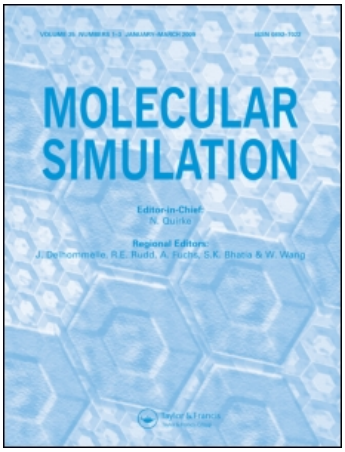

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Prediction of Solubilities of Complex Medium-sized Chemicals. II. Solutes in Mixed Solvents

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Prediction of Solubilities of Complex Medium-sized Chemicals. II. Solutes in Mixed Solvents

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Our systematic approach for predicting the solubility of sparingly soluble solid fine chemicals and pharmaceuticals in pure solvents is extended to all compositions of fully miscible mixed solvents. Group contribution correlations are used for computing the difference in solubility at infinite dilution in the system of interest from an optimal reference solvent. The method minimizes the impact of uncertainties in pure-solute properties, decreases the number of adjustable parameters to be determined by data reduction, and suggests an efficient experimental strategy to find any unknown parameters. Several examples illustrate the method for mixed systems.

Keywords: Mixed solvents; Fugacity; UNIFAC parameters; Binary parameters

INTRODUCTION

Though water is a natural and desirable solvent, poor aqueous solubility can cause difficulties in pharmaceutical processing [1]. Cosolvency, the addition of water miscible solvents, is commonly used to increase the solubility of non-polar drugs in aqueous vehicles. For example, parental dosage forms should incorporate the required dose as a true solution in the smallest volume of liquid as possible. Currently, cosolvents are used in 13% of FDA-approved parental products [1]. But, despite their popularity and utility, most cosolvent formulations are developed from experience and empirical descriptions of experimental results rather than systematically.

Recently [2], we proposed a method for evaluating pure solvents to solubilize a complex chemical. We assumed application of infinite dilution conditions and computed the difference of solubility between an optimally selected reference solvent, for which data are available, and a range of potential solvents, either known or to be measured. We also gave a procedure for obtaining the most important unknown group contribution parameters from data on substances with new groups. The results were more accurate than other common methods and avoided the consequences of uncertainties in pure solute properties and reduced restrictive assumptions about solute solid-phase behavior.

Here we extend the technique to reducing and predicting solubility data of complex chemicals in aqueous and other mixed solvents. We briefly review the thermodynamic and numerical frameworks of the method and then give examples.

FRAMEWORK OF THE METHOD

The basic relationships we use for describing low liquid solubility of solid components that are solid when pure at the system temperature are derived [2] from the equality of component fugacities in all phases. Then assumptions can be made about solid purity and whether the liquid non-ideality is

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equivalent to infinite dilution. For a component i pure in the solid (S) phase and soluble in the liquid (L) phase

$$\ln x_i \gamma_i(T,\{x\}) = \ln \frac{f_i^{0S}}{f_i^{0L}} \equiv \ln x_i^{id} \approx \frac{\Delta H_{mi}}{RT_{mi}}\left(1-\frac{T_{mi}}{T}\right) \quad (1)$$

where the "ideal" solubility, $\ln x_i^{id}$, has been approximated with only melting point properties, T_{mi} and ΔH_{mi}, though more complete expressions can be used [3]. Here the activity coefficient, γ_i is for the Lewis/Randall standard state (pure component as a liquid at the system T), a function of T and solution composition, $\{x\}$. We estimate γ_i with UNIFAC. Two *pure group* parameters for each solute, R_k and Q_k, are for size and shape, and are obtained on the basis of atomic structure [4]. Two *binary* interaction parameters for each pair, identified as $a_{mn} \neq a_{nm}$, are determined by fitting to reliable measured data on systems involving the group(s) of interest.

If the solubility is low enough ($x_i < 0.01$), the activity coefficient can be considered as at infinite dilution, then

$$\ln \gamma_i^{\infty}(T,\{x_S\}) \approx \ln \gamma_i(T,\{x\}) \quad (2)$$

where γ_i^{∞} is a function only of T and the solvent composition, $\{x_S\}$. At low concentrations, the solubility can be approximated,

$$\ln x_i \approx \frac{\Delta H_{mi}}{RT_{mi}}\left(1-\frac{T_{mi}}{T}\right) - \ln \gamma_i^{\infty}(T,\{x_S\}) \quad (3)$$

If one applies Eq. (3) to a pure or mixed solvent (m) and subtracts the same expression for a reference solvent j, there is a direct relation between the solubility in m with that in the reference solvent and predicted infinite dilution activity coefficients in the solvents

$$\ln x_{im} = \ln x_{ij} + \left[\ln \gamma_i^{\infty}\left(T,\{x_S\}_j\right) - \ln \gamma_i^{\infty}\left(T,\{x_S\}_m\right)\right] \quad (4)$$

Finally, if not all of the binary group parameters have been fitted, it is possible with regularization techniques to determine a large number of parameters from relatively few data. We recommend minimizing the objective function

$$S'' = \sum_{m<j} (\delta\Delta \ln x_{i,mj})^2 + \alpha \sum_{m\neq n} (\delta a_{mn})^2 \quad (5)$$

where

$$\delta\Delta \ln x_{i,mj} \equiv (\ln x_{im} - \ln x_{ij})^{exp} - (\ln x_{im} - \ln x_{ij})^{calc} = (\ln x_{im} - \ln x_{ij})^{exp} - \left[\ln \gamma_i^{\infty}\left(T,\{x_S\}_j\right) - \ln \gamma_i^{\infty}\left(T,\{x_S\}_m\right)\right] \quad (6)$$

and

$$\alpha \sum_{m\neq n} (\delta a_{mn})^2 = \alpha \sum_{m\neq n} \left(a_{mn} - a_{mn}^0\right)^2 \quad (7)$$

with α a small constant and a_{mn}^0 an initial guess of the parameter (commonly zero) to keep the data and parameter residuals in proper proportion. If the influence of the parameter is not strong, $a_{mn} \sim a_{mn}^0$ after the fitting.

The above procedure requires a reference solvent, j. An optimal choice is possible if only a single solute is considered and if one has experimental solubilities in N solvents. The optimal reference (j) would have

$$\ln x_{ij} + \ln \gamma_{ij}^{\infty} - \frac{1}{N}\sum_{k=1}^{N} \left(\ln x_{ik} + \ln \gamma_{ik}^{\infty}\right) = 0 \quad (8)$$

The procedure is to select the data successively, ultimately choosing the solvent (j) that most closely obeys Eq. (8) [2]. If the magnitudes of all residuals are of the same order, they will scatter about zero. Note that one cannot guarantee optimal predictions for solvents outside of the database used, but we have found good success when minimizing the numerical value of the lhs of Eq. (8).

