Using nonrandom two-liquid model for solvent system selection in counter-current chromatography

Da-Bing Ren, Yan-Hua Qin, Yong-Huan Yun, Hong-Mei Lu, Xiao-Qing Chen, Yi-Zeng Liang*

College of Chemistry and Chemical engineering, Central South University, Changsha 410083, China

ARTICLE INFO

ABSTRACT

Selection of an appropriate solvent system is of great importance for a successful counter-current chromatography separation. In this work, the nonrandom two-liquid (NRTL) model, a thermodynamic method, was used for predicting the partition coefficient based on a few measured partition coefficients. The NRTL method provides quite satisfactory results for model solutes in first correlating measured partition coefficient in a few representative biphasic liquid systems and then successfully predicting partition coefficient in other two-phase liquid systems. According to the predicted partition coefficient, a suitable solvent system can be screened. Assisted with the NRTL method, the solvent system composed of hexane/ethyl acetate/methanol/water (1:4:1:4, v/v) was rapidly screened for the successful separation of two major compounds with high purity from *Malus hupehensis* leaves. The results demonstrated that the NRTL model can offer a simple and practical strategy to estimate partition coefficients in support of CCC solvent system selection, which will significantly minimize the experimental efforts and cost involved in solvent system selection.

© 2014 Published by Elsevier B.V.

1. Introduction

Counter-current chromatography (CCC) has been accepted as a useful tool for separation and purification of natural products [1,2]. For a successful CCC separation, selection of an appropriate solvent system is the most crucial step. It is well accepted that the selection of an appropriate solvent system has been a significant issue that somehow blocks the wide application of CCC [1,3]. Therefore, many efforts have been made to give instructions on how to efficiently determine a suitable solvent system for CCC separation [3–7].

The partition coefficient (K) defined as the concentration of the target compound in the stationary phase divided by the concentration in the mobile phase is a key property related to the partition behavior of the solute between the stationary and mobile phase. Generally, solvent system selection or optimization is performed by measuring the K value of the target compound. Unfortunately, the determination of partition coefficient is time-consuming and labor-intensive. If the partition coefficient can be predicted without or with only a few experimental efforts, the efficiency of CCC

solvent system selection will be enhanced significantly. In fact, such predictions have been reported in previous works [6–8]. Recently, a quantum chemical method combined with thermodynamics (COMSO-RS) was used for the prediction of partition coefficient [7,9]. In addition, Ren et al. developed a semi-empirical predictive method by employing the nonrandom two-liquid segment activity coefficient (NRTL-SAC) model, which can predict the partition coefficient in a large number solvent systems based on a few measured partition coefficients [8]. In both of the aforementioned methods, the partition coefficient is calculated through the activity coefficient obtained from the thermodynamic model, COMSO-RS or NRTL-SAC. Thus, any method that can provide reliable activity coefficient values of the solute in both the stationary and mobile phase would be capable of estimating the partition coefficient in a biphasic solvent system.

Nonrandom two-liquid (NRTL) model developed by Renon and Prausnitz is a popular method that can be successfully used for representing the strongly non-ideal vapor–liquid equilibrium and liquid–liquid equilibrium [10]. It uses three adjustable parameters per binary system and can be applied to multi-component mixtures without additional parameters. The NRTL model has been widely used to calculate phase equilibrium, especially vapor–liquid equilibrium and liquid–liquid equilibrium [11]. The objective of this work is to test the applicability of the NRTL model as a tool

* Corresponding author. Tel.: +86 731 8830831; fax: +86 731 8830831.
  E-mail address: yizeng_liang@263.net (Y.-Z. Liang).

for predicting partition coefficient and screening a suitable solvent system.

2. Theory

Based on relevant thermodynamic theory, when the partition equilibrium of solute i in a biphasic system was achieved, the partition coefficient of the solute i (P_i) in the stationary phase (S) and the mobile phase (M) can be calculated from the thermodynamic equilibrium as follows:

$$P_i = \frac{x_i^S}{x_i^M} = \frac{\gamma_i^{S,\infty}}{\gamma_i^{M,\infty}}; \quad x_i \to 0. \tag{1}$$

where x_i^S is the molar fraction of solute in the stationary phase and x_i^M is the molar fraction of solute in the mobile phase. $\gamma_i^{S,\infty}$ and $\gamma_i^{M,\infty}$ are the infinite dilution activity coefficient of solute i in the stationary and mobile phase, respectively.

In practice, molar concentration rather than molar fraction is used to calculate the partition coefficient. Hence, the partition coefficient based on the molar fraction in Eq. (1) has to be transformed into the partition coefficient based on the molar concentration (K_i) through the following expression:

$$K_i = \frac{C_i^S}{C_i^M} = P_i \frac{V^M}{V^S} = P_i \frac{\sum\limits_{j=1}^{n} x_j^M V_{0j}}{\sum\limits_{j=1}^{n} x_j^S V_{0j}} \tag{2}$$

where j is the component index in the two phases. C_i^S and C_i^M are the molar concentration of the solute i in the stationary and mobile phase, respectively. V^S and V^M are the molar volume of stationary phase and mobile phase. V_{0j} is the molar volume of solvent j in the two liquid phases. It should be noted that the excess volume of mixing was neglected.

