Review

Revising Concepts on Liquid−Liquid Extraction: Data Treatment and Data Reliability

Alberto Arce, Alberto Arce, Jr., and Oscar Rodriguez*

Cite This: *J. Chem. Eng. Data* 2022, 67, 286−296

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ABSTRACT: The intention of this article is to clarify some concepts and relevant aspects of the experimental determination and treatment of liquid−liquid equilibrium data for ternary systems. Distinction is made between solubility curve and binodal curve, setting the stability limit which is defined by the spinodal curve. In addition, it is recommended to carry out the equilibrium data correlation using semiempirical models with a thermodynamic base, over the use of empirical equations. Moreover, the misuse of these empirical equations (Hand, Bachman, Othmer-Tobias, etc.) as proof of data quality or consistency is clarified.
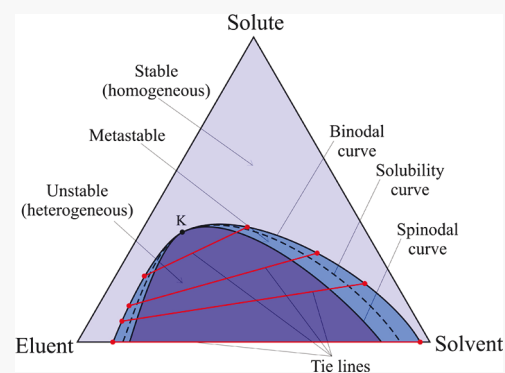
1. INTRODUCTION

As reviewers of liquid−liquid equilibria (LLE) manuscripts, we have detected and tried to correct some of these conceptual errors before publication. Among them all, probably the use of Othmer-Tobias, Hand, Bancroft, and similar empirical equations to evaluate the quality of LLE is the foremost conceptual error. For years, we have been requesting in our reviews the complete removal of such equations, while at the same time being pedagogic and explaining to all authors why that is a misuse. Clearly, we had little success, and the problem persists. This attitude in the review of LLE articles caught the attention of former editor Dr. Paul Mathias, with whom we have discussed our reviews, especially our concerns on the use of empirical equations to demonstrate the quality (or "reliability", sometimes even called "consistency") of LLE data. He proposed and encouraged us to prepare this article, which he considered pertinent for the phase equilibria community: An article that not only collects errors and misuses of LLE data, but that also provides some insights to improve data quality, in line with other reviews and editorials he promoted as an Associate Editor.[1]

Lots of attention has been given in phase equilibrium thermodynamics to the behavior of immiscible liquid phases, with emphasis not only in the experimental determination but also in the correlation relationships of the equilibrium compositions. In the past few decades, a significant number of articles have been published on liquid−liquid equilibria, with increasing attention to aqueous two-phase systems (ATPS). Although the experimental techniques and the correlation of the obtained data deserve being treated with care, there are some mistakes that have been published and maintained afterward in subsequent works. Because of that, the intention of this work is to provide a review of the subject and clarify some of these aspects.

2. THE EXPERIMENTAL DETERMINATION OF LLE

Experimental determinations of the liquid−liquid equilibrium were already carried out at the end of 19th century, such as the early works of Nernst[2] studying acetic acid distribution between two immiscible liquid phases of water and benzene. Also, some early works of Bancroft[3,4] were focused on LLE, both theoretically and experimentally. At the dawn of the LLE, the ternary mixtures studied experimentally were composed of a solute, frequently an acid, distributed between water and an organic compound (only partially miscible with water). Many of these early determinations were collected in the works of Hand[5] and Brancker and co-workers.[6] The purpose of the extraction would be to separate the water + solute mixture using the organic solvent. The choice of acetic acid was in the ease of analysis by titration. Indirect analysis could also be used, such as the measurement of physical properties (refraction index, viscosities), despite such methods having
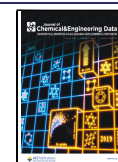
lower precision and requiring the availability of calibration curves for the mixtures.

The first technique to determine equilibrium data of ternary systems (the tie-lines) followed a two-stage procedure. In the first stage the solubility curve (the solubility limit, between homogeneous/one phase and heterogeneous/two phases) was determined visually using the so-called cloud-point method. In the second stage, mixtures of the three components were stirred vigorously and then allowed to settle. The time for stirring and settling needed to be enough to attain equilibrium and the complete separation of the phases. Syringes are still used today to withdraw samples of both equilibrium phases. The separated phases were analyzed by chemical means, yielding in this way the ends of the tie lines that represent the equilibrium between the immiscible liquid phases. The number of tie-lines obtained for a system was limited, due to the difficult and time-consuming procedure. Thus, tie-line interpolation methods were necessary with the aim of providing additional data without new experiments. This need of tie-line interpolation methods was explicitly stated by several authors, who developed empirical equations for that purpose.[6−8] That will be described ahead. Nowadays, the procedure for determining tie-lines experimentally is not that difficult, and it is not justified to provide a reduced number of tie-lines. Typically, at least six tie-lines should be provided covering the complete LLE region. Another unfortunate situation is the measurement of LLE data on aqueous two-phase systems, which typically cover only a small fraction of the LLE region, and this with few tie-lines (just three or four very close tie-lines in many cases). But there are no technical justifications for such a limitation. ATPS are typically used for extraction in biotechnology, and knowledge of the complete LLE region is important to any industrial application of the system for a separation. Even so, that is scarcely found in the literature. Moreover, the complete phase diagram, including solid phases when present, are even scarcer to find in the literature.[9,10] Considering all the above, it seems that providing the LLE data should cover the whole LLE region, starting from the binary subsystems (tie lines in the axes of the triangular diagram). Indeed, as for modeling purposes, the availability of LLE data for the binary systems (temperature−composition data) would be very useful for any ternary LLE data treatment.

An example of this a two-stage procedure described above can be found in the work from Woodman.[11] The cloudiness technique to obtain the solubility curve, also distribution curve, is detailed by Othmer and co-workers.[12] Curiously, many authors would misidentify this solubility curve as the binodal curve, and the mistake has been held for many years. It is important to note that at that time, Othmer and co-workers (probably the most used references for the cloud-point method) always applied the term solubility curve, rather than binodal curve, to refer to it in their works.[8,12,13] But even Treybal[14] in his textbook suggests that the equilibrium data of a ternary system can be determined carrying out the cloud-point procedure first to obtain the "*binodal curve*" and afterward match the solute compositions to that curve. The cloud-point method is not a rigorous method to obtain the binodal curve, since it depends on the visual perception of the observer to find the limit between immiscibility and homogeneity (and in some mixtures, clouding is not produced, just the appearance of drops of the immiscible phase that float -or sink- in the larger phase). Since the solubility curve is not a true equilibrium curve, using this curve in the determination of the tie-lines does not lead to the true equilibrium ends. For this, the previously described method must be questioned for the determination of tie lines.

