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Local composition models in pharmaceutical chemistry. I. Liquid–liquid distribution coefficients from COMMON UNIQUAC parameters

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Summary

A literature compilation of COMMON UNIQUAC parameters has been employed to correlate mutual solubilities in binary and ternary systems on one side and distribution coefficients between water and organic solvent of infinitely diluted liquid solutes, K_d, on the other. The following organic solvents were considered: butan-1-ol, 2-methylpropan-1-ol, ethyl acetate, chloroform, octan-1-ol, benzene, hexane, cyclohexane, heptane, octane and 2,2,4-trimethylpentane. Satisfactory K_d predictions were observed for various solutes in 2-methylpropan-1-ol/water and butan-1-ol/water and ethyl acetate/water. For all other systems, the reliability of predicted K_d values decreased with decreasing mutual saturabilities, outliers being most frequently found among alkane/water distribution coefficients of hydrogen-bonding and acidic solutes. These results are comparable to those of previous empirical correlation studies and much better than those produced by a solubility parameter concept.

Introduction

A very large number of pharmaceutically important solution processes, such as distribution, membrane transport and bioaccumulation, are ultimately determined by the tendency of most drug molecules to prefer a lipoid phase over an aqueous

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environment. This common basis of all the above processes has been confirmed by several observed linear relationships between, for example, solubility and distribution (Yalkowsky et al., 1983; Tewari et al., 1982; Hafkenscheid and Tomlinson, 1983a; Hafkenscheid, 1984), solubility and RP-HPLC retention (Hafkenscheid and Tomlinson, 1981 and 1983a; Hafkenscheid, 1984) and distribution and RP-HPLC retention (Hafkenscheid and Tomlinson, 1983b; Hafkenscheid, 1984). Eqn. 1 gives the general form of such a relationship:

$$\log Y = A \log X + B \qquad (1)$$

where A and B are regression constants. Y and X may represent solubility (S), liquid–liquid distribution (K_d) or chromatographic capacity factor (k′). Relationships of this type are undoubtedly of great practical value, for example, in the estimation of unknown solubilities or distribution coefficients from easily measurable k′ values (Hafkenscheid and Tomlinson, 1983b; Hafkenscheid, 1984). However, due to the *empirical* nature of their derivation, the validity of these equations is usually limited to the classes of compounds they were obtained from. The scope of the method can be generalized by attributing some statistical or physical meaning to the parameters A and B. Examples of this approach are given by the work of Seiler (1974), Rekker (1977) and Van de Waterbeemd and Testa (1983) on mutual correlations between distribution coefficients in two different systems, and by Hafkenscheid and Tomlinson (1983a) and Hafkenscheid (1984) for correlations between solubility and either chromatographic retention or distribution. However, these methods all remain essentially empirical and therefore limited to mutual correlations between two experimental parameters only. In our opinion, a more versatile alternative approach to such correlations in pharmaceutical chemistry may be found in the chemical engineering sector where application of so-called local composition models of intermolecular interactions has brought considerable progress to similar correlation problems (Sørensen et al., 1979; Sørensen and Arlt, 1980). Fig. 1 shows the specific features of this method, together with the contrasting empirical method described above.

The angular points of the triangle in Fig. 1 are formed by three physicochemical

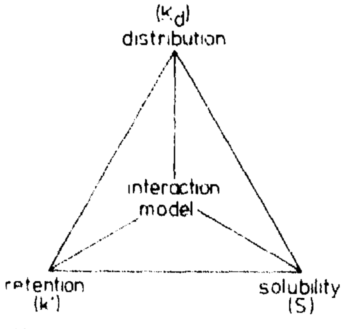

Fig. 1. Relationship between empirical and model-dependent approaches to correlations between solubility, retention and distribution. Key: K_d = distribution coefficient (in mol/litre) at infinite dilution in an organic solvent/water system. k′ = capacity factor in an RP-HPLC system with aqueous methanol as the mobile phase. S = aqueous solubility (in mol/litre).

phenomena of interest; for example, solubility, distribution and retention. Empirical relationships of the type of Eqn. 1 are visualized by considering the sides of the triangle only. However, the correlation scheme provided by a local composition model—or any other statistical model of intermolecular interactions in liquid mixtures—essentially consists of a two-step procedure using the pivot of the triangle. In the first step, the model is used to represent one of the three phenomena at the angular points as a function of the composition of the multicomponent system used for its measurement. Two types of model parameters are required for this purpose: *structural* parameters—such as molecular surface areas and volumes, and *interaction* parameters which account for the various binary interaction energies between neighbouring molecules in the mixture. Structural parameters are always readily available from the literature, whilst interaction parameters must be obtained from experimental data—such as mutual solubilities and vapour pressures—by means of curve fitting. A reliable set of interaction parameters, once derived from experiment, is thus applicable to the estimation of more than one other experimental parameter. Predictions outside the framework of Fig. 1 are feasible as well. An example is the prediction of retention-composition relationships of liquid solutes in RP-HPLC using interaction parameters derived from mutual solubilities and vapour pressure measurements (Grünbauer and Tomlinson, 1983).

