*International Journal of Pharmaceutics*, 18 (1984) 47–52
Elsevier

IJP 00610

# Solubility of biphenyl in binary solvent mixtures

William E. Acree, Jr.

*Department of Chemistry, Kent State University, Kent, OH 44242 (U.S.A.)*

(Received April 28th, 1983)
(Modified version received and accepted July 21st, 1983)

## Summary

Solubilities have been determined at 25°C for biphenyl in binary mixtures of cyclohexane with *n*-hexane, *n*-heptane and *n*-octane, and in binary mixtures of carbon tetrachloride with cyclohexane, *n*-hexane and *n*-heptane. The results of these measurements are compared to solution models previously developed. The Nearly Ideal Binary Solvent (NIBS) model predicts the binary solvent solubilities to within a maximum deviation of 1.3%, using as input data the solubility of biphenyl in the pure solvents. In comparison, the UNIFAC group contribution model predicts the experimental solubilities in both pure and binary solvents to within a maximum deviation of 49%. While the deviations for the later solution model appear quite large, the predicted values do represent a significant improvement over the ideal solubility approximation.

## Introduction

This work continues a systematic search for mixing models and equations which will provide predictions for the thermochemical properties of a solute at high dilution in binary solvent mixtures. In two earlier papers, Acree and Rytting (1982a and b) reported solubilities for benzil and *p*-benzoquinone in binary solvent mixtures containing carbon tetrachloride, in which the mole fraction solubility of benzil and *p*-benzoquinone cover a 14-fold and 6-fold range, respectively. The experimental data were interpreted with solution models developed previously for solubility in systems containing specific solute–solvent interactions and with models of purely non-specific interactions. A stoichiometric complexation model based entirely on specific interactions (non-specific interactions ignored) required several equilibrium constants to mathematically describe the experimental results, while the Nearly Ideal

---

*Correspondence:* W.E. Acree, Jr., Department of Chemistry, Kent State University, Kent, OH 44242, U.S.A.

0378-5173/84/$03.00 © 1984 Elsevier Science Publishers B.V.

Binary Solvent (NIBS) model, based on non-specific interactions, described adequately the observed solubilities without introducing a single equilibrium constant.

The success of the NIBS approach in predicting the binary solvent effect on benzil and *p*-benzoquinone solubilities suggested the possibility that this solution model may provide a foundation for approximations of the physical interactions even in a system known to contain chemical interactions. To pursue this idea further, Acree et al. (in press) extended the basic NIBS model to systems containing association between the solute (component A) and a complexing cosolvent (component C)

$$A_1 + C_1 \rightleftharpoons AC$$

$$K_{AC}^{\phi} = \frac{\phi_{AC}}{\phi_{A_1}\phi_{C_1}}$$

Postulating the formation of a 1 : 1 anthracene–benzene complex, the authors demonstrated that the solubility of anthracene in benzene + *n*-heptane and benzene + isooctane could be described to within a maximum deviation of 4% using a single equilibrium constant, $K_{AC}^{\phi} = 1.91$. More importantly, it was noted that the determination of solute–solvent equilibrium constants from solubility measurements does depend on the manner in which non-specific interactions are incorporated into the model.

In a follow-up study comparing iodine solubilities in binary solvent mixtures, Acree (1983) compared the solubility-based association constant for the iodine-benzene complex, $K_{AC}^{c} = 0.393\ M^{-1}$, to the spectroscopic values of Bhowmik (1971) determined in cyclohexane ($K_{AC}^{c} = 0.260\ M^{-1}$), methylcyclohexane ($K_{AC}^{c} = 0.252\ M^{-1}$) and *n*-heptane ($K_{AC}^{c} = 0.246\ M^{-1}$) solvents. Deviations of this magnitude are to be expected in comparing independently determined equilibrium constants, particularly in the case of weak association complexes as both specific and non-specific interactions play an important role in determining the total non-ideality of the solution.

As the final paper in the short series dealing with thermochemical investigations of associated solutions, I was hoping to describe the solubility of testosterone in binary cyclohexane + chloroform mixtures. In looking at the solubility data of James and Mehdizadeh (1981), I noted that testosterone is very soluble in chloroform, having a volume fraction solubility of $(\phi_A^{sat})_C \approx 0.489$. Calculation of testosterone–chloroform association constant(s) does present a small problem since one is not certain that the basic NIBS model will describe the thermochemical properties of very soluble solutes. Previous testing of the NIBS model was limited primarily to systems having solubilities on the order of $X_3^{sat} \leqslant 0.2$.