The system equilibrium curve is called the binodal curve, and it is obtained by joining all the true ends of the tie lines for the studied system. The correct procedure to obtain a system binodal curve is, after phase separation, to carry out a careful and precise analysis of the equilibrium compositions. This requires an equilibrium cell, a jacketed vessel connected to a thermostat, where appropriate amounts of the components are added, stirred vigorously to attain equilibrium, and then allowed to settle for phase separation. The analysis of the sampled phases must be very rigorous. Nowadays, the availability of different analytical techniques (namely chromatographic methods as GC and HPLC) facilitates acquisition of the LLE data. Gas chromatography (GC) is a very robust and precise analytical technique, broadly used whenever the components of the liquid mixture can be vaporized in the GC. The different types of detectors make them a very convenient choice for analysis. HPLC can be used whenever the components cannot be vaporized (polymers, salts, ionic liquids, etc.), but the analysis is not as robust and economic as that of the GC. Other analytical techniques (such as different spectroscopic analyses) can be used conveniently to quantify all or some of the components in the equilibrium phases. Also indirect methods based on physical properties, that can be measured to very high precision (e.g., density, refractive index, conductivity, among others), are reliable. The vast majority of these analytical procedures will need a calibration procedure. There is no need for the analysis of the equilibrium samples to be carried out at the same temperature as the equilibrium experiment, but there is the evident risk of phase splitting if the temperature of the equilibrium sample is changed (because the equilibrium condition of constant temperature has been changed). A diluent (typically, the component present in the largest quantity or a solvent for all components present) can be used to avoid such a problem. The use of the ternary diagram early times proved to be very practical for studying the distribution of components into the conjugated phases and, combined with the lever rule, for carrying out inherent calculations to the mass balances.[13]

From the experimentalist point of view, the use of adequate chemical analysis or even indirect methods based on physical properties is recommended rather than relying on visual methods such as the cloud-point. Very recently, a IUPAC Task Group published a list of recommended binary systems that should be used to test new methods for LLE.[15] While the article refers to binary LLE data, the methodologies tested with these binary systems can obviously be used successfully with ternary systems. As for the number of tie-lines, it is very important to cover the whole LLE region (but at least six tie-lines would be desirable). Nowadays many authors report the feed composition together with the ends of tie-lines. While the feed composition is obviously not a part of the LLE data, and unnecessary, it can be used as a check of the tie-line itself (at least internally, if not published in the article): the feed and the ends of the tie-lines must be on a straight line, which is a direct check in a graphical representation or evaluated by the coefficient of determination (most often with $r^2 > 0.99$).

3. FIRST LIQUID−LIQUID EQUILIBRIUM CORRELATIONS OF TERNARY SYSTEMS

Understanding the phase behavior was of prime interest from the earliest works by Nernst.[2] In his work, acetic acid was distributed between water and benzene immiscible liquid phases. The distribution coefficient $K = C_1/C_2$ did not remain constant (acetic acid composition ratio in both phases, with subscripts 1 and 2 representing the aqueous and organic phases, respectively). But the constancy was slightly improved using a modified coefficient: the ratio between the squared aqueous phase composition and the organic phase composition, $K' = C_1^2/C_2$. This modification was simply an empirical treatment that later authors tried to improve without success. The idea had further modifications such as using fractional exponents, for example $C_1^{1.2}/C_2$. Several justifications were provided for deviations from Nernst distribution law: The modification of the mutual solubilities of the immiscible liquids due to the addition of the cosolute, cases of a component association and/or dissociation in the mixture, or the possible polymerization, particularly in the high concentration region. A valuable review on these trials was carried out by Hand.[5]

Hand, studying the acetic acid−chloroform−water mixture, starts from the aforementioned relationship, $K = C_1^2/C_2$, and modifies the acetic acid compositions in both phases introducing the dissociation degree of the acid in the aqueous phase, a. The concentration of nondissociated molecules would be $C_1(1 − a)$. Considering that r is the ratio of acetic acid molecules distributed between water and chloroform, then $C_1(1 − a)/r$ would be the concentration of the acetic acid in the chloroform, and the concentration of the molecules associated would be $C_2 − C_1(1 − a)/r$. So, when applying the corrected mass action law, the result would be

$$K = \frac{[C_1(1 − a)/r]^2}{C_2 − [C_1(1 − a)/r]} \tag{1}$$

The previous expression required two new parameters, and the constancy of K was not totally satisfactory. On the other hand, it would be arguable to admit the constancy of these parameters for the whole range of the mixture compositions. A better approximation made by Hand would start based on the supposedly valid expression,

$$\frac{A_1}{(B_1 + kC_1)} = \frac{A_2}{(B_2 + kC_2)} \tag{2}$$

In the previous expression A is the solute masses, and B and C are the immiscible component masses. The subscripts refer to both phases. Equation 2 would be preferably valid for the case in which the system tie-lines were horizontal. Therefore, we can obtain the value of the parameter k to transform the experimental tie lines into horizontal tie lines. If we assume that the solute of each phase associates to each one of the immiscible components of the phase, we will write for each phase:

$$\frac{A_{1b}}{B_1} = \frac{A_{1c}}{kC_1} = \frac{A_1}{(B_1 + kC_1)} \quad A_{1b} + A_{1c} = A_1 \tag{3a}$$

$$\frac{A_{2b}}{B_2} = \frac{A_{2c}}{kC_2} = \frac{A_2}{(B_2 + kC_2)} \quad A_{2b} + A_{2c} = A_2 \tag{3b}$$

where: A_{1b} = mass of solute A held by B in phase 1; A_{1c} = mass of A held by C in phase 1; A_{2b} = mass of A associated with B in

phase 2; and A_{2c} = mass of A associated with C in phase 2; although these solute values associated with each immiscible component would be very difficult to specify.

Hand's calculations were verified by the experimental determination of the compositions of the ternary mixture components at constant temperature and plotted in the ternary diagram at the corresponding isotherm. The composition of the conjugated phases was generally carried out by chemical analysis of the components in each phase. The method to obtain the solubility curve consisted of adding components following the sequence "two liquids−cloudiness−homogeneity", which is typically known as the cloud-point titration method. This technique has been maintained over the years as can be seen still today in recent publications.

