Int J Thermophys (2018) 39:7
DOI 10.1007/s10765-017-2323-6

Solubility Determination and Modeling and Dissolution Thermodynamic Properties of Raspberry Ketone in Binary Solvent Mixtures of Ethanol and Water

Min Shu[1] · Liang Zhu[1] · Yan-fei Wang[1] · Jing Yang[1] · Liyu Wang[1] · Libin Yang[1] · Xiaoyu Zhao[1] · Wei Du[1]

Received: 13 March 2017 / Accepted: 24 October 2017

Abstract The solubility and dissolution thermodynamic properties of raspberry ketone in a set of binary solvent mixtures (ethanol + water) with different compositions were experimentally determined by static gravimetrical method in the temperature range of 283.15–313.15 K at 0.10 MPa. The solubility of raspberry ketone in this series of ethanol/water binary solvent mixtures was found to increase with a rise in temperature and the rising mole fraction of ethanol in binary solvent mixtures. The van't Hoff, modified Apelblat and 3D Jouyban–Acree–van't Hoff equations were increasingly applied to correlate the solubility in ethanol/water binary solvent mixtures. The former two models could reach better fitting results with the solubility data, while the 3D model can be comprehensively used to estimate the solubility data in all the ratios of ethanol and water in binary solvent mixtures at random temperature. Furthermore, the changes of dissolution thermodynamic properties of raspberry ketone in experimental ethanol/water solvent mixtures were obtained by van't Hoff equation. For all the above experiments, these dissolution processes of raspberry ketone in experimental ethanol/water binary solvent mixtures were estimated to be endothermic and enthalpy-driven.

Keywords 3D Jouyban–Acree–van't Hoff model · Binary solvent mixtures · Dissolution thermodynamic properties · Gravimetric method · Raspberry ketone · Solubility

✉ Liang Zhu
zhuliang@tust.edu.cn

[1] Tianjin Key Laboratory of Marine Resources and Chemistry, College of Material Science and Chemical Engineering, Tianjin University of Science and Technology, Tianjin 300457, People's Republic of China

Published online: 20 November 2017

1 Introduction

4-(4-hydroxyphenyl)-2-butanone (Raspberry ketone, $C_{10}H_{12}O_2$, CAS Registry No. 5471-51-2) as drawn in Fig. 1 has fruity perfume. For this reason, it is widely applied in the fields of edible food additive, perfumery, cosmetic and medicine [1]. Raspberry ketone is mainly extracted from red raspberry, and its anti-obese activity is as three times as capsaicin's [2]. Moreover, it is also conducive to enhance skin elasticity and promote hair growth as it can raise dermal IGF-I production in our bodies [3–5]. In Industry, the present preparation method of raspberry ketone mostly has focused on the polycondensation reaction by using raw materials of acetone and p-hydroxybenzaldehyde [6]. During the whole manufacturing process, crystallization plays a significant role in controlling the purity of raspberry ketone [7].

At this stage, the synthesis reaction of raspberry ketone is the main research content [8–10], but there is lack of thermodynamic data that can guide crystallization experiments. According to the relevant research reports and our daily experiment about raspberry ketone, it can provide a guidance that raspberry ketone is slightly soluble in distilled water while it is freely soluble in pure ethanol at the atmospheric temperature [11]. But the outbreak of nucleation will occur in a short time in the saturated solutions at 323.15 K during the cooling crystallization process from 323.15 K to 298.15 K in pure ethanol according to our daily experimental phenomenon. So co-solvents containing different compositions of water and ethanol could be applied in crystallization to purify raspberry ketone with good crystal morphology at low cost. Therefore, to improve the quality and reduce costs of raspberry ketone's purification process, the solubility in ethanol/water binary solvent mixtures is essential to be ascertained.

To measure the solubility of solute in experimental solvents, the most widely used method is static gravimetrical method [12–15]. Although the dynamic method takes less time to attain the solubility data, the final sample of raspberry ketone cannot be detected and disappears timely. As to raspberry ketone sample, it always floats on the surface of the solvents. So it is hard for the laser probe which is inserted to the solution to detect the dissolution processes of all samples . For this reason, the dynamic method is not suitable to precisely measure the solubility data of raspberry ketone in our experimental solvents. But the static method can solve this problem. The solubility data is determined through analyzing the solid and liquid phase composition in the equilibrium saturated solution which was withdrawn by a syringe with filter membrane. Therefore, the static gravimetrical method was utilized to determine the solubility of raspberry ketone in ethanol/water solvent mixtures.

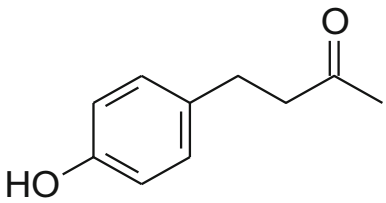

Fig. 1 Schematic diagram of molecular structure of raspberry ketone

In this work, the solubility of raspberry ketone in a set of ethanol/water binary solvent mixtures at the temperature range from 283.15 K to 313.15 K was determined by static gravimetrical method. The experimental data in ethanol/water binary solvent mixtures were correlated by three models of van't Hoff, modified Apelblat and 3D-Jouyban–Acree–van't Hoff equations [16–18]. The 3D figure about the solubility of raspberry ketone measured in this work was drawn to vividly describe the variation trend. Finally, all the changes of dissolution thermodynamic properties of raspberry ketone in these experimental ethanol/water solvent mixtures were evaluated by the van't Hoff equation.

2 Experiments

2.1 Materials

The raspberry ketone sample used in this work was kindly provided by Bestally Biological Technology Co., Ltd. (Zhangzhou, China). Then it was purified by recrystallization from the ethanol and water binary mixtures and dried in vacuum at 323.15 K. Its final purity was tested by high-performance liquid chromatography (HPLC) with a mass fraction $\geqslant$ 0.996. In the experiments, ethanol (mass fraction $\geqslant$ 0.995) which was purchased from Bolt Chemical Trade Co., Ltd. (Tianjin, China) was used without further purification. The distilled water used in our experiments was made by distillation in the laboratory. The above information of all the experimental materials is listed in detail in Table 1.

