Solubility of L-phenylalanine in water and different binary mixtures from 288.15 to 318.15 K

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ABSTRACT

The solubility of L-phenylalanine in water and binary mixtures (methanol + water and ethanol + water) at temperatures ranging from 288.15 to 318.15 K was investigated. The results obtained from these measurements were correlated with the temperature and the molar fraction of water by the combined nearly ideal binary solvent (CNIBS)/Redlich–Kister(R–K) model and the semiempirical Apelblat model. Both of the models demonstrated good fitting with the experimental data, while the CNIBS/R–K model gave a more accurate prediction. In addition, the thermodynamic properties of the solution process, including the Gibbs energy, enthalpy, and entropy, were obtained using the van't Hoff equation and the Gibbs equation. The experimental results showed that water was a better solvent for L-phenylalanine than methanol and ethanol, which could thus be used as effective anti-solvents in the crystallization process. For all the cases studied, the values of both the standard molar enthalpy change and standard molar Gibbs energy change of solution were positive, which indicated that the process was endothermic and not spontaneous.

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1. Introduction

L-Phenylalanine (Fig. 1), one of the essential amino acids, is an important intermediate for the synthesis of many biological chemicals, and has been widely used in the food, pharmaceutical and chemical industries, notably in the production of aspartame (one of the most popular sweeteners) and several drugs with antivirus and anticancer properties [1–5]. L-Phenylalanine exists in two different crystalline forms: the anhydrous form and the monohydrate form [6]. The anhydrous form is the commonly used crystalline form due to its high stability, granular crystal structure, good fluidity, and ease of packaging and storing.

In crystallization, the supersaturation of a solution has a direct effect on the quality of the crystals. Thus, the fundamental solubility data of amino acids are generally considered an essential factor in the design of crystallization processes. Recently, there have been many studies on the solubility of different kinds of amino acids. The solubility of four amino acids at different temperatures was measured by Carta [7]. Ji and Feng [8] applied the statistical associating fluid theory (SAFT) equation of state to modeling the amino acid solubility in water and in an aqueous solution. It was found that

the SAFT model described the L-phenylalanine solubility in water well in the temperature range from 0 to 100 °C. The effects of pH and the ions of the electrolyte solutions on the solubility of several kinds of amino acids including L-phenylalanine were also investigated [9–11]. Soto et al. [12] measured the solubility of two pairs of amino acids in different systems and developed a model to correlate the solubility of an amino acid in aqueous solutions with that of another amino acid. These works were valuable in the development of thermodynamic models for L-phenylalanine in terms of the effect of temperature and pH values in water. However, different solvents have a major impact on the solubility behavior. It is very important to investigate the solubility in different solvents when developing thermodynamic models, and for the efficient design of separation and crystallization processes [13,14]. Although it is well known that L-phenylalanine can be dissolved in the water and is insoluble in some organic solvents [1], there has been no detailed analysis of the influences of different compositions of organic solvents and temperature on the solubility data.

Methanol and ethanol, which are widely used as anti-solvents, were chosen for this study because they are hypotoxicity and can be easily removed from the solvents [15,16]. The solubilities of L-phenylalanine in water, methanol + water and ethanol + water in the temperature range from 288.15 to 318.15 K were investigated using the anhydrate form, in order to collect basic data for studies of the separation and crystallization of L-phenylalanine. The combined nearly ideal binary solvent (CNIBS)/Redlich–Kister model and

Nomenclature

A, a	parameter
B, b	parameter
C, c	parameter
$\sum(\%D)$	percentage deviation
G	molar Gibbs free energy
H	molar enthalpy
m	mass
M	molecular weight
n	number of the experimental data
R	gas constant
S	entropy change; parameter
T	temperature
V	volume
x	mole fraction

Greek letter

Δ	change

Superscripts

0	initial
$\circ$	standard molar
cal	calculated
exp	experimental

Subscripts

1	solute; parameter
2	water; parameter
3	organic solvent; parameter
4	parameter
s	solution

the semiempirical Apelblat model were used to correlate the solubility data. The thermodynamic properties for the solution process were also discussed.