A better approach from Hand for the mixture acetic acid−water−benzene was the equation:

$$\log_{10}(A_2/C_2) − 0.79 \log_{10}(A_1/B_1) = \text{const} \tag{4}$$

where A is the acetic acid quantity, B is for benzene, and C is for water, the immiscible liquids. Subscript 1 refers to the upper, organic phase, and subscript 2 refers to the lower, aqueous phase.

The general form of eq 4 is

$$\frac{(A_1/B_1)^m}{(A_2/C_2)} = \text{const} \tag{5}$$

where exponent m is an empirical constant, typically fitted to experimental data by linear regression in the log scale. Thus, a plot of A_1/B_1 against A_2/C_2 on logarithmic coordinates would provide a straight line. Several authors tested this equation with other mixtures yielding different deviations, although it would be an attempt for data reduction and useful for tie-line interpolation. Nevertheless, Hand himself admits that his previous equations separately are not sufficient to calculate the composition of a conjugated phase in equilibrium with a known phase, although together could help to find it.

If it is admitted that the law of mass action governs the composition of the saturated phases of a solute and two immiscible liquids, keeping constant the solute A quantity it can be supposed that the percentage decrease in amount of solvent B is proportional to the percentage increase in amount of diluent C, this is

$$\frac{dB}{B} = −n\frac{dC}{C} \tag{6}$$

or by integration, $\log_{10} B + n \log_{10} C = \log_{10} \text{const}$.

and with a constant solute amount we could write

$$\log_{10}(B/A) + n \log_{10}(C/A) = \log_{10} K \tag{7}$$

Equation 7 could be used to determine the component proportion in the saturated phase, even though it must be admitted that it is an empirical equation. In practice, plotting B/A against C/A on the logarithmic scale should yield a straight line from which constants n and K would be found.

Brancker and co-workers[6] plotted the diluent percentage in one phase against the solvent percentage in the other phase on a logarithmic diagram for several systems getting straight lines that would prove the validity of eq 7.

Bachman,[7] following Brancker's work, proposes that the equation curve relating the component compositions would be

$$xy = mx + ny \tag{8}$$

where x = weight percentage of C in C-rich phase, y = weight percentage of B in the B-rich phase, m, n = constants, with a solute A distributed among the immiscible liquids B and C.

The previous equation could be rewritten in the form

$$x = m\frac{x}{y} + n \tag{9}$$

which is a straight line when plotting x against x/y. This equation, totally empirical, was used with relative success to correlate the liquid–liquid equilibrium of diverse ternary systems. This equation is of little use since it only represents the compositions of the major component in each equilibrium phase. The two other components are not in the equation. Such representation would always give a straight line.

Othmer and Tobias[8] developed an equation able to relate equilibrium compositions of ternary systems. These authors modify Bachman's equation finally proposing the equation:

$$\log_{10}[(1 - b_1)/b_1] = n \log_{10}[(1 - c_2)/c_2] + S \tag{10}$$

where b_1 is the solvent fraction in the solvent-rich phase and c_2 is the diluent fraction in the diluent-rich phase. Plotting $(1 - b_1)/b_1$ against $(1 - c_2)/c_2$ on a logarithmic diagram would conduct to a straight line from where the parameters n and S could be obtained. The previous equation turned out useful in many ternary systems being used afterward in the following publications. It must be considered that it is an empirical equation, without thermodynamic basis, whose greatest utility has been the tie-line interpolation. This need of tie-line interpolation is due to the limited number of tie-lines obtained for each ternary system, as commented above. Othmer and Tobias[8] stated this need for a tie-line interpolation method in the very first paragraph of the article. Indeed, the statement is also in the beginning of the papers by Brancker and co-workers[6] and Bachman.[7]

It must be admitted that the Hand,[5] Brancker and co-workers,[6] Bachman,[7] and Othmer-Tobias[8] models were previous correlation attempts for phase equilibria treatment, questioned today for their empirical nature but useful for tie-line interpolation. But it is clear in the original articles that the authors did not pretend to prove the quality of the experimental data from the linearity obtained. But unfortunately, that is a purpose that is attributed nowadays: Many authors use these empirical equations as proof of the quality, "reliability" or even the consistency of the LLE data. Such "reliability" as concept is not defined, but the use of the term consistency is an important mistake: In Thermodynamics, consistency tests are used to prove that experimental vapor–liquid equilibrium data fulfill the Gibbs–Duhem equation (and thus, the data are "consistent" with the Gibbs–Duhem restriction). Attributing "consistency" to LLE data by fulfillment of empirical equations is just a fundamental error from the thermodynamics point of view.

A valuable critical review of both Hand and Othmer-Tobias correlations was presented by Carniti and co-workers[16] more than four decades ago. Their analysis was applied to the different types of error in the experimental determination of tie-line. Of course, the empirical equations were not able to detect the errors introduced in the data, and the interested reader is encouraged to evaluate the original paper for details. But it is important to note the tie-line equivalence in both methods, as explained by Carniti and co-workers and shown in Figure 1. Recalling eq 7 (Hand equation) and the terms in its logarithms, Figure 1 (left) shows that tie-lines AB and CD do
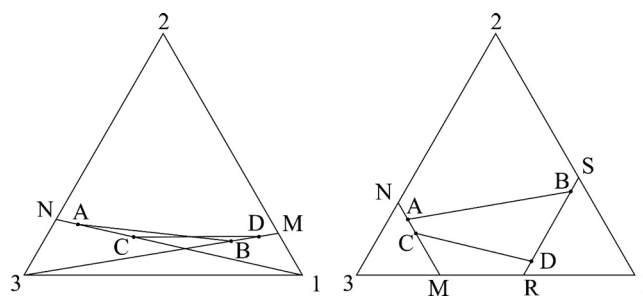
Figure 1. (Left) Equivalence of two tie-lines (AB, CD) in the Hand correlation. (Right) Equivalence of two tie-lines (AB, CD) in the Othmer-Tobias correlation. Adapted with permission from ref 16. Copyright 1978. Elsevier.

not change the equation linearity because all points in line 1N have a constant ratio between compositions of components 2 and 3, and likewise all points in line 3M have the same ratio between compositions of components 1 and 2. This means that any group of tie-lines for which the ends lie into lines 1N and 3M will provide a straight line in the Hand equation, even if they cross each other as in Figure 1(left), which is physically impossible. Similarly, recalling eq 10 (Othmer-Tobias equation) and the terms in its logarithms, Figure 1 (right) shows that tie-lines AB and CD again do not change the linearity of the Othmer-Tobias equation since all the points in lines MN and RS (lines parallel to the triangle side) have the same composition of the component shown in the opposite vortex (MN same composition of component 3, RS same composition of component 1). This is an evident proof that all these empirical equations do not provide a proof of LLE data quality, despite that they can be used as means of data reduction or interpolation.