2.2 Apparatus and Experiment

2.2.1 Characterization of Raspberry Ketone Sample

The polymorphism of raspberry ketone during the experiment processes including heating and stirring was tested by X-ray powder diffraction (XRPD). It was implemented on Puxi XD-3 automatic diffractometer system at the set experimen-

Table 1 The descriptions of experimental materials used in this paper

Chemical name	Source	Purification method	Mass fraction purity	Analysis method
Raspberry ketone	Bestally Biological Technology Co., Ltd. (Zhangzhou, China)	Recrystallization	$\geq$ 0.996	HPLC[a]
Ethanol	Bolt Chemical Trade Co., Ltd. (Tianjin, China)	No further	$\geq$ 0.995	GC[b]
Water	Laboratory	Distillation	Distilled-deionized water	–

[a] High performance liquid chromatography
[b] (Gas + liquid) chromatography

tal conditions: Cu K $\alpha(\lambda = 1.54187$ Å) radiation, scan range from 5° to 60°, scan step $\Delta 2\theta = 0.02$, scan speed 2°/min, tube voltage 36 kV and current 20 mA, respectively. The raw material and excess solid in ethanol/water solvent mixtures were analyzed by XRPD.

Melting properties (onset melting temperature T_m and enthalpy of fusion ΔH_{fus}) of the raspberry ketone sample were acquired by differential scanning calorimetry (NETZSH DSC-200F3) with a heating rate of $10\,K \cdot min^{-1}$ to provide a better understanding of the changes in energy with the rising temperature during the melting process. And onset melting temperature T_m was necessary to guide the determination of the experimental temperature range and the evaporation temperature to avoid the sample melting. The measurement experiments were repeated for three times in the temperature range from 313.15 K to 373.15 K.

2.2.2 Solubility Measurements of Raspberry Ketone Sample

All the experiments were conducted in an automatic crystallization reactor (EasyMax 102, Mettler Toledo, Switzerland) with a volume of 50 mL. Firstly, different ratios of the co-solvents of ethanol and water were prepared and added into the container with a lid at the top. After that, the crystallizer was maintained at the setting temperature with an accuracy of 0.05 K. Then excessive amount of raspberry ketone was added into the glass container. The mixture was continuously stirred for 16 h to reach solid–liquid equilibrium. The equilibrium time was determined in our preliminary experiment by sampling 1 mL solution with the uncertainty of ± 0.01 mL with filter membrane and measuring its weight every 30 min until the weight was constant. Then stirring was stopped for 4 h to allow the excess solid particles in the equilibrium solution to precipitate completely. After that the supernatant in the container was extracted by a syringe with a filter membrane (0.50 μm) and rapidly injected into a pre-weighed 10 mL evaporating dish with a lid. Finally, the evaporating dish with the mixture was weighed immediately and placed into a vacuum oven at $T = 323.15$ K until the weight remained constant. By analyzing the masses of dissolved solute and the ethanol/water binary solvent mixtures in the equilibrium saturated solution, the solubility data of raspberry ketone could be determined in experimental ethanol/water binary solvent mixtures.

The masses of raspberry ketone samples and solvents which were used during the experiment were weighed by an analytical balance (CP114, Ohaus Corp, USA) with an uncertainty of ± 0.0001g. To get better accuracy, every experiment was repeated three times.

The mole fraction (x_1) of raspberry ketone dissolved in the ethanol/water binary solvent mixtures was calculated by Eq. 1 [19]:

$$x_1 = \frac{m/M}{m/M + \sum (m_s/M_s)} \tag{1}$$

where m is the mass of raspberry ketone dissolved in the mixed solvent. m_s is the masses of pure solvents of ethanol and water used in the binary solvent mixtures, respectively. M and M_s represent the corresponding molecular masses of them.

2.3 Thermodynamic Models

In this work, the solubility value of raspberry ketone in experimental ethanol/water solvent mixtures was correlated by the following thermodynamic models which contain van't Hoff, modified Apelblat and Jouyban–Acree–van't Hoff equations.

2.3.1 van't Hoff Model

In general, van't Hoff equation can be used to describe the relative relationship between the solubility of experimental solute and temperature. It is expressed as a linear relationship between the natural logarithm of solubility data of solute dissolved in experimental solvent and the reciprocal of experimental temperature [20]:

$$\ln x_1 = A + \frac{B}{T} \tag{2}$$

where x_1 in Eq. 2 is mole fraction solubility of solute in the experimental solvent. A and B are the two constants of van't Hoff equation which can be calculated by the software of origin.

2.3.2 The Modified Apelblat Equation

The modified Apelblat equation is based on the solid–liquid equilibrium theory. It is a commonly used semi-empirical model to correlate solubility of solute and experimental temperature. Their relationship can be generally expressed as Eq. 3 [21,22]:

$$\ln x_1 = a + \frac{b}{T} + c \ln T \tag{3}$$

where x_1 in Eq. 3 represents the mole fraction solubility of solute dissolved in the solvent mixtures. a, b and c are the constants of modified Apelblat equation which can be attained by correlation of solubility data.

2.3.3 The 3D Jouyban–Acree–van't Hoff Model

The Jouyban–Acree model is a relatively comprehensive model to correlate the solubility with solvent composition and temperature simultaneously. The Jouyban–Acree equation is commonly described in Eq. 4 [17]:

$$\ln x_1 = x_2 \ln(x_1)_{2,T} + x_3 \ln(x_1)_{3,T} + \frac{x_2 x_3}{T} \sum_{i=0}^{2} J_i (x_2 - x_3)^i \tag{4}$$

where x_1 in Eq. 4 is the mole fraction solubility of solute dissolved in binary solvent mixtures of ethanol and water at T. x_2 and x_3 are the mole fraction of ethanol and water in pre-prepared ethanol/water solvent mixtures, respectively. $(x_1)_{2,T}$ and $(x_1)_{3,T}$ are the mole fraction solubility data of solute in pure solvents of ethanol and water at T,

respectively. J_i refers to the constant of Jouyban–Acree model used in this text [23]. i stands for the number of experimental pure solvent and equals to 0, 1, 2 in this work.