The best known local composition model is that due to Abrams and Prausnitz (1975). Called UNIversal QUAsi Chemical—or UNIQUAC—after the so-called quasi-chemical approximation employed for its derivation, the UNIQUAC model has been used by Sørensen and Arlt (1980) for their recently published compilation of structural and interaction parameters derived from several hundreds of mutual solubilities in phase-separated binary and ternary systems. Two different types of interaction parameters are given by these latter authors: SPECIFIC and COMMON UNIQUAC parameters. SPECIFIC parameters have been derived by fitting ternary systems individually to the UNIQUAC model. These parameters are therefore valid only for the system from which they were obtained. COMMON UNIQUAC parameters on the other hand have been derived from a much larger data base and may be considered as best estimates of interaction parameters accounting for a particular A–B interaction in an arbitrary multicomponent system where A and B are two of the constituents.

The above compilation of COMMON UNIQUAC parameters has been chosen by us as the starting point of a series of studies on the applicability of local composition models in pharmaceutical chemistry. The present paper is the first of the series. It is concerned with calculation of log K_d values from COMMON UNIQUAC parameters in some relevant organic solvent/water systems. The line passing from the solubility angular point to the pivot of Fig. 1 is thus extended towards the angular point indicated by distribution. The ultimate aim of this study is to investigate whether or not reliable K_d estimates can result from such extrapolations. Evidence for affirmative answers to this question is of great interest as the observation of reliable K_d predictions in a particular distribution system imply that, at a later stage, experimental K_d values in that system can be employed to obtain interaction parameters suitable for both the estimation of drug solubilities in mixed solvents, and the correlation of such solubilities with distribution coefficients and RP-HPLC retention data.

In this present study the following organic solvents have been considered: butan-1-ol, 2-methylpropan-1-ol, octan-1-ol, ethyl acetate, chloroform, benzene, cyclohexane, hexane, heptane, octane and 2,2,4-trimethylpentane. Calculated values of K_d have been tested using either experimental K_d values (Hansch and Leo, 1979) and/or fragment summations of K_d (Rekker, 1977). The reliability of the UNIQUAC method has been subsequently compared to that of the empirical method described above. Finally, using cyclohexane/water as an example, the effect of replacing UNIQUAC by a solubility parameter approach has been evaluated.

Methods

The thermodynamic distribution coefficient K_d^x of a solute (component 3) in a two-phase system composed of water (component 1) and an organic solvent (component 2) on the mole fraction concentration scale is given by:

$$K_d^x = \frac{x'_3}{x_3} = \frac{\gamma_3}{\gamma'_3} \tag{2}$$

where x_3 and γ_3 represent the mole fraction and activity coefficient (based on Raoult's law) of the solute in the aqueous phase, respectively. Corresponding quantities in the organic phase are indicated by primes. According to the UNIQUAC model the activity coefficient of the solute, γ_3, in the aqueous phase is given by (Abrams and Prausnitz, 1975):

$$\begin{aligned} \ln \gamma_3 = {} & \ln \frac{\Phi_3}{\theta_3} + \frac{z}{2} q_3 \ln \frac{\theta_3}{\Phi_3} + \ell_3 - \frac{\Phi_3}{x_3}(x_1\ell_1 + x_2\ell_2 + x_3\ell_3) \\ & - q_3 \ln(\theta_1\tau_{13} + \theta_2\tau_{23} + \theta_3) + q_3 - \frac{q_3\theta_1\tau_{13}}{\theta_1 + \theta_2\tau_{21} + \theta_3\tau_{31}} \\ & - \frac{q_3\theta_2\tau_{23}}{\theta_1\tau_{12} + \theta_2 + \theta_3\tau_{32}} - \frac{q_3\theta_3}{\theta_1\tau_{13} + \theta_2\tau_{23} + \theta_3} \end{aligned} \tag{3}$$

where

$$\ell_j = \frac{z}{2}(r_j - q_j) - (r_j - 1) \tag{3a}$$

$$\tau_{ij} = \exp\{-(u_{ij} - u_{jj})/RT\} \tag{3b}$$

$$A_{ij} = (u_{ij} - u_{jj})/R \tag{3c}$$

$i = 1, 3 \qquad j = 1, 3$

In these equations, z represents a lattice coordination number which is usually set equal to 10 (Abrams and Prausnitz, 1975). Mole fractions, area fractions and volume fractions are indicated by x, θ and Φ, respectively. The structural parameters q_i and r_i are (relative) measures of the Van der Waals volume and area of molecule i, respectively. These parameters as well as the interaction parameters A_{ij} are found in the data compilation of Sørensen and Arlt (1980). An expression for $\log \gamma_3^\infty$, the solute activity coefficient at infinite dilution in the aqueous phase is readily obtained from Eqn. 3 by taking the limit for $x_3 \rightarrow 0$ and transformation to Naperian logarithms. $\log \gamma_3'^\infty$, the limiting activity coefficient of the solute in the organic phase is expressed in a similar way. Finally, the distribution coefficient K_d on the molar concentration scale is calculated from (Grünbauer et al., 1982):