RESULTS WITH KNOWN UNIFAC PARAMETERS

Using the above procedure, we have determined solubilities for example solutes in mixed solvents. The group assignments are given in Table I and the pure solute properties are given in Table II. We first consider naphthalene solubility [5] in mixtures of ethanol and water, for which there are many data in the literature and all groups necessary for making calculations are available. Naphthalene has only a single main group, so if any data have complex behavior, the cause is probably due to its molecular size and shape [6]. As shown in Fig. 1, the available UNIFAC model parameters used in equations (1), (3), and (4) capture well the trends of the data. Table III shows numerical results for pure ethanol as the reference solvent. In this case the reference was pure; this is not necessary and Fig. 2 shows a mixed solvent reference in the case of biphenyl in n-heptane/carbon tetrachloride mixtures [7]. Figure 2 shows that both Eqs. (1) and (2) are inaccurate due to the high solubility and inaccurate UNFAC parameters. However, the figure and Table III show that Eq. (3) is quite successful in describing the data.

RESULTS WITH UNIFAC PARAMETER FITTING

The rest of the substances studied here (Table II) require new parameters for main- and subgroups.

TABLE I Solute group assignments

Solute, i						
Naphthalene	8 × ACH	2 × AC				
Biphenyl	10 × ACH	2 × AC				
Paracetamol	4 × ACH	1 × ACOH	1 × CH_3CO	1 × AC-NH—		
Sulfanilamide	4 × ACH	1 × AC	1 × $ACNH_2$	1 × SO_2-NH_2		
Phenobarbital	1 × CH_3	1 × CH_2	1 × C	5 × ACH	1 × AC	1 × $C_3N_2O_3$
Vinbarbital	3 × CH_3	2 × CH_2	1 × C	1 × CH═C	1 × $C_3N_2O_3$	

Table IV summarizes the situation. For paracetamol, the group AC-NH— is needed. Our geometric properties are:

$$R_{\text{AC-NH-}} = R_{\text{AC-CH}_3} + R_{\text{CH}_3\text{-NH-}} - 2R_{\text{CH}_3} \quad (9)$$

$$Q_{\text{AC-NH-}} = Q_{\text{AC-CH}_3} + Q_{\text{CH}_3\text{-NH-}} - 2Q_{\text{CH}_3} \quad (10)$$

For sulfanilamide the group SO_2-NH_2 is needed. We use:

$$R_{\text{SO}_2\text{-NH}_2} = R_{\text{AC-NH}_2} + R_{\text{SO}_2} - R_{\text{AC}} \quad (11)$$

$$Q_{\text{SO}_2\text{-NH}_2} - Q_{\text{AC-NH}_2} + Q_{\text{SO}_2} - Q_{\text{AC}} \quad (12)$$

Finally, for the barbitals the group $C_3N_2O_3$ is introduced. We find:

$$R_{\text{C}_3\text{N}_2\text{O}_3} = 2\left(R_{\text{-(C=O)N(CH}_3)_2} - 2R_{\text{CH}_3}\right) + R_{\text{CH}_2\text{CO}} - R_{\text{CH}_2} \quad (13)$$

$$Q_{\text{C}_3\text{N}_2\text{O}_3} = 2\left(Q_{\text{-(C=O)N(CH}_3)_2} - 2Q_{\text{CH}_3}\right) + Q_{\text{CH}_2\text{CO}} - Q_{\text{CH}_2} \quad (14)$$

Numerical R and Q values are given in Table V.

First we examine the paracetamol data in ethyl acetate/ethanol mixtures given by Romero *et al.* [8]. Figure 3 compares the measured solubilities with those found with equations (1), (2) and (4) using current UNIFAC parameters for known groups and all AC-NH— interaction parameters set to zero. The agreement is poor and Eqs. (1) and (2) give different results; most of the data have x_i from 0.018 to 0.08 so assuming infinite dilution is not fully valid for these cases. Table III lists the statistics for this case.

As expected, overall agreement improves by adjusting the interaction parameters of AC-NH— with the solute groups, ACOH, ACH and CH_3CO, and the solvent groups, CH_2, OH and CH_2COO; a total of 10 parameters as listed in Table IV. If S'' is minimized and solubilities are calculated with Eq. (4), the interactions among solute–solute groups make no contribution and are thus not necessary to find so there are only 6 parameters to fit. Figure 4 shows the results graphically and Table VI gives the statistics. The optimal reference solvent is pure ethanol using Eq. (8). With optimal parameters and reference solvent, the results are quite good, even though the solubilities are slightly high for the infinite dilution assumption to be valid.

Next, we consider the sulfanilamide data in water/ethanol mixtures of Bustamente *et al.* [9]. We do the same fitting procedure for this case as for paracetamol. Calculations with zero AC-NH— interaction parameters are again poor, as indicated in Table III. Figure 5 shows the graphical results from fitting and Tables III, VI and VII show the numerical results. Because this system is aqueous, the solubility values are lower, making the results of Eqs. (1) and (2) nearly the same. Table IV shows the parameters of SO_2-NH_2 with the solvent groups, CH_2, H_2O and OH to be fitted, a total of 6 parameters. There are also interaction parameters of SO_2-NH_2 with the solute groups, $ACNH_2$ and ACH (Table II), needed for applying Eq. (1), but these are not necessary for Eq. (4). The reference solvent is the mixture listed in Table VI, found from Eq. (8).

Finally, we consider the two sets of barbital data of Breon and Paruta [10] in the manner above and in predictive mode. The solute vinbarbital differs from phenobarbital only with an aromatic ring (i.e. ACH groups) in the one 5-position replaced by a hydrocarbon chain containing a single double bond (or C═C group). The numerical aspects are found in Tables I–VII. As shown in Figs. 6–8, the solubility data of this aqueous system covers several orders of magnitude, depending upon the solvent composition, with the calculations of Eqs. (1) and (2) being essentially identical. Figure 6 shows results for phenobarbital and Fig. 7 shows results for vinbarbital with independent adjustment of the parameters for $C_3N_2O_3$ interactions with CH_2, OH and H_2O as needed for Eqs. (2)–(4). Though the interaction parameters with ACH and with C═C might also have been adjusted for Eqs. (2) and (3), their values have no impact on S'', so the fitting led to zero

TABLE II Pure solute properties

Solute, i	T_{mi}/K	ΔH_{mi}/kJ kmol^{-1}	M_i/g mol^{-1}
Naphthalene	353.43	0.1898×10^5	128.174
Biphenyl	342.37	0.1858×10^5	154.211
Paracetamol	443.6	0.271×10^5	151.1640
Sulfanilamide	437.65	0.23416×10^5	172.2014
Phenobarbital	447.15	0.2774×10^5	232.2384
Vinbarbital	436.0	0.29786×10^5	224.26