To address this concern, I have measured the solubility of biphenyl in several binary solvent mixtures. Biphenyl was chosen as the solute molecule because the enthalpy of fusion is available in the literature. This allows the activity of the solid solute to be estimated at temperatures removed from the normal melting point. Furthermore, one can estimate the molar volume of the supercooled liquid, $\bar{V}_3 = 149.4$ cm$^3$/mole, from the experimental data of Good and coworkers (1953).

## TABLE 1

## OBSERVED AND PREDICTED VALUES OF THE SOLUBILITY OF BIPHENYL IN SEVERAL BINARY SOLVENTS AT 25°C

| Solvent 1 + Solvent 2 | $X_1^0$ | $X_3^{sat}$ | % Deviations of calculated values [a] | | |
|---|---|---|---|---|---|
| | | | (XV) | (VV) | UNIFAC |
| **Cyclohexane** | **0.0000** | **0.1233** | – | – | +49.4 |
| **+ *n*-hexane** | **0.2134** | **0.1378** | +0.1 | +0.2 | +46.0 |
| | **0.3618** | **0.1476** | +0.9 | +0.9 | +44.2 |
| | **0.5311** | **0.1609** | +0.5 | +0.6 | +40.9 |
| | **0.6844** | **0.1727** | +0.3 | +0.3 | +38.5 |
| | **0.8179** | **0.1817** | +0.3 | +0.4 | +37.3 |
| | **1.0000** | **0.1921** | – | – | +37.0 |
| Carbon tetrachloride | 0.0000 | 0.1233 | – | – | +49.4 |
| + *n*-hexane | 0.1733 | 0.1538 | +1.3 | +1.3 | +43.1 |
| | 0.2982 | 0.1843 | −0.4 | −0.5 | +34.5 |
| | 0.4731 | 0.2268 | +0.4 | +0.4 | +24.7 |
| | 0.6387 | 0.2691 | +0.3 | +0.3 | +16.0 |
| | 0.8319 | 0.3103 | +0.8 | +0.6 | +9.7 |
| | 1.0000 | 0.3421 | – | – | +6.4 |
| Cyclohexane | 0.0000 | 0.1480 | – | – | +21.9 |
| + *n*-octane | 0.1463 | 0.1539 | +0.2 | +0.3 | +22.6 |
| | 0.3314 | 0.1601 | +1.1 | +1.1 | +25.0 |
| | 0.5016 | 0.1675 | +0.7 | +0.9 | +27.3 |
| | 0.7318 | 0.1789 | −0.1 | 0.0 | +30.8 |
| | 0.8293 | 0.1825 | −0.1 | 0.0 | +33.2 |
| | 1.0000 | 0.1921 | – | – | +37.0 |
| Carbon tetrachloride | 0.0000 | 0.1381 | – | – | +32.0 |
| + *n*-heptane | 0.1369 | 0.1594 | −0.3 | +0.1 | +28.9 |
| | 0.3185 | 0.1938 | −0.4 | +0.2 | +23.1 |
| | 0.5046 | 0.2340 | +0.8 | +0.9 | +19.0 |
| | 0.7099 | 0.2815 | +0.9 | +1.0 | +12.5 |
| | 0.8131 | 0.3051 | +0.6 | +0.5 | +9.5 |
| | 1.0000 | 0.3421 | – | – | +6.4 |
| Cyclohexane | 0.0000 | 0.3421 | – | – | +6.4 |
| + carbon tetrachloride | 0.1654 | 0.3213 | +1.1 | +1.0 | +10.2 |
| | 0.3387 | 0.3015 | +0.4 | +0.3 | +13.3 |
| | 0.5215 | 0.2740 | +0.7 | +0.6 | +18.9 |
| | 0.6833 | 0.2474 | +0.8 | +0.7 | +24.5 |
| | 0.8507 | 0.2184 | +0.5 | +0.5 | +30.8 |
| | 1.0000 | 0.1921 | – | – | +37.0 |
| Cyclohexane | 0.0000 | 0.1381 | – | – | +32.0 |
| + *n*-heptane | 0.1831 | 0.1477 | −0.2 | +0.2 | +31.2 |
| | 0.3654 | 0.1571 | +0.1 | +0.5 | +32.4 |
| | 0.5455 | 0.1663 | +0.4 | +0.8 | +33.7 |
| | 0.7386 | 0.1765 | +0.7 | +1.0 | +35.0 |
| | 0.8511 | 0.1845 | +0.3 | −0.1 | +35.6 |
| | 1.0000 | 0.1921 | – | – | +37.0 |

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

## Materials and Methods

Biphenyl (Aldrich) was recrystallized several times from methanol, giving a melting point of 69.5 ± 0.5°C (literature value 71°C; Weast, 1981). Cyclohexane (Aldrich Gold Label), *n*-heptane (Fisher Spectroanalyzed), *n*-octane (Aldrich Gold Label), *n*-hexane (Aldrich 99%) and carbon tetrachloride (Fisher Spectroanalyzed) were stored over molecular sieves (Type 4A) to remove trace amounts of water. Binary solvent mixtures were prepared by weight so that solvent compositions could be calculated to 0.0001 mole fraction.