4. THERMODYNAMIC FORMALISM

For many years, the treatment of phase equilibrium data has been based on models with a strong thermodynamic basis. Prior to presenting these sections, it is necessary to define the thermodynamic criteria for equilibrium that will be applied in such methodologies. The vast majority of experimental setups used in the acquisition of LLE data use closed systems, and the equilibrium condition for a closed system at constant temperature T and pressure P is a minimum in the Gibbs energy of the system,[17−19] that is, $dG = 0$ and $d^2G > 0$.

$$dG = 0 \quad \text{and} \quad d^2G > 0 \tag{11}$$

From the definition of the Gibbs energy as a function of temperature, pressure, and the number of moles of each component, it is straightforward to define the equilibrium condition as a function of the chemical potential of all components μ_i of the mixture in the equilibrium phases α and β:

$$\mu_i^{\alpha} = \mu_i^{\beta} \tag{12}$$

Then, using the definition of fugacity and activity of a component in a mixture:

$$f_i^{\alpha} = f_i^{\beta} \quad \text{and} \quad a_i^{\alpha} = a_i^{\beta} \tag{13}$$

where f_i is the fugacity of component i in the liquid mixture, and similarly a_i is its activity. The superscript indicates the equilibrium phase (the liquid mixture where the component is located, α or β), and the definition of activity: $a_i^{\alpha} = f_i^{\alpha}/f_i^{0}$, with

f_i^0 as the fugacity of any component i in some arbitrary reference state 0. But all these magnitudes, chemical potential, fugacity, or activity, are not measured experimentally in the laboratory. Thus, the concept of activity coefficient as the ratio between activity and mole fraction of the component i is introduced to relate activity with the actual composition of the component:

$$\gamma_i = a_i/x_i \qquad (14)$$

Then, eqs 13 and 14 are combined:

$$x_i^\alpha \gamma_i^\alpha = x_i^\beta \gamma_i^\beta \qquad (15)$$

Equation 15 establishes the liquid−liquid equilibrium condition for a closed system at constant temperature and pressure. This equation relates the equilibrium compositions for each component of the mixture in both equilibrium phases, α and β, a magnitude that can be measured accurately in the lab. Indeed, the set of compositions that fulfill this equation are the ends of the tie-lines, that is, the line segments that are represented in a LLE phase diagram. The activity coefficient needs to be calculated with a suitable model, typically an excess Gibbs model (also called the activity coefficient model) such as those presented ahead. Much more detail on this equilibrium formalism can be found in Thermodynamics textbooks.[17−19]

5. THE CONSISTENCY OF PHASE EQUILIBRIUM DATA

The great advantage of working in the experimental determination of vapor−liquid equilibrium (VLE) data over LLE data is the use of consistency tests to prove the correctness of experimental VLE data. The effort to apply these consistency tests provides an independent proof of the quality or correctness of the equilibrium data obtained. The recent review of Wisniak and co-workers on consistency tests is recommended.[20] Unfortunately, such a tool does not exist for LLE data. In thermodynamics, the consistency of the data refers to their compliance with the Gibbs−Duhem equation. Different consistency tests have been developed for VLE data using the Gibbs−Duhem equation, either for complete VLE data sets, or point-to-point tests. Consistency tests are critical tools to trust published equilibrium data, and have been required for many years in the main journals publishing phase equilibrium data.[15] That is the reason why many authors are looking for any test or proof for the consistency of their LLE data sets. As commented in the previous section, empirical equations such as Hand or Othmer-Tobias cannot be considered as a validation procedure. But Othmer and Tobias did propose a data validation technique for LLE that uses the partial pressures together with LLE data.[21] Unfortunately, partial pressures and similar VLE data are scarcely measured together with LLE data, so this procedure, while recommended by NIST, has not been applied in the literature.[22]

In fact, there is no indication of consistency tests for LLE data in any Thermodynamics textbooks, only consistency tests for VLE data sets (see, for instance, Prausnitz and co-workers,[17] Sandler,[18] and Smith and co-workers[19]). The reason for that comes from the equilibrium condition and the source of the consistency: the Gibbs−Duhem equation:

$$\left(\frac{\delta M}{\delta P}\right)_{T,x} dP + \left(\frac{\delta M}{\delta P}\right)_{P,x} dT - \sum_i x_i d\bar{M}_i = 0$$

$$\sum_i x_i d\bar{M}_i = 0$$

$$(T, P, \text{constants}) \qquad (16)$$

where M is a mixing property such as the variation of Gibbs energy of the mixture, the bar above M indicates a partial molar quantity, P and T are pressure and temperature, and x_i refers the mole fraction of component i in the liquid phase. In VLE data at low to moderate pressures, the modified Raoult's law can be applied, assuming fugacity coefficients are equal to unity:

$$y_i P = \gamma_i x_i P_i^{\text{sat}} \qquad (17)$$

where y_i is the mole fraction of component i in the vapor phase, γ_i is the activity coefficient in the liquid phase, and P_i^{sat} is the saturation pressure of component i. From this equation it is straightforward to calculate the activity coefficient from the VLE experimental data. Then, it can be checked that the activity coefficients (or Gibbs excess energies) satisfy the Gibbs−Duhem equation. On the other hand, recalling the equilibrium condition for LLE given in eq 15, it is clear that activity coefficients cannot be calculated from the experimental data: there are two unknowns (two activity coefficients) in each defined equation (each component).

6. EQUILIBRIUM DATA CORRELATION USING SEMI-EMPIRICAL METHODS

Different equations based on the excess Gibbs energy can be used to correlate equilibrium data, such as the equations from Margules, van Laar, or Redlich−Kister. In this work, we highlight the Wilson, nonrandom two liquid (NRTL), and universal quasichemical (UNIQUAC) equations as semi-empirical methods since they have thermodynamic fundament. The three equations have a common base using the dimensionless excess Gibbs energy, G^E/RT, that relates to the activity coefficient of the components in the mixture (R is the gas constant and T is the temperature).