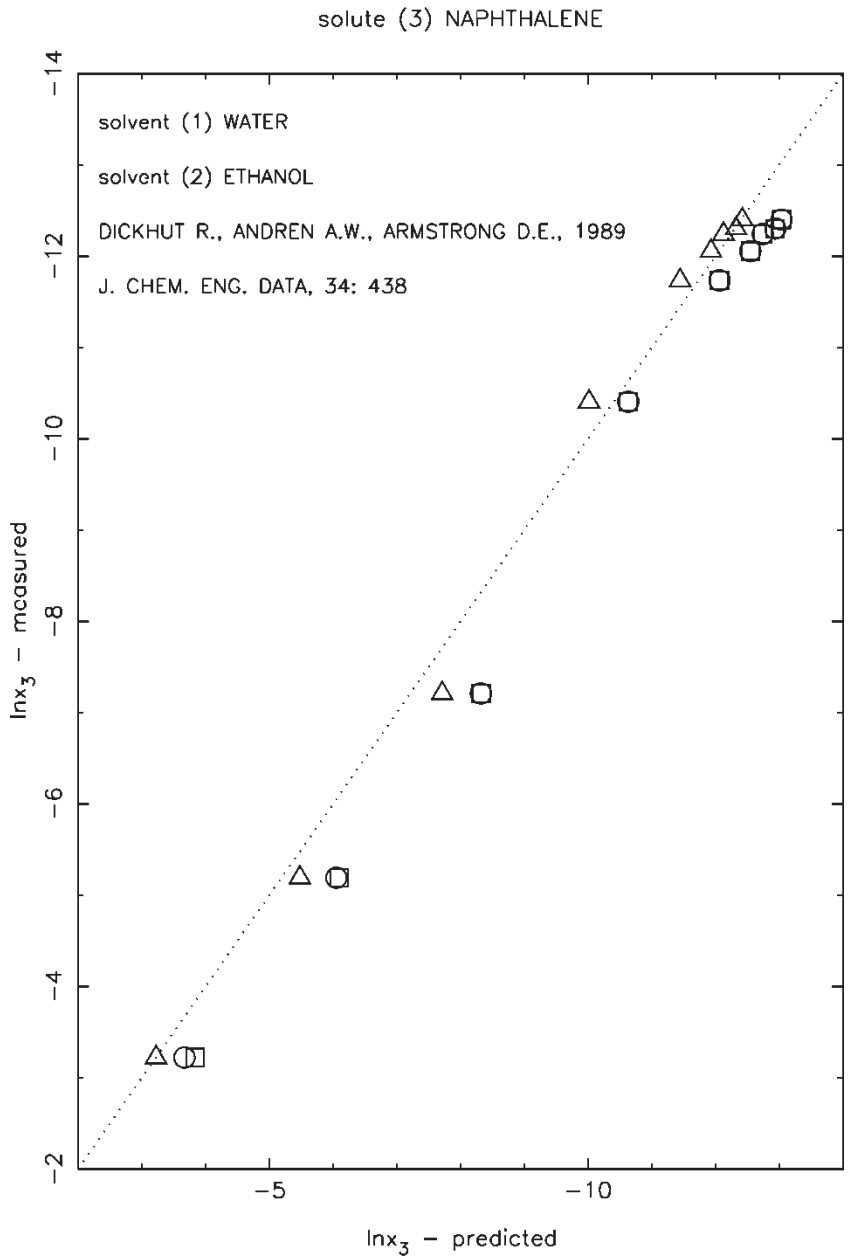

FIGURE 1 Naphthalene in water/ethanol mixtures ($T = 298.15$ K) with no parameter-fitting. ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent (pure ethanol) Eqs. (4) and (8).

values. Table VII also shows that the other barbital parameters are similar in magnitude for both substances, suggesting that simultaneous fitting and predictive treatment should be satisfactory. Figure 8 and Table VI show the results from using vinbarbital parameters to predict the phenobarbital data. The accuracy is satisfactory, while not as good as those from regression.

To examine the influence of varying the value of α, Table VIII gives the residual ($\|\delta \ln x_3\|_2$) and

TABLE III Optimal reference solvent mixture; without parameter fitting

Solute (3)	*(1)*	*(2)*	x_1	*AAPE(ln x_3) %*	*AAE (ln x_3)*
Naphthalene	Water	Ethanol	0	2.3	0.194
Biphenyl	CCl_4	Heptane	0.318500	2.2	0.0326
Paracetamol	Ethyl Acetate	Ethanol	0.372859	24.0	0.699
Sulfanilamide	Water	Ethanol	0.764378	17.0	0.885
Vinbarbital	Ethanol	Water	0.290506	8.8	1.15
Phenobarbital	Ethanol	Water	0.281115	7.9	1.00