Then a combination model of Jouyban–Acree and van't Hoff has been put forward to provide more comprehensive presentation of the relationship between solubility of solute and temperature in mixed ethanol/water solvents.

$$\ln x_1 = x_2\left(A_2 + \frac{B_2}{T}\right) + x_3\left(A_3 + \frac{B_3}{T}\right) + \frac{x_2 x_3}{T}\sum_{i=0}^{2} J_i (x_2 - x_3)^i \tag{5}$$

where A_2, B_2 and A_3, B_3 are the constant parameters of van't Hoff model of solute in pure solvents (ethanol, water), respectively, at temperature T.

Then 3D Jouyban–Acree–van't Hoff equation can be simplified as:

$$\ln x_1 = k_0 + k_1/T + k_2 x_2 + \left(k_3 x_2^4 + k_4 x_2^3 + k_5 x_2^2 + k_6 x_2\right)/T \tag{6}$$

where k_0 to k_6 are the model parameters calculated by MATLAB.

3 Results and Discussion

3.1 Characterization Results of Raspberry Ketone Sample

3.1.1 XRPD Pattern of Raspberry Ketone Sample

The original raspberry ketone sample and the excess sample after stirring at experimental temperature were characterized by X-ray powder diffraction (XRPD). The contrast result is displayed in Fig. 2. Seen from it, there is no new diffraction peak, which explains that the crystal form of raspberry ketone does not change during all the dissolution process. In other words, the polymorphism has not occurred during the experiment.

3.1.2 Melting Properties of Raspberry Ketone Sample

The melting temperature (T_m) and enthalpy of fusion (ΔH_{fus}) of raspberry ketone were measured by DSC. As detailedly demonstrated in Fig. 3, T_m and ΔH_{fus} of raspberry ketone are about 355.0 K ($n = 3$, n is defined as the number of experiments; the uncertainty is U = 0.5 K, 0.95 confidence interval) and 24.7 kJ · mol^{-1} ($n = 3$, the uncertainty is U = 0.1 kJ · mol^{-1}, 0.95 confidence interval), respectively. The deviation is specified as the mean standard deviation of three times of experiments. The onset melting temperature of raspberry ketone is defined as the intersection of left tangent of the crest and the horizontal line. The value of it is consistent with the reported value in the literature (355.15 K to 356.15 K) [24]. The result means that the samples of raspberry ketone used in this work are quite pure to attain the accurate solubility data of raspberry ketone. So the experimental temperature should be set below the onset melting temperature of raspberry ketone.

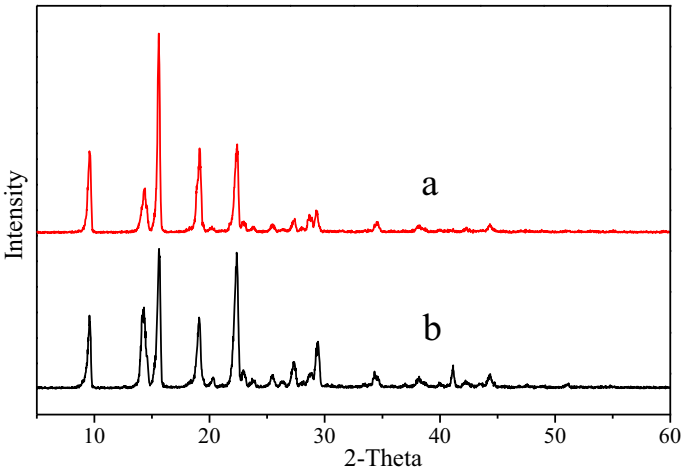

Fig. 2 X-ray powder diffraction patterns of raspberry ketone in different conditions: (a) raw material; (b) excess solid in (ethanol + water) binary solvents

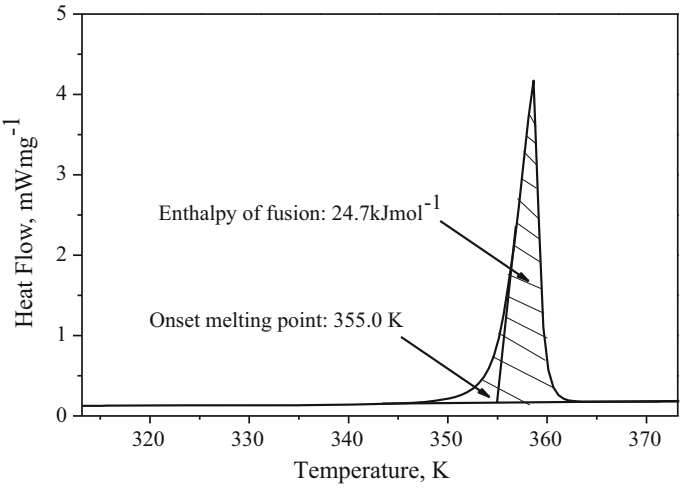

Fig. 3 DSC thermogram of raspberry ketone sample

In addition, the value of the entropy of fusion (ΔS_{fus}) was estimated to be 69.6 J $\cdot$ $\mathrm{mol}^{-1}\cdot\mathrm{K}^{-1}$ ($n = 3$, the uncertainty is $\mathrm{U} = 0.2\,\mathrm{J}\cdot\mathrm{mol}^{-1}\cdot\mathrm{K}^{-1}$, 0.95 confidence interval) by using the following equation [25]:

$$\Delta S_{\mathrm{fus}} = \frac{\Delta H_{\mathrm{fus}}}{T_{\mathrm{m}}} \tag{7}$$

3.2 Solubility Data of Raspberry Ketone in Ethanol/Water Binary Solvent Mixtures

The solubility data of raspberry ketone in the binary system of ethanol and water at different temperatures are listed in Table 2 and plotted in Fig. 4 which shows that the experimental solubility (x_1) of raspberry ketone is found to increase with rising temperature. In addition, the solubility also increases with a rise in mole fraction of ethanol in the ethanol/water binary solvent mixtures at the experimental temperature, which is in accordance with the research that raspberry ketone is freely soluble in ethanol and is slightly soluble in water.