2. Experimental

2.1. Materials

The anhydrate form of L-phenylalanine (mass fraction ≥ 99%) was obtained by recrystallization. The number of waters of crystallization was measured using differential scanning calorimetry (STA449C, NETZSCH Gerätebau GmbH, Germany). The moisture content of L-phenylalanine was below 0.05% (mass fraction), as
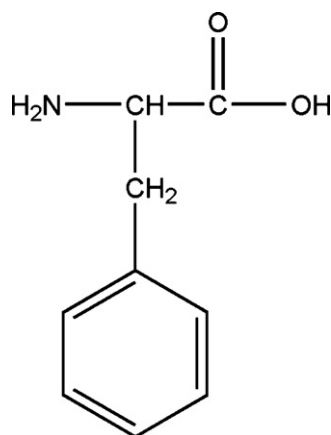

Fig. 1. Molecular structure of L-phenylalanine.

determined by the loss on drying under normal pressure method [17]. The standard sample of L-phenylalanine used for the establishment of the calibration curve was purchased from Sigma Chemical Co. Methanol (mole fraction ≥ 99.5%) and ethanol (mole fraction ≥ 99.7%) obtained from Shanghai Chemistry Reagent Co. (China) were of analytical reagent grade. Distilled deionized water which was obtained from the triple distilled water generator (SZ-97, Shanghai Yarong Biochemical Instrument Co. Ltd., China) was used in all cases.

2.2. Solubility measurement

The solubility of L-phenylalanine in water and binary mixtures (methanol + water, and ethanol + water) was determined from 288.15 to 318.15 K using an isothermal method.

For each experiment, the binary solvent was mixed with known mass of organic solvent and water which was measured by an electronic balance (BS-124S, Sartorius, Germany) with uncertainty of ±0.1 mg. The initial mole fraction composition of the binary solvent (x_2^0) was calculated. Then an excess of L-phenylalanine was added to the solution. Test tubes were sealed to prevent solvent evaporation. The experiments were carried out in a constant temperature water bath (type DC-2030, Shanghai Sunny Hengping Scientific Instrument Co. Ltd., China), which controlled the temperature at a constant value within ±0.05 K. The phase equilibrium was ensured by the preliminary experiments in which the concentration of L-phenylalanine in each mixture was measured every 30 min. The equilibrium cell was heated and held at the temperature for at least 5 h with continuous stirring. After 5 h, the stirring was stopped, and the solution was held for around 1 h. Then the solution was poured into the filter funnel to remove the excess of solid. The filter funnel and the filter tanks had been dried in an oven for at least 24 h and kept at experimental temperature before use. And during the filtration process, the filter tanks were kept in the constant temperature water bath to avoid the errors evoked by the temperature changing. The concentrations of L-phenylalanine in the filtrate were measured at 260 nm using high performance liquid chromatography (1200 Series, Agilent1100, USA) with a SepaxHP-C18 column (4.6 mm × 250 mm, 5 μm, Sepax (Jiangsu) Technologies, Inc., Changzhou, China), and calculated by a calibration curve method. The mobile phase was 30% (v/v) methanol. The column temperature was 298.15 K and the flow rate was 1.0 ml/min. Then the mole fraction solubility of L-phenylalanine (x_1) in the solution was calculated. Each test was carried out three times to get a mean value, and the relative error was less than 3%.

3. Results and discussion

3.1. Solubility data

The mole fraction solubility of L-phenylalanine (x_1) in water (2), water (2) + methanol (3) and water (2) + ethanol (3), at various initial mole fraction composition of binary solvent (x_2^0) from 288.15 K to 318.15 K were calculated using Eq. (1) and the results are listed in Table 1 . The initial mole fraction composition of the binary solvent (x_2^0) was defined by Eq. (2).