$$\log K_d = \log \gamma_3^\infty - \log \gamma_3'^\infty + C \tag{4}$$

where the conversion factor C is given by:

$$C = \log \frac{r_1 x_1 + r_2 x_2}{r_1 x_1' + r_2 x_2'} \tag{4a}$$

In conclusion: $\log K_d$ values are immediately calculable from Eqn. 3 and 4 by substitution of the known composition of the distribution system considered and the appropriate values for q_i, r_i and A_{ij}.

Eqn. 5, which gives $\log K_d$ in terms of solubility parameters, is readily derived in a similar way (Srebrenik and Cohen, 1976; Anderson et al., 1983), i.e.:

$$\log K_d = \frac{\bar{v}_3}{2.303RT}\left\{(\delta_1 - \delta_3)^2 - (\delta_2 - \delta_3)^2\right\} + C \tag{5}$$

where the solubility parameters of water, organic solvent and solute have been indicated by δ_1, δ_2 and δ_3, respectively. These parameters are comparable to the interaction parameters of UNIQUAC whereas the corresponding structural parameter is formed by $\bar{v}_3$, the molar volume of the solute.

Results

There exists only partial overlap between all possible K_d values that are calculable from the data compilation of Sørensen and Arlt (1980) and those given in the listing of experimental K_d values published by Hansch and Leo (1979). Extension of the latter by application of a fragmental system (Rekker, 1977) has been necessary, although the empirical nature (Grünbauer, 1981) as well as the predictive limitations (Le Therizien et al., 1980; Lewis et al., 1983; Hansch and Leo, 1979) of such systems must be kept in mind. In Figs. 2–10, fragment summations are therefore only included when experimental data were not available. Those K_d values from UNIQUAC for which neither experimental data nor fragment summations could be obtained have been omitted.

Fig. 2 summarizes results obtained for the systems butan-1-ol/water and 2-methylpropan-1-ol/water. It is seen that for solutes having low K_d values, there is good agreement between calculated and experimental or estimated K_d values, with values within 0.5 log units from each other. Some solutes having higher K_d values deviate to a greater extent, i.e. 3-methylbutan-1-ol in 2-methylpropan-1-ol/water and benzene and decane in butan-1-ol/water. However, these two solutes have K_d values estimated using a fragmental approach which has to be extrapolated far outside its accepted area of validity.

Calculated K_d values in ethyl acetate/water are compared to experimental values in Fig. 3. Excellent agreement is observed throughout, with all predictions being within 0.4 log units from experimental data. For chloroform/water and octan-1-ol/water, UNIQUAC K_d values may be calculated for only a small number of solutes. The resulting plots, given in Figs. 4 and 5, respectively, show an increased scatter, as compared to those found for isomeric butanol/water and ethyl acetate/water. Significant outliers—i.e. deviating more than 0.5 log units—are propanoic acid in chloroform/water and pyridine in octan-1-ol/water.

Fig. 6 gives a plot of 22 predicted K_d values versus observed K_d values in benzene/water. Here the largest deviations from experiment are observed for molecules having significant hydrogen-bonding capabilities, such as acetic and propanoic acid, propan-2-ol, pyridine and 2-methylpyridine. Poor agreement with predictions of the fragmental system is also found for hexane and heptane which have relatively high K_d values. The significance of this observation is, however, uncertain due to the absence of any experimentally obtained K_d values and the

Fig. 2.

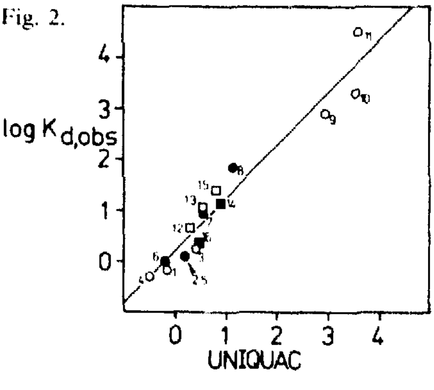

Fig. 3.

