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Solubility and solution thermodynamics of ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophenecarboxylate in nine organic solvents at evaluated temperatures

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ABSTRACT

Knowledge of solubility for ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophenecarboxylate (ACET) in different solvents is essential for its purification and further theoretical studies. In this paper, the solubility of ACET in selected pure solvents, including methanol, ethanol, 1-butanol, *n*-propanol, isopropanol, toluene, ethyl acetate, acetonitrile and acetone were acquired by a high-performance liquid chromatography (HPLC) at T = (273.15, 278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, 313.15 and 318.15) K under pressure of 0.1 MPa. Generally, they obeyed the following order from high to low in different solvents: acetone > ethyl acetate > acetonitrile > methanol > ethanol > isopropanol > *n*-propanol > 1-butanol > toluene. The obtained solubility data of ACET in selected solvents were correlated by the van't Hoff equation, modified Apelblat equation, λh equation, Wilson model and NRTL model. The correlated values of the five equations agreed well with the experimental values and the Wilson model gives better correlation results than other models. Furthermore, the standard dissolution enthalpy and excess enthalpy for dissolution process of ACET were calculated from the experimental solubility by using the van't Hoff equation. The solubility values of ACET in different solvents and thermodynamic relations would be invoked as fundamental data and models regarding the crystallization process of ACET.

1. Introduction

Ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophene carboxylate (also named as ACET, CAS No. 58168-20-0, structure shown in figure 1) is often used in preparation of tetraethyl ranelate, which is an important intermediate in the synthesis of anti-osteoporosis drugs [1–12]. In the present publications, many methods have been proposed to prepare ACET [13–17]. During the production process of ACET, however, some by-products (unknown at present) are also generated. The obtained product is a mixture of ACET, unknown by-product and unreacted raw materials. The crude product restricts its further use in many fields. A valuable method to purify ACET with low cost is solvent crystallization [13–18]. During the purification process of ACET by using solvent crystallization, the solubility data has a direct effect on the purity and quality of the final product. Therefore, the solubility of ACET in different solvents and dissolution thermodynamic properties are important factors in the optimisation process of crystallization. Nevertheless, to the best of the authors' present knowledge, many studies have been focused on the production of ACET, few has been tried to construct purification methods to achieve high purity products. Moreover, physicochemical information on its solubility in solvents is very scarce. The aims of this work are to (1) measure the melting enthalpy of ACET at 0.1 MPa; (2) determine the solubility of ACET in different organic solvents at temperatures ranging from (273.15 to 318.15) K (generally, crystallization of ACET in solvents is performed in the temperature range) using the method of high-performance liquid phase chromatograph, (3) correlate the solubility results with different thermodynamic models, and (4) calculate the dissolution thermodynamic properties (dissolution enthalpy and excess enthalpy) from solubility for the dissolution process of ACET in solvents.

2. Experimental

2.1. Materials

Ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophene carboxylate provided by Shanghai Xuxin Chemical Technology Co., Ltd and having a mass fraction of 0.985 was recrystallized

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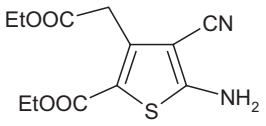

FIGURE 1. Chemical structure of ACET.

three times in acetone. The content of the purified sample was determined by high-performance liquid phase chromatograph (HPLC), which had a purity of 0.997 in mass fraction. All the solvents including methanol, ethanol, 1-butanol, *n*-propanol, isopropanol, toluene, ethyl acetate, acetonitrile, acetone and trichloromethane with analytical grade were purchased from Merck and used without additional purification. The detailed information of these materials was presented in table 1.

2.2. Melting and density properties measurements

The melting temperature T_m of ACET was determined previously [19–20], however the difference between them is a large (T = 410.15 K, determined by Wierzbicki [19]; and T = (401.15 to 402.15) K, by Wei [20]). In addition, the fusion enthalpy $\Delta_{fus}H$ of ACET has not been reported so far. In the present work, the melting enthalpy $\Delta_{fus}H$ of ACET was obtained by means of a differential scanning calorimetric instrument (Pyris-Diamond, PerkinElmer) under a nitrogen atmosphere. Before experiment, the DSC instrument was pre-calibrated with indium as the reference material. About 4 mg of ACET was placed in a DSC pan, and then the sample was heated with a heating rate of T = 2 K·min^{-1} at temperatures ranging from (350 to 550) K. The standard uncertainty for T_m is 0.5 K and for $\Delta_{fus}H$, 400 J·mol^{-1}.

