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Thermodynamic analysis and correlation of solid–liquid equilibrium of hyodeoxycholic acid in ethanol + (acetone, ethyl acetate) binary solvent mixtures

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ABSTRACT

Data on corresponding solid–liquid equilibrium of hyodeoxycholic acid (HDCA) are essential for a preliminary study of industrial applications. In this paper, we focused on solubility and solution thermodynamics of HDCA. By gravimetric method, the solubility of HDCA was measured in ethanol + (acetone, ethyl acetate) binary solvent mixtures from 278.15 K to 328.15 K under atmospheric pressure. The data of equilibrium solubility were then fitted using modified Apelblat equation, a variant of the combined nearly ideal binary solvent/Redich–Kister (CNIBS/R–K) model and Jouyban–Acree model. In addition, the thermodynamic properties of the solution process, including the Gibbs energy, enthalpy, and entropy, were calculated by the van't Hoff analysis.

1. Introduction

Hyodeoxycholic acid (Fig. 1, $C_{24}H_{40}O_4$, CASRN: 83-49-8) is also known as 3α,6α-dihydroxy-5β-cholan-24-oic acid or HDCA, which is a secondary bile acid that is one of the metabolic byproducts of intestinal bacteria. It is widely used in treatment of hypertension and coronary artery disease [1,2]. Besides, HDCA was used as an anti-inflammatory drug to treat chronic bronchitis and infantile viral respiratory tract inflammation. More recently, HDCA is investigated for its propensity to prevent cholesterol-induced gallstones in animals fed with a lithogenic diet [3].

HDCA is mainly extracted from pig bile, and the extraction process is divided into saponification reaction and purification (decoloration, filtration, crystallization). Therefore, the solid–liquid equilibrium of HDCA plays an important role in purification. The solubility data laid the foundation for the later study in the solute crystallization process [4,5]. It is a process that requires adding an anti-solvent to the solution to reach a certain degree of saturation, resulting in solute precipitation. Based on the previous solubility data of HDCA in pure organic solvents, we choose binary solvents to reduce the saturation in the mother liquid. The significance of measuring solubility in binary solvents is to select the best anti-solvent for industrial production. Meanwhile, the cost and safety of the anti-solvents should be considered. So the solubility of HDCA in ethanol + (acetone, ethyl acetate) binary solvent mixtures was investigated across different temperature ranges in our study.

In this work, the solubility of HDCA in ethanol + (acetone, ethyl acetate) binary solvent mixtures was measured from 278.15 K to 328.15 K under atmospheric pressure. The modified Apelblat equation, CNIBS/R–K model and Jouyban–Acree model were applied to correlate with the experimental data. The thermodynamic properties of the dissolution process, including enthalpy, entropy and Gibbs energy, were calculated by means of van't Hoff analysis and Gibbs equation. This study aims to provide theoretical solubility data as a platform for manipulating the HDCA crystallization process.

2. Experimental

2.1. Materials and apparatus

Hyodeoxycholic acid, a white crystalline powder with a mass fraction purity of ≥0.980, was obtained from Aladdin Reagent Co., Ltd. Ethanol, acetone and ethyl acetate (Shanghai Shenbo Chemical Co., Ltd.) were of analytical reagent grade with a purity higher than 0.997. More details about the solvents along with their CAS registry numbers were listed in Table 1. Analytical balance (model CPA225D) was provided by Satorius Scientific Instrument (Beijing) Co., Ltd. with an uncertainty of ±0.00001 g. Smart thermostatic bath (model: DC-2006) was provided by Ningbo Scientz Biotechnology Co., Ltd. with an uncertainty of ±0.1 K.

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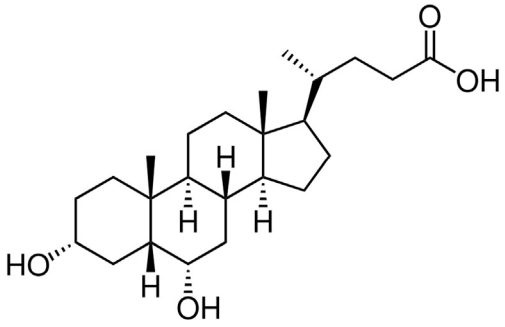

Fig. 1. Chemical structure of hyodeoxycholic acid.

