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Measurement and correlation of the solubility of antipyrine in ten pure and water + ethanol mixed solvents at temperature from (288.15 to 328.15) K

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ABSTRACT

The aim of this experiment is to obtain new antipyrine solubility data and the correlation equation parameters and thermodynamic parameters of the dissolution process. The solubility of antipyrine was experimentally measured in ten mono-solvents (methanol, ethanol, acetone, *n*-propanol, isopropanol, methyl acetate, *n*-butanol, isobutanol, ethyl acetate, water) and binary mixed solvents (ethanol–water) at 288.15 to 328.15 K using a gravimetric method under atmospheric pressure. In addition, the experimental solubility in the mono- and mixed solvents was correlated using the λh equation, modified Apelblat equation, nonrandom two-liquid equation, Wilson equation, and van't Hoff equation. Good agreement was found between the experimental values and correlation values calculated by all the selected equations. The thermodynamic parameters, Gibbs energy (ΔG°_{sol}), molar enthalpy of dissolution (ΔH°_{sol}), and molar entropy of dissolution (ΔS°_{sol}) were also calculated. These experimental results are crucial for optimization of the antipyrine crystallization process.

1. Introduction

Antipyrine (CAS: 60-80-0), a colorless crystal or white crystalline powder, is an important pharmaceutical intermediate and analytical reagent. Its formula is $C_{11}H_{12}N_2O$, and its relative molecular mass is 188.23 g/mol. The chemical structure of antipyrine is presented in Fig. 1.

Antipyrine (AT) is a well-known analytical reagent for nitric acid, nitrous acid, iodine, and elements that form complex cations. Therefore, more stringent requirements for crystallization of antipyrine are needed. More importantly, antipyrine is an important intermediate of Analgin. The synthesis route of Analgin is shown in Fig. 2 [1, 2]. Owing to its ease of use, efficacy, low cost, and diverse dosage forms, Analgin plays an important role in clinical medicine [3]. The literature shows that 4,4′-two methylene antipyrine methane, the single impurity present in the largest quantities in Analgin, is produced during the production of antipyrine [4]. Therefore, it is essential to remove this impurity from antipyrine; thus, it is vital to study the crystallization process of antipyrine. It is well known that understanding the solid–liquid equilibrium data of target substances in various solvents and at multiple temperatures points is particularly important for studying the crystallization process effectively [5–8].

In this experiment, the solubility of antipyrine in mono-solvents (methanol, ethanol, acetone, *n*-propanol, isopropanol, methyl acetate, *n*-butanol, isobutanol, ethyl acetate, and water) and binary mixed solvents from 288.15 to 328.15 K at atmospheric pressure was measured. In addition, the experimental antipyrine solubility in the mono- and mixed solvents was correlated using the Wilson, λh, van't Hoff, nonrandom two-liquid (NRTL), and modified Apelblat equations. Furthermore, the entropy change (ΔS°_{sol}), Gibbs free energy change (ΔG°_{sol}), and enthalpy change (ΔH°_{sol}) in the dissolution of antipyrine in the mono- and mixed solvents were calculated.

2. Experimental section

2.1. Materials

Antipyrine was purchased from Beijing HWRK Chem Co., Ltd. The chemical was used without prior treatment. The solvents for the experiment are analytical research-grade reagents with mass fraction purities exceeding 0.995, and they were purchased from Beijing Chemical Works of China. The water was obtained from an

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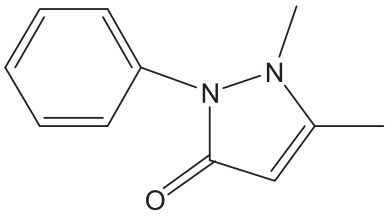

Fig. 1. Chemical structure of antipyrine.

ultrapure water machine. The details of the chemicals are listed in Table 1.

2.2. Differential scanning calorimetry

The melting temperature T_m and heat of fusion $\Delta_{fus}H$ were measured as the basic thermal characteristics by a differential scanning calorimetry (DSC) instrument (TGA/DSC1/1600LF, Mettler Toledo Co., Switzerland) under nitrogen atmosphere. Approximately 5.8 mg of antipyrine was added to a hermetically sealed DSC pan and heated from 288.15 to 328.15 K at a rate of 20 K/min. The standard uncertainty for T_m is 0.2 K [9, 10]. The melting point of antipyrine was 111.9 K. $\Delta_{fus}H$ was 118 J/g. The DSC curve is shown in Fig. 3.

