Fluid Phase Equilibria 427 (2016) 549–556

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Determination and correlation of solubility and solution thermodynamics of ethenzamide in different pure solvents

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ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form
11 August 2016
Accepted 11 August 2016
Available online 13 August 2016

Keywords:
Ethenzamide
Solubility
Solution thermodynamics
Mixing thermodynamic properties

ABSTRACT

The solubility of ethenzamide in methanol, ethanol, 1-propanol, isobutanol, ethyl acetate and acetonitrile was determined via the gravimetric method in the temperature range from 288.15 K to 323.15 K at atmospheric pressure. Five thermodynamic models were employed to correlate the experimental solubility data. The correlated results were analyzed and compared with the experimental results. It was found that all the thermodynamic models give satisfactory correlation results, in which the modified Apelblat model shows the best fitting result. In addition, the molecular modeling studies were carried out to give the explanation for the sequence of solubility in various solvents. The dissolution enthalpy and entropy of ethenzamide were obtained by using the Van't Hoff equation. Furthermore, the mixing thermodynamic properties of ethenzamide, including the mixing Gibbs energy, the mixing enthalpy and entropy, as well as the infinite-dilution activity coefficient and the infinitesimal concentration reduced excess enthalpy, were also obtained by using the Wilson model and the experimental solubility values.

1. Introduction

In the past decades, crystallization has been an essential separation and purification technologies in the industry, which affects the quality and quantity of the final products especially in the pharmaceutical field [1,2]. Among the factors concerning crystallization, solubility is one of the most significant physicochemical properties. It is intensely beneficial to the study of drugs in biological, chemical, pharmaceutical and environmental industries [3,4]. Therefore, accurate solubility data of chemicals is indispensable for process and product design.

Ethenzamide (2-ethoxybenzamide, CAS: 938-73-8, shown in Fig. 1) is an extremely poorly water soluble nonsteroidal anti-inflammatory drug, which is mainly used for the treatment of mild to moderate pain, combination with other ingredients such as acetaminophen, aspirin, dipyrone, allylisopropylacetylurea, caffeine, and ibuprofen [5–7]. Crystallization process is crucial in the production and purification process of ethenzamide to improve the performance. In order to design an optimum crystallization strategy for ethenzamide, it is vital to obtain its complete physicochemical data such as solubility and dissolution enthalpy in different solvents. However, from the point of literatures review, there is no report regarding the solution thermodynamics, especially the solubility data of ethenzamide in most of organic solvents.

In this work, the solubility of ethenzamide in various solvents (methanol, ethanol, 1-propanol, isobutanol, ethyl acetate and acetonitrile) at temperatures ranging from (288.15–323.15) K at atmospheric pressure was measured by using the gravimetric method. According to the solubility data, the thermodynamic analysis and correlation of solubility of ethenzamide were studied in details. The experimental results were correlated by five thermodynamic models, including the modified Apelblat equation, Van't Hoff equation, λh equation, Wilson model and NRTL model. In addition, study about molecular simulation was carried out to interpret the sequence of solubility of ethenzamide in the selected solvents. Furthermore, to better identify the dissolution behavior of ethenzamide in the appointed solution, solution thermodynamic data involving the mixing Gibbs energy, mixing enthalpy and mixing entropy was calculated on the basis of the Wilson model.

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http://dx.doi.org/10.1016/j.fluid.2016.08.019
0378-3812/

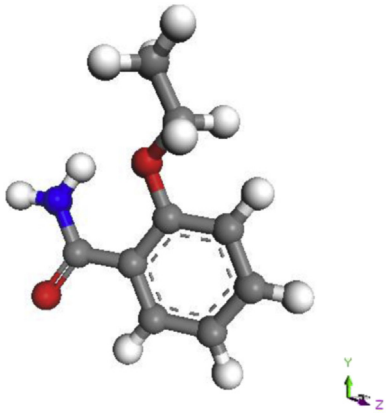

Fig. 1. Sketch of the molecular structure of ethenzamide.

2. Experimental

2.1. Materials

Ethenzamide (mass fraction purity > 0.990) was purchased from Alfa Aesar. The analytic reagent grade of methanol, ethanol, 1-propanol, isobutanol, ethyl acetate and acetonitrile (mass fraction purity >0.995) used in this work were purchased from Tianjin Jiangtian Chemical Co. Ltd., China. All chemicals were used directly as supplied by the manufacturers without further purification. The detailed information of the materials is listed in Table 1.

