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The Mobile Order Theory Versus UNIFAC and Regular Solution Theory-Derived Models for Predicting the Solubility of Solid Substances

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The theory of mobile order of Huyskens is tested against the UNIFAC model, the regular solution model, and the extended Hildebrand or Hansen solubility approaches in predicting the solubility of naphthalene in both polar and nonpolar solvents at 40°C. While all models correctly predict the solubility in nonpolar and moderately polar solvents, a substantial improvement is achieved by Huyskens' model, particularly in alcohols. This improvement originates from the correct description of the entropy effects as well as of the hydrophobic effects in the particular case of the alcohols. The model necessitates the knowledge of only one parameter not known a priori, i.e., the naphthalene modified nonspecific solubility parameter, the value of which is deduced from its solubility in hexane.

KEY WORDS: solubility prediction; mobile order; solution thermodynamics; UNIFAC; naphthalene.

INTRODUCTION

The ability to estimate solubility is important in many fields, including pharmaceutical technology to select solvent systems with adequate drug solubility, stability, and bioavailability for topical, oral, or parenteral delivery. A remarkable improvement of solubility prediction has been achieved with the theory of the mobile order of Huyskens (1–3). The quantitative development of this theory (4) has led to equations describing the effect of solvent–solvent, solute–solvent, and solute–solute hydrogen bonds on the chemical potential of the solute. A universal equation predicting the solubility of solid substances has been derived.

The aim of this paper was to examine the prediction accuracy of Huyskens' model for the solubility of naphthalene in various solvents ranging from hydrocarbons to alcohols at 40°C. The results were tested against those obtained by other predictive methods, in particular, by the Scatchard–Hildebrand regular solution theory (5), by the extended Hildebrand solubility approach and the extended Hansen solubility approach of Martin (6,7), and by the universal-quasi-chemical (UNIQUAC) model of Abrams and Prausnitz (8). While the first three models are concerned mainly with enthalpic effects, the last model includes both enthalpic and entropic contributions to the activity coefficients. According to this method, the total activity coefficient is divided into a "combinatorial" and a "residual" part. The combinatorial contribution is only entropy-governed and is obtained by the number of ways of forming a solution with molecules (solute and solvent) of which the size and shape are given. The residual contribution is calculated from interaction parameters which are either determined experimentally or obtained by adding interaction parameters of functional groups (UNIFAC) (9,10).

Although naphthalene, having no functional groups, hetero-atoms, or side chains, is a poor prototype of a drug molecule, it is a convenient model to analyze the efficiency of Huyskens' model in predicting the solubility of crystalline substances in pure solvents. Moreover, naphthalene is one of the few molecules for which solubility values have experimentally been measured and calculated by the four previous predictive models in numerous solvents.

THE PREDICTIVE EQUATION DERIVED FROM THE THEORY OF THE MOBILE ORDER

The solubility of naphthalene in volume fraction, Φ_B, as far as the hydrogen bonding between the solute and the solvent can be ignored, is expressed by the product of four terms [Eq. (1)], accounting for the ideal solubility, the entropy of placing, the changes in the nonspecific cohesion forces upon mixing, and the hydrophobic effect of the associated solvents such as alcohols on the solubility of an inert substance.

$$\Phi_B = e^{-A}\, e^{B}\, e^{-D}\, e^{-F} \tag{1}$$

The physical meaning and the mathematical expression of each of these terms are discussed in our previous paper (4). Briefly, the fluidization constant, A, in the above equation depends only on the crystal and should normally be expressed by

$$\begin{aligned} A = {} & \Delta_{\mathrm{melt}}H\,(1/T - 1/T_m)/R \\ & + \Delta C_p\,[(T_m/T - 1) \\ & - \ln(T_m/T)]/R \end{aligned} \tag{2}$$