2.2. Methods

The solid–liquid equilibrium data of HDCA in ethanol + (acetone, ethyl acetate) binary solvent mixtures were measured by the analytical stirred-flask method. 8 mL solvent mixtures and some excess HDCA were added into a 10 mL glass test tube with a stopper. The test tube was kept in a jacket glass vessel full of water, whose temperature was maintained at the desired value by circulating water through the outer jacket from a smart thermostatic water-circulator bath. Magnetic stirrers were used to mix the solid and solvent mixtures adequately. In order to ensure the solution reaching equilibrium, this stirring process should last at least 24 h. Then stop the magnetic stirrers and let the solution settle down, which would take another 6 h. Finally, a 1 mL supernatant solution was transferred into a 5 mL beaker with a cover and weighted immediately. Of course, this beaker had been weighted previously. All beakers were put into a dryer and weighted weekly until reaching constant weight. Each experiment was conducted three times, and the mean value was used to calculate the mole fraction solubility [6–8]. The mole fraction solubility of HDCA (x) in ethanol + (acetone, ethyl acetate) binary solvent mixtures is calculated by Eq. (1). The mole fraction of ethanol (x_A) in binary solvent mixtures is defined using Eq. (2).

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{1}$$

$$x_A = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \tag{2}$$

where m_1, m_2, and m_3 represent the mass of HDCA, ethanol, organic solvent (acetone or ethyl acetate), and M_1, M_2, and M_3 represent the molar mass of HDCA, ethanol, organic solvent (acetone or ethyl acetate), respectively.

3. Results and discussions

3.1. Solid–liquid equilibrium data

The solubility data of HDCA (x) in ethanol + (acetone, ethyl acetate) binary solvent mixtures with the temperature ranging from 278.15 K to 328.15 K are presented in Tables 2–3. In order to compare the solubility data under different conditions vividly, these data are presented in Figs. 2–3.

3.2. Thermodynamic models

3.2.1. Modified Apelblat equation

On the basis of the solid–liquid phase equilibrium theory, the changing trends of solubility data against temperature in the solvent with same ratio are described by the modified Apelblat equation. This model is firstly used by Apelblat [9,10], which can give a relatively accurate correlation with three parameters:

$$\ln x = A + \frac{B}{T/K} + C\ln(T/K) \tag{3}$$

where x represents the mole fraction solubility of HDCA, T is the experimental temperature in K, and A, B and C are the regression curve parameters which are listed in Table 4.

3.2.2. CNIBS/R–K model

The changing trends of solubility data against different ratios of ethanol under isothermal condition are described by the combined nearly ideal binary solvent/Redich–Kister (CNIBS/R–K) model [11–13], which is one of the theoretical models for calculating the solute solubility in binary solvents and is represented in Eq. (4):

$$\ln x = x_A \ln X_A + x_B \ln X_B + x_A x_B \sum_{i=0}^{N} S_i (x_A - x_B)^i \tag{4}$$

where x represents the mole fraction solubility of HDCA. x_A and x_B represent the initial mole fraction composition of binary solvent mixtures when the solute is not added. X_A and X_B represent the saturated mole solubility data of HDCA in pure ethanol and organic solvent (acetone or ethyl acetate), respectively. S_i is the model constant and N can be equal to 0, 1, 2 and 3. When N = 2 and substituting $(1 - x_A)$ for x_B, Eq. (4) can be rearranged as:

$$\begin{aligned}\ln x = {} & \ln X_B + (\ln X_B + S_0 - S_1 + S_2)x_A(-S_0 + 3S_0 - 5S_2)x_A^2 \\ & + (-2S_1 + 8S_2)x_A^3 + (-4S_2)x_A^4.\end{aligned} \tag{5}$$

This equation can be simplified as:

$$\ln x = B_0 + B_1 x_A + B_2 x_A^2 + B_3 x_A^3 + B_4 x_A^4. \tag{6}$$

This is a variant of the CNIBS/R–K model. The parameters B_i could be obtained by regressing.

The values of parameters are listed in Table 5. However, the CNIBS/R–K model can only be used to describe the solubility data and to predict solubility data for different concentrations of a mixed solvent at a fixed temperature. To describe the effect of both solvent compositions and temperature on the solubility of HDCA, we adopt another equation.

3.2.3. Jouyban–Acree model

This is a relatively more versatile model to describe the solubility of a solute with the variation of both temperature and initial composition of binary solvent mixtures [14]:

$$\ln x = x_A \ln X_A + x_B \ln X_B + x_A x_B \sum_{i=0}^{N} \frac{J_i (x_A - x_B)^i}{T} \tag{7}$$

Table 1
Mass fraction purities of hyodeoxycholic acid and solvents with CAS registry number.

Compound	Source	Mass fraction purity	CAS no.
Hyodeoxycholic acid	Aladdin Reagent Co., Ltd.	≥0.980	83-49-8
Ethanol	Shanghai Shenbo Chemical Co., Ltd.	≥0.997	67-56-1
Acetone	Shanghai Shenbo Chemical Co., Ltd.	≥0.997	67-64-1
Ethyl acetate	Shanghai Shenbo Chemical Co., Ltd.	≥0.997	141-78-6