2.2. X-ray diffraction analysis

Powder X-ray diffraction (PXRD) was carried out to identify the crystal form of ethenzamide used in the experiments. The PXRD patterns were measured on Rigaku D/MAX 2500 diffractometer (Cu Kα radiation, 1.5406 Å) at 100 mA and 40 kV. The measurements were performed at 2θ degrees from 2° to 50°, with a scanning rate of 8°/min.

2.3. Differential scanning calorimetry

The melting temperature (T_{melt}) and enthalpy of fusion ($\Delta_{fus}H$) of ethenzamide were measured by Differential scanning calorimetry (DSC 1/500, Mettler-Toledo, Switzerland). About 5.0 mg of ethenzamide was used and the heating rate was 10 K/min under the protection of nitrogen.

2.4. Solubility measurements

The gravimetric methods [8–10] were employed to measure the solubility of ethenzamide. Firstly, the excessive ethenzamide was added into various organic solvents (methanol, ethanol, 1-propanol, isobutanol, ethyl acetate and acetonitrile). Experiments were carried out in several 50 mL sealed Erlenmeyer flasks. The temperature (from 288.15 to 323.15 K) was controlled by a constant-temperature water bath, with an uncertainty of ±0.06 K. The solution was kept shaking for at least 24 h to ensure that the thermodynamic equilibrium was reached. Then static settlement of the suspension was arranged for 5 h to ensure the solid precipitated. After that, 2 mL samples of the upper clear solution were collected by using a pre-heated (or pre-cooled) syringe and filtered through a 0.45 μm membrane into a pre-weighed Petri dish and weighed them again quickly. Finally, the sample was dried in the vacuum oven (DZF-6020, Shanghai Yi Heng Scientific Instrument Co., Ltd., China) at 323.15 K for 18 h until the weight remained constant and the ultimate weight was determined. All the masses in this study were weighted employing an analytical balance (Satorius model TE214S, Switzerland) with an accuracy of ± 0.0001 g. Each experiment was carried out three times and the average value was used as the final result. The residual bottom solids were filtered and characterized by PXRD and DSC.

The mole fraction (x_1) of ethenzamide was calculated as follows:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

Where m_1 and m_2 stand for the mass of ethenzamide and solvent (methanol, ethanol, 1-propanol, isobutanol, ethyl acetate and acetonitrile), respectively. M_1 and M_2 represent the molar mass of ethenzamide and solvents, respectively.

2.5. Simulation methods

Previously, DMol^3 module in Materials Studio was successfully employed to analyze the experimental solubility sequence of various compounds in different solvents [4,11–13]. In this study, molecules of ethenzamide and different solvents were optimized by using the density functional theory method with the generalized gradient approximation (GGA) and the Perdew-Burke-Ernzerhof (PBE) functional form [14]. A double numerical polarized (DNP) basis set was employed [15] which was equivalent to 6-31G* basis set. The convergence criteria of the self-consistent-field calculation was 10^{-5} Hartree, the tolerances of energy, maximum force, and maximum displacement for the geometry optimization were 1.0×10^{-4} au, 0.02 au, and 0.05 au, respectively. The geometry of all involving molecules was optimized at this level, and the interaction energy was defined as:

$$E_{inter} = E_{eth-sol} - E_{eth} - E_{sol} \quad (2)$$

where E_{eth}, E_{sol}, and $E_{eth\text{-}sol}$ are the total energies of ethenzamide,

Table 1
The detailed information of all the materials used in this work.

Chemicals	Molar mass ($g \cdot mol^{-1}$)	Polarity (water 100)[a]	Molar volume ($cm^3 \cdot mol^{-1}$)	Source	Mass fraction purity
Ethenzamide	165.19		123.30[b]	Alfa Aesar	>0.990
Methanol	32.04	76.2	40.40[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995
Ethanol	46.07	65.4	58.68[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995
1-propanol	60.10	61.7	75.14[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995
Isobutanol	74.12	55.2	92.91[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995
Ethyl acetate	88.11	23.0	98.50[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995
Acetonitrile	41.05	46.0	52.86[a]	Tianjin Jiangtian Chemical Co. Ltd.	>0.995

[a] Literature data from Ref. [29].
[b] Literature data from Ref. [31].