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{1}$$

$$x_2^0 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \tag{2}$$

in which 1, 2 and 3 refer to L-phenylalanine, water and organic solvents, respectively. m and M are the masses and the molecular

Table 1
The mole fraction solubility of L-phenylalanine (x_1) in water (2), water (2) + methanol (3), water (2) + ethanol (3), at various initial mole fraction composition of binary solvent (x_2^0) from 288.15 K to 318.15 K.

x_2^0 (mole fraction)	$10^4 x_1^{exp}$ (mole fraction)	$10^2(x_1^{exp} - x_1^{cal})/x_1^{exp}$ (CNIBS)	$10^2(x_1^{exp} - x_1^{cal})/x_1^{exp}$ (Apelblat)
Water (2) + methanol (3)			
$T = 288.15 \pm 0.05$ K			
1.0000	22.43 ± 0.04	0.4840	−0.3756
0.8827	15.03 ± 0.08	−2.2129	−1.9269
0.8176	14.21 ± 0.07	1.6649	−1.1066
0.7378	13.08 ± 0.03	−0.5558	−1.2401
0.6921	13.13 ± 0.04	2.1422	−0.5929
0.5997	11.96 ± 0.05	−1.9091	0.7172
0.3597	8.44 ± 0.05	0.3291	−0.2593
0.0000	3.23 ± 0.02	−0.0252	−1.0717
$T = 293.15 \pm 0.05$ K			
1.0000	25.13 ± 0.05	0.6151	0.4533
0.8827	18.89 ± 0.07	−1.5606	2.3628
0.8176	17.24 ± 0.06	−1.4917	0.4290
0.7378	16.54 ± 0.08	2.8025	2.8148
0.6921	15.82 ± 0.03	2.5723	3.0522
0.5997	13.64 ± 0.06	−3.6672	−0.4457
0.3597	10.12 ± 0.07	0.6084	1.9416
0.0000	4.15 ± 0.02	−0.0450	−1.7310
$T = 298.15 \pm 0.05$ K			
1.0000	27.45 ± 0.11	0.3866	−0.4237
0.8827	21.80 ± 0.07	−1.8275	1.2798
0.8176	20.46 ± 0.03	0.9927	2.2643
0.7378	18.79 ± 0.08	2.4134	−1.0178
0.6921	17.07 ± 0.07	−1.8156	−3.2598
0.5997	15.54 ± 0.02	−0.3704	−1.4719
0.3597	11.24 ± 0.03	0.1664	−2.5306
0.0000	5.67 ± 0.01	−0.0146	8.0717
$T = 303.15 \pm 0.05$ K			
1.0000	30.55 ± 0.16	0.3362	1.6722
0.8827	24.28 ± 0.05	−1.5088	−0.4214
0.8176	22.83 ± 0.07	0.5785	−0.4132
0.7378	21.46 ± 0.11	2.6687	−1.8142
0.6921	19.60 ± 0.06	−2.0087	−2.3769
0.5997	18.21 ± 0.03	−0.2695	0.5285
0.3597	13.20 ± 0.03	0.1464	0.5158
0.0000	5.89 ± 0.02	−0.0130	−4.6463
$T = 308.15 \pm 0.05$ K			
1.0000	31.96 ± 0.05	0.5089	−1.2352
0.8827	26.59 ± 0.04	−0.9193	−1.0470
0.8176	24.74 ± 0.12	−2.4308	−2.2001
0.7378	24.94 ± 0.09	3.9469	1.5498
0.6921	23.53 ± 0.06	1.3780	3.8094
0.5997	20.86 ± 0.07	−3.1599	0.4826
0.3597	15.23 ± 0.03	0.5419	0.5383
0.0000	6.18 ± 0.02	−0.0401	−3.0656
$T = 313.15 \pm 0.05$ K			
1.0000	34.15 ± 0.06	0.3076	−0.9414
0.8827	28.19 ± 0.13	−1.0601	−2.3454
0.8176	27.08 ± 0.08	−0.2562	1.6158
0.7378	26.81 ± 0.09	2.5517	−0.5634
0.6921	25.35 ± 0.05	−0.9440	0.1613
0.5997	24.03 ± 0.08	−0.8353	1.1873
0.3597	17.53 ± 0.05	0.2052	2.1887
0.0000	7.75 ± 0.01	−0.0164	0.9655
$T = 318.15 \pm 0.05$ K			
1.0000	36.67 ± 0.04	0.0841	0.8182
0.8827	30.85 ± 0.14	−0.5573	1.9896
0.8176	29.88 ± 0.07	0.5303	1.7301
0.7378	29.03 ± 0.07	0.9894	0.1876
0.6921	27.80 ± 0.09	−1.4534	−1.0019
0.5997	26.82 ± 0.03	0.4029	−1.0273
0.3597	18.99 ± 0.02	−0.0152	−1.4513
0.0000	8.20 ± 0.01	0.0000	0.9524
Water (2) + ethanol (3)			
$T = 288.15 \pm 0.05$ K			
1.0000	22.43 ± 0.05	1.6357	−0.3756
0.9156	14.66 ± 0.07	−5.9727	−0.3235
0.8660	13.04 ± 0.08	1.2842	−1.5569
0.8023	11.24 ± 0.08	7.9451	−0.1363
0.7641	8.86 ± 0.06	−4.0052	−2.1366
0.6835	7.31 ± 0.03	−1.8721	0.3739
0.4475	4.89 ± 0.03	0.3796	0.9142
0.0000	0.84 ± 0.00	−0.0175	0.1433