Excess solute and solvent were placed in amber glass bottles and allowed to equilibrate in a constant temperature bath at 25.0°C for several days. Random duplicate samples were allowed to equilibrate for a longer period of time, but no significant difference in the saturation solubility was observed. Aliquots of saturated biphenyl solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample, and diluted quantitatively with cyclohexane. Concentrations were determined spectrophotometrically at 250 nm on a Cary 118 spectrophotometer. Experimental solubilities of biphenyl in several binary solvent mixtures are given in Table 1. The experimental results at each composition represent the average of 10 determinations with a maximum deviation of about 1%.

## Results and Discussion

The general NIBS expressions for predicting solubilities in systems with non-specific interactions depend on two different models of solution ideality:

$$\mathrm{RT}\ln\left(a_3^{\mathrm{solid}}/X_3^{\mathrm{sat}}\right) = \left(1-\phi_3^{\mathrm{sat}}\right)^2\Big[\phi_1^0\left(\Delta\overline{G}_3^{\mathrm{ex}}\right)^{\infty}_{X_1^0=1} + \phi_2^0\left(\Delta\overline{G}_3^{\mathrm{ex}}\right)^{\infty}_{X_2^0=1}$$

$$- \overline{V}_3\left(X_1^0\overline{V}_1 + X_2^0\overline{V}_2\right)^{-1}\Delta\overline{G}_{12}^{\mathrm{ex}}\Big] \qquad \text{(Eqn. XV)}$$

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

$$+ \phi_2^0\left(\Delta\overline{G}_3^{\mathrm{fh}}\right)^{\infty}_{X_2^0=1} - \overline{V}_3\left(X_1^0\overline{V}_1 + X_2^0\overline{V}_2\right)^{-1}\Delta\overline{G}_{12}^{\mathrm{fh}}\Big] \qquad \text{(Eqn. VV)}$$

Eqn. XV is based on Raoult's Law, and Eqn. VV is based on the Flory-Huggins model. In the above expressions $X_i$ is mole fraction, $\phi_i$ is volume fraction, $\Delta\overline{G}_{12}^{\mathrm{ex}}$ is the molar excess Gibbs free energy of the binary solvent relative to Raoult's Law [1], and $a_3^{\mathrm{solid}}$ is the activity of the solid solute (component 3) relative to the pure

---

[1] For a binary mixture, the excess molar Gibbs free energy over the predictions of the Flory-Huggins equation is related to the defined excess free energy by:

$$\Delta\overline{G}_{12}^{\mathrm{fh}} = \Delta\overline{G}_{12}^{\mathrm{ex}} = \mathrm{RT}\left[\ln\left(X_1^0\overline{V}_1 + X_2^0\overline{V}_2\right) - X_1^0\ln\overline{V}_1 - X_2^0\ln\overline{V}_2\right]$$

hypothetical supercooled liquid. The numerical value of $a_3^{solid}$ can be calculated from the solute's melting point temperature ($T_m$) and molar enthalpy of fusion ($\Delta H_3^{fus}$)

$$\ln a_3^{solid} = \ln X_3^{sat}\gamma_3^{sat} = \int_{T_m}^{T} (\Delta H_3^{fus}/RT^2)dT \approx -\frac{\Delta H_3^{fus}(T_m - T)}{RTT_m} \tag{1}$$

assuming that $\Delta H_3^{fus}$ is constant through the temperature interval. For biphenyl this will be a good approximation as one is extrapolating over a very small temperature interval—46°C.

Comparisons of experimental and predicted values are shown in Table 1 for biphenyl in the 6 binary solvent systems studied. Properties used in the calculations include: $a_3^{solid}$ ($= 0.3844$) calculated from the enthalpy of fusion data, $\Delta H_3^{fus} = 4400$ cal/mole (from Plato and Glasgow, 1969, and $\bar{V}_3$ ($= 149.4$ cm$^3$/mole) estimated from the experimental data of Good et al. (1953). Literature references for the $\Delta\bar{G}_{12}^{ex}$ values are tabulated in earlier papers (Acree and Bertrand, 1977 and 1983; Acree and Rytting, 1983a). In general, Eqns. XV and VV are comparable with overall average (rms) deviations of 0.6 and 0.7%, respectively.