3.3 The Parameter Estimation and Error Analysis of Three Thermodynamic Models

In this work, the root-mean-square deviation (RMSD) was calculated to evaluate and compare the applicability and advantages of three models [15].

$$\mathrm{RMSD} = \left[\frac{1}{N}\sum_{i=1}^{N}\left(x_i - x_i^{\mathrm{cal}}\right)^2\right]^{1/2} \tag{8}$$

$$\mathrm{ORMSD} = \frac{1}{M}\sum_{i=1}^{M}\mathrm{RMSD} \tag{9}$$

where x_i is the experimental solubility data and x_i^{cal} is the calculated solubility data of raspberry ketone, which i stands for the solvent in which the solubility data of raspberry ketone measured. N is the number of experimental points which is seven per set experiments and M is the number of the different ratios solvents which is eight in this study.

The parameter estimation and error analysis of three thermodynamic models which cover van't Hoff, modified Apelblat and Jouyban–Acree–van't Hoff equations are calculated and listed in Tables 3, 4 and 5 correspondingly. The van't Hoff equation and Apelblat equation can only describe the trend of solubility versus the temperature, while the 3D Jouyban–Acree–van't Hoff equation could indicate the solubility of raspberry ketone at different T in ethanol/water binary solvent mixtures of full range of compositions. The van't Hoff model is better to correlate the experimental solubility data of raspberry ketone: the value of 10^3 ORMSD is 3.59 which is less than other two models'. And the 3D Jouyban–Acree–van't Hoff equation can be well correlate the solubility data at $x_2 > 0.2001$ in ethanol/water binary solvent mixtures. For a lower fraction of ethanol in ethanol/water binary mixtures, the results of the error analysis indicate that the 3D Jouyban–Acree–van't Hoff model may bring little errors to the value of solubility. But it can predict the solubility of raspberry ketone in all kinds of compositions of binary solvent (ethanol + water) at any temperature.

As to the relative deviations between the experimental data and the values calculated by van't Hoff model and modified Apelblat model, Fig. 5 is visually displayed which is in accordance with the error analysis in Tables 3, 4 and 5.

Table 2 Experimental and correlated mole solubility of raspberry ketone with different initial mole fraction of ethanol (x_2) in ethanol + water solvent mixtures from 283.15 K to 313.15 K under 0.1 MPa

T/K	$10^2 x_1^{\mathrm{b}}$	$10^2 x_1^{\mathrm{cal}}$		
		van't Hoff	Modified Apelblat	3D Jouyban–Acree–van't Hoff
$x_2 = 0.0000$				
283.15	0.0532	0.0534	0.0544	0.0316
288.15	0.0702	0.0684	0.0688	0.0489
293.15	0.0867	0.0868	0.0867	0.0746
298.15	0.1060	0.1093	0.1087	0.1121
303.15	0.1386	0.1366	0.1358	0.1662
308.15	0.1698	0.1695	0.1690	0.2433
313.15	0.2085	0.2088	0.2095	0.3519
$x_2 = 0.2001$				
283.15	0.7820	0.7256	0.7966	0.6853
288.15	1.3295	1.3187	1.3832	1.4479
293.15	2.2622	2.3484	2.3852	2.0471
298.15	3.9614	4.1024	4.0874	3.9515
303.15	6.7978	7.0348	6.9588	5.4014
308.15	12.3337	11.8537	11.7727	9.7949
313.15	19.4766	19.6446	19.7926	17.0148
$x_2 = 0.3998$				
283.15	4.9739	5.6849	5.8179	5.8436
288.15	7.4414	7.7834	7.8554	7.9638
293.15	10.3380	10.5410	10.5430	10.5624
298.15	14.6383	14.1323	14.0653	13.9580
303.15	19.3470	18.7650	18.6570	18.3462
308.15	24.9062	24.6882	24.6112	23.8641
313.15	31.7426	32.1966	32.2946	30.5469
$x_2 = 0.5003$				
283.15	7.5189	8.1249	8.1259	7.5842
288.15	10.3582	10.5102	10.5102	10.0497
293.15	13.8751	13.4771	13.4761	13.1582
298.15	17.0287	17.1377	17.1357	17.1485
303.15	22.0643	21.6203	21.6173	22.1570
308.15	27.2381	27.0701	27.0661	28.3874
313.15	33.3219	33.6519	33.6489	35.9647
$x_2 = 0.6011$				
283.15	9.1825	9.8925	10.0265	8.5683
288.15	12.1098	12.3818	12.4338	11.1794
293.15	15.3968	15.3794	15.3515	14.4580
298.15	19.4419	18.9649	18.8749	18.6451