From expressions (1) and (2), it can be learned that once the infinite dilution activity coefficient of component i in the two phases ($\gamma_i^{M,\infty}$ and $\gamma_i^{S,\infty}$), the two phase compositions (x_j^M and x_j^S) and the molar volume of pure solvent j (V_{0j}) are known, the partition coefficient of the component i (K_i) can be calculated. The molar volume of pure solvent can be obtained easily from the literature, and also the phase composition can be obtained from phase equilibrium calculation by employing thermodynamic method such as the NRTL model. Therefore, for the calculation of the partition coefficient of a given solute, the main challenge encountered is how to determine the infinite dilute activity coefficient of the solute ($\gamma_i^{M,\infty}$ and $\gamma_i^{S,\infty}$) in both the stationary and mobile phase through a simple and reasonable method.

In the present study, the activity coefficient γ_i needed in Eq. (1) is determined from the NRTL model. The activity coefficient of component i in a solvent mixture can be expressed with NRTL equation [10] as:

$$\ln \gamma_i = \frac{\sum_j \tau_{ji} G_{ji} x_j}{\sum_k G_{ki} x_k} + \sum_j \frac{x_j G_{ij}}{\sum_k G_{kj} x_k} \left(\tau_{ij} - \frac{\sum_k x_k \tau_{kj} G_{kj}}{\sum_k G_{kj} x_k} \right) \tag{3}$$

where x_i is the mole fraction of solute i, and:

$$G_{ij} = \exp(-\alpha_{ij} \tau_{ij}); \quad \alpha_{ij} = \alpha_{ji} = 0.2 \tag{4}$$

where τ_{ij} is the interaction parameter between component i and j, and α_{ij} is the third non-randomness parameter that was set to 0.2 in this study. For some commonly used solvent system families, such as hexane/ethyl acetate/methanol/water and chloroform/methanol/water solvent system family, the NRTL binary
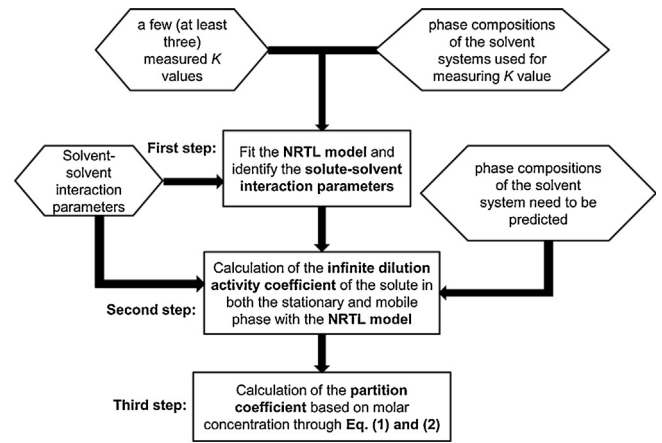

Fig. 1. Scheme of the procedure used for the calculation of partition coefficient; hexagon represent data input and rectangles represent calculations; NRTL, nonrandom two-liquid.

solvent–solvent interaction parameters have been reported in previous works [11,12]. Also if the phase equilibria data are available, one can easily determine the solvent–solvent interaction parameters through regression. Hence, we focus in the present study on how to determine the binary solute–solvent interaction parameters.

Determination of the solute–solvent interaction parameters involves regression of available experimental partition coefficients of the solute in a few biphasic liquid solvent systems. In the process of regression, the solvent–solvent parameters were taken from the literature or obtained through regression of available phase equilibria data. The solute–solvent binary interaction parameters (τ_{ij}) are the only adjustable parameters in the process of regression. The genetic algorithm (GA) method, a popular global optimization method, was used for the regression of NRTL parameters. The regression was performed with minimization of the root-mean square deviation of the partition coefficient for a given solute:

$$\text{RMSD} = \sqrt{\frac{1}{n} \sum_1^n (K_{i,cal} - K_{i,exp})^2} \tag{5}$$

where n is the number of data used for regression, $K_{i,exp}$ and $K_{i,cal}$ are the experimental partition coefficients and the calculated data, respectively.

Once the solute–solvent interaction parameters are identified, the infinite activity coefficient of the solute can be calculated from the NRTL model, and then the partition coefficient of the solute can be calculated through Eqs. (1) and (2). Fig. 1 presents the whole procedure for the calculation of the partition coefficient by using the NRTL method.

3. Experimental

3.1. Chemical and materials

Aspirin, coumarin, 2-mercapbenzimidazole, 8-hydroxyquinoline, salicylic acid and 2-(4-chlorophenoxy)-2-methylpropionic acid were purchased form TCI (Shanghai, China). The above compounds were used as model solutes for investigating and evaluating the performance of the NRTL model. The Chinese medicine *Malus hupehensis* was purchased from Yichang, China.

All organic solvents used for preparation of biphasic solvent system were analytical grade and purchased from Tianjin Hengxing Chemical Preparation Co. Ltd. (Tianjin, China). Methanol and acetonitrile used in high-performance liquid chromatography