

RECENT PROGRESS IN MIXED SOLVENT SOLUBILITY ESTIMATION

Solute-free nonideality

Martin E. Christensen,* Jens Abildskov

CAPEC, Department of Chemical and Biochemical Engineering, Build. 229,
Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

John P. O'Connell

Department of Chemical Engineering, University of Virginia, Charlottesville, VA 22904-4741, U.S.A.

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INTRODUCTION

The solubility of sparingly soluble solid drugs in liquid solvents has undergone extensive study in the past¹⁻³. The importance of proper description of solid/liquid equilibrium has facilitated the need for a more fundamental approach to the modeling framework. The complexity of the solid/liquid equilibrium increases significantly when more than one liquid solvent is present. Models in the literature are frequently empirical in nature and this usually makes the reason(s) for their failure unclear. In order to increase the solubility of a solid in a solvent (e.g. water) an organic solvent is usually added to increase certain properties (e.g. hydrophobicity). The cosolvency effect associated with this solvent blending is frequently sought through a trial-and-error approach, requiring substantial laboratory efforts.

The 'excess' solubility is one convenient way of measuring the cosolvency effect in terms of solubility. For a solute, i , in a mixed solvent it is defined:

$$\ln x_i^E \equiv \ln x_{i,m} - \sum_{j \neq i} x'_j \ln x_{i,j}. \quad (1)$$

Here $x_{i,m}$ is the mole fraction solubility of i in the mixture, $x_{i,j}$ is the solubility of i in pure solvent j , and x'_j is the mole fraction of solvent j on a solute-free basis. Thus if the excess solubility is

*Corresponding author. Tel.: (+45) 4525 2808. Fax: (+45) 4593 2906. E-mail: mec@kt.dtu.dk.

known a more effective search for solvent candidates could be performed.

Recently⁴ a new method was developed for estimating the excess solubility of a solid solute in a binary solvent mixture. The method originates from statistical mechanical fluctuation solution theory⁵⁻⁷. It requires one parameter characterizing the interaction between the solute with each of the solvents. Also required are parameter(s) for a G^E-model describing the nonideality of the solvent mixture. However, these may be found independently of the solute, e.g. from binary vapor/liquid equilibrium data.

The excess solubility of a solid solute (1) in a mixed, binary solvent (2,3) may be estimated through⁴

$$\ln x_1^E = -\frac{x_3'}{2} \left(\frac{\partial \ln \gamma_3}{\partial x_3} \right)_{T,P,N_2}^+ [1 + x_2' f_{12}^0 + x_3' f_{13}^0]. \quad (2)$$

Here the parameters of the model are the factors f_{12}^0 and f_{13}^0 which characterizes the nonideality of the solute/solvent interaction, independent of other solvent species. Superscript + denotes that the solute is at infinite dilution in the mixed solvent, whereas ⁰ denotes infinite dilution in the pure solvent. The derivative term in equation (2) is the composition derivative of the Rewis/Randall normalized activity coefficient in the solute-free binary. The solute/solvent parameters in equation (2) appear linearly and therefore estimation of these and their corresponding standard deviations is straightforward⁸. The parameters are found from regression of experimental mixed solvent solubility data.

In the following we will report our investigations into the influence of the nonideality of the solute-free solvent mixture on the excess solubility of a solid in a mixed, binary solvent.

RESULTS

In the above expression the nonideality of the solvent mixture appears explicitly. This means that if the solvent mixture is ideal ($\partial \ln \gamma_3 / \partial x_3 = 0$) the excess solubility is zero. This is in agreement with experimental data. Figure 1 shows characteristic profiles of the excess solubility as function of solvent composition. Positive and negative deviations from ideal mixing often follow a smooth, parabolic profile. In Figure 1 these are displayed as symmetric but this is rarely the case. The solvent mixtures in these two situations often form strongly nonideal solutions, typically aqueous alcohol mixtures.

