Chinese Journal of Chemical Engineering 22 (2014) 1141–1144

Contents lists available at ScienceDirect

Chinese Journal of Chemical Engineering

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

Chemical Engineering Thermodynamics

Determination and Correlation of Solubility of Nonivamide in Different Solvents☆

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ARTICLE INFO

Article history:
Received 20 December 2012
Received in revised form 13 April 2013
Accepted 6 May 2013
Available online 4 September 2014

Keywords:
Solubility
Nonivamide
Hydrogen-bonding interaction
Modified Apelblat equation
van't Hoff plotting

ABSTRACT

The solubility of nonivamide in dimethyl sulfoxide, methanol, acetone, ethyl acetate, methyl *tert*-butyl ether, acetonitrile, *n*-hexane and water over the temperature range of 293.2 K to 323.2 K was measured. The results reveal that the solubility of nonivamide is greatly influenced by the hydrogen-bond basicity of solvent and increases with temperature. The experimental data were correlated with the modified Apelblat equation. The dissolution enthalpy and entropy of nonivamide in different solvents were obtained from the correlation of ln$x$ with 1/T using the van't Hoff equation. The calculated nonivamide solubility is in good agreement with experimental data for most of the solvents.

1. Introduction

Nonivamide (CAS Registry Number 2444-46-4, molecular weight 293.4, Fig. 1) is a minor constituent of capsicum oleoresin [1]. It shows many biological and pharmacological effects, such as antibacterial, anti-inflammatory, and analgesic [2–4]. It is considered as an alternative of capsaicin, because it is similar to capsaicin structurally and biologically [5], and could be easily manufactured synthetically, costing less than the natural capsaicin isolated from capsicum. The solubility of nonivamide in solvents is of great importance for separation and purification of nonivamide. However, as far as we know, no experimental solubility data of pure nonivamide in organic solvents or water have been reported.

In this study, the solubility of nonivamide in eight solvents over the temperature range of 293.2 K to 323.2 K was measured, including polar amphiprotic solvent methanol, polar aprotic solvents dimethyl sulfoxide (DMSO), acetone, ethyl acetate, acetonitrile and methyl *tert*-butyl ether (MTBE), non-polar aprotic solvent *n*-hexane, and highly polar solvent water. The experimental solubility data were explained on the basis of the solvatochromic parameters of the solvents and correlated with the modified Apelblat equation and the van't Hoff equation.

2. Experimental

2.1. Materials

Nonivamide was obtained from Hangzhou Great Forest Biomedical Ltd. (China), with purity higher than 99.6% [High Performance Liquid Chromatography(HPLC)]. Methanol, acetone, ethyl acetate, MTBE, acetonitrile and *n*-hexane were purchased from Tedia (USA) and were of HPLC grade with a mass fraction over 99.5%. DMSO was purchased from Sinopharm Chemical Reagent Co., Ltd. (China) and was of analytical grade with a mass fraction over 99.0%. The deionized water was obtained from Hangzhou Wahaha Group Co., Ltd. (China).

2.2. Apparatus and procedure

The solubilities of nonivamide in DMSO, methanol, acetone, ethyl acetate, methyl *tert*-butyl ether and acetonitrile were determined by a dynamic method [6]. The experiments were carried out in a magnetically stirred, jacketed glass vessel (about 15 cm^3). A constant temperature was maintained by circulating water through the outer jacket from a thermostatically controlled bath (uncertainty of ±0.1 K). The actual temperature in the vessel was measured by a microthermometer with an uncertainty of ±0.01 K. For solubility measurements, predetermined mass of nonivamide was weighed by an electronic balance with an accuracy of ±0.0001 g and transferred into the vessel. The solvent was added dropwise to the vessel in the early stage of the experiment, and towards the end of experiments, 10 μl solvent was added to the vessel each time until the solute was completely dissolved, which was

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☆ Supported by the National Natural Science Foundation of China (20936005, 21222601) and the National High Technology Research and Development Program of China (2012AA040211).

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http://dx.doi.org/10.1016/j.cjche.2013.05.001
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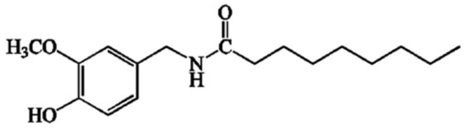

Fig. 1. Molecular structure of nonivamide.

Table 1
Mole fraction solubility of nonivamide in different solvents

T/K	x_i	$10^2[(x_i - x_i^{cal}) / x_i]$	x_i	$10^2[(x_i - x_i^{cal}) / x_i]$
	DMSO		methanol	
293.2	0.2565	2.78	0.2189	−4.75
298.2	0.3149	−2.60	0.2801	0.30
303.2	0.4032	−0.60	0.3492	2.81
308.2	0.4947	0.05	0.4278	3.78
313.2	0.5945	1.41	0.4893	−1.82
318.2	0.6712	−0.81	0.5834	−3.16
323.2	0.7628	0.08	0.7363	1.46
	acetone		ethyl acetate	
293.2	0.1613	−0.27	0.0625	−7.23
298.2	0.2287	1.55	0.1168	−2.28
303.2	0.2988	−1.2	0.1987	1.08
308.2	0.3901	−0.64	0.3088	2.83
313.2	0.4988	1.03	0.421	−1.39
318.2	0.6001	−0.36	0.566	−0.38
323.2	0.7144	0.03	0.7124	0.27
	MTBE		acetonitrile	
293.2	0.019	−5.53	0.0118	−16.85
298.2	0.0472	−18.46	0.0357	−17.38
303.2	0.1142	−13.48	0.0943	−11.12
308.2	0.2697	6.49	0.2318	6.08
313.2	0.4275	2.60	0.3799	0.08
318.2	0.5693	−3.50	0.5532	−1.54
323.2	0.7289	1.04	0.7143	0.29
	n-hexane		water	
293.2	0.4063×10^{-4}	15.15	0.1636×10^{-4}	1.04
298.2	0.6996×10^{-4}	4.83	0.1926×10^{-4}	−1.01
303.2	0.1192×10^{-3}	0.30	0.2320×10^{-4}	0.16
308.2	0.1893×10^{-3}	−4.1	0.2706×10^{-4}	−0.98
313.2	0.2965×10^{-3}	−2.76	0.3235×10^{-4}	1.15
318.2	0.4573×10^{-3}	3.50	0.3701×10^{-4}	−0.24
323.2	0.5951×10^{-3}	−0.99	0.4270×10^{-4}	−0.06