Table 2 continued

T/K	$10^2 x_1^{\mathrm{b}}$	$10^2 x_1^{\mathrm{cal}}$		
		van't Hoff	Modified Apelblat	3D Jouyban–Acree–van't Hoff
303.15	23.8426	23.2246	23.1126	23.6863
308.15	28.4512	28.2542	28.1932	29.9968
313.15	33.6075	34.1595	34.2615	36.5548
$x_2 = 0.7999$				
283.15	10.1947	10.7827	10.8017	9.8874
288.15	13.0298	13.3168	13.3288	12.5280
293.15	16.1895	16.3275	16.3335	15.8247
298.15	20.3281	19.8821	19.8841	19.8604
303.15	24.8602	24.0552	24.0562	24.7563
308.15	29.0795	28.9235	28.9315	30.59 648
313.15	33.9850	34.5730	34.5990	36.4546
$x_2 = 0.9008$				
283.15	10.5919	11.2899	11.4409	10.6574
288.15	13.5749	13.8909	13.9459	13.3387
293.15	17.0556	16.9702	16.9366	16.6594
298.15	21.1589	20.5939	20.4939	20.6468
303.15	25.4180	24.8320	24.7140	25.3209
308.15	29.8707	29.7617	29.7037	30.9357
313.15	34.9394	35.4644	35.5864	36.6897
$x_2 = 1.0000$				
283.15	11.1430	11.7680	11.8250	11.2742
288.15	14.0896	14.4036	14.4306	13.9536
293.15	17.9628	17.5068	17.5088	17.1418
298.15	21.4964	21.1404	21.1244	20.9439
303.15	25.8193	25.3703	25.3523	25.5143
308.15	30.0085	30.2665	30.2715	30.7852
313.15	35.7029	35.9039	35.9699	36.9135

Standard uncertainties u are $u(T) = 0.05$ K, $u(p) = 0.01$ MPa. The relative standard uncertainty u_{r} is $u_{\mathrm{r}}(x_2) = 0.001$, $u_{\mathrm{r}}(x_1) = 0.05$
x_1^{b} and x_1^{cal} are the experimental and calculated solubility data, respectively

3.4 Dissolution Thermodynamic Properties of Raspberry Ketone

It is essential to study the dissolution properties of the raspberry ketone in ethanol/water binary solvents of different compositions which were calculated in this study.

The changes of dissolution thermodynamic functions including molar enthalpy and Gibbs free energy can be deduced from the plot of $\ln x_1$ versus $1/T$. To reduce the error, the average temperature T_{mean} was introduced and defined in Eq. 10 [15]:

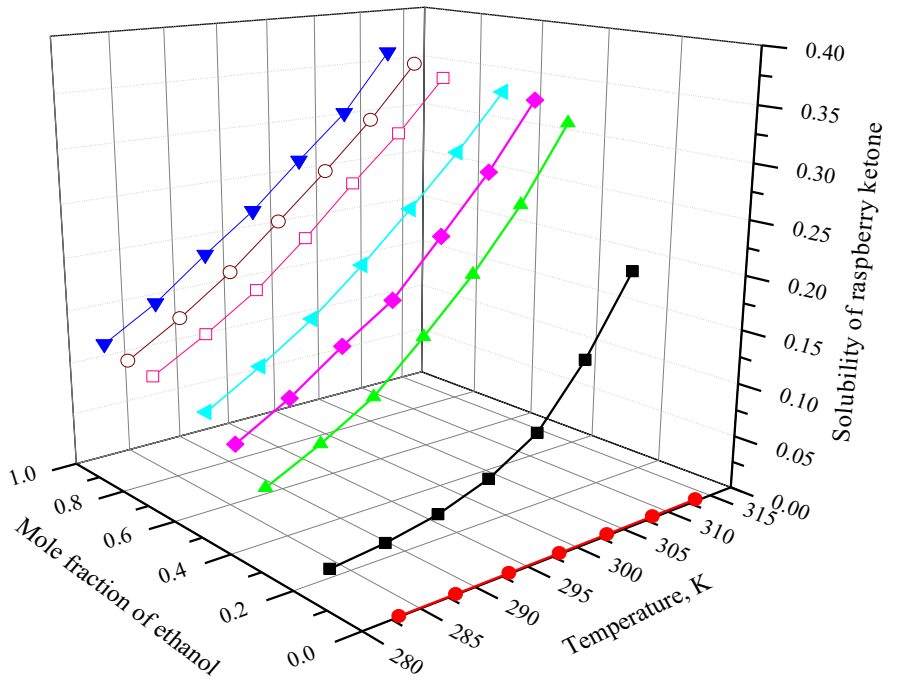

Fig. 4 Mole fraction solubility of raspberry ketone in ethanol/water binary solvent mixtures at temperatures ranging 283.15–313.15 K versus the mole fraction of ethanol: •, $x_2 = 0.0000$; ■, $x_2 = 0.2001$; ▲, $x_2 = 0.3998$; ♦, $x_2 = 0.5003$; ►, $x_2 = 0.6011$; □, $x_2 = 0.7999$; ○, $x_2 = 0.9008$; ▼, $x_2 = 1.0000$

$$T_{\text{mean}} = N / \sum_{i=1}^{N} (1/T) \tag{10}$$

where N presents the number of the set of experimental points. And in this study, $T_{\text{mean}} = 297.81$ K is estimated to calculate the thermodynamic functions.

Assuming that the heat capacity of solution can be considered constant in a short range of temperature, and change of molar enthalpy of solution can be derived from van't Hoff equation in Eq. 11 [26]:

$$\Delta H_{\text{diss}} = -R \left[\frac{\partial \ln x}{\partial (1/T)} \right] = -R \left[\frac{\partial \ln x}{\partial (1/T - 1/T_{\text{mean}})} \right] \tag{11}$$

For the ethanol/water binary solvents, the $\ln x_1$ versus $10^4(1/T - 1/T_{\text{mean}})$ plots are demonstrated in Fig. 6. Deduced from it, the molar enthalpy change of solution $\Delta H^{\circ}_{\text{diss}}$ could be calculated. This figure shows that the solubility data show a linear relationship with the reciprocal of temperature. The value of the slope, intercept and R^2 of each plot is listed in Table 6. All of R^2 in the tables are higher than 0.99, which indicates that the van't Hoff equation can be well used to calculate the thermodynamic properties of raspberry ketone in ethanol/water binary solvent mixtures.