Also depicted in Figure 1 is an example of a system where the excess solubility changes sign (s-shape). Although shown as symmetric, this is also rarely the case. For aqueous mixtures the zero is usually located in the water rich end of the concentration scale. The s-shape can be accomplished in two ways:

1. The parameters of the solute with each of the solvents are of opposite sign, c.f. the last term in equation (2).

2. The derivative in equation (2) changes sign.

The latter does not occur frequently and mostly in binaries with small excess Gibbs energies (close to ideal). An example of #1 in the above list is shown in Figure 2 (a)-(b) with L-alanine in water/1-propanol. In this system the parameters of equation (2) are reduced using the data of Orella and Kirwan⁹ and are of opposite sign and the VLE¹⁰ of water and 1-propanol does not show an extremum in the activity coefficients. An example of #2 include mixtures with the binary solvent mixture of water and 1,2-propanediol. The vapor/liquid equilibrium data of Lancia and coworkers¹¹ allows for reduction to obtain parameters for the Wilson¹² and modified Margules¹³ equations. Reduction of VLE data is done using Barker’s method where the sum of squared vapor pressure differences is minimized by adjusting parameters in the G^E-model. The results for water/1,2-propanediol are shown in Figure 3. Although quantitatively different the Wilson and Margules equation give qualitatively similar behavior, with an extremum in the activity coefficients at a water mole fraction of ~ 0.25 . Other examples of excess solubility behavior than shown in Figure 1 may also occur, e.g. zero excess solubility. This situation may arise if the solvent binary is ideal but may also, in practice, occur if the factors in equation (2) – f_{12}^0 and f_{13}^0 – are zero. The solvent/solvent nonideality term in equation (2) alone does not contribute greatly to the excess solubility, so it is possible for a nonideal solvent mixture to exhibit negligible excess solubility when the solute is introduced. Examples of this phenomena include alcohol/hydrocarbon mixtures with nonpolar organic solutes.

Previously⁴ we have classified binary solvent mixtures according to a parameter, f_{23}^+ , which is a function of the derivative in equation (2):

$$f_{23}^+ = -\frac{\frac{1}{x'_2} \left(\frac{\partial \ln \gamma_3}{\partial x'_3} \right)_{T,P,N_2}^+}{1 + x'_3 \left(\frac{\partial \ln \gamma_3}{\partial x'_3} \right)_{T,P,N_2}^+}. \quad (3)$$

The variation of the above quantity with solvent composition provides an indication of the non-ideality of the binary (as does the excess Gibbs energy). Given that f_{23}^+ is of a derivative quantity it is highly sensitive to the G^E-model expression which is advantageous since equation (2) requires this derivative. This may provide a better indication of the nonideality. An example is illustrated in Figure 2 (c)-(d). The figure shows the variation of the quantity in equation (3) with solvent composition for water and 1-propanol using the Wilson and four-parameter Margules equations. There is little difference in the two upper figures but f_{23}^+ is quantitatively different. The sharp peak in Figure 2 (d) is usually observed when more than two parameters are used in the Margules model. This does, however, not seem to influence the excess solubility estimate nor does it influence the parameter estimation. The parameter values and standard deviations obtained using the Wilson and Margules equations are summarized in Table 1. Negligible difference is found between the pairs, suggesting that the choice of G^E-model is not important. This is also observed when extending to

Table 1. Parameter estimates and standard deviations for L-alanine (1) in water (2) and 1-propanol (3) for equation (2) using Wilson or Margules equation for solvent nonideality.

| G^E -model | f_{12}^0 | f_{13}^0 |
|--------------|------------------|-----------------|
| Wilson | -1.42 ± 0.18 | 1.99 ± 0.64 |
| Margules | -1.46 ± 0.18 | 1.94 ± 0.60 |

other solutes such as beta carotene and anthracene in various polar/nonpolar solvents. Figure 4 shows an example of anthracene in the highly nonideal mixed solvent of n-hexane and 1-butanol. The parameters for this system are regressed with other data sets where the solute appears with each of the solvents. Both G^E -models yield similar solute/solvent parameter values. However, the excess solubility when the four-parameter Margules model is used exhibit unusual behavior in mid-concentration region. Discrepant behavior is also observed in the two bottom figures which shows the f_{23}^+ for the Wilson and Margules models. Figure 5 shows the activity coefficients and excess Gibbs energy of the binary; both models yield similar infinite dilution activity coefficients and the curvature of both models appear similar. However, since the quantity in equation (3) requires the derivative of the activity coefficient it may reveal additional information regarding the reliability of the subsequent excess solubility estimate.

CONCLUSIONS

The excess solubility of solids in mixed solvents are driven by the nonideality of the solute-free solvent mixture. When the solvent mixture is ideal, or close to ideal, the excess solubility is zero. On the other hand, if the solvent mixtures is nonideal, the excess solubility is pending the size of the solute/solvent interactions. If these are zero the excess solubility will also be close to zero, but if these are different from zero there will be an excess solubility. Solvent mixtures where the solvent activity coefficients exhibit extremes will result in s-shaped excess solubility profile when the solute is introduced.