The density of ACET was measured by using the flotation method [21] at T = 298.15 K. The measurement was carried out in a glass stoppered tube of about 15 mm diameter, which was immersed in a small water-bath with transparent windows in the sides. The temperature of the water-bath was controlled by a smart thermostatic water unit (model: DZKW-4) with a standard uncertainty of T = 0.02 K provided by Ningbo Scientz Biotechnology Co., Ltd. Trichloromethane and 1-butanol were employed in density determination because of lower solubility of ACET in the two solvents. Ten (10.00) mL of trichloromethane and a certain quantity of ACET were put into the glass tube, and then 1-butanol was added drop wise from the burette. After each 1-butanol addition, the contents of the tube were mixed completely. 1-Butanol was added until the solid ACET was suspended in the liquid mixture. The density of ACET equalled to that of the liquid mixture.

2.3. Solubility determination

The solubility of ACET were determined by the high-performance liquid chromatography (HPLC) [22–24] under 0.1 MPa in the temperatures range from (273.15 to 318.15) K. The temperature of solutions was regulated by employing the smart thermostatic water bath. The mass of the solvent, solute and saturated solution was weighed by an analytical balance (standard uncertainty: 0.0001 g).

The experimental saturated solutions were prepared in an Erlenmeyer flask by adding excess ACET in a solvent with a volume of about 50 mL. A condenser was attached to the Erlenmeyer flask to prevent the solvent from volatilising. The temperature of the Erlenmeyer flask equipped with a magnetic stirring was kept at a constant by circulating water from the smart thermostatic water bath through the outer jacket. The real temperature was shown by a mercury glass micro thermometer (standard uncertainty: 0.02 K) immersed into the inner chamber of the Erlenmeyer flask. For assurance of equilibrium, the solution was agitated continuously for 30 h. The liquid phase was taken out every two hours with a 0.2 μm pore syringe filter, and then analysed by HPLC. We believed the system was in equilibrium if two analytical results were the same. Results showed that 18 h was enough to make the system equilibriate. When the mixture arrived at equilibrium, the agitation was stopped for thirty minutes to allow any solid to be settled from the mixture. About 3 mL (standard uncertainty: 0.01 mL) of upper clear liquid was taken out with a 5 mL syringe equipped with a 0.2 μm pore filter, which was pre-heated in the thermostatic water bath. The sample was transferred instantly into a glass flask of 25 mL covered with a rubber stopper, weighed using the analytical balance, diluted with the same solvent, and then taken out to test using HPLC. Once the solubility was measured

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

Chemicals	Molar mass/ g·mol^{-1}	Melting temperature/ K	Melting molar enthalpy/ kJ·mol^{-1}	Density/ kg·m^{-3}	Source	Purification method	Mass fraction purity	Analysis method
Ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophenecarboxylate	282.32	410.05[a] 410.15[b] 401.15–402.15[c]	40.88[a]	1297[d]	Shanghai Xuxin Chemical Technology Co., Ltd	Recrystallization	0.997	HPLC[f]
1-Butanol	74.12			810.5[e]	Merck	None	0.995	GC[g]
n-Propanol	60.01			804.8[e]		None	0.997	GC
Isopropanol	60.06			786.9[e]		None	0.996	GC
Ethanol	46.07			790.5[e]		None	0.997	GC
Methanol	32.04			792.5[e]		None	0.995	GC
Toluene	92.14			867[e]		None	0.998	GC
Ethyl acetate	88.11			900.6[e]		None	0.995	GC
Acetonitrile	41.05			982[e]		None	0.998	GC
Acetone	58.08			789[e]		None	0.996	GC
Trichloromethane	119.38			1480[e]		None	0.994	GC

[a] This work was determined under 0.1 MPa. The standard uncertainty u are $u(T)$ = 0.5 K, $u(p)$ = 450 Pa, $u(\Delta_{fus}H)$ = 400 J·mol^{-1}.
[b] Taken from references [19,20,34], respectively.
[c] Taken from references [19,20,34], respectively.
[d] This work was determined at T = 298.15 K and 0.1 MPa. The standard uncertainty u are $u(T)$ = 0.02 K, $u(p)$ = 450 Pa, $u(\rho)$ = 0.9 kg·m^{-3}.
[e] Taken from references [19,20,34], respectively.
[f] High-performance liquid chromatography.
[g] Gas chromatography.