Table 3 Parameters of van't Hoff model and error analysis results of raspberry ketone in ethanol + water solvent mixtures

Model	Parameters	x_2							
		0.0000	0.2001	0.3998	0.5003	0.6011	0.7999	0.9008	1.0000
van't Hoff	A	6.6898	29.5061	15.2325	12.3235	10.6227	9.9348	9.7669	9.5037
	10^{-3} B	− 4.0276	− 9.7494	− 5.1250	− 4.2002	− 3.6629	− 3.4437	− 3.3831	− 3.2968
	10^3 RMSD	0.02	2.22	4.65	3.58	4.68	4.88	4.70	4.02
	10^3 ORMSD	3.59							
	R^2	0.9988	0.9986	0.9968	0.9980	0.9961	0.9956	0.9960	0.9971

Table 4 Parameters of modified Apelblat model and error analysis results of raspberry ketone in ethanol + water solvent mixtures

Model	Parameters	x_2							
		0.0000	0.2001	0.3998	0.5003	0.6011	0.7999	0.9008	1.0000
Modified Apelblat	*a*	− 77.34	− 245.31	− 76.50	11.61	− 56.95	3.77	− 58.99	− 11.59
	b	− 255.59	2682.63	− 997.28	− 4168.10	− 633.05	− 3166.81	− 302.13	− 2352.03
	c	12.53	40.92	13.67	0.11	10.08	0.92	10.25	3.15
	10^3 RMSD	0.02	2.60	5.51	3.58	5.57	4.96	5.68	4.28
	10^3 ORMSD	4.02							
	R^2	0.9984	0.9975	0.9944	0.9974	0.9931	0.9943	0.9928	0.9958

Table 5 Parameters of 3D Jouyban–Acree–van't Hoff model correlated to experimental solubility of raspberry ketone in ethanol + water solvent mixtures

Parameters	Value
k_0	17.09
k_1	− 7120.34
k_2	− 6.84
k_3	− 4312.15
k_4	13357.12
k_5	− 15368.57
k_6	9921.23
10^3 ORMSD	19.15
R^2	0.9878

In general, the change of molar Gibbs free energy of dissolution process of raspberry ketone can be calculated by Eq. 12 [26]:

$$\Delta G_{\text{diss}} = -RT_{\text{mean}} \times \text{Intercept} \tag{12}$$

where the intercept in Eq. 12 is the value of intercept of the plot. The intercepts are all negative which means $\Delta G^{\circ}_{\text{diss}}$ always tends to be positive based on Eq. 12.

Then change of $T_{\text{mean}}\Delta S_{\text{diss}}$ can be calculated by Eq. 13:

$$T_{\text{mean}}\Delta S_{\text{diss}} = \Delta H_{\text{diss}} - \Delta G_{\text{diss}} \tag{13}$$

The estimated values of $\Delta H^{\circ}_{\text{diss}}$, ΔG_{diss} and $T_{\text{mean}}\Delta S_{\text{diss}}$ in water/ethanol mixtures of different compositions are listed in Table 7. From the table, it indicates that all the changes of dissolution enthalpy and Gibbs energy of raspberry ketone are positive, which manifest that these dissolutions are endothermal, not spontaneous, correspondingly. Furthermore, the order of $\Delta G^{\circ}_{\text{diss}}$ value reverses the change of solubility data. In general, the solubility of raspberry ketone in the set of ethanol/ water solvent mixtures increases with raising temperature in the above experiments. Then the value of $\frac{\partial \ln x}{\partial(1/T)}$ always tends to be negative. Based on Eq. 11, the value of $\Delta H^{\circ}_{\text{diss}}$ always tends to be positive. Moreover, according to Eq. 13, the value of $\Delta H^{\circ}_{\text{diss}}$, $T_{\text{mean}}\Delta S^{\circ}_{\text{diss}}$ and $\Delta G^{\circ}_{\text{diss}}$ is all positive, which means the value of $\Delta H^{\circ}_{\text{diss}}$ is bigger than $T_{\text{mean}}\Delta S^{\circ}_{\text{diss}}$. Therefore, the change of dissolution enthalpy is the main contributor to the positive dissolution Gibbs energy change in all experimental ethanol/water binary solvent mixtures.

Furthermore, to visually compare the relative contribution of enthalpy and entropy to the Gibbs free energy change, $\%\xi_H$ and $\%\xi_{TS}$ represented respective contribution value of enthalpy and entropy and were calculated by Eqs. 14 and 15 [27]:

$$\%\xi_H = \frac{\left|\Delta H^{\circ}_{\text{diss}}\right|}{\left|\Delta H^{\circ}_{\text{diss}}\right| + \left|T\Delta S^{\circ}_{\text{diss}}\right|} \times 100 \tag{14}$$

$$\%\xi_{TS} = \frac{\left|T\cdot\Delta S^{\circ}_{\text{diss}}\right|}{\left|\Delta H^{\circ}_{\text{diss}}\right| + \left|T\Delta S^{\circ}_{\text{diss}}\right|} \times 100 \tag{15}$$