The model presented previously does not seem to depend greatly on the G^E -model chosen; Wilson or Margules equation. However some excess solubility profiles exhibit unusual behavior in the mid-concentration range. This is not indicated in the excess Gibbs energy of the solvent binary, but is seen in the characteristic quantity defined by equation (3), suggesting that working with quantities of a derivative basis may be advantageous.

LITERATURE CITED

1. T.L. Nielsen, J. Abildskov, P.M. Harper, I. Papaconomou, and R. Gani. J. Chem. Eng. Data 46 (2001) 1041.
2. J. Marrero and J. Abildskov. Solubility and related properties of large complex chemicals - Part 1. DECHEMA, 2003.

3. J. Abildskov. Solubility and related properties of large complex chemicals - Part 2. DECHEMA, 2005.
4. M.E. Christensen, J.P. O'Connell, and J. Abildskov. AIChE J. Submitted for publication.
5. J.G. Kirkwood and F. Buff. J. Chem. Phys. 19 (1951) 775.
6. J.P. O'Connell. Mol. Phys. 20 (1971) 27.
7. J.P. O'Connell. AIChE J. 17 (1971) 658.
8. R. Fletcher. Practical methods of optimization. Wiley, 1987.
9. C.J. Orella and D.J. Kirwan. Ind. Eng. Chem. Res. 30 (1991) 1040.
10. J. Zielkiewicz and A. Konitz. J. Chem. Therm. 23 (1991) 59.
11. A. Lancia, D. Musmarra, and F. Pepe. J. Chem. Eng. Japan 29 (1996) 449.
12. G.M. Wilson. J. Am. Chem. Soc. 86 (1964) 127.
13. M.M. Abbott and H.C. van Ness. AIChE J. 21 (1975) 62.
14. V. Rodriguez, J. Pardo, M.C. Lopez, F.M. Royo, and J.S. Urieta. J. Chem. Eng. Data 38 (1993) 350.

LIST OF SYMBOLS

- f Parameter in equation (2).
 G Gibbs energy.
 N Mole number.
 P Pressure.
 T Absolute temperature.
 x Mole fraction.
 γ Activity coefficient.

SUPERSCRIPTS AND SUBSCRIPTS

- $'$ Solute-free basis.
 0 Infinite dilution in pure solvent.
 $+$ Infinite dilution in mixed solvent.
 E Excess property.
 $_{i,j}$ Components.
 $_m$ Mixture property.
 $_{1-3}$ Components.