2.3. Measurement of the solubility of antipyrine

The gravimetric method was used to measure the solubility of antipyrine in mono-solvents and mixed solvents at atmospheric pressure. Excess solute was added to a 100 mL conical flask containing approximately 40 mL of a solvent [11]. The conical flask was brought to a certain temperature using sonication in a water bath (Shanghai Yiheng Scientific Instrument Co., Ltd.) for 72 h. The solution was then allowed to settle for 12 h to reach solid–liquid equilibrium. Then, the supernatant was removed and filtered, and the filtrate was poured into an evaporating dish that had been weighed by an analytical balance (Sartorius CP124S, Germany) with an accuracy of ±0.0001 g. Finally, the samples were dried in a vacuum drying oven (Tianjin Taisite Instrument Co., Ltd.) and weighed [12]. All experiments were repeated three times to obtain the mean values [13].

3. Theoretical basis

3.1. Solubility equations

The mole fraction solubility of antipyrine (x_1) in mono solvents is calculated by Eq. (1) [14].

$$x_1 = \frac{m_1/M_1}{m_1/M_2 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the mass of the antipyrine and solvent, M_1 and M_2 are the respective molar mass.

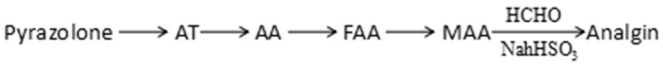

Fig. 2. Synthesis route of Analgin.

Table 1
Purity and sources of experimental chemicals.

Chemical	Mass fraction purity	Source
Antipyrine	99%	Beijing HWRK Chem Co., Ltd.
Methanol	≥99.5%	Beijing Chemical Works, China
Ethanol	≥99.5%	Beijing Chemical Works, China
n-Propanol	≥99.5%	Beijing Chemical Works, China
Isopropanol	≥99.5%	Beijing Chemical Works, China
n-Butanol	≥99.5%	Beijing Chemical Works, China
Isobutanol	≥99.5%	Beijing Chemical Works, China
Acetone	≥99.5%	Beijing Chemical Works, China
Methyl acetate	≥99.5%	Beijing Chemical Works, China
Ethyl acetate	≥99.5%	Beijing Chemical Works, China
Water		Double-distilled in lab

The mass fraction of ethanol (w) in mixed solvents varied from 0.1 to 0.9 in intervals of 0.1. The mass fraction of ethanol inmixed solvents is obtained by Eq. (2).

$$w = \frac{m_3}{m_2 + m_3} \tag{2}$$

where m_2 and m_3 represent the mass of water and ethanol, respectively.

The mole fraction solubility of antipyrine (x_1) in different ethanol concentration of the mixed solvents at different temperatures is obtained by Eq. (3).

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{3}$$

where m_1, m_2 and m_3 represent the mass of antipyrine, water and ethanol; M_1, M_2 and M_3 are the relative molecular weight of antipyrine, water and ethanol.

The experimental solubility of antipyrine in mono and mixed solvents were presented in Tables 2 and 3, with the corresponding graph plotted in Figs. 4 and 5.

3.2. Correlation equations

The modified Apelblat equation, Wilson equation, NRTL equation, van't Hoff equation and λh equation are used to correlate the solubility of antipyrine in mono and binary mixtures solvents. The obtained equation parameters can be used to predict the solubility of antipyrine in

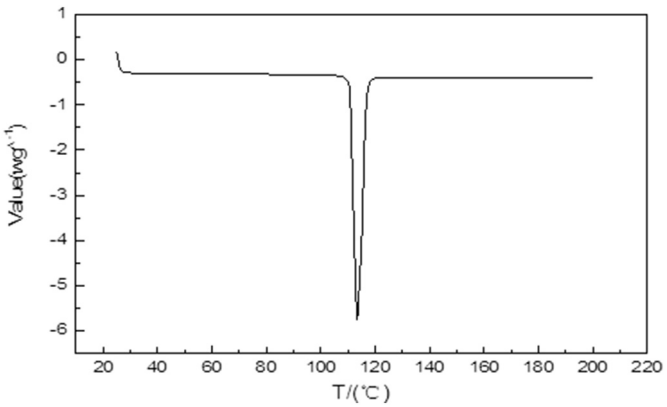

Fig. 3. DSC spectrum of antipyrine.