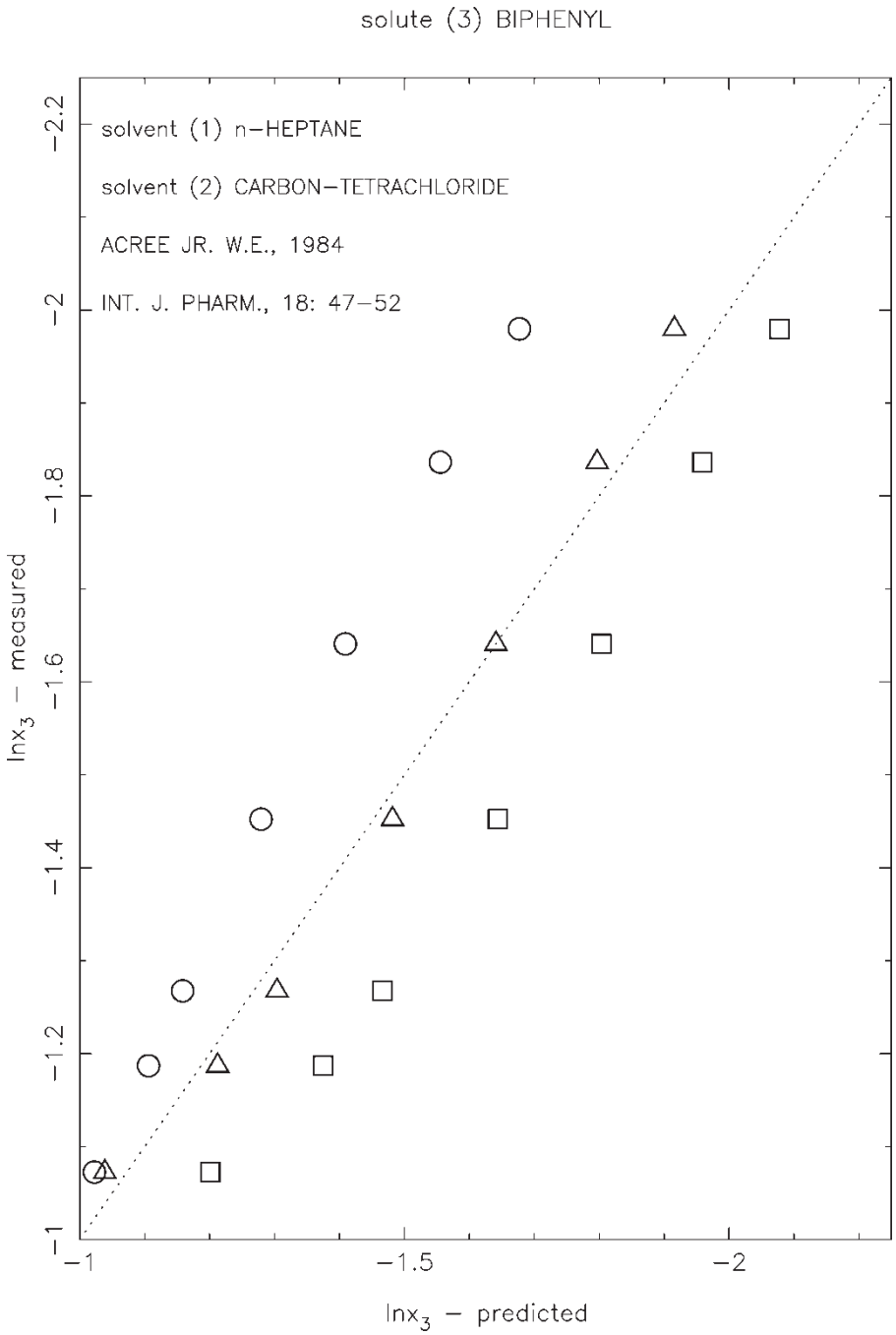

FIGURE 2 Biphenyl in n-heptane/CCl_4 mixtures ($T = 298.15$ K) with no parameter fitting. ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{heptane} = 0.6815$) Eqs. (4) and (8).

TABLE IV Example systems for parameter estimation

Solute, i	*Sulfanilamide*	*Paracetamol*	*Phenobarbital*	*Vinbarbital*
New Group	SO_2-NH_2	AC-NH—	$C_3N_2O_3$	$C_3N_2O_3$
Solvent 1	Water	Ethyl acetate	Ethanol	Ethanol
Solvent 2	Ethanol	Ethanol	Water	Water
Unknown system interaction parameters				
Solute–Solute	ACH, $ACNH_2$	ACOH, ACH, CH_3CO	CH_2, ACH	CH_2, C═C
Solute–Solvent	OH, CH_2, H_2O	OH, CH_2, CH_2COO	OH, CH_2, H_2O	OH, CH_2, H_2O
Adjustable	10	12	8	8
Adjusted	6	6	6	6

TABLE V Geometric parameters for new groups

New group	SO_2-NH_2	AC-NH—	$C_3N_2O_3$
R_k	2.033	0.8978	2.8701
Q_k	1.736	0.516	2.356

parameter ($\|a\|_2$) norms obtained from data reductions based on different α. For large α the residual norms are large, but decrease when α decreases. However, at some α the residual norm does not decrease any further. Yet the parameter norm, which increases as α decreases, continues to increase after the residual norm has reached an almost constant value. This shows the danger of inappropriate parameter estimate variances if the regressions are done with low values of α. On the other hand, the data/model agreement may not be satisfactory for values above a suitable level. Based on Table VII, we adopt the parameter estimates made with $\alpha = 10^{-5}$ for both these solutes.

Figures 6–8 show that even the fitted reference solvent results drift away from the diagonal at low solubility. We expect that

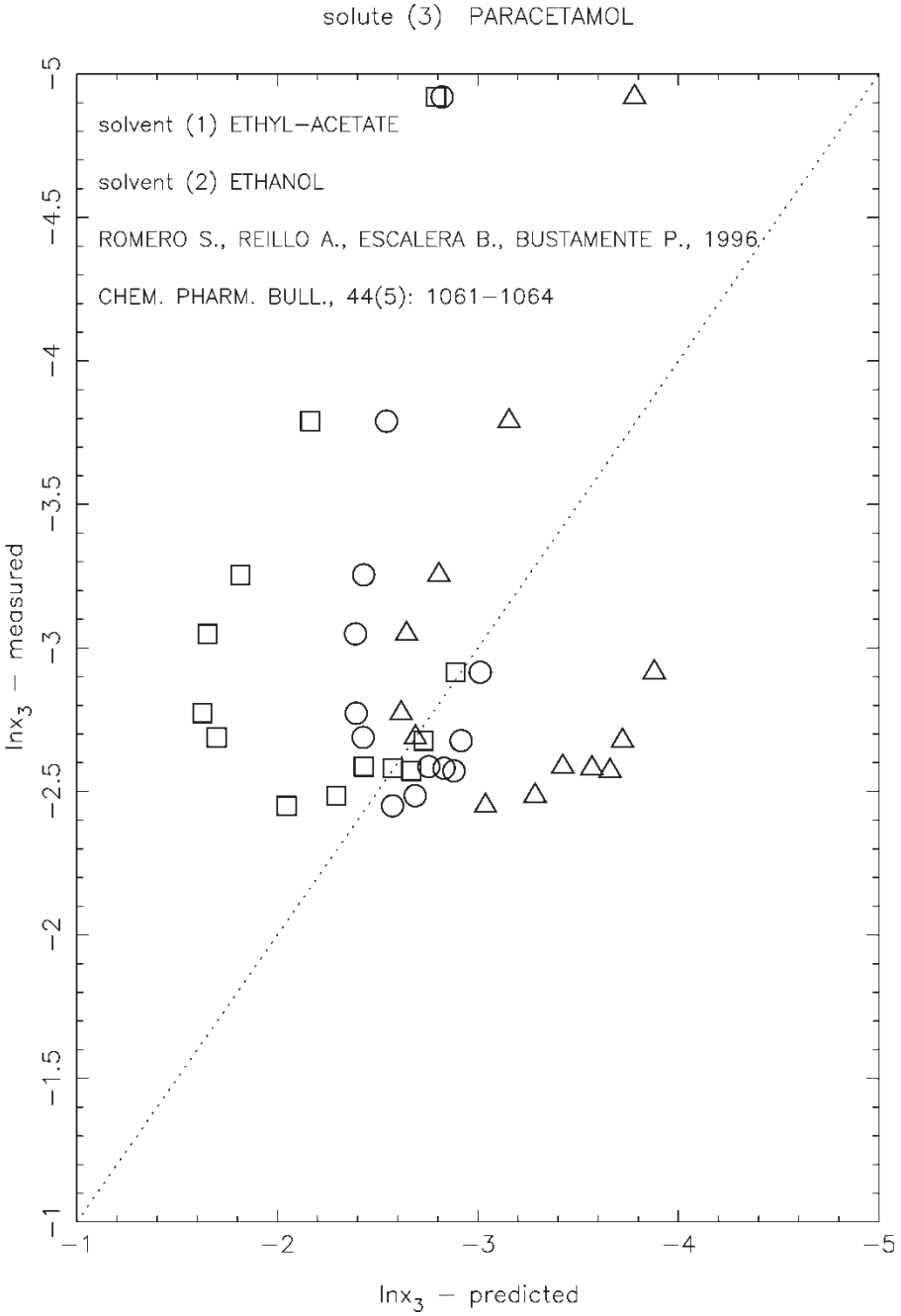

FIGURE 3 Paracetamol in ethyl-acetate/ethanol mixtures ($T = 298.15$ K) with no parameter fitting. ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 0.63$) Eqs. (4) and (8).