where $\Delta_{\mathrm{melt}}H$ is the molar heat of fusion, T_m and T are the absolute melting point and the temperature of interest, respectively, and ΔC_p is the difference in heat capacity between the crystalline and the molten forms of the substance. However, as ΔC_p is usually quite small and as $(T_m/T - 1)$ is approximately equal to $\ln(T_m/T)$, the last term in Eq. (2) can be ignored without any significant loss of accuracy. Therefore, as a reasonable approximation, the fluidization constant, A, is calculated by

$$A = \Delta_{\mathrm{melt}}H\,(1/T - 1/T_m)R \tag{2'}$$

As a result, the predictions of the naphthalene solubility in pure solvents using Eq. (1) necessitate only one parameter that is not a priori known, i.e., its modified nonspecific solubility parameter δ_B', the value of which is deduced from *one experimental solubility* at the desired temperature.

RESULTS AND DISCUSSION

The melting point of naphthalene is 353.35 K (7), and its molar heat of fusion, determined by differential thermal analysis (10), is 18.803 kJ mol^{-1}. These values lead to a fluid-

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ization constant A of 0.822 at 40°C. By using Eq. (2) with the ΔC_p value of 8.901 J mol^{-1} K^{-1} given by Choi *et al.* (11), the fluidization constant would decrease to only 0.813. The molar volume of naphthalene, formed of eight C–H aromatic groups (14.9 cm^3) and of two C aromatic carbons (5.5 cm^3), amounts to 130.2 cm^3 mol^{-1} as calculated from group contributions (4). This value, which is somewhat larger than the value of 123 cm^3 mol^{-1} used by Martin *et al.* (6,7), corresponds to the molar liquid volume (130.9 cm^3 mol^{-1}) of naphthalene measured at the melting point (11).

The molar volumes, V_S, and the modified nonspecific solubility parameters, δ_S', of the solvents used are given in Table V of our previous paper (4), except for the six following molecules: 1,1-dichloroethane, 1,1-dibromoethane, 1,2-dibromoethane, chlorobenzene, nitrobenzene, and carbon disulfide. For these nonassociated solvents, the modified solubility parameter values, δ_S', have been determined from Hansen's partial solubility parameters, δ_d and δ_p (12), by means of Eq. (3). As for the five remaining associated solvents given in Ref. 7, they cannot be used for the solubility comparison without the experimental determination of their δ_S'.

$$\delta_S' = (\delta_d^2 + \delta_p^2)^{1/2} \qquad (3)$$

The modified solubility parameter, δ_B', of naphthalene for the nonspecific cohesion forces has been deduced from its experimental solubility in *n*-hexane, for which Gmehling *et al.* (10) have reported a molar fraction value X_B of 0.222 at 40°C. As the term F in Eq. (1) for this solvent vanishes, one calculates a value δ_B' of 19.30 MPa$^{1/2}$, which, in this particular case, corresponds to the square root of the sum of squares of Hansen's dispersive δ_d and polar δ_p solubility parameters of naphthalene given by Barton (12).

From this unique experimental solubility value, Huyskens' model, represented by Eq. (1), allows us to predict the naphthalene solubility in 18 solvents at 40°C. The results are listed in the third column in Table I and are compared to the solubilities (7), either determined experimentally or calculated from the four above-mentioned models. Contrary to the extended Hildebrand or Hansen solubility approaches of Martin *et al.* (6,7), Eq. (1) does not imply adjustable parameters, yielding therefore really predicted values.

In nonpolar or moderately polar solvents, all mentioned methods predict or reproduce quite correctly the solubility of naphthalene at 40°C. Accuracies are good and the ratios of predicted-to-experimental values for solvents ranging from toluene to acetone (Fig. 1) lay between 0.77 and 1.23, i.e., the deviations do not exceed ±24%.