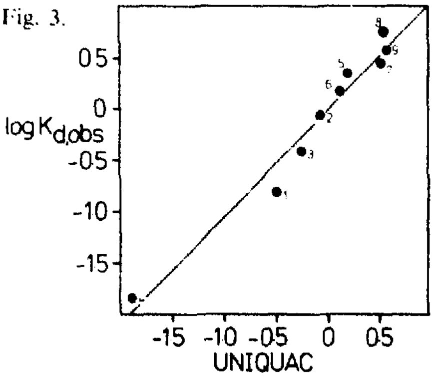

Fig. 2. Relationship between observed and predicted distribution coefficients in butan-1-ol/water (circles) and 2-methylpropan-1-ol/water (squares). The solid line represents the regression line given in Table 1. Observed values are experimentally determined (■ or ●) or calculated from fragmental constants (□ or ○). Key: 1 = methanol; 2 = acetic acid; 3 = ethanol; 4 = 1,2-ethanediol; 5 = 2-hydroxypropanoic acid; 6 = succinic acid; 7 = 2-methylpropan-1-ol; 8 = benzene; 9 = hexane; 10 = heptane; 11 = decane; 12 = propan-1-ol; 13 = butan-1-ol; 14 = 3-methylbutanoic acid; 15 = 3-methylbutan-1-ol; 16 = ethyl acetate.

Fig. 3. Relationship between experimental and predicted distribution coefficients in ethyl acetate/water. The solid line represents the regression line given in Table 1. Key: 1 = methanol; 2 = acetic acid; 3 = ethanol; 4 = 1,2-ethanediol; 5 = propanoic acid; 6 = propan-1-ol; 7 = butanoic acid; 8 = butan-1-ol; 9 = furfural.

inability of fragmental systems to predict very high distribution coefficients (Hansch and Leo, 1979).

A relatively large number of COMMON UNIQUAC parameters are available for aliphatic hydrocarbon/water systems. Results for cyclohexane/water are given in Fig. 7. Outliers are again observed among acids and alcohols although predictions for methyl acetate and tetrahydrofuran are also poor.

For hexane/water (Fig. 8), the overall agreement with experiment is similar to that for cyclohexane/water. Apart from acids and alcohols, N,N-dimethylformamide and 1,2-ethanediol are seen to be outliers. Experimental reference data are, however, not available for these solutes.

Predicted heptane/water distribution coefficients are plotted in Fig. 9. A pattern similar to that for the other hydrocarbon/water systems can be observed. For heptanoic acid, a reference log value of 0.05 obtained by fragment summation was preferred over an experimental value of 2.66 which appeared out of line with respect to other homologues of the carboxylic acid series. Fragment summations of 3.61 for the dimethylbenzenes are in better agreement with experimental values of 3.4–3.5 than UNIQUAC predictions ranging from 2.3 to 2.9.

The octane/water and 2,2,4-trimethylpentane/water systems are summarized in Fig. 10. Except for nitroethane in octane/water and octane in 2,2,4-trimethylpentane/water, the quality of UNIQUAC K_d values is satisfactory. Interestingly, prediction of K_d using both fragmental method and UNIQUAC for these latter two exceptions deviate strongly from experiment, although values predicted using both methods are in excellent agreement.

The results can be summarized as follows: the reliability of predicted K_d values increases with increasing mutual saturabilities of the distribution systems considered.

Fig. 4.

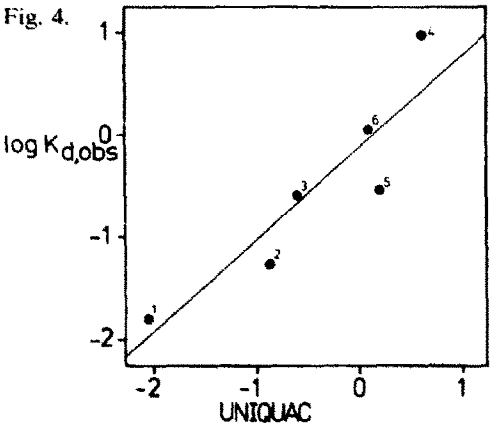

Fig. 5.

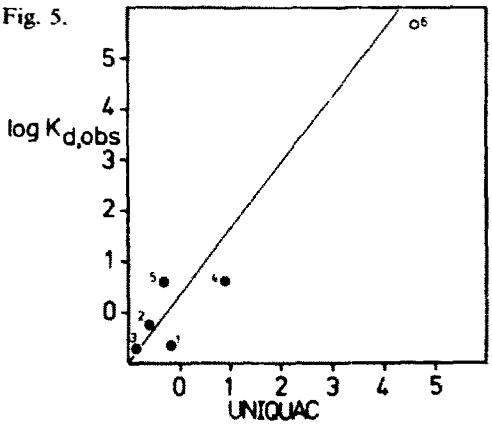

Fig. 4. Relationship between experimental and predicted distribution coefficients in chloroform/water. The solid line represents the regression line given in Table 1. Key: 1 = formic acid; 2 = acetic acid; 3 = ethanol; 4 = acetone; 5 = propanoic acid; 6 = propan-2-ol.

