Journal of Molecular Liquids 216 (2016) 771–780

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Thermodynamic solubility of tetraethyl ranelate in ten organic solvents at different temperatures

Wanxin Li [a], Jinting Chen [a], Shuo Han [b], Cunbin Du [b], Hongkun Zhao [b,*]

[a] Jiangsu Provincial Key Laboratory of Coastal Wetland Bioresources and Environmental Protection, Yancheng Teachers University, Yancheng, Jiangsu 224002, PR China
[b] College of Chemistry & Chemical Engineering, YangZhou University, YangZhou, Jiangsu 225002, PR China

ARTICLE INFO

Article history:
Received 19 September 2015
Accepted 2 February 2016
Available online xxxx

Keywords:
Tetraethyl ranelate
Solubility
Thermodynamic model
Dissolution property

ABSTRACT

The solubility of tetraethyl ranelate in cyclohexane, 1-butanol, *n*-propanol, isopropanol, ethanol, methanol, toluene, ethyl acetate, acetonitrile and acetone were measured by a high-performance liquid phase chromatograph at temperatures from 283.15 to 323.15 K under 0.1 MPa. The solubility of tetraethyl ranelate in the selected solvents increase with an increase in temperature. The solubility data in acetone, ethyl acetate, acetonitrile and toluene are larger than those in the other solvents. In general, they follow the order for all the studied solvents: (acetone, ethyl acetate) > (acetonitrile, toluene) > methanol > *n*-propanol > ethanol > 1-butanol > isopropanol > cyclohexane. The modified Apelblat equation, λ*h* equation, Wilson model and NRTL model were employed to correlate the obtained solubility data. The four models all provided good precision for the systems of tetraethyl ranelate in the solvents. Based on the solubility determined in this work, the dissolution and mixing properties, including the change of molar Gibbs energy, molar enthalpy, and molar entropy for saturated solutions of tetraethyl ranelate were calculated, and the dissolution process of tetraethyl ranelate in these solvents was discussed.

1. Introduction

Tetraethyl ranelate (CAS No. 58194-26-6),also named as 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-2-(ethoxycarbonyl)-3-thiopheneacetic acid ethyl ester, is an important intermediate in the synthesis of strontium ranelate [1–9], which has very valuable properties of pharmacology and therapy, especially distinct anti-osteoporotic properties. The chemical structure of tetraethyl ranelate is shown in Fig. 1.

A lot of investigations were made for production of tetraethyl ranelate in previous publications [10–17]. The main method of producing tetraethyl ranelate comprises two steps of: (a) reacting malononitrile with acetone dicarboxylate to acquire intermediate (ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophenecarboxylate), and (b) reacting the intermediate with sulfur in ethanol to obtain the tetraethyl ranelate. The crude product contains some unreacted material (ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophenecarboxylate), which limits its further application in many fields. In order to obtain higher purity of tetraethyl ranelate, the crude product must be purified by solvent crystallization. It is well known that the solubility data are of importance in the separation process of tetraethyl ranelate. The crystallization process of tetraethyl ranelate requires a large amount of accurate solubility data. Unfortunately, physicochemical information on its solubility in solvent is very scarce, the dependence of solubility of tetraethyl ranelate on temperature is not available in previous publications. As a result, obtaining the accurate solubility data of the tetraethyl ranelate in different solvents and the thermodynamic properties of solutions are quite necessary to determine the crystallization process and increase the purity and yield of tetraethyl ranelate.

The aims of the present work are to (1) measure the solubility data of tetraethyl ranelate in cyclohexane, 1-butanol, *n*-propanol, isopropanol, ethanol, methanol, toluene, ethyl acetate, acetonitrile and acetone at temperatures of 283.15 to 323.15 K, (2) fit the solubility data with the modified Apelblat equation, λ*h* equation, Wilson model and NRTL model, and (3) calculate the dissolution and mixing thermodynamic properties for tetraethyl ranelate in selected solvents.

2. Experimental section

2.1. Materials

The tetraethyl ranelate (purity 0.984 in mass fraction) was provided by Shanghai Xuxin Chemical Technology Co., Ltd. It was recrystallized four times with acetone to produce a purified sample having a purity of 0.996, which was further checked by a high-performance liquid phase chromatograph. The solvents, including cyclohexane, 1-butanol, *n*-propanol, isopropanol, ethanol, methanol, toluene, ethyl acetate, acetonitrile and acetone with analytical grade were purchased from Merck

* Corresponding author.
E-mail address: hkzhao@yzu.edu.cn (H. Zhao).

http://dx.doi.org/10.1016/j.molliq.2016.02.002
0167-7322/

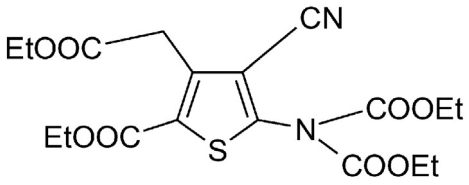

Fig. 1. Chemical structure of tetraethyl ranelate.

and used without further refining. The details of these materials are presented in Table 1.

