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Solubilities of evodiamine in twelve organic solvents from $T = (283.2$ to $323.2)$ K

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ABSTRACT

The values of the solubility of evodiamine in chloroform, dichloromethane, acetone, ethyl acetate, 1-butanol, isopropanol, ethanol, methanol, ethyl ether, cyclohexane, *n*-pentane and *n*-hexane were measured at $T = (283.2, 293.2, 303.2, 313.2,$ and $323.2)$ K. The solubility of evodiamine in all the organic solvents studied increases with the increase of the temperature. The experimental solubility values were correlated by a simplified thermodynamic equation and the modified Apelblat equation. The values of the dissolution enthalpy and entropy of evodiamine in all organic solvents were calculated using the van't Hoff equation. The findings showed that the dissolution process was endothermic and entropy-driven. These data of solubility can be used to guide the processes of extraction, purification in the industry.

1. Introduction

Evodiae fructus (Chinese name: Wuzhuyu) is the dried, immature fruit of *Evodia rutaecarpa* (Juss.) Benth. Or *E. rutaecarpa* (Juss.) Benth. var. *officinalis* (Dode) Huang, and E. *rutaecarpa* (Juss.) Benth. var. *bodinieri* (Dode) Huang belong to the family Rutaceae. They are cultivated in East Asian nations including China, Korea, and Japan, and in recent years their extracts are exported to European countries from China [1,2]. *E. fructus* has been used for a long time as a traditional Chinese medicine for the treatment of gastrointestinal disorders, headache and postpartum hemorrhage [3]. Evodiamine (figure 1, CAS Registry Number 518-17-2) is a major alkaloidal component of *E. fructus* [4] and has been shown to exhibit antitumour, bronchocontractive, anti-nociceptive, catecholamine secretory, vasorelaxant and nitric oxide inductive properties [3,5].

Evodiamine is usually extracted from *E. fructus* by using various solvents and should be isolated from these extracts for some purpose [2]. Moreover, knowledge of (solid + liquid) equilibrium is very important for the design of separation and purification processes, and the development of models for prediction of drugs in various solvent [6–8]. Therefore, to obtain a high yield and separation efficiency by selecting the optimal solvent, knowledge of the solubility of evodiamine in various solvents is a prerequisite [9]. Only at $T = 298.15$ K, the solubility of evodiamine with different purities were measured in several solvents by Chen *et al.* [10]. However, to the best of our knowledge, the solubility of evodiamine in organic solvents have not been were not systematically demonstrated. Therefore, in this work, the solubility of evodiamine in chloroform, dichloromethane, acetone, ethyl acetate, 1-butanol, isopropanol, ethanol, methanol, ethyl ether, cyclohexane, *n*-pentane and *n*-hexane was measured at $T = (283.2, 293.2, 303.2, 313.2,$ and $323.2)$ K by a synthetic method and correlated by a simplified thermodynamic equation and the modified Apelblat equation.

2. Experimental

2.1. Materials

The evodiamine (mass fraction purity $\geqslant 0.98$) was purchased from Shaanxi Sciphar Biotechnology Co. Ltd, Shanxi, China (table 1), and used without further treatment. Its structure was identified by the UV and H NMR spectra, and the purity of evodiamine was checked by HPLC-DAD. All of the organic solvents were of analytical grade and purchased from the Damao Chemical Reagents Co., Tianjin, China and was used without further treatment.

2.2. Solubility measurements

The solubility was measured according to a literature method with some modification by using the high-performance liquid chromatography (HPLC) analysis method [8,9,11–14]. A vial with a rubber stopper was used to prepare saturated solutions (about 15 cm^3) of solute, in which excess solid solute was dissolved in the organic solvents. The vial was stoppered, sealed up with tape, and fastened with a rubber band to prevent evaporation of the

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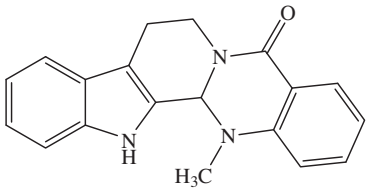

FIGURE 1. Structure of evodiamine.

TABLE 1
The sample provenance and mass fraction purity of evodiamine.

Sample	Provenance	Mass fraction purity[a]
Evodiamine	Shananxi Sciphar Biotechnology Co. Ltd., Shanxi, China	⩾0.98

[a] The purity of evodiamine was checked by HPLC-DAD.

solvents. Then the vial was placed in a low temperature thermostatic reaction bath (type DFY5/40, China) with an uncertainty of ±0.1 K. The solution was stirred by an electric magnetic stirrer, and the temperature of the system was determined by a microthermometer (type 60-11, shanghai science chemical plant, China) with an uncertainty of ±0.1 K. The vial was allowed to settle for about 48 h to ensure equilibrium and stand for 4 h before sampling. For each vial, three samples of approximately (0.1 to 0.5) cm^3 were withdrawn from the clear saturated solution with the preheated glass syringes. The glass syringes with saturated solution were weighed on an analytical balance (type FA1104 N, Shanghai, China) with an uncertainty of ±0.1 mg. To prevent evaporation of the solvent during the weighing process, the needle was closed with silicon rubber. The saturated solution was injected into the volumetric flasks (10 cm^3) immediately to prevent precipitation. After that, the mass of the glass syringes with the remaining solution was weighed, and the mass of the saturated solution in the volumetric flasks can be determined. The sample solution was diluted to the mark prior to HPLC determination. Each experiment was repeated at least twice to check the repeatability of the solubility determination, and three samples were taken for each solvent at each temperature. In this work, the measuring relative uncertainty of the experimental solubility value was within ±5%.