Fig. 5. Relationship between predicted and observed distribution coefficients in octan-1-ol/water The solid line represents the regression line given in Table 1. Observed values are experimental (●) or fragment summations (○). Key: 1 = methanol; 2 = acetone; 3 = 2-hydroxypropanoic acid; 4 = diethyl amine; 5 = pyridine; 6 = decane.

Fig. 6.

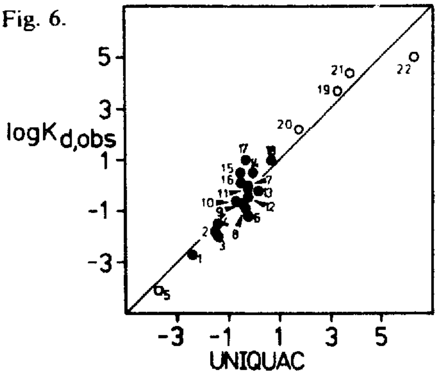

Fig. 7.

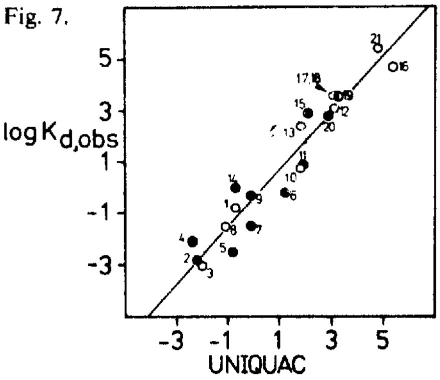

Fig. 6. Relationship between observed and predicted distribution coefficients in benzene/water. The solid line represents the regression line given in Table 1. Observed values are experimental (●) or fragment summations (○). Key: 1 = formic acid; 2 = methanol; 3 = acetic acid; 4 = ethanol; 5 = 1,2-ethanediol; 6 = propanoic acid; 7 = acetone; 8 = propan-2-ol; 9 = propan-1-ol; 10 = 2-methylpropan-2-ol; 11 = 2-methylpropan-1-ol; 12 = butan-1-ol; 13 = butan-2-ol; 14 = furfural; 15 = pyridine; 16 = piperidine; 17 = 2-methylpyridine; 18 = aniline; 19 = cyclohexane; 20 = butyl acetate; 21 = hexane; 22 = heptane.

Fig. 7. Relationship between observed and predicted distribution coefficients in cyclohexane/water. The solid line represents the regression line given in Table 1. Observed values are experimental (●) or fragment summations (○). Key: 1 = nitromethane; 2 = methanol; 3 = acetic acid; 4 = ethanol; 5 = propanoic acid; 6 = methyl acetate; 7 = propan-1-ol; 8 = propan-2-ol; 9 = butan-2-one; 10 = tetrahydrofuran; 11 = diethyl ether; 12 = cyclopentane; 13 = benzene; 14 = aniline; 15 = toluene; 16 = heptane; 17 = 1,4-dimethylbenzene; 18 = 1,2-dimethylbenzene; 19 = 1,3-dimethylbenzene; 20 = ethylbenzene; 21 = 2,2,4-trimethylpentane.

Fig. 8.

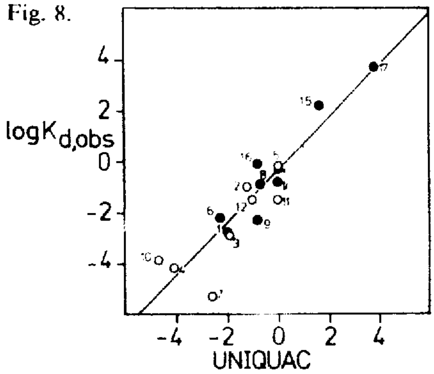

Fig. 9.

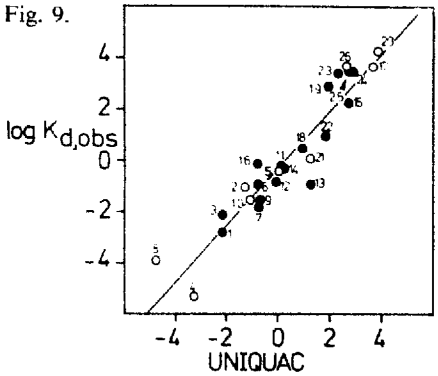

Fig. 8. Relationship between observed and predicted distribution coefficients in hexane/water. The solid line represents the regression line given in Table 1. Observed values are experimental (●) or fragment summations (○). Key: 1 = methanol; 2 = acetonitrile; 3 = acetic acid; 4 = N-methylformamide; 5 = nitroethane; 6 = ethanol; 7 = 1,2-ethanediol; 8 = acetone; 9 = propanoic acid; 10 = N,N-dimethylformamide; 11 = propan-1-ol; 12 = propan-2-ol; 13 = butan-2-one; 14 = butan-1-ol; 15 = benzene; 16 = aniline; 17 = methylcyclopentane.