FIGURES

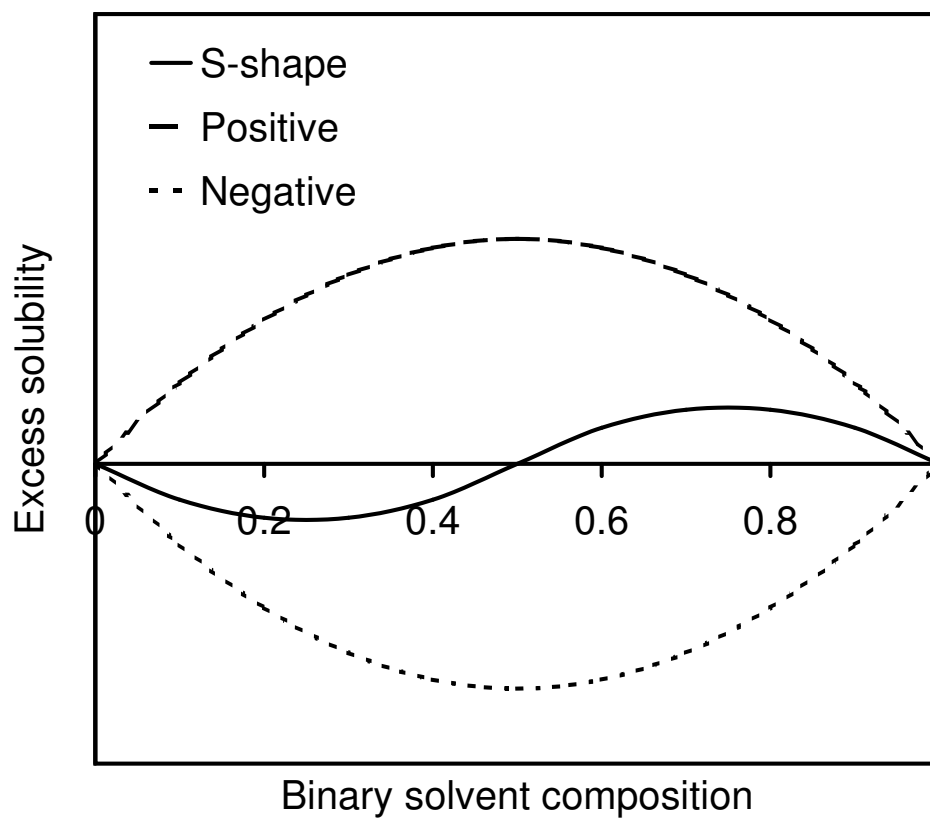


Figure 1. Characteristic variations of excess solubility with solvent composition. Although shown as symmetric frequently this is not the case.

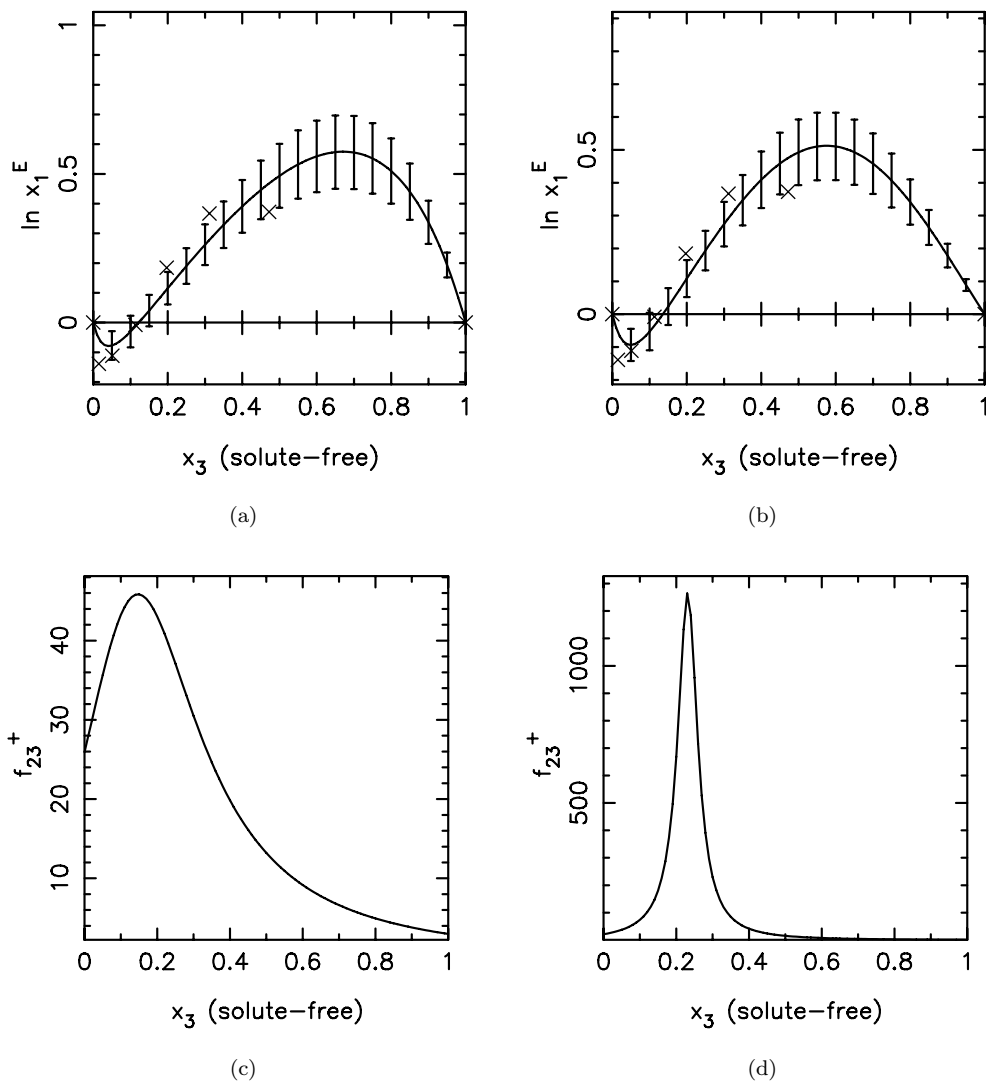


Figure 2. Excess solubility and solvent nonideality of L-alanine (1) in water (2) and 1-propanol (3). Figures (a)-(b) show the excess solubility correlated with equation (2). Figures (c)-(d) show the development of f_{23}^+ from equation (3) as function of solvent composition. Left side: Wilson equation and right side: Four-parameter Margules equation.

