.

The UNIFAC model divides the activity coefficient into two parts: the combinatorial contribution, due mostly to differences in molecular size and shape, and the residual contribution, arising primarily from differences in intermolecular forces of attraction. The activity coefficient of component i in a multicomponent solution is given by

$$\ln \gamma_i = \ln \gamma_i^{com} + \ln \gamma_i^{res} \tag{5}$$

$$\ln \gamma_i^{com} = \ln(\phi_i/X_i) + \frac{Z}{2} q_i \ln(\theta_i/\phi_i) + l_i - (\phi_i/X_i)\sum_j X_j l_j \tag{6}$$

where

$$l_i = \frac{Z}{10}(r_i - q_i) - (r_i - 1) \tag{7}$$

The coordination number Z is taken to be 10. The area fraction θ and the segment fraction ϕ are related to the mole fraction compositions via

$$\theta_i = \frac{X_i q_i}{\sum\limits_j X_j q_j} \quad \text{and}\ \phi_i = \frac{X_i r_i}{\sum\limits_j X_j r_j} \tag{8}$$

where pure-component parameters r_i and q_i represent measures of molecular volumes and molecular surface areas, respectively. These, in turn, are given by group contributions R_k and Q_k according to

$$\begin{aligned} r_i &= \sum_k \nu_k^{(i)} R_k \\ q_i &= \sum_j \nu_k^{(i)} Q_k \end{aligned} \tag{9}$$

where $\nu_k^{(i)}$ is the number of groups of type k in molecule i. Numerical values of the group contributions R_k and Q_k have been tabulated by Fredenslund et al. (1977a and b) and Gmehling et al. (1982).

The residual contribution to the activity coefficient γ_i is given by

$$\ln \gamma_i^{res} = \sum_{\substack{\text{all groups in} \\ \text{the solution}}} \nu_k^{(i)} \left[\ln \Gamma_k - \ln \Gamma_k^{(i)} \right] \tag{10}$$

where Γ_k is the group residual activity coefficient and $\Gamma_k^{(i)}$ is the residual activity coefficient of group k in a reference solution containing only molecules of type i. The term involving $\ln \Gamma_k^{(i)}$ arises because of the normalization condition that the activity coefficient γ_i becomes unity as X_i approaches one.

The group residual activity coefficient Γ_k (or $\Gamma_k^{(i)}$) is related to the mixture composition and temperature through

$$\ln \Gamma_k = Q_k \left[1 - \ln \sum_{m} \theta_m \Psi_{mk} - \sum_{m} \left(\theta_m \Psi_{km} / \sum_{n} \theta_n \Psi_{nm} \right) \right] \tag{11}$$

In the above expression the summations extend over all groups and θ_m is the area fraction of group m which is calculated using

$$\theta_m = \frac{X_m Q_m}{\sum_n X_n Q_n} \tag{12}$$

the mole fractions of the various groups X_n in the solution. The group interaction parameter Ψ_{mn} is defined as

$$\Psi_{mn} = \exp[-(U_{mn} - U_{nn})/RT] = \exp[-a_{mn}/T] \tag{13}$$

with U_{mn} representing the interaction energy between groups m and n. Numerical values of a_{mn} and a_{nm} ($a_{mn} \neq a_{nm}$) have been evaluated from a large number of vapor-liquid and liquid-liquid equilibrium studies (Fredenslund et al., 1977a, b and Gmehling et al., 1982).

Results and discussion

Naphthalene solubilities were calculated in several binary solvent mixtures using Eqns. 2 and 4 with the activity coefficients calculated from the UNIFAC model. Although naphthalene lacks the functional groups and side-chains typically encountered in pharmaceutical systems, it is one of the few molecules whose solubility has been reported in binary solvent mixtures. Solutes such as benzil, benzoic acid and *p*-benzoquinone could not be used because the required UNIFAC group interaction parameters have not been tabulated.