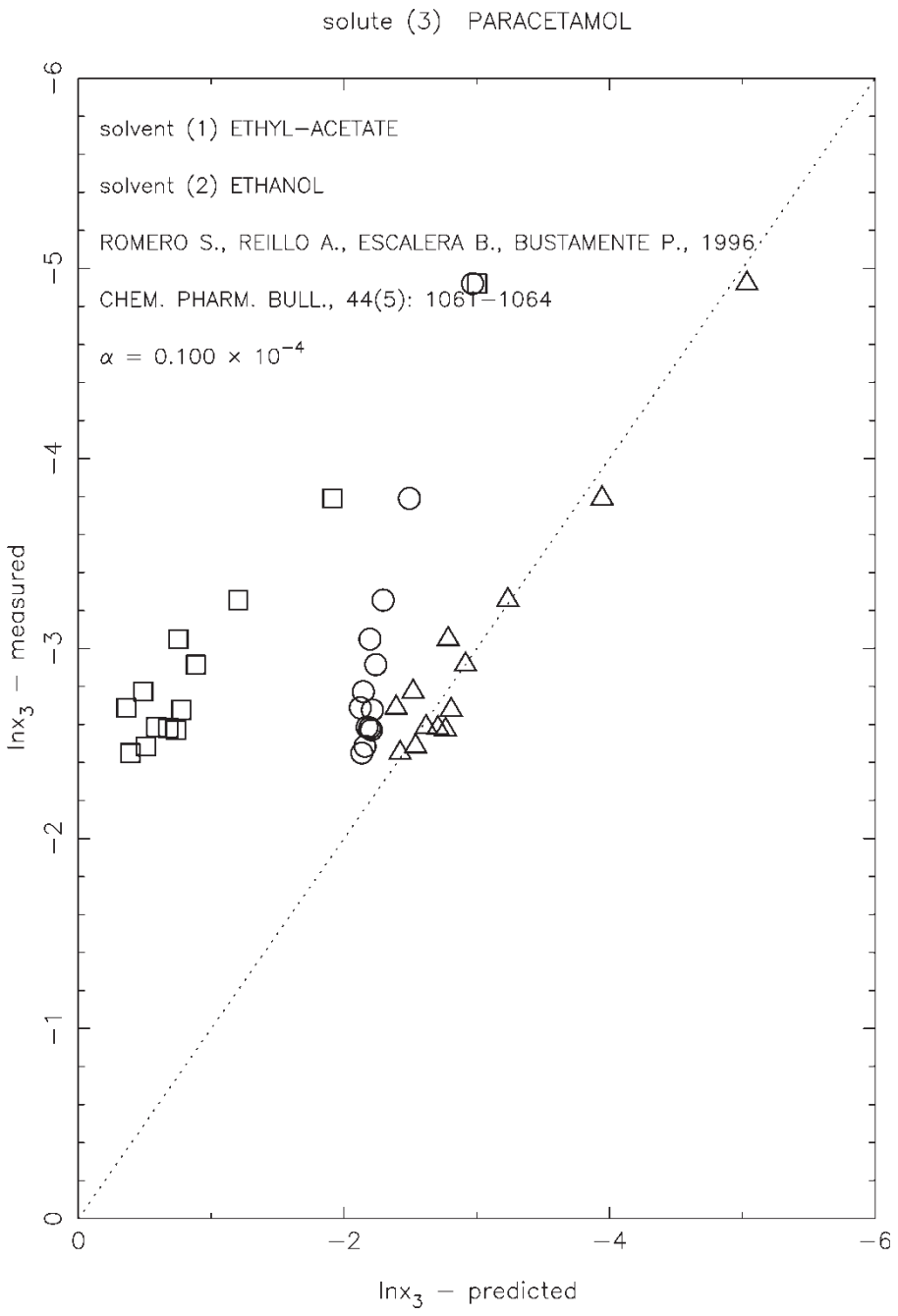

FIGURE 4 Paracetamol in ethyl-acetate/ethanol mixtures ($T = 298.15$ K) with parameter fitting via Eq. (5). ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 1.0$) Eqs. (4) and (8).

this occurs because these systems involve nearly pure water where few general methods are reliable.

DISCUSSION

The present investigations suggest that our previously recommended procedures [2] for evaluating optimal pure solvents and new parameters are also effective for mixed solvents.

A remaining practical issue is that some drugs can persist in one or more metastable solid modifications (polymorphism), in addition to the thermodynamically stable state. For example, paracetamol is known to exist in different modifications [11]. Depending upon the solid form and sample history, such effects can persist for appreciable periods of time [12]. Such modifications will change $\ln x_i^{id}$ used in Eqs. (1) and (3). If there is no solvent effect on the (pure) solid structure and $\ln x_i^{id}$ is available, Eq. (1) will still be reliable. So will Eq. (3) at low concentrations. Equation (4) is less restrictive in this sense. Its application only requires that the solid properties