6.1. Wilson Equation. Wilson[23] relates the local molar fractions of molecules 1 (x_{11}) and of molecules 2 (x_{21}) in the immediate neighborhood of molecule 1 to their molar fractions in the global mixtures x_1 and x_2, using interaction energies among the pair 1−2 and 1−1. The final relationship for the excess molar Gibbs energy developed by Wilson is

$$G^E/RT = -x_1 \ln(x_1 + A_{12}x_2) - x_2 \ln(x_2 + A_{21}x_1) \qquad (18)$$

where x_1, x_2, = molar fractions of component 1 and 2 and A_{12}, A_{21} = fitting parameters.

The activity coefficients γ_1 and γ_2 are calculated from

$$\ln \gamma_1 = -\ln(x_1 + A_{12}x_2) + x_2\left[\frac{A_{12}}{(x_1 + A_{12}x_2)} - \frac{A_{21}}{(x_2 + A_{21}x_1)}\right]$$

$$\ln \gamma_2 = -\ln(x_2 + A_{21}x_1) + x_1\left[\frac{A_{21}}{(x_2 + A_{21}x_1)} - \frac{A_{12}}{(x_1 + A_{12}x_2)}\right]$$

$$(19)$$

Wilson's equation has been very useful in vapor−liquid equilibria, but it cannot be applied directly to liquid−liquid equilibria because this equation cannot predict phase separation.[17] Even so, it has been successfully used by several

authors to develop more complex models combining different theories. It has been clearly helpful in ATPS, where the combination of components of different chemical natures (water, polymers, and electrolytes) makes the modeling quite complex. Just as an example (not an exhaustive list), the groups of Professors Macedo[24] or Zafarani-Moattar[25] have developed and used models for ATPS combining the Wilson equation with others to cover the variety of interactions present in such systems.

6.2. NRTL Equation. Renon and Prausnitz[26] proposed the nonrandom two liquid equation, NRTL, using the same local-composition concept developed by Wilson, and introducing the nonrandomness parameter for modifying the interaction energies between molecules 1 and 2. Renon and Prausnitz used the local composition concept from Wilson, the Guggenheim's quasichemical theory, and the Scott's two-liquid theory of binary mixtures. The relationships for the local compositions with the global compositions are

$$\frac{x_{21}}{x_{11}} = \frac{x_2 \exp(-\alpha_{12}g_{21}/RT)}{x_1 \exp(-\alpha_{12}g_{11}/RT)}$$

$$\frac{x_{12}}{x_{22}} = \frac{x_1 \exp(-\alpha_{12}g_{12}/RT)}{x_2 \exp(-\alpha_{12}g_{22}/RT)}$$

$$x_{21} + x_{11} = 1$$

$$x_{12} + x_{22} = 1 \tag{20}$$

where g_{11} and g_{21} are the interaction energies between a $1-1$ and $1-2$ pair of molecules (with $g_{12} = g_{21}$), and x_1 and x_2 being the global molar fractions. The x_{21} and x_{12} values, with the same meaning as in Wilson's equation, can be readily obtained from previous relationships. For α_{12} the values are estimated and positive, between 0.1 and 0.3, even though in later works this nonrandomness parameter was treated as an open parameter the values of which would depend on the more satisfactory adjustment of the equilibrium data treated.

According to Scott's two-liquid theory, it is assumed that in a binary mixture there are cells, the centers of which are occupied by one molecule 1 or 2 surrounded by molecules 2 or 1. In the cells for molecule 1 the interaction energy is given by

$$g^{(1)} = x_{11}g_{11} + x_{21}g_{21} \tag{21}$$

Similarly, in cells for molecule 2

$$g^{(2)} = x_{12}g_{12} + x_{22}g_{22} \tag{22}$$

and

$$g_{\text{pure}}^{(1)} = g_{11}$$

$$g_{\text{pure}}^{(2)} = g_{22}$$

$$g_{12} = g_{21} \tag{23}$$

Renon and Prausnitz postulate the relationship for the excess Gibbs energy

$$G^{\text{E}}/RT = x_1(g^{(1)} - g_{\text{pure}}^{(1)}) + x_2(g^{(2)} - g_{\text{pure}}^{(2)}) \tag{24}$$

Substituting eqs 21 and 22 takes the form

$$G^{\text{E}}/RT = x_1 x_2(g_{21} - g_{11}) + x_2 x_1(g_{12} - g_{22}) \tag{25}$$

Introducing x_{21} and x_{12} values gives the NRTL equation. In this equation, the excess Gibbs energy would be a function of the component compositions x_1 and x_2 along with g_{11}, g_{12}, g_{22}, and g_{21}. The interaction energies can be grouped together with the terms:

$$\tau_{12} = (g_{12} - g_{22})/RT$$

$$\tau_{21} = (g_{21} - g_{11})/RT \tag{26}$$

Therefore, the NRTL equation is defined by three parameters τ_{12}, τ_{21}, and α.

It can be also written in the form:

$$G^{\text{E}}/RT = x_1 x_2[\tau_{21}g_{21}/(x_1 + x_2 g_{21})] + \tau_{12}g_{12}/(x_2 + x_1 g_{12})$$

$$g_{12} = \exp(-\alpha\tau_{12})$$

$$g_{21} = \exp(-\alpha\tau_{21}) \tag{27}$$

The activity coefficients can be calculated from

$$\ln \gamma_1 = \frac{G^{\text{E}}}{RT} + x_2 \frac{\partial(G^{\text{E}}/RT)}{\partial x_1}$$

$$\ln \gamma_2 = \frac{G^{\text{E}}}{RT} + x_1 \frac{\partial(G^{\text{E}}/RT)}{\partial x_2} \tag{28}$$

If we compare the NRTL equation with older equations as those developed by Wohl,[27] Redlich–Kister,[28] or Black,[29] these models require three or more adjustable parameters while the NRTL only requires two parameters per binary, although it requires a third empirical constant, the non-randomness parameter, selected according with the chemical properties of the mixture components.[17]

The NRTL equation can be applied to predict ternary vapor–liquid equilibria and ternary liquid–liquid equilibria based solely in binary data. It can be generally applied to multicomponent mixtures for predicting excess Gibbs energy only from binary data, for which it becomes an excellent tool for phase equilibria correlation of liquid mixtures.