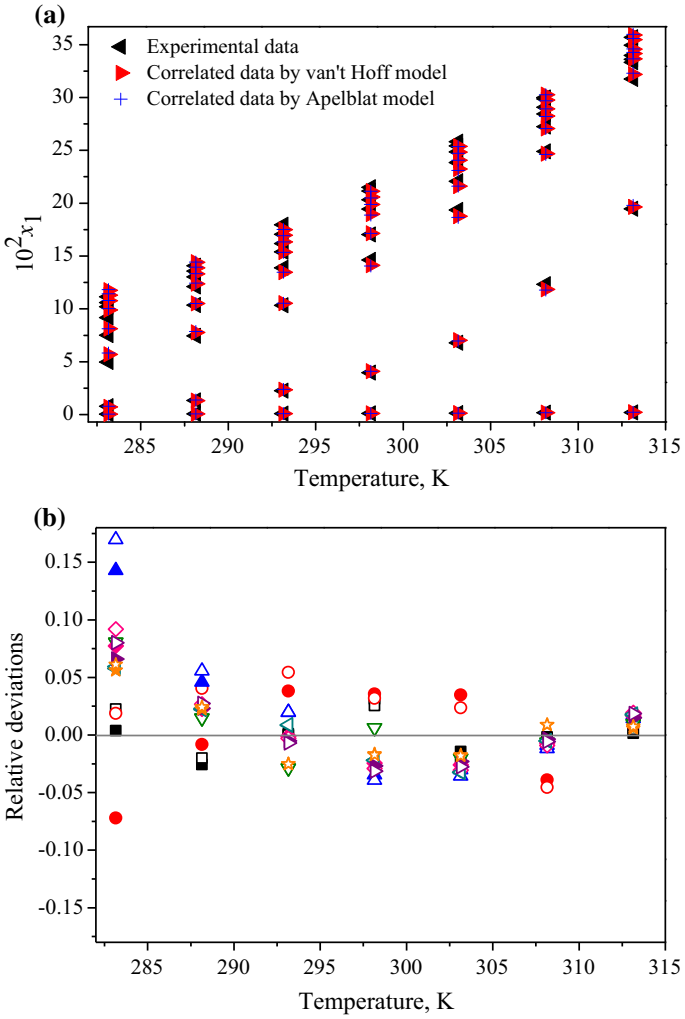

Fig. 5 (a) The experimental data as well as their correlations by the van't Hoff model and the Apelblat model; (b) The relative deviations between the experimental data and the correlated data by the van't Hoff model as well as the Apelblat model: ■, $x_2 = 0.0000$; ●, $x_2 = 0.2001$; ▲, $x_2 = 0.3998$; ▼, $x_2 = 0.5003$; ♦, $x_2 = 0.6011$; ◄, $x_2 = 0.7999$; ►, $x_2 = 0.9008$; ★, $x_2 = 1.0000$. Solid symbols, relative deviations from van't Hoff model; open symbols, relative deviations from Apelblat model

The values of $\%\xi_H$ and $\%\xi_{TS}$ in binary solvents of ethanol + water are reported in Table 7. It is indicated that the main contributor to the mole Gibbs energy is the enthalpy during the dissolution process of raspberry ketone because the values of $\%\xi_H$ are all more than 50.

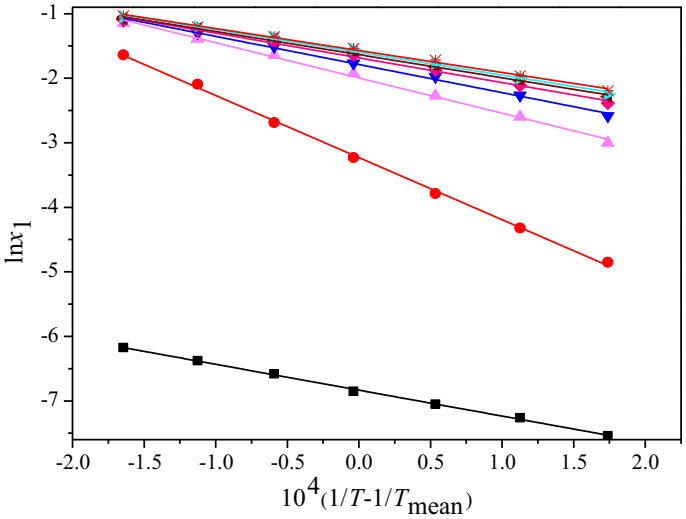

Fig. 6 Van't Hoff plots of logarithm mole fraction solubility (x_1) of raspberry ketone in ethanol + water mixed solutions versus $10^4(1/T - 1/T_{mean})$: (■), $x_2 = 0.0000$; (●), $x_2 = 0.2001$; (▲), $x_2 = 0.3998$; (▼), $x_2 = 0.5003$; (♦), $x_2 = 0.6011$; (◄), $x_2 = 0.7999$; (►), $x_2 = 0.9008$; (✳), $x_2 = 1.0000$

Table 6 Slope and intercept of the $\ln x_1$ versus $10^4(1/T - 1/T_{mean})$ plot in the binary ethanol + water solvent mixtures

x_2	Slope	Intercept	R^2
0.0000	− 0.4014	− 6.8342	0.9985
0.2001	− 0.9626	− 3.2303	0.9986
0.3998	− 0.5461	− 1.9961	0.9955
0.5003	− 0.4356	− 1.7880	0.9964
0.6011	− 0.3833	− 1.6843	0.9957
0.7999	− 0.3584	− 1.6352	0.9963
0.9008	− 0.3528	− 1.5990	0.9957
1.0000	− 0.3407	− 1.5711	0.9958

4 Conclusions

In the current research, the solubility data of raspberry ketone in ethanol/water solvent mixtures were measured by static gravimetrical method in the temperature range of 283.15–313.15 K. The results generally reveal that the temperature has a direct effect on the solubility of raspberry ketone in all experimental ethanol/water binary solvent mixtures. The solubility of raspberry ketone in binary solvent mixtures of ethanol and water also increases with increasing mole fraction of ethanol in the mixture solution. The three models of van't Hoff, modified Apelblat and Jouyban–Acree–van't Hoff were applied to correlate the solubility data in ethanol/water binary solvent mixtures and had a better applicability and accuracy. As raspberry ketone is slightly soluble in the water and the value of its solubility is too small in ethanol/water binary solvent mixtures of low fraction of ethanol, the solubility value of raspberry ketone in ethanol/water

Table 7 Thermodynamic functions (ΔH_{diss}, ΔG_{diss}, $T_{\text{mean}}\Delta S_{\text{diss}}$,) related to dissolution process of raspberry ketone at $T_{\text{mean}} = 297.81$K with the different mole fraction of ethanol in the binary mixture solvent of ethanol and water

x_2	ΔH_{diss} ($\text{kJ} \cdot \text{mol}^{-1}$)	ΔG_{diss} ($\text{kJ} \cdot \text{mol}^{-1}$)	$T_{\text{mean}}\Delta S_{\text{diss}}$ ($\text{kJ} \cdot \text{mol}^{-1}$)	$\%\xi_H$	$\%\xi_{TS}$
$T_{\text{mean}} = 297.81$K					
0.0000	33.37	16.92	16.45	66.98	33.02
0.2001	80.03	8.00	72.03	52.63	47.37
0.3998	45.40	4.94	40.46	52.88	47.12
0.5003	36.22	4.43	31.79	53.25	46.75
0.6011	31.87	4.17	27.70	53.50	46.50
0.7999	29.80	4.05	25.75	53.64	46.36
0.9008	29.33	3.96	25.37	53.62	46.38
1.0000	28.33	3.89	24.44	53.69	46.31

binary solvent mixtures of low mole fraction of ethanol could not fit very well to the 3D model. Dissolution thermodynamic studies indicate endothermic and enthalpy-driven dissolution process of raspberry ketone in this set of ethanol/water binary solvent mixtures.