Table 1 (*Continued*)

x_2^0(mole fraction)	$10^4 x_1^{exp}$(mole fraction)	$10^2(x_1^{exp} - x_1^{cal})/x_1^{exp}$(CNIBS)	$10^2(x_1^{exp} - x_1^{cal})/x_1^{exp}$(Apelblat)
$T = 293.15 \pm 0.05$ K			
1.0000	25.13 ± 0.08	1.4731	0.4533
0.9156	17.74 ± 0.07	−5.7308	1.5855
0.8660	16.68 ± 0.05	2.6175	5.0211
0.8023	14.28 ± 0.03	3.7179	2.7232
0.7641	12.49 ± 0.02	−0.4433	3.5850
0.6835	10.26 ± 0.05	−2.2822	3.9546
0.4475	6.42 ± 0.04	0.3618	−0.8503
0.0000	0.96 ± 0.01	−0.0161	−0.5174
$T = 298.15 \pm 0.05$ K			
1.0000	27.45 ± 0.07	1.5102	−0.4237
0.9156	19.90 ± 0.08	−3.7466	−1.5852
0.8660	17.75 ± 0.06	−1.6386	−4.4573
0.8023	15.95 ± 0.04	2.7418	−4.6895
0.7641	15.17 ± 0.09	5.6398	−0.8170
0.6835	11.65 ± 0.08	−5.5489	−9.7116
0.4475	8.20 ± 0.02	0.6203	−2.0117
0.0000	1.13 ± 0.00	−0.0253	0.1017
$T = 303.15 \pm 0.05$ K			
1.0000	30.55 ± 0.07	0.9937	1.6722
0.9156	22.56 ± 0.11	−2.8222	−1.3394
0.8660	20.92 ± 0.03	−0.2568	−1.5974
0.8023	19.48 ± 0.05	1.8921	−0.5293
0.7641	18.80 ± 0.05	2.7597	1.1812
0.6835	16.24 ± 0.04	−3.0634	1.8506
0.4475	10.78 ± 0.02	0.3641	2.9214
0.0000	1.35 ± 0.01	−0.0151	1.6334
$T = 308.15 \pm 0.05$ K			
1.0000	31.96 ± 0.07	0.4659	−1.2352
0.9156	25.86 ± 0.05	−1.7065	2.1344
0.8660	24.50 ± 0.06	0.4677	2.4520
0.8023	23.15 ± 0.08	2.3584	3.0334
0.7641	21.43 ± 0.04	−1.2897	−2.9296
0.6835	19.75 ± 0.05	−0.4463	3.0712
0.4475	12.39 ± 0.04	0.1012	−2.6506
0.0000	1.52 ± 0.01	−0.0047	−2.5557
$T = 313.15 \pm 0.05$ K			
1.0000	34.15 ± 0.05	0.6031	−0.9414
0.9156	27.43 ± 0.08	−2.3002	−0.0847
0.8660	26.59 ± 0.09	1.0432	0.7422
0.8023	25.37 ± 0.04	1.7302	0.7676
0.7641	24.23 ± 0.03	−0.4057	−0.1099
0.6835	22.84 ± 0.05	−0.8613	2.7775
0.4475	15.49 ± 0.02	0.1440	2.9851
0.0000	1.87 ± 0.01	−0.0065	1.4096
$T = 318.15 \pm 0.05$ K			
1.0000	36.67 ± 0.06	1.0065	0.8182
0.9156	29.08 ± 0.15	−3.3329	−0.4458
0.8660	28.39 ± 0.04	0.7299	−0.8925
0.8023	27.30 ± 0.06	2.0984	−1.3742
0.7641	26.49 ± 0.07	1.4808	1.0801
0.6835	24.20 ± 0.09	−2.4074	−2.9890
0.4475	17.05 ± 0.05	0.3136	−1.4700
0.0000	2.18 ± 0.02	−0.0133	−0.2723