2.2. Melting properties measurement

Although the melting temperature *T*m of tetraethyl ranelate was determined in the literatures [18–20], the melting enthalpy $\Delta_{fus}H$ was not reported. In the present paper, the melting enthalpy $\Delta_{fus}H$ of tetraethyl ranelate was obtained by using a differential scanning calorimetric instrument (Pyris-Diamond, PerkinElmer) under a nitrogen atmosphere. The temperature and heat flow of the DSC instrument were precalibrated by using indium as the reference materials before experiment. About 4 mg of tetraethyl ranelate was introduced to a DSC pan, and then the sample was heated with a heating rate of 2 $K \cdot min^{-1}$ at temperatures ranging from 313 to 500 K. The standard uncertainties of the experiments for the temperature were estimated to be 0.5 K for temperature and 400 $J \cdot mol^{-1}$ for the melting enthalpy.

2.3. Solubility determination

During the experiment, the solution temperature was controlled by employing a smart thermostatic water bath (model, DZKW-4; standard uncertainty: 0.02 K), which was produced by Ningbo Scientz Biotechnology Co., Ltd. An analytical balance (standard uncertainty: 0.0001 g) was used to weigh the mass of the solvent, solute and saturated solution.

The solubility of tetraethyl ranelate under 0.1 MPa in the temperature range from 283.15 to 323.15 K were analyzed by a high-performance liquid phase chromatograph. They were determined by equilibrating excessive tetraethyl ranelate in the selected solvents. The mixture of an excessive amount of tetraethyl ranelate and solvent was put into an Erlenmeyer flask with a volume of about 50 mL. The temperature of the Erlenmeyer flask equipped with a magnetic stirrer was maintained constant by circulating water from the smart thermostatic water bath by the outer jacket. The actual temperature was displayed through a mercury glass micro thermometer (standard uncertainty: 0.02 K) placed into the inner chamber of the Erlenmeyer flask. In order to prevent the solvent from volatilizing, a condenser was attached to the Erlenmeyer flask. The mixture was stirred continuously for 30 h. For assurance of equilibrium, the liquid phase was got out at intervals of two hours with a 0.2 μm pore syringe filter and analyzed by a high-performance liquid phase chromatograph. The system was believed to be in equilibrium if two analysis results were identical. Results indicated that 11 h was sufficient to attain system equilibrium. Once the solution reached equilibrium, the magnetic agitation was stopped to allow any solid to be settled from the solution. About 3 mL (standard uncertainty: 0.01 mL) of equilibrium upper liquid was extracted with a 5 mL syringe equipped with a 0.2 μm pore filter which was preheated in the thermostatic water bath, and then transferred instantly into a glass flask of 25 mL. The flask was covered with a rubber stopper, and weighed with the analytical balance, and then diluted using corresponding solvent. 1 μL of the sample solution was taken out to analyze by means of the high-performance liquid phase chromatograph. After the solubility was measured at a temperature, the remaining solution containing excess solid was heated to another temperature, and the determination procedure was carried out repeatedly.

2.4. Analysis

The content of equilibrium liquid phase was determined by a Shimadzu-6A high-performance liquid phase chromatograph (HPLC), which was equipped with a Shimadzu SPD-6A UV single wavelength spectrophotometric detector. The type of column was a unimicro Kromasil C18, 5 μm (250 mm × 4.6 mm) and the column temperature was set to 308 K. The wavelength of the detector was set to 322 nm. The mobile phase was pure methanol. The relative standard uncertainty of the measurement is less than 2.1% in mole fraction. Each experiment was performed three times, and the mean value was regarded as the final solubility data.

Table 1
Source and purity of the materials used in the work.

Chemicals	Molar mass	Melting point	Melting molar enthalpy	Density	Source	Purification method	Mass fraction purity	Analysis method
	$g \cdot mol^{-1}$	K	$kJ \cdot mol^{-1}$	$kg \cdot m^{-3}$				
Teraethyl ranelate	454.49	376.53[a] 378–379[b] 376–379[c] 376[d]	33.60[a]	1281[e]	Wuhan Fortuna Chemical Co., Ltd	Recrystallization	0.996	HPLC[g]
Cyclohexane	84.16			778.4[f]	Sinopharm Chemical Reagent Co., Ltd., China	None	0.995	GC[h]
1-Butanol	74.12			810.5[f]		None	0.995	GC
n-Propanol	60.01			804.8[f]		None	0.997	GC
Isopropanol	60.06			786.9[f]		None	0.996	GC
Ethanol	46.07			790.5[f]		None	0.997	GC
Methanol	32.04			792.5[f]		None	0.995	GC
Toluene	92.14			867[f]		None	0.998	GC
Ethyl acetate	88.11			900.6[f]		None	0.995	GC
Acetonitrile	41.05			982[f]		None	0.998	GC
Acetone	58.08			789[f]		None	0.996	GC

[a] This work, determined under 0.1 MPa. The standard uncertainties *u* are $u(p) = 350$ Pa, $u(\Delta_{fus}H) = 400\ J \cdot mol^{-1}$.
[b] Taken from ref. [18].
[c] Taken from ref. [19].
[d] Taken from ref. [20].
[e] This work, determined at 293.15 K and 0.1 MPa. The standard uncertainties *u* are $u(T) = 0.02$ K, $u(p) = 350$ Pa, $u(\rho) = 0.9\ kg \cdot m^{-3}$.
[f] Taken from ref. [22].
[g] High-performance liquid phase chromatograph.
[h] Gas chromatography.