Acknowledgements The financial support of the Tianjin Research Program of Application Foundation and Advanced Technology (Grant No. 14JCZDJC40900) and the National Natural Science Foundation of China (Grant No. 21506162) are sincerely acknowledged.

References

1. M. Larsen, L. Poll, Z. Lebensm. Unters. Forsch. **191**, 129–131 (1990)
2. L. Bredsdorff, E.B. Wedebye, N.G. Nikolov, T.H. Møller, K. Pilegaard, Regul. Toxicol. Lett. **229S**, S171 (2014)
3. C. Fuganti, G. Zucchi, J. Mol. Catal. B Enzym. **4**, 289–293 (1998)
4. Y. Ogawa, M. Akamatsu, Y. Hotta, A. Hosoda, H. Tamura, B. Med, Chem. Lett. **20**, 2111–2114 (2010)
5. N. Harada, K. Okajima, N. Narimatsu, H. Kurihara, N. Nakagata, Growth Horm. IGF Res. **18**, 335–344 (2008)
6. W. Hoelderich, V. Ritzerfeld, Appl. Catal. A Gen. **504**, 654–663 (2015)
7. H. Matsuda, K. Mori, M. Tomioka, N. Kariyasu, T. Fukami, K. Kurihara, K. Tochigi, K. Tomono, Fluid Phase Equilib. **406**, 116–123 (2015)
8. B. Kosjek, W. Stampfer, R.V. Deursen, K. Faber, W. Kroutil, Tetrahedron **59**, 9517–9521 (2003)
9. M. Lakshmy, B.M. Chandrasekhar, B.S. Jai Prakash, Y.S. Bhat, Clay Miner. **50**, 573–581 (2015)
10. J. Beekwilder, I.M. van der Meer, O. Sibbesen, M. Broekgaarden, I. Qvist, J.D. Mikkelsen, R.D. Hall, Biotechnol. J. **2**, 1270–1279 (2007)
11. L. Bredsdorff, E.B. Wedebye, N.G. Nikolov, T.H. Møller, K. Pilegaard, Regul. Toxicol. Pharm. **73**, 196–200 (2015)
12. H.R. Rafiee, F. Frouzesh, J. Chem. Thermodyn. **102**, 95–104 (2016)
13. L.N. Zelenina, T.P. Chusova, A.V. Isakov, J. Chem. Thermodyn. **102**, 89–94 (2016)
14. M.Y. Tao, H. Sun, Z. Wang, P.L. Cui, J.K. Wang, Fluid Phase Equilib. **352**, 14–21 (2013)
15. G. Wang, Y.L. Wang, Y.G. Ma, H.X. Hao, Q.H. Luan, H.H. Wang, J. Chem. Thermodyn. **77**, 144–150 (2014)
16. A. Mehrdad, A.H. Miri, Fluid Phase Equilib. **425**, 51–56 (2016)

17. K.F. Zhao, P. Yang, S.C. Du, K.L. Li, X.N. Li, Z.F. Li, Y.M. Liu, L.L. Lin, B.H. Hou, J.B. Gong, J. Chem. Thermodyn. **102**, 276–286 (2016)
18. Y.Y. Yang, P. Yang, S.C. Du, K.L. Li, K.F. Zhao, S.J. Xu, B.H. Hou, J.B. Gong, J. Chem. Thermodyn. **103**, 432–445 (2016)
19. F.X. Zou, W. Zhuang, J.L. Wu, J.W. Zhou, Q.Y. Liu, Y. Chen, J.J. Xie, C.J. Zhu, T. Guo, H.J. Ying, J. Chem. Thermodyn. **77**, 14–22 (2014)
20. L.Y. Wang, X.C. Li, L. Zhu, Z.L. Sha, Y.F. Wang, L.B. Yang, J. Mol. Liq. **208**, 211–218 (2015)
21. L.P. Xiao, Y.L. Wang, J.X. Yang, F.H. Yuan, C. Jiang, B.H. Hou, C. Xie, J. Chem. Thermodyn. **102**, 199–210 (2016)
22. P. Yang, S.C. Du, Y.J. Qin, K.F. Zhao, K.L. Li, B.H. Hou, J.B. Gong, J. Chem. Thermodyn. **101**, 84–91 (2016)
23. W.E. Acree, M.Y. Horton, J. Chem. Thermodyn. **104**, 61–66 (2017)
24. K. Koeduka, B. Watanabe, S. Suzuki, J. Hiratake, J. Mano, K. Yazaki, Biochem. Biophys. Res. Commun. **412**, 104–108 (2011)
25. H.W. Shi, Y. Xie, C.B. Du, Y. Cong, J. Wang, H.K. Zhao, J. Chem. Thermodyn. **102**, 79–88 (2016)
26. K. Nam, E.S. Ha, J.S. Kim, D.H. Kuk, D.H. Ha, M.S. Kim, C.W. Cho, S.J. Hwang, J. Chem. Thermodyn. **104**, 45–49 (2017)
27. R.R. Pawar, C.S. Aher, J.D. Pagar, S.L. Nikam, M. Hasan, J. Chem. Eng. Data **57**, 3563–3572 (2012)