Fig. 9. Relationship between observed and predicted distribution coefficients in heptane/water. The solid line represents the regression line given in Table 1. Observed values are experimental (●) of fragment summations (○). Key: 1 = methanol; 2 = acetonitrile; 3 = ethanol; 4 = 1,2-ethanediol; 5 = propanoic acid, nitrile; 6 = acetone; 7 = propanoic acid; 8 = N,N-dimethylformamide; 9 = propan-1-ol; 10 = propan-2-ol; 11 = butan-2-one; 12 = butan-1-ol; 13 = pentanoic acid, 14 = 3-methylbutan-1-ol; 15 = benzene; 16 = aniline; 17 = cyclohexane; 18 = hexan-1-ol; 19 = toluene; 20 = methylcyclohexane; 21 = heptanoic acid; 22 = heptan-1-ol; 23 = 1,2-dimethylbenzene; 24 = 1,3-dimethylbenzene; 25 = 1,4-dimethylbenzene; 26 = ethylbenzene.

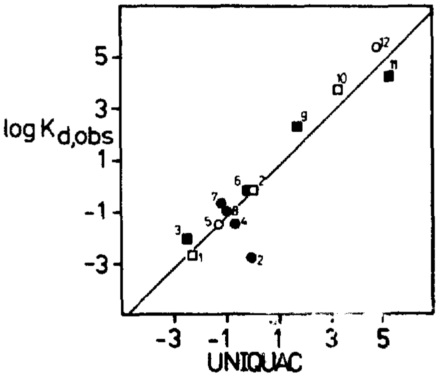

Fig. 10. Relationship between observed and predicted distribution coefficients in octane/water (circles) and 2,2,4-trimethylpentane/water (squares). The solid line represents the regression line given in Table 1. Observed values are experimental (■ or ●) of fragment summations (□ or ○). Key: 1 = methanol; 2 = nitroethane; 3 = ethanol; 4 = propan-1-ol; 5 = propan-2-ol; 6 = butan-2-one; 7 = furfural; 8 = phenol; 9 = benzene; 10 = cyclohexane; 11 = octane; 12 = 2,2,4-trimethylpentane.

The limits of the method are particularly noticeable for distributions in alkane/water systems of molecules with significant hydrogen bonding capabilities such as carboxylic acids and alcohols. The position of other types of solutes in alkane/water systems is somewhat uncertain due to the lack of a sufficient number of calculable predictions and/or experimental reference values.

Discussion

Linear regression analysis has been applied to the data given in Figs. 2–10, and the results are summarized in Table 1. The statistical quality of the regressions is satisfactory, especially if it is realized that the larger part of the solutes considered belongs to the class of small hydrogen-bonding solutes, which is difficult to manage using either a fragmental approach (Rekker, 1977) or empirical correlations of the type of Eqn. 1. For example, Hafkenscheid and Tomlinson (1981, 1983a) also found systematic deviations for alcohols and acids in correlations between solubilities and reversed-phase HPLC retention using methanol/water as the mobile phase. In addition, relatively poor correlations—as compared to neutral and basic compounds—were found between retention and octan-1-ol/water distribution for these compounds. As in their study, the quality of regressions in Table 1 could have been improved by introduction in the regression equation of a dummy parameter accounting for systematically deviating alcohols and acids. Statistical correction factors of this type are, however, not compatible with the model-dependent approach of Fig. 1, since their inclusion would obstruct the future use of experimental K_d values as a data source for the deviation of interaction parameters. It will be shown below that the discrepancies observed in Figs. 2–10 can be shown to arise from problems with the original derivation of COMMON UNIQUAC parameters.

Deviations shown in Figs. 2–10 are most readily explained in terms of self-association of alcohols and acids in inert organic solvents and/or hydrophobic hydration phenomena in aqueous phases containing almost pure water. This viewpoint is formed after considering a crucial, but problematic, assumption on interaction energies, which is implicit in not only local composition models but also in many other interaction models of liquid mixtures. That is, the interaction energy of an adjacent pair of molecules is treated as an adjustable constant, irrespective of the type and behaviour of surrounding molecules. As shown by Sørensen and Arlt (1980), this assumption is sufficiently accurate for the purpose of correlating mutual solubilities in phase-separated binary and ternary systems. However, in certain extreme cases, the interaction energy of a neighbouring pair of molecules is probably strongly dependent on its solvent environment. For example, aliphatic alcohols and carboxylic acids are well known to exhibit self-association and/or dimerization in inert solvents such as carbon tetrachloride or alkanes (Fletcher and Heller, 1967; Prausnitz, 1969; Chen and Bagley, 1978). As a consequence, the interaction energy between, for example, two acetic acid molecules in water is likely to be significantly different from that in, say, hexane. Moreover, hexane–acetic acid interactions at high concentrations of acid are probably predominantly determined by relatively favourable interactions between hexane and acetic acid dimers. It follows that interaction parameters derived from data at high acetic acid concentrations are likely to predict too high K_d values since, at conditions of infinite dilution, self-association and/or dimerization is less important (the data of Hansch and Leo, 1979, have usually been corrected for these effects). A similar reasoning has been presented by Grünbauer et al. (1982) for structured aqueous phases where interactions between neighbouring molecules were considered to depend on the solvent environment as well. Predicted K_d values are affected by *both* phenomena in a positive direction with respect to experimental data. The analysis is further confirmed by the very satisfactory results obtained for these solutes in butanol- and 2-methylpropan-1-ol/water and ethyl acetate/water, the only systems where both self-association/dimerization and structural effects are likely to be less important. It can be concluded that