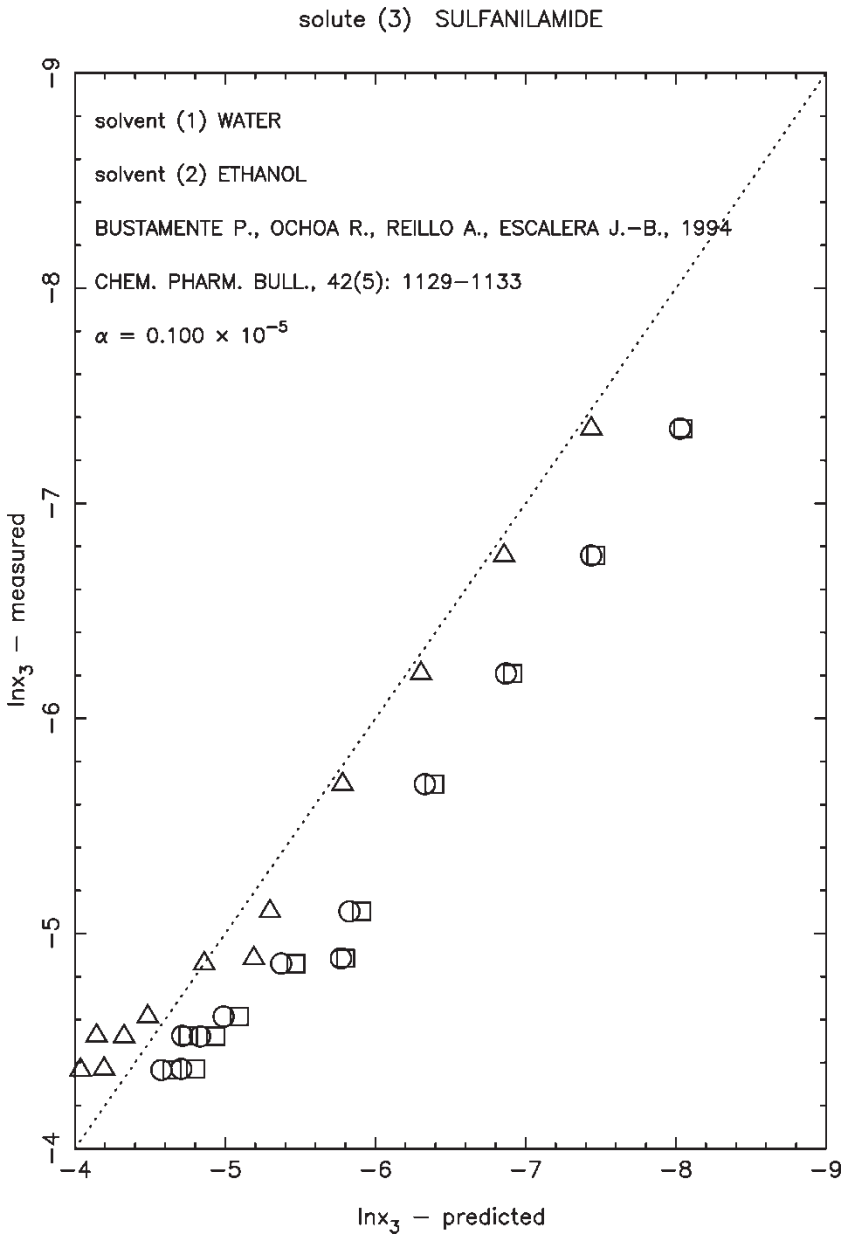

FIGURE 5 Sulfanilamide in water/ethanol mixtures ($T = 298.15$ K) with parameter fitting via Eq. (5). ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 0.24$) Eqs. (4) and (8).

are solvent independent. However, solvent-induced effects on crystal forms are not uncommon. Apparently caffeine [13], cholesterol [14,15], and dextropropoxyphene napsylate [16] vary with composition in solvent mixtures. Unfortunately, only experiment can indicate if such issues will affect predictions and correlations.

Finally, we note that we have only treated prototypes of moderately flexible, polyfunctional molecules. While this may be representative of

TABLE VI Optimal reference solvent mixture; after parameter fitting

Solute (3)	*(1)*	*(2)*	x_1	*AAPE (ln x_3) %*	*AAE (ln x_3)*
Paracetamol	Ethyl Acetate	Ethanol	0	4.4	0.128
Sulfanilamide	Water	Ethanol	0.764378	4.4	0.219
Vinbarbital	Ethanol	Water	0.827034	1.2	0.175
Phenobarbital*	Ethanol	Water	0.394578	1.2	0.169
Phenobarbital†	Ethanol	Water	0.394578	2.0	0.247

*Fit to phenobarbital data. †Predicted from fit to vinbarbital data.

TABLE VII Binary parameters

i	j	a_{ij}/K	a_{ji}/K
Parameters from fitting phenobarbital data			
CH_2	$C_3N_2O_3$	155.70	1438.92
ACH	$C_3N_2O_3$	0.00	0.00
OH	$C_3N_2O_3$	141.28	164.40
H_2O	$C_3N_2O_3$	− 296.98	716.24
Parameters from fitting vinbarbital data			
CH_2	$C_3N_2O_3$	154.76	980.38
C═C	$C_3N_2O_3$	0.00	0.00
OH	$C_3N_2O_3$	140.40	123.12
H_2O	$C_3N_2O_3$	− 295.15	570.51

older substances, newer drugs can be significantly more complex. In such cases, solution models such as UNIFAC may not be accurate. But the techniques used here can be applied, regardless of the model chosen to relate molecular structure to solution non-ideality. In particular, the limitations on Eq. (4) will only be that of the model, not the thermodynamic and numerical frameworks. All systems considered here are at 298.15 K; thus temperature dependence is not considered, and the possibility of extrapolating results to other temperatures is not known.

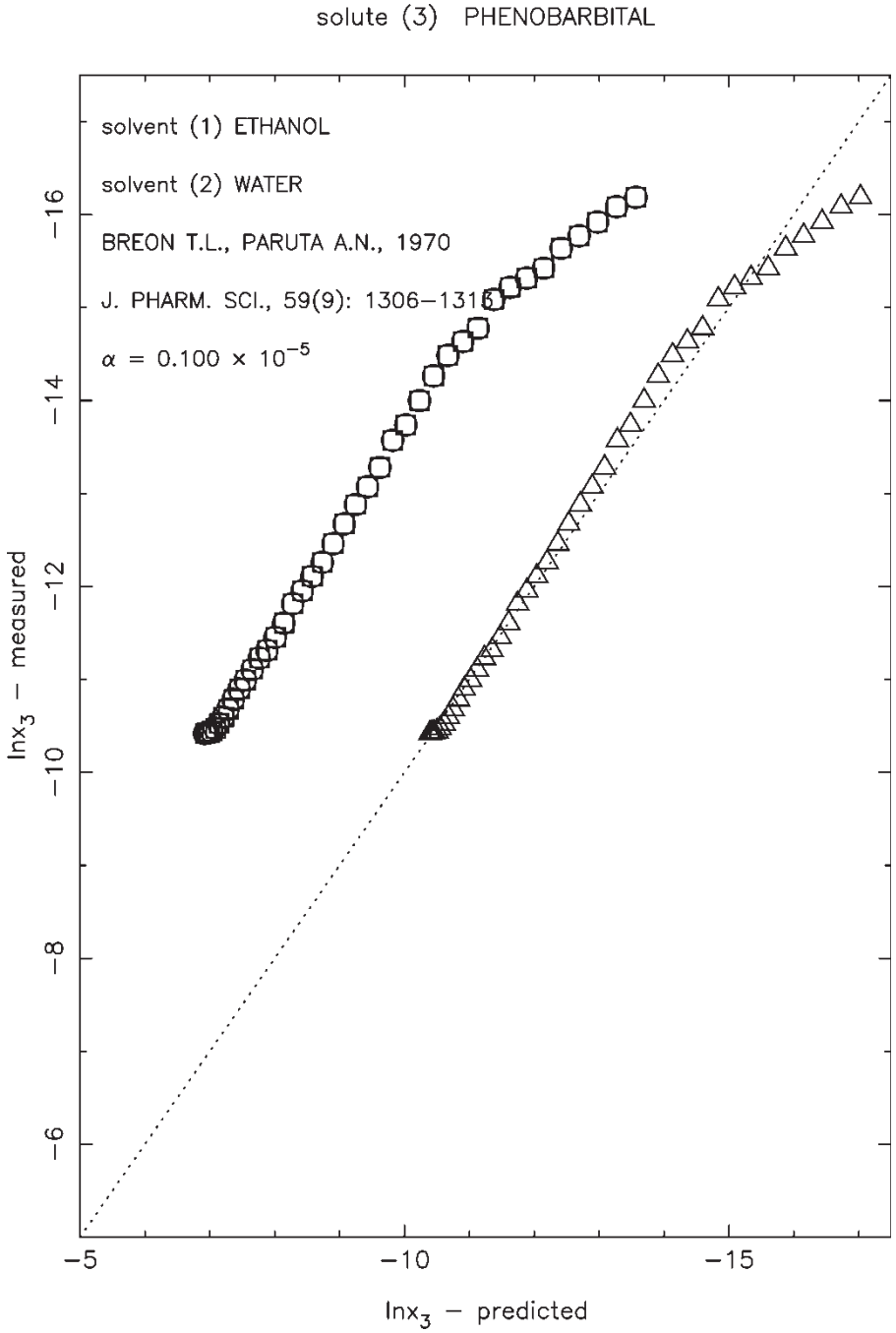

FIGURE 6 Phenobarbital in water/ethanol mixtures ($T = 298.15$ K) with parameter fitting via Eq. (5). ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 0.39$) Eqs. (4) and (8).