6.3. UNIQUAC Equation. A more proper model for phase equilibria correlation was developed by Abrams and Prausnitz[30] that uses the concept of local area fraction. They propose an expression for the excess Gibbs energy as the summation of two terms, one called combinatorial and other called residual:

$$(G^{\text{E}}/RT) = (G^{\text{E}}/RT)_{\text{combinatorial}} + (G^{\text{E}}/RT)_{\text{residual}} \tag{29}$$

They derive the universal quasichemical (UNIQUAC) equation from the Guggenheim's quasi-chemical theory. Multicomponent mixtures containing both polar and nonpolar liquids, including liquids with tendency to form hydrogen bonds, have been successfully modeled by this equation, which can be applied to a large variety of mixtures. This equation only requires two parameters per binary pair, and its extension for multicomponent mixtures does not require ternary or higher parameters.

The local fraction area concept considers a molecule of component 1 as a set of bonded segments having the same size, r_1, although they differ in the external contact area with the nearest neighbors whose number is a function of the lattice coordination number, z, and proportional to the molecule's external surface parameter, q_1. These parameters for

component 2 are r_2 and q_2. The local fraction area, θ_{21}, is the fraction of sites around molecule 1 that are occupied by molecule's 2 segments. Likewise, the local fraction area θ_{11} is the fraction of sites around molecule 1 occupied by molecule's 1 segments. The local fraction areas for molecule 2, θ_{12} and θ_{22}, are defined similarly. Since these are fractions:

$$\theta_{11} + \theta_{21} = 1 \quad \text{and} \quad \theta_{12} + \theta_{22} = 1 \tag{30}$$

The combinatorial term of the excess Gibbs energy accounts for the number of possible configurations in a mixture with N_1 and N_2 molecules of component 1 and 2, respectively. The $G^{E(combinatorial)}$ value is given by the relationship:

$$\left(\frac{G^E}{RT}\right)_{combinatorial} = x_1 \ln \frac{r_1}{(x_1 r_1 + x_2 r_2)} + x_2 \ln \frac{r_2}{(x_1 r_1 + x_2 r_2)}$$
$$+ \left(\frac{z}{2}\right)\left[q_1 x_1 \ln \frac{q_1(x_1 r_1 + x_2 r_2)}{r_1(x_1 q_1 + x_2 q_2)} \right.$$
$$\left. + q_2 x_2 \ln \frac{q_2(x_1 r_1 + x_2 r_2)}{r_2(x_1 q_1 + x_2 q_2)} \right] \tag{31}$$

The coordination number z usually set equal to 10.

The residual term $G^{E(residual)}$ is related to the interaction energies between the components. This term is defined by the relationship:

$$\left(\frac{G^E}{RT}\right)_{residual} = -q_1 x_1 \ln \left[\frac{x_1 q_1}{(x_1 q_1 + x_2 q_2)} \right.$$
$$\left. + \frac{x_2 q_2}{(x_1 q_1 + x_2 q_2)} \exp\left(\frac{-u_{12} - u_{22}}{RT}\right) \right]$$
$$- q_2 x_2 \ln \left[\frac{x_1 q_1}{(x_1 q_1 + x_2 q_2)} \right.$$
$$\left. + \frac{x_2 q_2}{(x_1 q_1 + x_2 q_2)} \exp\left(\frac{-u_{12} - u_{11}}{RT}\right) \right] \tag{32}$$

In these relationships, the structural parameters r and q represent, respectively, the size and surface parameters of the pure component, calculated from the angles and bond distances. The values r and q for the molecules of some fluids have been published in the Abrams and Prausnitz work and in works afterward by other authors. Necessarily, the correlation of equilibrium data using UNIQUAC equation requires the calculation of $(-u_{12} - u_{22})$ and $(-u_{12} - u_{11})$ by regression.

The original UNIQUAC equation was widely used for the correlation of phase equilibria, but further modifications were developed. Anderson and Prausnitz[31,32] modify the structural parameters for a better fitting of vapor−liquid equilibria of binary and ternary systems containing alcohols. Maurer and Prausnitz[33] multiply the residual term by a constant C ($C < 1$) representing the molecular surface reduction. A variety of modifications has been carried out by Nagata and co-workers. Nagata and Katoh[34] introduce an additional parameter in their effective UNIQUAC model. Nagata[35] develops the extended UNIQUAC model. Nagata and Ohtsubo[36] applied an associated-solution UNIQUAC theory to alcohols. Later, Nagata[37] modifies the extended UNIQUAC equation introducing additional parameters for the liquid−liquid equilibria of ternary and quaternary systems. Subsequent works form Nagata and other authors assessed the application of the UNIQUAC model and its modifications to several

systems supporting its great usefulness for the correlation of phase equilibria.

Without doubt, both NRTL and UNIQUAC models would be recommended for the correlation of equilibrium data, specifically for liquid−liquid and vapor−liquid equilibria. An outstanding contribution from Professor John M. Prausnitz, these equations have demonstrated their usefulness in the liquid−liquid equilibria correlation in an unequal way. Both have a thermodynamic base since their models depend on the nature of the mixture components, so these equations are preferred before other totally empirical models.

Curiously, the most used equation for the correlation of liquid−liquid equilibria is NRTL, while the UNIQUAC equation is preferred for vapor−liquid equilibria. The NRTL equation requires two parameters, g_{12} and g_{21}, and the nonrandomness parameter, α, per binary pair. The UNIQUAC equation only requires two parameters per binary, considering that the structural parameters can be calculated individually for each molecule. Even so, the quality of the LLE data correlation strongly depends on the quality of LLE data and, very important, that the experimental data used cover the whole composition range. Important errors may arise when incomplete or limited data sets are used in the data correlation.[38] This problem is of particular relevance in aqueous two-phase systems since in most cases a very limited set of tie-lines are provided, and the extension of the LLE region is studied in very few cases.[9,10]

7. EQUILIBRIUM DATA PREDICTION

The best approximations provided for the prediction of liquid−liquid equilibrium have been achieved by the methods of ASOG (Analytical Solution of Groups) developed by Kojima and Tochigi[39] and UNIFAC from Fredenslund and co-workers.[40] Although both methods were developed for the prediction of vapor−liquid equilibrium, their assumptions were also applied to the liquid−liquid equilibrium.

Both methods assume that the logarithm of the activity coefficient is the summation of a combinatorial term that depends on the molecule size and shape, and a residual term for the interaction of groups:

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \tag{33}$$

The residual term is shared in both methods. In the combinatorial term, the ASOG method uses the Flory−Huggins theory, defining the molecule size as a function of the number of atoms in the molecules (except hydrogen), while UNIFAC takes the UNIQUAC equation developed by Abrams and Prausnitz.