TABLE 1

COEFFICIENTS A AND B TOGETHER WITH THEIR 95% CONFIDENCE LIMITS OF REGRESSION EQUATIONS: $\log K_d(\text{obs}) = A \log K_d(\text{pred.}) + B$.

Solvent	A	B	n	*r*	s	F
isomeric butanols	1.02 ± 0.14	0.22 ± 0.22	16	0.97	0.34	232
ethyl acetate	1.03 ± 0.19	−0.03 ± 0.14	9	0.98	0.18	161
chloroform	0.91 ± 0.56	−0.39 ± 0.57	6	0.91	0.45	20.1
octan-1-ol	1.14 ± 0.39	0.19 ± 0.76	6	0.97	0.64	67.4
benzene	0.99 ± 0.14	−0.01 ± 0.29	22	0.96	0.64	226
cyclohexane	1.10 ± 0.15	−0.37 ± 0.39	21	0.96	0.76	220
hexane	1.02 ± 0.26	−0.40 ± 0.55	17	0.91	0.95	72.9
heptane	1.12 ± 0.17	−0.15 ± 0.37	26	0.94	0.89	187
isomeric octanes	0.99 ± 0.22	−0.18 ± 0.54	14	0.95	0.92	101

Key: n = number of data points; *r* = correlation coefficient; s = standard error of estimate; F = Fisher's variance ratio.

COMMON UNIQUAC parameters can be used to correlate mutual solubilities with experimental K_d values in these systems. Improvement of such correlations in other systems can probably be made by introducing alternative methods for the determination of interaction parameters. This point will be considered in detail in a forthcoming study on the effects of different choices of structural parameters.

The model-dependent correlation method via the pivot of Fig. 1 is evidently not restricted to local composition models. Consequently, it appeared worthwhile to compare predictions using UNIQUAC with results produced by some other relevant model. The solubility parameter concept based on regular solution theory has been selected to this purpose, mainly because this concept has received much recent attention (Schoenmakers et al., 1981; Anderson et al., 1983; Hafkenscheid and Tomlinson, 1983b).

The regular solution model of liquid mixtures was originally considered to be not applicable to phase-separated mixtures since, according to Hildebrand and Scott (1949), two regular solutions should be miscible in all proportions. As a consequence, at least one of the two phases of a partially miscible system must be non-regular. However, later work (Wakahayashi et al., 1964; Srebrenik and Cohen, 1976 and Shinoda, 1978), showed that solubility parameter concepts based on regular solution theory could be applied successfully to phase-separated aqueous mixtures. Such studies considered the solubility parameter of water as an adjustable parameter. For example, values of 23.53 and 16.35 for the solubility parameter of water were derived from mutual solubilities of water and liquid hydrocarbons (Black et al., 1948; Shinoda, 1978) and distribution coefficients of β-diketones (Wakahayashi et al., 1964), respectively. The solubility parameter concept can thus be used to replace UNIQUAC in the correlation scheme of Fig. 1. That is, values for the solubility parameter of water derived from mutual solubilities or other external sources can be substituted into Eqn. 5 to yield predicted K_d values in a similar way as before.

The cyclohexane/water system has been chosen for study. K_d values calculated by substitution of $\delta_1 = 23.53$ in Eqn. 5 are given in Table 2. As expected from the previous work of Hafkenscheid and Tomlinson (1983b), the agreement with experiment or fragment summation is very poor. This implies that, unlike UNIQUAC, a δ_1 value derived from mutual solubilities is not compatible at all with distribution coefficients at infinite dilution. As suggested by Anderson et al. (1983), improved predictions (Table 2), are indeed obtained by substituting $\delta_1 = 16.35$ (as first proposed by Wakahayashi et al., 1964). However, the improvement is somewhat artefactual since this δ-value has previously also been derived from hydrocarbon/water distribution coefficients. The limitations of the solubility parameter concept are quite evident when Eqn. 5 is solved for δ_1 by substituting fragment summations for K_d. It follows directly from Eqn. 5 that:

$$\delta_1 = \delta_3 \pm \left\{ \frac{2.303RT}{\bar{v}_3} (\Sigma f - C) - (\delta_2 - \delta_3)^2 \right\}^{1/2} \qquad (6)$$