observed visually. The solution was stirred constantly using a magnetic stirrer. The sample was taken by a preheated glass dropper and transferred into a pre-weighted volumetric flask. Then, the total mass of the sample and flask was weighed using the electronic balance. After that, the sample was diluted with methanol for HPLC analysis.

For very low solubilities of nonivamide in hexane and water, the dynamic method was not applicable and the static equilibrium method was used. The procedure was described in our previous work [7,8]. The experiments were carried out in a magnetically stirred, jacketed glass vessel (about 150 cm^3), in which the temperature was controlled to be constant by circulating water through the outer jacket from a thermostatically controlled bath (uncertainty of ±0.1 K). A microthermometer was used to measure the actual temperature in the vessel with an uncertainty of ±0.01 K. For each measurement, an excess mass of nonivamide was added to a known amount of solvent. To prevent solvent volatilization, a cold-water condenser tube was connected to the vessel. The solution was stirred constantly using a magnetic stirrer for 10 h to reach phase equilibrium and then allowed to settle for at least 4 h before sampling. The upper clear phase was withdrawn using a preheated glass syringe, transferred into a pre-weighed volumetric flask, weighed using the electronic balance, then appropriately diluted and analyzed by HPLC.

To validate the methods of solubility measurement, the solubility of KCl in water was determined in the temperature range of 293.2 K to 323.2 K by both methods and the solubilities obtained are similar to the values reported in literature [9]. Each experiment was repeated three times and the average value was reported. The deviations of the solubility data were all less than 6% with the dynamic method and less than 5% with the static equilibrium method.

2.3. Sample analysis

To determine the solubility of nonivamide, an HPLC system (Waters, US) equipped with a 1525 HPLC pump, a 717 plus autosampler and a 2487 UV detector set at 280 nm was used. Separation of nonivamide was performed using an X-Bridge C18 column (150 mm × 3.9 mm I.D., 5 μm, Waters) at 30 °C. The mobile phase was a methanol/water (70/30, by volume) mixture with a flow rate of 1 $ml \cdot min^{-1}$.

3. Results and Discussion

The mole fraction solubility of nonivamide in DMSO, methanol, acetone, ethyl acetate, MTBE, acetonitrile, *n*-hexane and water at temperatures ranging from 293.2 K to 323.2 K is listed in Table 1.

The chemical structure of nonivamide in Fig. 1 shows that nonivamide molecule contains a benzene ring, a hydrogen-bond acidic phenolic hydroxyl group, a hydrogen-bond basic amide group and a hydrophobic alkyl chain. Based on the results and the solvatochromic parameters of the solvents (dipolarity/polarizability π^*, hydrogen-bond acidity α and hydrogen-bond basicity β) [10,11], the relation between the solubility of nonivamide and the hydrogen-bond basicity of organic solvent is given in Fig. 2. The solubility of nonivamide increases with the increase of hydrogen-bond basicity of solvent. As DMSO exhibits high hydrogen-bond basicity, the solubility of nonivamide in DMSO is higher than that in other solvents.

The hydrogen-bond basicity of solvent is a key factor, but is not the only factor to determine the solubility. The high solubility of nonivamide in methanol could be partly ascribed to the high hydrogen-bond acidity of the solvent, which could enhance the Hydrogen-bonding interaction strength between solute and solvent. The low dipolarity/polarizability of MTBE decreases the dissolution of nonivamide in it. Although the hydrogen-bond basicity value of MTBE is equal to that of ethyl acetate, the solubility of nonivamide in MTBE is lower than that in ethyl acetate. The low solubility of nonivamide in hexane may result from the fact that weak interaction forms between hexane and nonivamide. Of all the solvents studied, water shows the lowest solubility; one possible explanation is that the hydrophobic groups in nonivamide make the hydrophobic interaction a key factor that determines the solubility of nonivamide in water.

The results reveal that the experimental solubility of nonivamide increases with temperature. The differences among the solubilities of

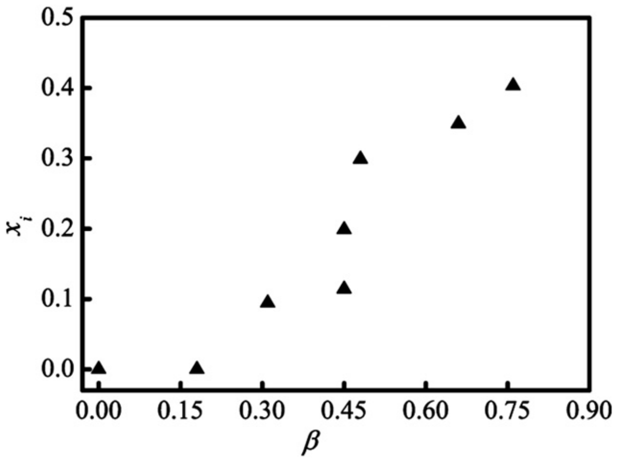

Fig. 2. Mole fraction solubility of nonivamide in different solvents at 303.2 K *versus* the hydrogen-bond basicity of solvent.