While the two methods have been popularly applied for the prediction of vapor−liquid equilibrium, their use in liquid−liquid equilibrium is more limited because of the large deviations usually yielded.

7.1. Use of Equations of State (EoS).
Nowadays, equations of state are often used in the prediction and correlation of LLE data. While conventional EoS typically present problems for LLE data correlation and prediction, SAFT EoS variants and the CPA EoS have in general overcome such limitations.[41] Indeed, the book of Kontogeorgis and Folas contains many examples on the successful application of EoS to LLE, namely the CPA EoS. Similar success can be found with different SAFT variants. In particular, the group of Prof. Sadowski has demonstrated the capability of the PC-SAFT and

electrolyte-PC-SAFT to correlate and even predict the phase diagram of aqueous two-phase systems (ATPS), both (polymer + polymer) and (polymer + salt),[42−44] or complex liquid−liquid−liquid equilibrium.[45] The presentation of these models is beyond the purpose of this article: An extensive and detailed description of these EoS and many others is given in the book of Kontogeorgis and Folas.[41] A recent special issue in *J. Chem. Eng. Data* celebrating 30 years of the SAFT EoS family collects recent developments of the whole variety of the SAFT family of EoS.[46] While the majority of articles dealing with LLE data use excess Gibbs energy models for activity coefficients (such as those presented in previous sections and others), it has been proven that advanced EoS are capable of correlating, and in many cases predicting the LLE data with good accuracy and very few fitting parameters (or none). It is clear that in the future we will see LLE data treatment using EoS increasing.

8. STABILITY OF SYSTEMS IN OF LIQUID−LIQUID EQUILIBRIUM

The thermodynamic stability in liquid−liquid equilibrium is understood as the inequalities to be satisfied for the existence of a homogeneous system. In a binary system at constant temperature and pressure it must be fulfilled that[47]

$$\frac{\partial \ln a_1}{\partial x_1} = x_2 \frac{\partial^2 (G^M/RT)}{\partial x_1^2} \geq 0 \tag{34}$$

where a_1 is the chemical activity of component 1, G^M/RT is the dimensionless Gibbs energy of mixing, and x_1 and x_2 are the mole fractions of components 1 and 2.

The previous equation can be reduced to

$$\partial \ln a_1/\partial x_1 = x_2 G11 \geq 0 \tag{35}$$

And the $G11$ value is given by

$$G11 = \frac{1}{x_1 x_2} + \frac{\partial^2 (G^E/RT)}{\partial x_1^2} \tag{36}$$

In a homogeneous liquid system, a plot of $\ln a_1$ against x_1 would yield a monotonously increasing function, and there cannot exist two compositions with the same activity, for which the system cannot separate in two liquid phases. If this condition is not satisfied in a certain mixture concentration range, the mixture will be separated in two phases and their compositions will set the system stability limit.

Then the relationship

$$\partial \ln a_1/\partial x_1 = x_2 G11 = 0 \tag{37}$$

defines the system stability limit, and all composition fulfilling this equality will lie on the system limit of stability, which is called the spinodal curve.

For multicomponent systems the thermodynamic stability condition is given by the inequality

$$D_a = \begin{vmatrix} \partial \ln a_1/\partial x_1 & \partial \ln a_1/\partial x_2 & \cdots & \partial \ln a_1/\partial x_{N-1} \\ \partial \ln a_2/\partial x_1 & \partial \ln a_2/\partial x_2 & \cdots & \partial \ln a_2/\partial x_{N-1} \\ \vdots & \vdots & \vdots & \vdots \\ \partial \ln a_{N-1}/\partial x_1 & \partial \ln a_{N-1}/\partial x_2 & \cdots & \partial \ln a_{N-1}/\partial x_{N-1} \end{vmatrix} \geq 0 \tag{38}$$

where a_i is the chemical activity of component i and D is the stability determinant. That can be written as

$$D = \begin{vmatrix} G11 & G21 & \cdots & G1(N-1) \\ G12 & G22 & \cdots & G2(N-1) \\ \vdots & \vdots & \vdots & \vdots \\ G1(N-1) & G2(N-1) & \cdots & G(N-1)(N-1) \end{vmatrix} \geq 0 \tag{39}$$

where

$$G11 = \frac{\partial^2 (G^M/RT)}{\partial x_1^2} = \frac{1}{x_1 x_2} + \frac{\partial^2 (G^E/RT)}{\partial x_1^2}$$

$$G12 = \frac{\partial^2 (G^M/RT)}{\partial x_1 \partial x_2}$$

$$G22 = \frac{\partial^2 (G^M/RT)}{\partial x_2^2}$$

and so on. (G^M is the Gibbs energy of mixing.)

For a ternary system the stability determinant would be

$$D = G11 G22 - (G12)^2 \geq 0 \tag{40}$$

where $G11 > 0$ and $G22 > 0$

The points lying in the spinodal curve fulfill the condition

$$G11 G22 - (G12)^2 = 0 \tag{41}$$

The spinodal curve can be easily plotted if the LLE data are correlated with a model based on the dimensionless excess Gibbs energy, G^E/RT as in the case of NRTL and UNIQUAC equations.

According to all the above, in a liquid−liquid ternary system two curves are to be considered. One is the binodal curve that defines the phase equilibrium state between two phases. The other is the spinodal curve that sets the system stability limit. Both curves merge in the critical point as depicted in Figure 2a.
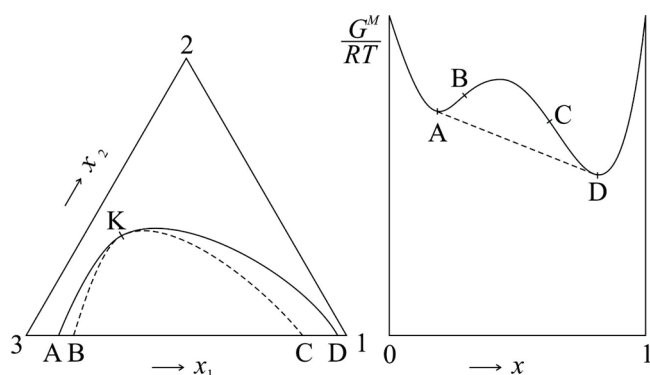
Figure 2. Stability in ternary systems. The curve AKD is the binodal curve, while curve BKC is the spinodal curve. K is the critical (or plait) point. (Left) ternary diagram. (Right) Mixing Gibbs energy in a binary system, for instance, the (1−3) axis in the ternary diagram.