Biphenyl solubilities can be used to test other solution models as well. The UNIFAC (Universal-functional-group-activity-coefficient) model (Fredenslund et al., 1975 and 1977) is a relatively new group contribution approach developed in chemical engineering laboratories for estimating activity coefficients, $\gamma_i$, of multicomponent mixtures.

$$\begin{aligned} \ln \gamma_i = {} & \ln(\phi_i/X_i) + \tfrac{1}{2}Zq_i \ln(\theta_i/\phi_i) + l_i \\ & - (\phi_i/X_i)\sum_j X_j l_j + \sum_{\substack{\text{all groups in} \\ \text{solution}}} \nu_k^{(i)}\left[\ln \Gamma_k - \ln \Gamma_k^{(i)}\right] \end{aligned} \tag{2}$$

Definitions of the UNIFAC terms are found in papers by Fredenslund et al.

To test the predictive abilities of the UNIFAC model, biphenyl solubilities were calculated for all 6 binary solvent mixtures studied. Results of these calculations are summarized in the last column of Table 1. Deviations expressed in percentages are on the order of 20–35% for most of the binary solvent mixtures and are comparable in magnitude to the deviations noted in an earlier paper (Acree and Rytting, 1983b) for naphthalene solubilities. While the deviations may seem large compared to the experimental biphenyl solubilities, the predicted values do represent a significant improvement over the ideal solubility approximation $(X_3^{sat})_{ideal} = a_3^{solid} = 0.3844$.

Inspection of the last 3 columns of Table 1 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 does limit their application.

The UNIFAC model, on the other hand, predicts the solute's thermochemical properties from a group contribution approach, with the various input parameters being determined, in many cases, from liquid–vapor equilibrium 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 systems contain 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. Much testing, though, still needs to be done so that the limitations and applications of the UNIFAC model can be properly assessed.

## References

Acree, W.E., Jr., Thermochemical investigations of associated solutions. 2. Calculation of iodine–benzene equilibrium constants from solute solubility in binary solvent mixtures. Int. J. Pharm., 15 (1983) 159–165.

Acree, W.E., Jr. and Bertrand, G.L., Thermochemical investigations of nearly ideal binary solvents. 3. Solubility in systems of nonspecific interactions. J. Phys. Chem., 81 (1977) 1170–1173.

Acree, W.E., Jr. and Bertrand, G.L., Thermochemical investigations of nearly ideal binary solvents. 6. Solubilities of iodine and benzil in systems of nonspecific interactions. J. Solution Chem., 12 (1983) 101–113.

Acree, W.E., Jr., McHan, D.R. and Rytting, J.H., Thermochemical investigations of associated solutions. 1. Calculation of solute–solvent equilibrium constants from solubility measurements. J. Pharm. Sci., in press.

Acree, W.E., Jr. and Rytting, J.H., Solubility in binary solvent systems. I. Specific vs nonspecific interactions. J. Pharm. Sci., 71 (1982a) 201–205.

Acree, W.E., Jr. and Rytting, J.H., Solubility in binary solvent systems. II. The importance of nonspecific interactions. Int. J. Pharm., 10 (1982b) 231–238.

Acree, W.E., Jr. and Rytting, J.H., Solubility in binary solvent systems. III. Predictive expressions based on molecular surface areas. J. Pharm. Sci., 72 (1983a) 292–296.

Acree, W.E., Jr. and Rytting, J.H., Solubility in binary solvent systems. IV. Prediction of naphthalene solubilities using the UNIFAC group contribution model. Int. J. Pharm., 13 (1983b) 197–204.

Bhowmik, B.B., Solvent effect on the charge transfer intensity of benzene–iodine complex. Spectrochim. Acta, 27A (1971) 321–327.

Fredenslund, Aa., Jones, R.L. and Prausnitz, J.M., Group-contribution estimation of activity coefficients in nonideal liquid mixtures. AIChE J., 21 (1975) 1086–1099.

Fredenslund, Aa., Gmehling, J., Michelson, M.L., Rasmussen, P. and Prausnitz, J.M., Computerized design of multicomponent distillation columns using UNIFAC group contribution method for calculation of activity coefficients Ind. Eng. Chem. Process Des. Dev., 16 (1977) 450–462.

Good, R.J., Hard, E.E., Ellenburg, A.M. and Richards, H.B., Jr., The solubility of *p*-terphenyl in *o*- and *m*-terphenyls and in biphenyl. J. Am. Chem. Soc., 75 (1953) 436–442.

James, K.C. and Mehdizadeh, M., Some solute–solvent complexes involving testosterone and testosterone propionate. J. Pharm. Pharmacol., 33 (1981) 9–13.

Plato, C. and Glasgow, A.R., Jr., Differential scanning calorimetry as a general method for determining the purity and heat of fusion of high-purity organic chemicals. Applications to 95 compounds. Anal. Chem., 41 (1969) 330–336.

Weast, R.C., Handbook of Chemistry and Physics, 61st Edn., Chemical Rubber, Cleveland, OH, 1980, p. C-182.