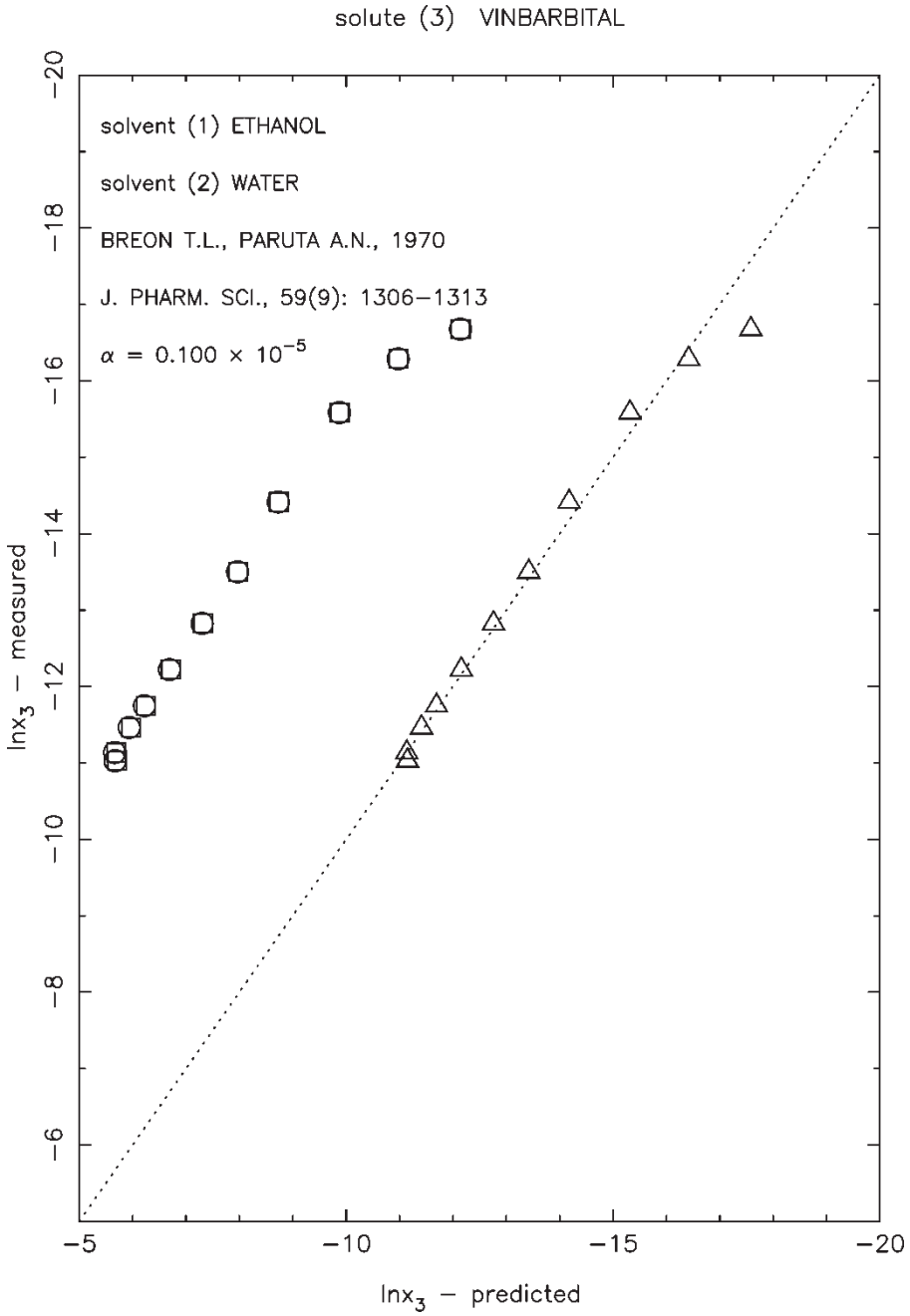

FIGURE 7 Vinbarbital in water/ethanol mixtures ($T = 298.15$ K) with parameter fitting via Eq. (5). ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 0.82$) Eqs. (4) and (8).

Current work investigates the incorporation of terms at different temperatures in S''.

SUMMARY & CONCLUSION(S)

Our systematic approach for using UNIFAC group contributions for predicting the solubility of sparingly soluble solid fine chemicals and pharmaceuticals in pure solvents has been extended to all compositions of fully miscible mixed solvents. Uncertainties in pure-solute properties and the number of adjustable parameters to be determined by data reduction are minimized. Examples illustrate that the method is as successful for mixed systems as for pure solvents.

Abbreviations: AAE(**x**), Average absolute error ($=\Sigma_i^N|\delta x_i|/N$); AAPE(**x**), Average absolute percent error ($= [\Sigma_i^N|\delta x_i/x_i|/N] \times 100\%$)