Fig. 1 and Tables 1 and 2 compare the calculated values to the experimental naphthalene solubilities determined by Heric and Posey (1964a and b, 1965) at 25°C. Deviations expressed in percentages were of the order of 10–20% for most binary solvent mixtures, and are comparable in magnitude to the deviations noted in the pure solvents. It is interesting to note that all of the deviations between the experimental solubilities and the UNIFAC predictions are positive in Tabel 1. Although the causes of the positive deviation were not addressed in this work, one explanation is a possible bias in the numerical values of the UNIFAC parameters. In

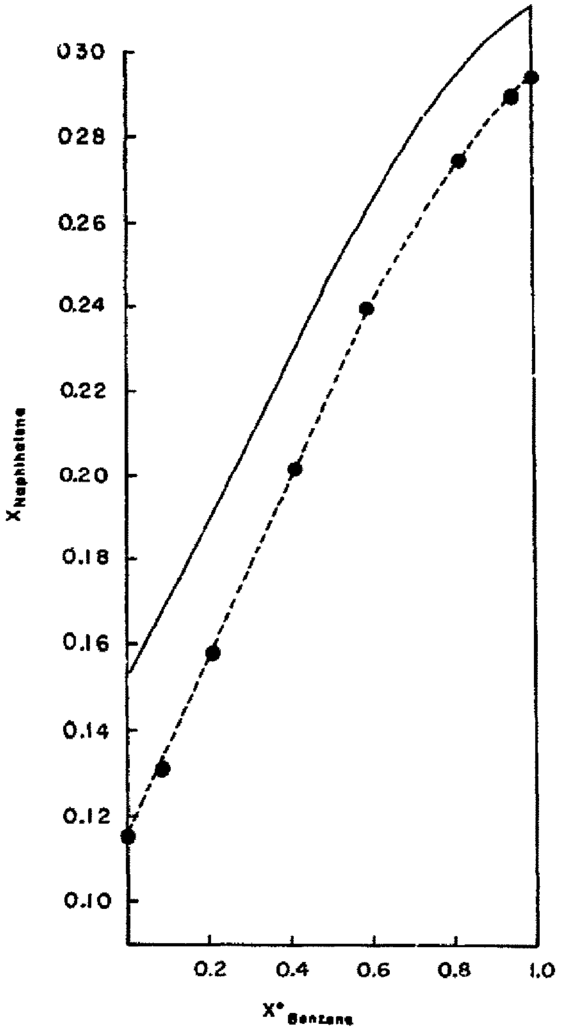

Fig. 1. Comparison between the experimental naphthalene solubilities (●) and the predictions of the UNIFAC (———) and NIBS (- - - - -) models for the benzene + *n*-hexane solvent system.

determining the group interaction parameters for aromatic hydrocarbons, Fredenslund et al. (1977a and b) used vapor–liquid equilibria data for binary mixtures containing benzene. Naphthalene has 2 carbon atoms (i.e. those without H) which differ from the 6 identically substituted carbon atoms in benzene.

Included in this comparison are the corresponding predictions of the Nearly Ideal Binary Solvent model (Acree and Bertrand, 1977). Inspection of the last two columns of Tables 1 and 2 reveals that the NIBS predictions are far superior to those of the UNIFAC model. It must be remembered, however, that the objectives of the two solution models are quite different. The Nearly Ideal Binary Solvent model was developed for predicting the thermochemical properties of the solute (which in this case is the solubility) in binary solvent mixtures from the measured properties in the two pure solvents. The fact that the NIBS expressions require a priori knowledge of the properties in the pure solvents limits its application to existing molecules.

TABLE 1

COMPARISON BETWEEN THE UNIFAC PREDICTIONS, NIBS PREDICTIONS AND EXPERIMENTAL SOLUBILITIES FOR NAPHTHALENE IN SELECTED BINARY SOLVENT MIXTURES AT 25°C