weights of L-phenylalanine, water and organic solvent, respectively.

3.2. Mole fraction of solvent-dependent equilibrium

In this work, the CNIBS/Redlich–Kister model [18,19] was used to describe the solubility data related to the mole fraction of water. The function can be given as follows:

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=0}^{n} S_i(x_2^0 - x_3^0)^i \tag{3}$$

in which, x_2^0 and x_3^0 represent the initial mole fraction composition of the binary solvent when the solute was not added; S_i is the model constant and n could be equal to 0, 1, 2 or 3; and $(x_1)_i$ is the mole fraction solubility of the solute in pure solvent i. When $n = 2$ and

$x_3^0 = 1 - x_2^0$ are combined with Eq. (3), the function can be written as:

$$\ln x_1 = B_0 + B_1 x_2^0 + B_2 (x_2^0)^2 + B_3 (x_2^0)^3 + B_4 (x_2^0)^4 \tag{4}$$

with

$$B_0 = \ln(x_1)_3 \tag{5}$$

$$B_1 = \ln(x_1)_2 - \ln(x_1)_3 + S_0 - S_1 + S_2 \tag{6}$$

$$B_2 = -S_0 + 3S_1 - 3S_2 \tag{7}$$

$$B_3 = -2S_1 + 6S_2 \tag{8}$$

$$B_4 = -4S_2 \tag{9}$$

where B_0, B_1, B_2, B_3, and B_4 are the parameters of this model and are listed in Table 2. When the confidence level was above 95%, the Levenberg–Marquardt (LM) algorithm was employed to fit Eq. (3) and determine the parameters.

Table 2
Fitted parameters of CNIBS model for L-phenylalanine in binary solution at different temperature.

T/K	B_0	B_1	B_2	B_3	B_4	$\sum(\%D)$
Water (2) + methanol (3)						
288.15	−8.0361	1.3592	9.2294	−19.5561	10.8988	1.1654
293.15	−7.7868	2.5192	1.7161	−6.7968	4.3559	1.6704
298.15	−7.4754	2.0440	0.2508	−2.4383	1.7170	0.9984
303.15	−7.4370	2.4612	0.4878	−4.0689	2.7625	0.9412
308.15	−7.3886	2.4089	2.2899	−7.2397	4.1785	1.6157
313.15	−7.1625	1.6619	4.8777	−11.0826	6.0229	0.7721
318.15	−7.1068	1.6301	5.4288	−11.9189	6.3576	0.5041
						$\sum\sum(\%D)/n = 1.0953$
Water (2) + ethanol (3)						
288.15	−9.3875	9.1373	−19.1324	19.6106	−6.3445	2.8890
293.15	−9.2465	7.3430	−9.9125	7.2204	−1.4056	2.0803
298.15	−9.0869	8.2933	−12.3359	8.9622	−1.7458	2.6839
303.15	−8.9131	5.0936	3.5543	−13.9844	8.4486	1.5209
308.15	−8.7915	5.3756	2.0098	−10.8443	6.4998	0.8551
313.15	−8.5843	5.2429	3.5417	−14.2722	8.3863	0.8868
318.15	−8.4294	5.2069	3.0200	−13.4446	8.0286	1.4228
						$\sum\sum(\%D)/n = 1.7627$