2.3. HPLC conditions

The concentrations of evodiamine were determined by using HPLC (Agilent 1100, Agilent Technologies, USA). The HPLC system was composed of a vacuum degasser (type G1379A), a quaternary pump (type G1311A), an autosampler (type G1313A), and a diode-array detector (type G1315A). The detection wavelength was 225 nm. The separation column was a Hypersil BDS-C18 column (4.6 × 200 mm, 5 μm) with a mobile phase composed of methanol and water in a volume ratio of 68:32 at a flow rate of 1.0 $cm^3 \cdot min^{-1}$. The temperature of the column was 303.2 K. The injected volume of each sample was 0.010 cm^3.

3. Results and discussion

The solubility data of evodiamine in chloroform, dichloromethane, acetone, ethyl acetate, 1-butanol, isopropanol, ethanol, methanol, ethyl ether, cyclohexane, *n*-pentane and *n*-hexane at various temperatures are presented in table 2, respectively (see also figure 2). The values of the solubility of evodiamine in dichloromethane, ethyl ether and *n*-pentane was measured below $T = 303.2$ K, because these solvents have a lower boiling point. The result revealed that the solubility of evodiamine in all selected solvents increased with the increase of the temperature.

To find a proper equation to represent the solubility values for evodiamine, a simplified thermodynamic equation and the modified Apelblat equation were used in this paper. According to the (solid + liquid) phase equilibrium theory, the relationship between solubility and temperature is described as [15]

$$\ln\left(\frac{1}{\gamma_x x}\right) = \frac{\Delta_{fus}H}{RT_t}\left(\frac{T_t}{T}-1\right) - \frac{\Delta C_p}{R}\ln\left(\frac{T_t}{T}-1\right) + \frac{\Delta C_p}{R}\ln\left(\frac{T_t}{T}\right), \quad (1)$$

where γ_x is the activity coefficient of Evodiamine on a mole fraction basis, x the mole fraction solubility of evodiamine in the organic solvent, $\Delta_{fus}H$ the fusion enthalpy of evodiamine, ΔC_p the heat capacity difference between the solid and the liquid forms of evodiamine, T the equilibrium temperature (K), T_t the triple point temperature, and R is the gas constant, respectively. After equation (1) is simplified [14,16,17], the simplified thermodynamic equation (equation (2)) can be obtained from equation (1)

$$\ln x = \frac{A}{T/K} + B, \quad (2)$$

where A and B are parameters. The data for solubility of evodiamine in different solvents were correlated with equation (2), and the results are given in table 3, together with the root-mean-square deviations (rmsd's) which are defined as equation (3)

$$rmsd = \left[\frac{\sum_{i=1}^{n}(x_i^c - x_i)^2}{n}\right]^{1/2}, \quad (3)$$

where n was the number of experimental points; $x^c{}_i$ and x_i was the calculated and experimental solubility of evodiamine, respectively.

The solubility of the evodiamine as a function of temperature was also correlated by the modified Apelblat equation (equation (4)) [13,18–25]

$$\ln(x) = a + \frac{b}{T/K} + c\ln(T/K), \quad (4)$$

where a, b, and c are the parameters of the equation. The parameters of a, b, and c were obtained by using a non-linear regression and are presented in table 3, together with the root-mean-square deviations (rmsd's) calculated by equation (3).

From table 3, it can be found that equations (2) and (4) can be used to correlate the experimental results of the solubility of the evodiamine in the organic solvents at different temperatures. Equation (2) is a simplified thermodynamic equation with two parameters. Equation (4) is the modified Apelblat equation with three parameters. Comparing the fitted results, we can see that the correlated results of equation (2) are a little better.

For real solutions, the logarithm of mole fraction of a solute is a linear function of the reciprocal of the absolute temperature, which could be described as the van't Hoff equation (equation (5)) [22,26–29]:

$$\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R}, \quad (5)$$

where x is mole fraction solubility, ΔH_d and ΔS_d are the dissolution enthalpy and entropy, respectively, T is absolute temperature, and R is the gas constant. The van't Hoff equation plots obtained from the linear fit of ln x versus $1/T$ are shown in figure 3. The solution enthalpy and entropy of evodiamine in pure solvents shown in table 3 could be calculated from the slope and intercept of these plots. According to table 4, the course of evodiamine dissolving in each solvent within the experimental temperature range was endothermic. The positive ΔH_d and ΔS_d revealed that the dissolution of evodiamine in each solvent was an entropy-driven process.