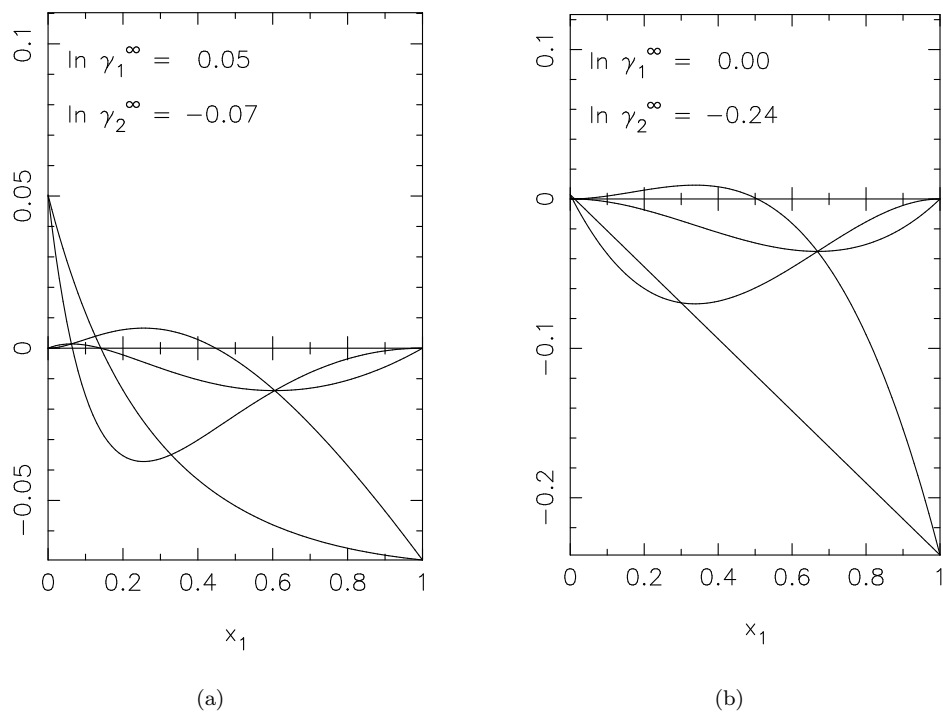


Figure 3. Reduced vapor/liquid equilibrium¹¹ of water (1) and 1,2-propanediol (2) using the (a) Wilson and (b) two-parameter Margules models.