The resulting δ_1-values are also summarized in Table 2. A large variation in δ_1 from

TABLE 2

PREDICTION OF CYCLOHEXANE/WATER DISTRIBUTION COEFFICIENTS BY MEANS OF A SOLUBILITY PARAMETER CONCEPT

Solute	$\bar{v}_3$ (cm^3)	δ_3 (cal$^{1/2}$·cm$^{-3/2}$)	log K_d ($\delta_1 = 23.53$)	log K_d ($\delta_1 = 16.35$)	δ_1 (from Σf)	Σf
nitromethane	53.954 [a]	12.90 [a]	2.81	−1.19	17.55	−0.80
methanol	40.733 [b]	14.50 [a]	0.47	−1.87	− *	−2.73
acetic acid	57.541 [b]	13.01 [a]	2.91	−1.29	− *	−3.03
ethanol	58.685 [b]	12.78 [a]	3.29	−1.14	− *	−2.11
propanoic acid	74.980 [b]	12.47 [a]	4.94	−0.96	− *	−2.41
methyl acetate	79.882 [a]	9.46 [a]	10.72	1.91	13.32	−0.00
propan-1-ol	75.145 [b]	12.18 [a]	5.44	−0.70	13.86	−1.50
propan-2-ol	76.923 [b]	11.44 [a]	6.87	−0.02	− *	−1.50
butan-2-one	90.169 [b]	9.45 [a]	12.22	2.26	13.02	−0.04
tetrahydrofuran	81.70 [c]	9.11 [c]	11.62	2.31	14.28	0.77
diethyl ether	104.78 [a]	7.53 [a]	18.85	5.16	12.66	1.21
cyclopentane	94.714 [a]	8.10 [a]	15.75	3.95	15.56	3.08
benzene	89.407 [b]	9.16 [a]	12.69	2.55	16.17	2.38
aniline	91.15 [c]	11.73 [c]	7.69	−0.19	16.68	0.02
toluene	106.86 [b]	8.93 [a]	15.87	3.49	15.92	3.00
heptane	147.47 [b]	7.50 [a]	26.95	7.64	14.68	4.74
1,4-dimethylbenzene	124.00 [a]	8.83 [a]	18.82	4.32	15.81	3.61
1,2-dimethylbenzene	121.22 [a]	9.06 [a]	17.76	3.88	16.14	3.61
1,3-dimethylbenzene	123.48 [a]	8.88 [a]	18.60	4.23	15.88	3.61
ethylbenzene	123.11 [a]	8.84 [a]	18.66	4.27	15.84	3.61
2,2,4-trimethylpentane	166.08 [b]	6.86 [a]	32.83	9.97	14.08	5.36

Key: $\bar{v}_i$ = molar volume; δ_i = solubility parameter; K_d = distribution coefficient on the mol/litre scale at infinite dilution; Σf = fragment summation according to Rekker (1977). Solubility parameters and molar volumes have been taken from: [a] Hoy, (1970); [b] Riddick and Bunger, (1970); [c] Kumar and Prausnitz, (1975). * Eqn. 6 cannot be solved for these solutes (see text).

12.66 (diethyl ether) to 17.55 (nitromethane) can be observed. For methanol, acetic acid, ethanol, propanoic acid and propan-2-ol, Eqn. 6 cannot be solved at all since, in these cases,

$$\Sigma f < \frac{\bar{v}_3(\delta_2 - \delta_1)^2}{2.303RT} + C \qquad (7)$$

which leads to physically meaningless negative square-roots. It can be concluded that, at its best, a solubility parameter concept may yield a semi-quantitative description of K_d values for related sets of solutes provided that the δ_1-values involved are derived from K_d values as well. Comparison of the concept with the

UNIQUAC model clearly favours the latter. This result is not surprising since Abrams and Prausnitz (1975) have demonstrated that the solubility parameter concept merely represents a special case of UNIQUAC.

Conclusions

The compilation of COMMON UNIQUAC parameters employed in the present study has been observed to yield good reproductions of mutual solubilities in phase-separated ternary mixtures. The present results clearly suggest that, as far as solvent/water systems are concerned, this capability can only be extended towards distribution coefficients at infinite dilution in systems with significant mutual solubilities. Predicted K_d values in all other systems show an increased scatter with systematic deviations being found for organic electrolytes and hydrogen bonding solutes in alkane/water systems. A significant similarity is further observed between the present results and those of previous studies using empirical correlation methods. The overall agreement with experiments is comparable and, in both approaches, discrepancies are observed for essentially the same solute classes. Finally, it can be concluded that UNIQUAC appears to be much better suited to the purpose of quantitatively representing a multicomponent system than a solubility parameter concept.

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