Component 1 + Component 2	X_1^0	X_3^{exp}	Predicted values		Deviations[a] (%)	
			UNIFAC	NIBS[b]	UNIFAC	NIBS
Benzene + carbon tetrachloride	1.0000	0.2946	0.3127	–[c]	+6.0	–[c]
	0.8604	0.2904	0.3080	0.2939	+5.9	+1.2
	0.6634	0.2828	0.2997	0.2890	+5.8	+2.2
	0.3866	0.2723	0.2849	0.2790	+4.5	+2.4
	0.2880	0.2702	0.2807	0.2747	+3.8	+1.6
	0.0000	0.2591	0.2620	–	+1.1	–
Carbon tetrachloride + cyclohexane	1.0000	0.2591	0.2620	–	+1.1	–
	0.7630	0.2351	0.2538	0.2354	+7.4	−0.1
	0.5883	0.2169	0.2442	0.2164	+11.9	−0.2
	0.3971	0.1955	0.2313	0.1944	+16.8	−0.6
	0.1939	0.1723	0.2144	0.1708	+21.9	−0.9
	0.0000	0.1487	0.1940	–	+26.6	–
Benzene + *n*-hexane	1.0000	0.2946	0.3127	–	+6.0	–
	0.9506	0.2905	0.3093	0.2919	+6.3	+0.5
	0.8219	0.2744	0.2958	0.2777	+7.5	+1.2
	0.5960	0.2400	0.2662	0.2387	+10.4	−0.6
	0.4109	0.2028	0.2312	0.1985	+13.1	−2.1
	0.2121	0.1590	0.1916	0.1562	+18.7	−1.8
	0.0743	0.1313	0.1634	0.1299	+21.9	−1.1
	0.0000	0.1168	0.1492	–	+24.5	–
n-Hexane + cyclohexane	1.0000	0.1168	0.1492	–	+24.5	–
	0.7986	0.1255	0.1575	0.1244	+22.8	+0.8
	0.6013	0.1319	0.1665	0.1324	+23.3	+0.3
	0.3996	0.1396	0.1783	0.1392	+24.5	−0.3
	0.1553	0.1453	0.1877	0.1463	+25.6	+0.7
	0.0000	0.1487	0.1940	–	+26.6	–

[a] Deviations (%) = $100 \cdot \ln(X_3^{cal}/X_3^{exp})$.

[b] The NIBS predictions were based on the following expression:

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

Symbols and calculational procedures are described elsewhere (Acree and Bertrand, 1977, 1981; Acree and Rytting, 1982a and b).

[c] The NIBS model cannot predict solubility in a pure solvent.

The UNIFAC model, on the other hand, predicts the solute's thermochemical properties from a group contribution approach, with the various input parameters R_m, Q_m and a_{mn} being determined, in many cases, from liquid–vapor equilibrium

TABLE 2

SUMMARIZED COMPARISON BETWEEN THE UNIFAC PREDICTIONS, NIBS PREDICTIONS AND EXPERIMENTAL SOLUBILITIES FOR NAPHTHALENE IN SEVERAL BINARY SOLVENT MIXTURES AT 25°C

Solvent system	RMS deviations (%) of calcd. values [a,b]	
	UNIFAC	NIBS
Benzene + cyclohexane	+15.8	−1.1
Benzene + carbon tetrachloride	+4.8	+1.9
Benzene + *n*-hexane	+15.3	1.4
Cyclohexane + *n*-hexadecane	12.7	+1.4
n-Hexane + *n*-hexadecane	12.7	+0.8
Carbon tetrachloride + cyclohexane	+16.7	−0.6
Benzene + *n*-hexadecane	7.6	+0.7
Carbon tetrachloride + *n*-hexane	+15.6	+0.5
Cyclohexane + *n*-hexane	+24.6	0.6
Benzene + toluene	+5.1	+0.6
Carbon tetrachloride + toluene	+2.7	−1.5
Cyclohexane + toluene	+14.9	−0.8
Carbon tetrachloride + *n*-hexadecane	7.1	+2.4
Toluene + *n*-hexane	+14.3	–
Toluene + *n*-hexadecane	6.9	–
Ethylbenzene + benzene	3.4	–

[a] RMA deviation (%) = $(100/N^{1/2})\{\Sigma[\ln(X_3^{cal}/X_3^{exp})]^2\}^{1/2}$; an algebraic sign indicates that all deviations were of the same sign.

[b] The NIBS model requires measured solubilities in the pure solvents, whereas the UNIFAC model requires no mixture data.

data of binary systems having the desired functional groups. Reduction of a large body of experimental data to just a few representative parameters reduces the predictive ability of the UNIFAC model for any one particular system or small set of systems, as the group parameters represent averages over the entire data set. This loss in predictive ability is more than compensated for by the fact that the UNIFAC expressions can be used to predict the thermodynamic properties of systems not included in the original data reduction, provided the system contains only molecules having known group parameters. The potential to estimate the solubility of hypothetical drug molecules in any given solvent environment might make the UNIFAC model useful in the area of drug design.

Acknowledgements

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