The best results, however, are obtained with Huyskens' model, for which the greatest relative error of prediction [Eq. (4)] corresponds to 9.8% for acetone.

$$\text{deviation } (\%) = 100\,(X_i^{\text{cal}} - X_i^{\text{exp}})/X_i^{\text{exp}} \qquad (4)$$

In alcohols, solubility predictions are generally more difficult because alcohols are associated solvents forming single H-bonded chains. Nevertheless, for such solvents, the results obtained by Eq. (1) are superior to those obtained by the other models, and the prediction accuracies of the Huyskens model in alcohols are of the same order of magnitude as those obtained previously with the non-H-bonded solvents [the largest deviation amounting to 13% for 2-propanol (Fig. 1a). In comparison, the Scatchard–Hildebrand regular solution theory completely fails in predicting the solubilities of a molecule as simple as naphthalene in alcohols, with deviations as high as 400% (Fig. 1b). It is therefore unrealistic to expect that such a model could provide satisfactory solubility estimations of drug molecules. Extended Hildebrand or Hansen solubility approaches (Figs. 1c and d)

Table I. Experimental and Predicted Solubilities in Molar Fraction, X_i, of Naphthalene at 40°C

		Model				
Solvent	Experimental[a]	Huyskens	Regular solution[a]	Extended Hildebrand[a]	Extended Hansen[a]	UNIFAC[a]
Toluene	0.422	0.433	0.453	0.434	0.407	0.442
Benzene	0.428	0.443	0.460	0.444	0.419	0.450
Carbon tetrachloride	0.395	0.414	0.446	0.431	0.396	0.407
Chloroform	0.467	0.445	0.464	0.448	0.408	0.469
1,1-Dichloroethane	0.437	0.442	0.458	0.445	0.428	—
1,2-Dichloroethane	0.452	0.435	0.461	0.439	0.455	—
1,1-Dibromoethane	0.456	0.442	0.462	0.437	0.423	0.384
1,2-Dibromoethane	0.439	0.435	0.359	0.339	0.374	0.383
Chlorobenzene	0.444	0.441	0.466	0.443	0.424	0.398
Nitrobenzene	0.432	0.405	0.433	0.395	0.481	—
Carbon disulfide	0.494	0.451	0.464	0.450	0.411	0.420
Acetone	0.378	0.415	0.466	0.448	0.442	0.363
Methanol	0.041	0.040	0.005	0.035	0.048	0.049
Ethanol	0.073	0.072	0.123	0.049	0.061	0.055
Propanol	0.094	0.094	0.334	0.081	0.083	0.094
2-Propanol	0.076	0.086	0.396	0.116	0.098	0.095
Butanol	0.116	0.116	0.401	0.113	0.110	0.112
2-Butanol	0.112	0.102	0.437	0.150	0.145	0.113

[a] See Ref. 7.