Over a ternary diagram three regions would then be observed: The stable region above the binodal curve, the unstable region below the spinodal curve, and the metastable region between both curves. The solubility curve that is obtained by the cloud-point method, described previously, would lie within the metastable region. An excellent description of the stability of liquid−liquid extraction systems can be found in the book from Novak, Matous, and Pick,[47] as well as in the book from Tester and Model.[48]

When plotting the composition of a ternary mixture on the triangle, if the point lies above the binodal curve it will produce a homogeneous state of three components. This space corresponds to the system stable region. On the contrary, if the point lies below the spinodal curve, that state will be unstable and be separated into two phases, corresponding to the heterogeneous region. The space enclosed between the binodal and the spinodal curves corresponds to the system metastable region, where the solubility curve would be drawn.

Then, in a ternary liquid−liquid equilibrium system, three regions (stable, unstable, and metastable) and three curves (binodal, spinodal, and solubility curve) are defined on the ternary diagram; all of them are characteristic of such a system.

For a binary system, when plotting the function $G11$ against composition x_1, the curve shows a concave shape with a minimum. If both components are miscible the $G11$ values are positive within the whole concentration range. When the two components are partially miscible, $G11$ values are zero at the two compositions that set the system stability limit (spinodal points), considering that $G11 > 0$ was set as the limit condition for a binary system. Then, the positive values of $G11$ represent the homogeneous region while the negative values correspond to the heterogeneous region of the binary system. This is represented in Figure 3.
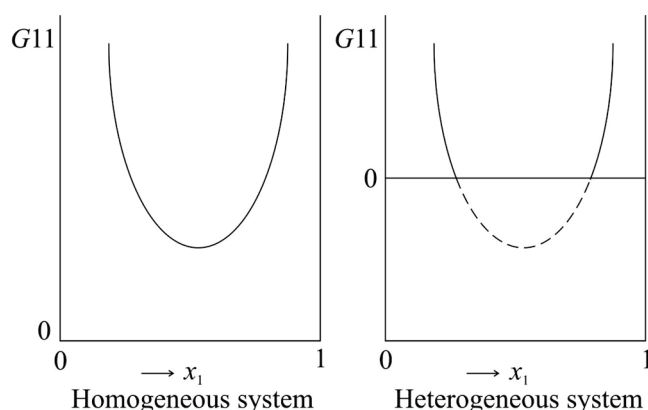

Figure 3. Miscibility conditions in a binary system.

When plotting G^M/RT against the compositions, the shape of the curve will show a minimum for miscible binary systems, while for partially miscible binaries the curve G^M/RT will have two minimums corresponding to the limit compositions at the coexisting phases, the points A and D shown in Figure 2(right) which are binodal points. The inflection points B and C are spinodal points.

In liquid−liquid equilibrium, for a Treybal ternary system of type I (one pair of immiscible components) when plotting the $G11$ values for the two binary pairs solute-eluent and solute−solvent, the tie lines point toward the more stable pair (higher $G11$ minimum). The same occurs in type II systems. Thus, the $G11$ values can give approximate information regarding the position of the tie lines of the ternary. Figure 4 shows the curves corresponding to two ternary systems (water + methanol + benzene) and (water + 1-propanol + benzene) where this effect can be observed.

In the liquid−liquid equilibrium of quaternary systems, the spinodal and binodal are surfaces that can be plotted on a tetrahedron, the four vortex of which represent the pure components. In systems having more components the plot
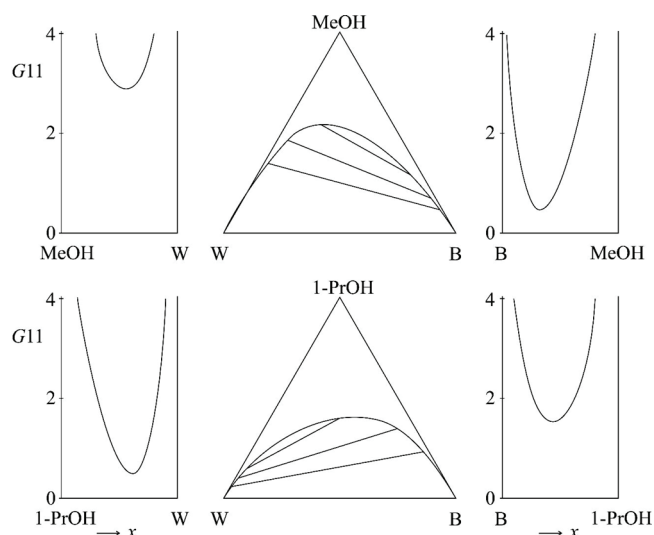

Figure 4. Tie-line slopes in ternary systems according to the $G11$ values of the corresponding binaries.

would be hypercubic. Some authors treat quaternary systems as pseudoternaries, considering a mixture of two components as a pure component. This is not correct since it cannot be guaranteed that this mixture (pseudocomponents) will keep the same proportion in both phases.

9. CONCLUSIONS

Because of the lack of a thermodynamic consistency test for liquid−liquid equilibria in the studies of liquid−liquid extraction, some concepts must be handled with care. In this article these concepts have been thoroughly reviewed and some recommendations have been suggested. Since the major interest lies in ternary systems for the ease of representation on the ternary diagram, it is critical to distinguish between binodal or equilibrium curve and solubility curve. The system stability limit is defined by the spinodal curve. The binodal curve must be determined using a precise analysis of the separated equilibrium phases. The spinodal curve can be obtained using the excess Gibbs energy following suitable models as those described herein, or others. The solubility curve lies in a metastable region within the phase diagram, between the binodal and the spinodal curve. Tie-line interpolation can be carried out following any empirical model, although the liquid−liquid equilibria correlation must be carried out using the semiempirical thermodynamic models based on the excess Gibbs energy or equations of state. For the prediction of liquid−liquid equilibria the UNIFAC or ASOG methods can be used although the results usually show large deviations from experimental data.

■ AUTHOR INFORMATION

Corresponding Author

Oscar Rodriguez − *Department of Chemical Engineering and CRETUS Institute, Universidade de Santiago de Compostela, E-15782 Santiago de Compostela, Spain;* ● orcid.org/0000-0002-8416-8534; Email: oscar.rodriguez@usc.es

Authors

Alberto Arce − *Department of Chemical Engineering, Universidade de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*

Alberto Arce, Jr. − *School of Engineering, Universidade de A Coruña, E-15403 Ferrol, Spain;* orcid.org/0000-0002-5954-8199

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