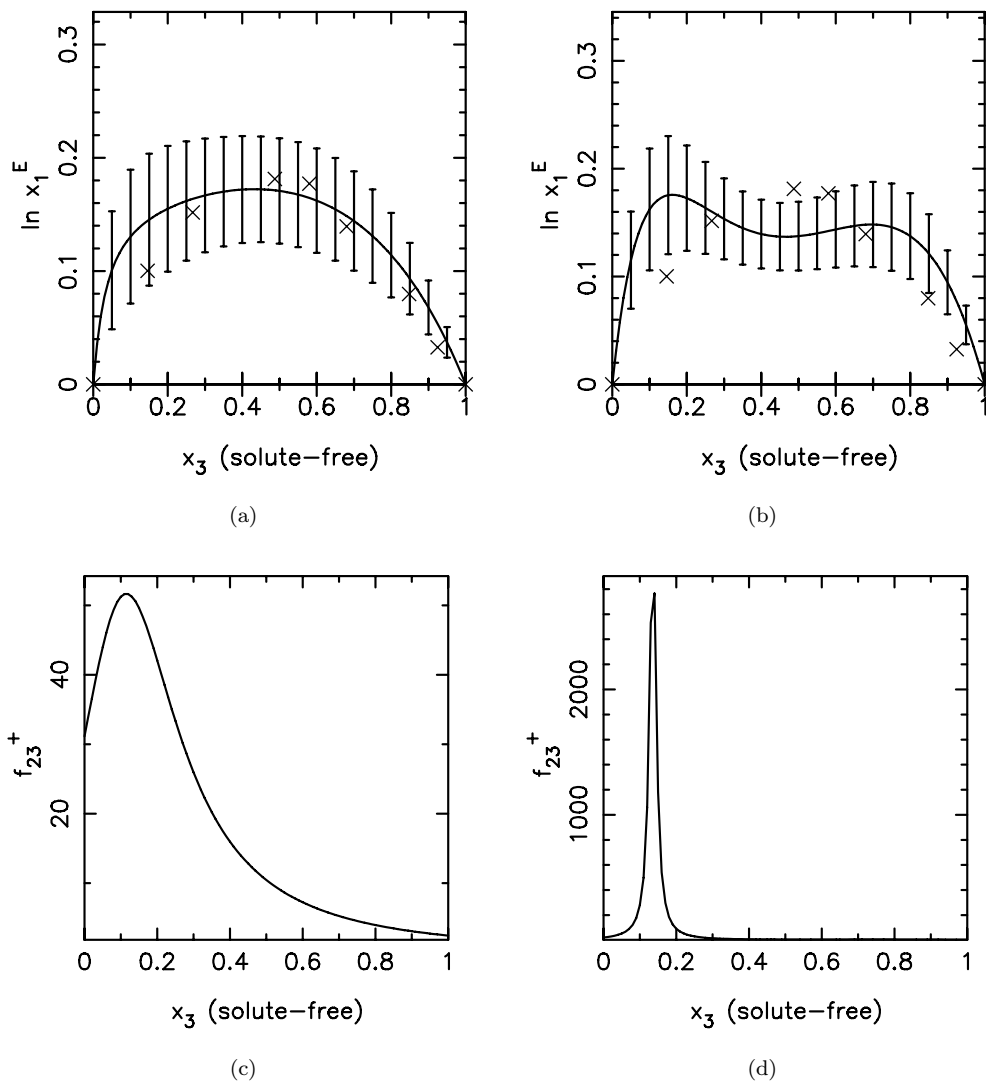


Figure 4. Excess solubility and solvent nonideality of anthracene (1) in n-hexane (2) and 1-butanol (3). Figures (a)-(b) show the excess solubility correlated with equation (2). Figures (c)-(d) show the development of f_{23}^+ from equation (3) as function of solvent composition. Left side: Wilson equation and right side: Four-parameter Margules equation.

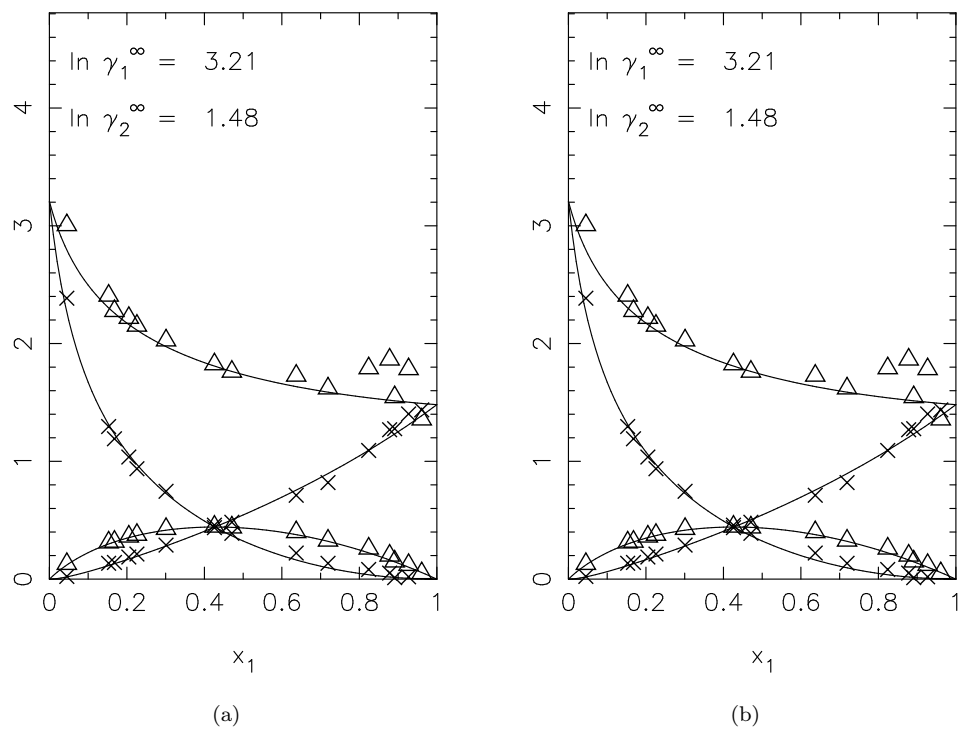


Figure 5. Reduced vapor/liquid equilibrium¹⁴ of 1-butanol (1) and n-hexane (2) using the (a) Wilson and (b) four-parameter Margules models.