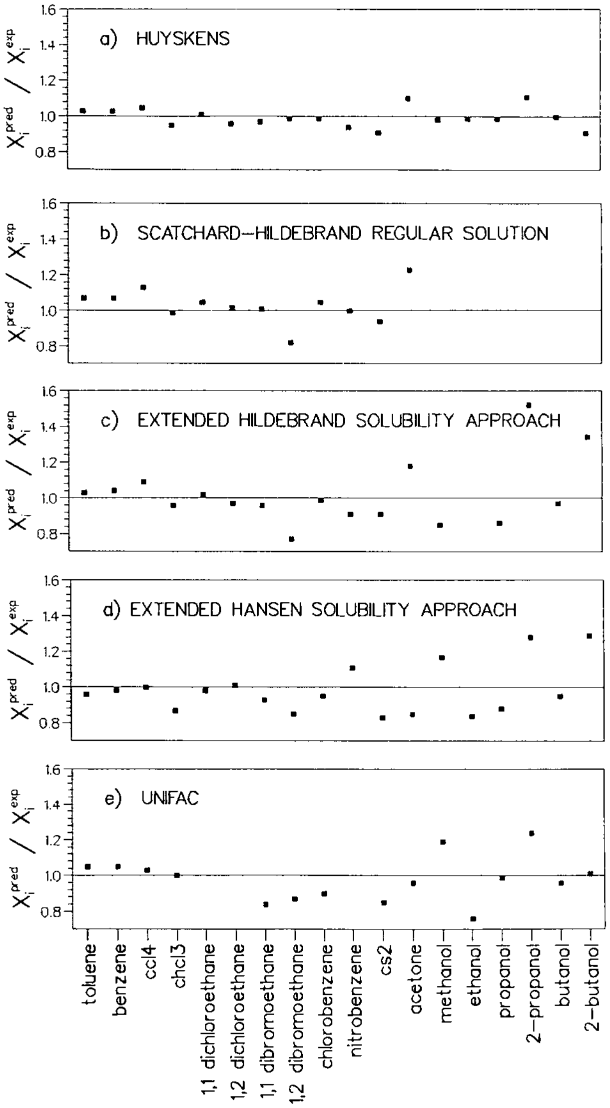

Fig. 1. Accuracy of naphthalene solubility predictions at 40°C expressed as the ratio of the predicted to the experimental solubility, X_i^{pred}/X_i^{exp}. Comparison of the results obtained by five models.

yield an accuracy similar to that of the UNIFAC method (Fig. 1e). However, the UNIFAC method requires only the knowledge of the physical properties of the pure substance to make reasonable predictions, while Martin's methods imply solubility determinations in the initial step to obtain the solvent–solute interaction energy.

The success of the present equation with respect to the models used for comparison originates from the correct description of the "hydrophobic effect." According to the mobile order theory of Huyskens, the hydrophobic effect of the alcohols on an inert substance such as naphthalene is no longer considered a result of a change in interaction energies but is taken into account as a lowering of entropy because of a temporary correlation in the displacements in the liquid of two or more hydroxylic groups of solvent molecules. These correlated displacements create a "mobile order" for which a detailed description was given previously (13). A detailed analysis of the effect of H bonds in alcohols on the solubility of polycyclic aromatic hydrocarbons is in preparation. In short, it is the hydrophobic effect which is at the origin of the lower solubility of naphthalene (predicted and observed) in alcohols with respect to the nonassociated solvents. The quantitative treatment of this effect [F term in the general solubility equation, Eq. (1)] shows that, at equilibrium, the solubility in alcohols, $\ln\Phi_B$, is diminished by an amount equal to $\Phi_S V_B/V_S$. A direct consequence of this effect is that any increase in the ratio of the molar volumes V_B/V_S, promotes the solubility of nonpolar substances in nonassociated solvents and disfavors it in alcohols (Fig. 2).

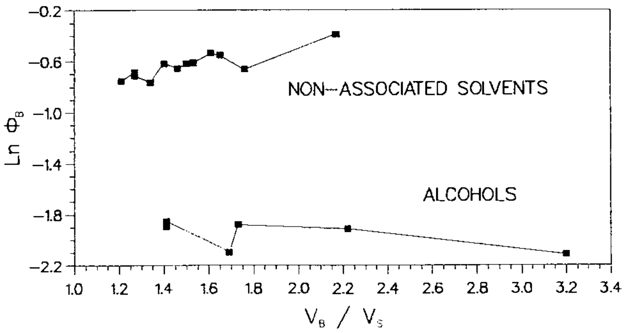

Fig. 2. Variation of the solubility, $\ln\Phi_B$, of naphthalene at 40°C versus the ratio V_B/V_S of the molar volumes of naphthalene, B, and the solvent, S.

CONCLUSION

The prediction of the naphthalene solubility in various solvents by means of the "mobile order theory" is based on the knowledge of a single parameter, e.g., its modified nonspecific solubility parameter, the value of which is calculated from its experimental solubility in hexane at 40°C. Except for 2-propanol, Huyskens' model yields predictions to within 10% of experimental values. The largest improvement of this model over the four other methods currently used for the prediction of naphthalene solubility is achieved for the alcohols. The success originates from the correct description of the entropic and hydrophobic effects. The last effect implies, in particular, that alcohols will never form "regular solutions" for which deviations from ideality are due exclusively to energetic effects. Accordingly, models based on regular solution theory do not correctly predict solubilities of substances, whether apolar or polar, in hydrogen-bonded solvents such as alcohols.

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