

## Comment on "Margules Equations Applied to PAH Solubilities in Alcohol–Water Mixtures"

SIR: In a recent publication appearing in this Journal, Fan and Jafvert (1) report solubility data for select polycyclic aromatic hydrocarbons (PAHs) dissolved in binary aqueous–alcohol solvent mixtures. The experimental solubilities,  $S_2$ , were mathematically described by means of a Margules equation

$$Af_w^2 + Bf_c^2 + (A + B - C + D)f_w f_c = -\ln S_2 - (\Delta S_{\text{melt}}/R)[(T_m/T) - 1] \quad (1)$$

where  $f_w$  and  $f_c$  refer to the volume fractions of water and organic cosolvent in the mixture, respectively. In the above equation  $A$  and  $B$  denote the Margules constants which are determined from measured solubilities in water and neat organic cosolvent,  $C$  is a solute-independent constant determined from cosolvent vapor pressure above the water–cosolvent mixtures, and  $D$  is a solute–water–cosolvent interactional parameter. The numerical value of the latter parameter, which is different for each system, is deduced for each data set by nonlinear least-squares analysis using the values of  $A$ ,  $B$ , and  $C$  previously determined. The quantity  $\Delta S_{\text{melt}}$  in eq 1 denotes the solute's entropy of fusion at its normal melting point temperature,  $T_m$ .

Our purpose is not to criticize the work of Fan and Jafvert but rather to suggest alternative mathematical forms for the representation of experimental solubility data. At a constant temperature, we note that both the entropy of fusion and Margules constants in eq 1 have fixed numerical values. By substituting  $f_w = 1 - f_c$  into eq 1 it is possible to express the solubility in terms of power series expansion in  $f_c$

$$\ln S_2 = L_0 + L_1 f_c + L_2 f_c^2 + L_3 f_c^3 \quad (2)$$

where  $L_0 - L_3$  are the model constants which are calculated using a least-squares analysis. As an informational note, eq 2 was originally presented as an empirical model (2). Recently (3) a theoretical justification was provided for eq 2 using various theoretical cosolvency models.

Williams and Amidon (4) presented the excess free energy models to calculate the solute solubility in both binary and ternary solvent systems. The three suffix excess free energy model expresses the logarithm of the solute solubility in binary solvent mixtures in terms of

$$\ln S_2 = f_c \ln(S_2)_c + f_w \ln(S_2)_w - A_{1-3} f_c f_w (2f_c - 1)(q_2/q_c) + 2A_{3-1} f_c^2 f_w (q_2/q_w) + C_2 f_c f_w \quad (3)$$

a volume fraction average of the solute's logarithmic solubility in the two neat solvents,  $\ln(S_2)_c$  and  $\ln(S_2)_w$ , plus additional terms describing water–cosolvent interactions. The quantities  $q_c$ ,  $q_2$ , and  $q_w$  refer to the molar volumes of the three components. The interactional parameters,  $A_{1-3}$  and  $A_{3-1}$ , are obtained from vapor–liquid equilibrium data. Through suitable algebraic manipulation, it is possible to rearrange eq 3 into the mathematical form given by eq 2.

A third theoretical model for calculating solute solubility in mixed solvents is the Combined Nearly Ideal Binary Solvent (NIBS)/Redlich–Kister (5, 6)

$$\ln S_2 = f_c \ln(S_2)_c + f_w \ln(S_2)_w + f_c f_w \sum_{i=0}^3 3W_i (f_c - f_w)^i \quad (4)$$

The model's curve-fit parameters,  $W_i$ , are calculated via regressing  $[\ln S_2 - f_c \ln(S_2)_c - f_w \ln(S_2)_w]$  versus  $f_c f_w (f_c - f_w)^i$  terms using a no intercept analysis (7). Equation 4 has been shown to provide a very accurate mathematical representation of anthracene and pyrene solubilities in a wide range of binary organic solvent mixtures (8–10) and of several drug molecules dissolved in various aqueous–organic solvent mixtures (11–15). We have compared the predictive/descriptive ability of the Combined NIBS/R–K model to other solution models and have noted that eq 4 often provides the best mathematical description for how the measured solubility varies with binary solvent composition. Moreover, we have shown that the ternary solvent form of the Combined NIBS/R–K model (16–18)

$$\begin{aligned} \ln x_2^{\text{sat}} = & x_B \ln(x_2^{\text{sat}})_B + x_C \ln(x_2^{\text{sat}})_C + x_D \ln(x_2^{\text{sat}})_D + \\ & x_B x_C \sum_{i=0}^r W_{i,BC} (x_B - x_C)^i + x_B x_D \sum_{j=0}^s W_{j,BD} (x_B - x_D)^j + \\ & x_C x_D \sum_{k=0}^t W_{k,CD} (x_C - x_D)^k \quad (5) \end{aligned}$$

can predict mole fraction solubilities of the solute,  $x_2^{\text{sat}}$ , dissolved in ternary solvents from measured solute solubility data in the three contributing sub-binary solvent systems. In eq 5  $x_i$  denotes the mole fraction composition of solvent component  $i$ , calculated as if the solute were not present. We have considered both the mole fraction (8–10) and volume fraction (11–15) versions of the Combined NIBS/Redlich–Kister model. Both versions have been found to provide accurate mathematical representations of experimental solubility data. The details of these comparisons are reported elsewhere (11–15).

Most of the solution models that employ curve-fit parameters are able to reproduce the experimental solubility data and are able to predict the solute solubility at other binary solvent compositions by interpolation and/or extrapolation methods, once the curve-fit parameters are known. Few of the models are able to make an outright prediction. In the case of the Combined NIBS/Redlich–Kister equation we have shown that it is possible to calculate the solubility of structurally related drugs in water–cosolvents. Numerical values of the  $W_i$  coefficients were determined from one set of drug molecules. The coefficients were then utilized to predict the solubility behavior of a second set of structurally similar drug molecules not used in the original regressional analysis. The mean percent error in the predicted solubilities was 17.6% for benzoate derivatives dissolved in propylene glycol–water and for sulfonamides dissolved in dioxane–water mixtures (11).

In closing we note that eqs 1–4 share a common mathematical form. Through suitable algebraic manipulations, substitutions, and rearrangements it is possible to convert from one equation to another. While all equations do provide fairly accurate descriptions for how the measured solubility data varies with solvent composition, it has been our experience that the Combined NIBS/R–K model provides the more accurate mathematical representation. Based upon this observation and its capability for making solubility predictions at various temperatures (10), description of

multiple peaks in solubility profiles (10), and ability to predict the solubility of structurally related solutes in mixed solvent systems (11), we would like to propose the Combined NIBS/R-K equation as the best equation for ecotoxicological and pharmaceutical applications.

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