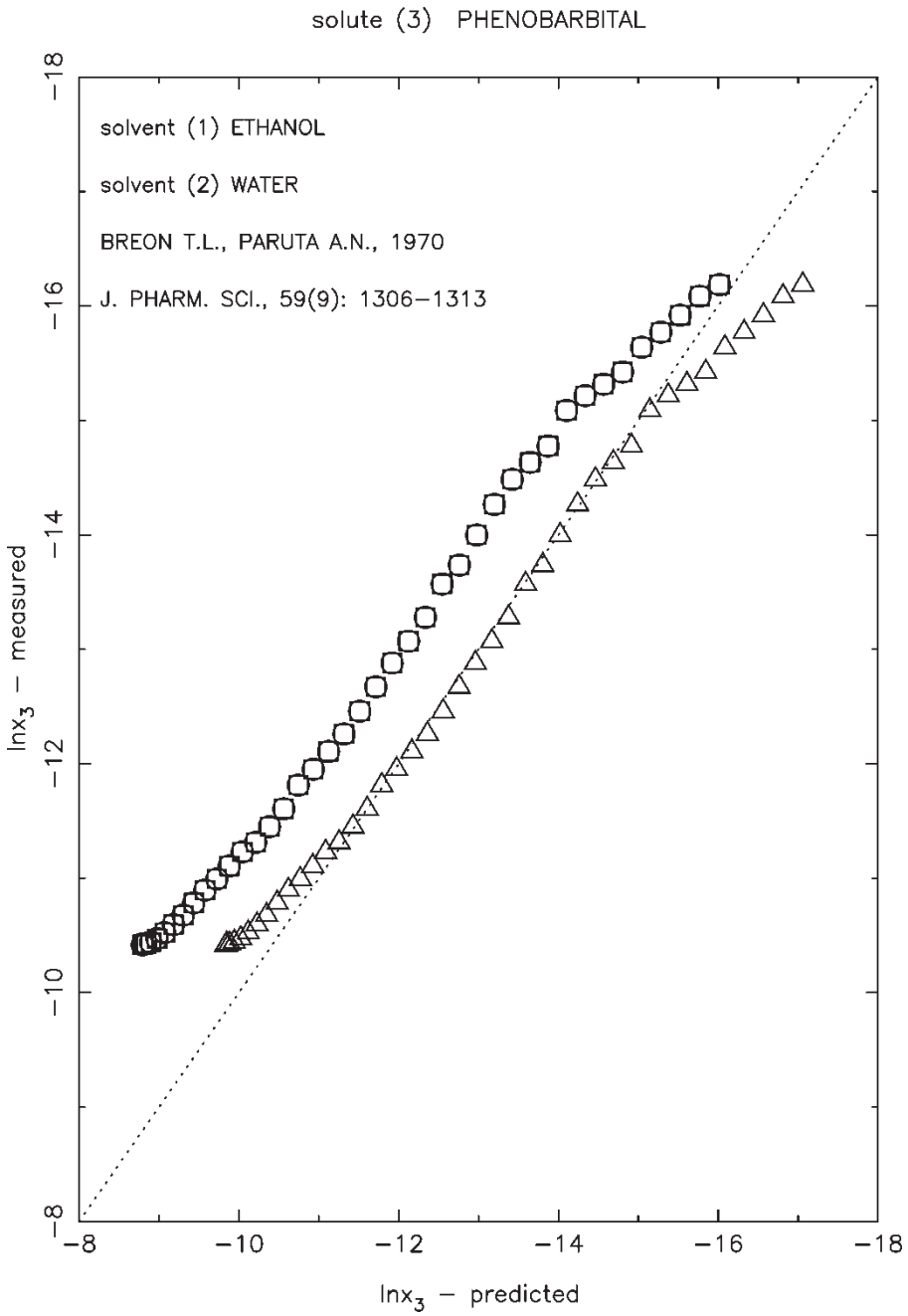

FIGURE 8 Phenobarbital in water/ethanol mixtures ($T = 298.15$ K) with parameters fitted to vinbarbital solubilities. ○ UNIFAC Eq. (1): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3$; □ UNIFAC Eq. (2): $\ln x_3 = \ln x_3^{id} - \ln \gamma_3^{\infty}$; Δ UNIFAC Reference Solvent ($x_{ethanol} = 0.39$) Eqs. (4) and (8).

LIST OF SYMBOLS

a_{mn} UNIFAC interaction energy parameter
f fugacity
M molecular weight
N number of data points in a particular set
Q_k surface area parameter of group k
R gas constant
R_k volume parameter of group k
S'' objective function for parameter fitting
T temperature
x_i mole fraction of component i, in liquid phase

Greek Letters

α regularization parameter, Eq. (5)
γ_i activity coefficient of component i in solution

TABLE VIII Impact of α on data reduction

	Vinbarbital		*Phenobarbital*	
$log_{10}(\alpha)$	$ln\|\|\delta ln\, x_3\|\|_2$	$ln\|\|a\|\|_2$	$ln\|\|\delta ln\, x_3\|\|_2$	$ln\|\|a\|\|_2$
−12	1.2	8.1	2.3	8.2
−11	1.2	8.1	2.3	8.2
−10	1.2	8.1	2.3	8.2
−9	1.2	8.1	2.3	8.1
−8	1.2	7.9	2.3	8.1
−7	1.2	7.5	2.3	7.8
−6	1.2	7.1	2.3	7.4
−5	1.4	6.5	2.3	7.0
−4	1.6	5.9	2.4	6.4
−3	2.0	5.3	2.7	5.9
−2	2.5	4.2	3.1	5.4
−1	2.7	2.2	3.7	4.1

δa a-residual: a(measured) − a(calculated)
Δ change (i.e. ΔH_{mi} denotes enthalpy of melting of component i)

Subscripts

i component i
ij i in j
m melting property (i.e. T_{mi} denotes temperature of melting of component i)

Superscripts

id ideal solution
L liquid state
S solid state
∞ at infinite dilution

References

[1] Millard, J.W., Alvarez-Núñez, F.A. and Yalkowsky, S.H. (2002) "Solubilization by cosolvents: Establishing useful constants for the log-linear model", *Int. J. Pharm.* **245**, 153–166.
[2] Abildskov, J. and O'Connell, J.P. (2003) "Predicting the solubilities of complex chemicals I. solutes in different solvents", *Ind. Eng. Chem. Res.* **42**, 5622–5634.
[3] Gracin, S., Brinck, T. and Rasmuson, A.C. (2002) "Prediction of solubility of solid organic compounds in solvents by UNIFAC", *Ind. Eng. Chem. Res.* **41**, 5114–5124.
[4] Bondi, A. (1968) *Properties of Molecular Crystals and Glasses* (Wiley, New York).
[5] Dickhut, R.M., Andren, A.W. and Armstrong, D.E. (1989) "Naphthalene solubility in selected organic solvent/water mixtures", *J. Chem. Eng. Data* **34**, 438–443.
[6] Abildskov, J., Gani, R., Rasmussen, P. and O'Connell, J.P. (2001) "Analysis of infinite dilution activity coefficients of solutes in hydrocarbons from UNIFAC", *Fluid Phase Equilibria* **181**, 163–186.
[7] Acree, W.E., Jr. (1984) "Solubility of biphenyl in binary solvent mixtures", *Int. J. Pharm.* **18**, 47–52.
[8] Romero, S., Reillo, A., Escalera, B. and Bustamente, P. (1996) *Chem. Pharm. Bull.* **44**(5), 1061–1064.
[9] Bustamente, P., Ochoa, R., Reillo, A. and Escalera, J.-B. (1994) *Chem. Pharm. Bull.* **42**(5), 1129–1133.
[10] Breon, T.L. and Paruta, A.N. (1970) *J. Pharm. Sci.* **59**(9), 1306–1313.
[11] Granberg, R.A. and Rasmusson, Å.C. (2000) "Solubility of paracetamol in binary and ternary mixtures of water + acetone + toluene", *J. Chem. Eng. Data* **45**, 478–483.
[12] Sangster, J. (1999) "Phase diagrams and thermodynamic properties of binary systems of drugs", *J. Phys. Chem. Ref. Data* **28**(4), 889–930.
[13] Bogardus, J.B. (1983) "Crystalline anhydrous-hydrate phase changes of caffeine and theophylline in solvent-water mixtures", *J. Pharm. Sci.* **72**, 837–838.
[14] Flynn, G.L., Shah, Y., Prakongpan, S., Kwan, K.H., Higuchi, W.I. and Hofmann, A.F. (1979) "Cholesterol solubility in organic solvents", *J. Pharm. Sci.* **68**(9), 1090–1097.
[15] Domañska, U., Klotufar, C. and Paljk, Š. (1994) "Solubility of cholesterol in selected organic solvents", *Fluid Phase Equilibria* **97**, 191–200.
[16] Nicklasson, M. and Brodin, A. (1984) *Int. J. Pharm.* **18**, 149–156.