In order to judge the fitting of each model to the experimental data, the percentage deviation ($\sum(\%D)$) was used, as defined in Eq. (10) [20].

$$\sum(\%D) = 100 \sum_{i=1}^{n} \left| \frac{(x_1^{exp} - x_1^{cal})/n}{x_1^{exp}} \right| \qquad (10)$$

where x_1^{exp} and x_1^{cal} are the experimental data and the calculated value from the model, respectively, and n is the number of the experimental data for each system. The experimental solubility values of L-phenylalanine (x_1) in water (2) + methanol (3) and water (2) + ethanol (3) at different temperatures and the solubility curve fitted by the CNIBS/Redlich–Kister model are shown in Figs. 2 and 3. It is clear that CNIBS/Redlich–Kister model demonstrates good fitting with the experimental data at different temperatures. The small discrepancy between the experimental data and the calculated values listed in Table 1 and the percentage deviation ($\sum(\%D)$) (Table 2) indicated that the CNIBS/Redlich–Kister model could give a good prediction of the solubility for different concentrations of the mixed solvents.
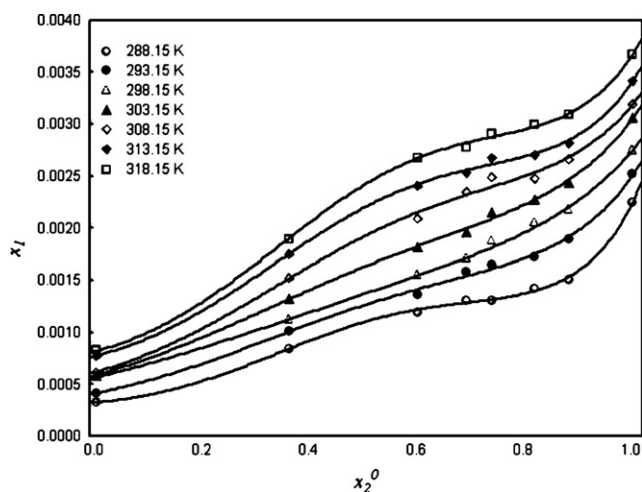
It is obvious from the experimental results that the maximal solubility value of L-phenylalanine was obtained in the aqueous solution at any given temperature. This is due to the properties of L-phenylalanine and water. The molecular structure of L-phenylalanine is shown in Fig. 1. As can be seen, there is a pair of unshared electrons on the nitrogen atom from the amino group, which make the amino group alkaline with an affinity for protons. Therefore, L-phenylalanine can act as a Lewis acid to establish hydrogen bonds with a protonic solvent (Eq. (11)) [21,22]:

$$R–NH_2 + H_2O \rightleftharpoons R–NH_3^+ + OH^- \qquad (11)$$
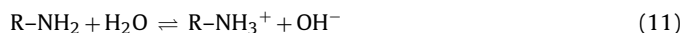
In addition, the carboxyl group with electron acceptance is a hydrophilic group. So L-phenylalanine undergoes the following change in water [21,22]:

$$R–COOH \rightleftharpoons R–COO^- + H^+ \qquad (12)$$

Both the amino group and carboxyl group could be associated with water via hydrogen bonds, producing solvated ions (shown in Fig. 4). Compared with organic solvents, water has a smaller molecular structure and stronger polarity with a high dielectric constant
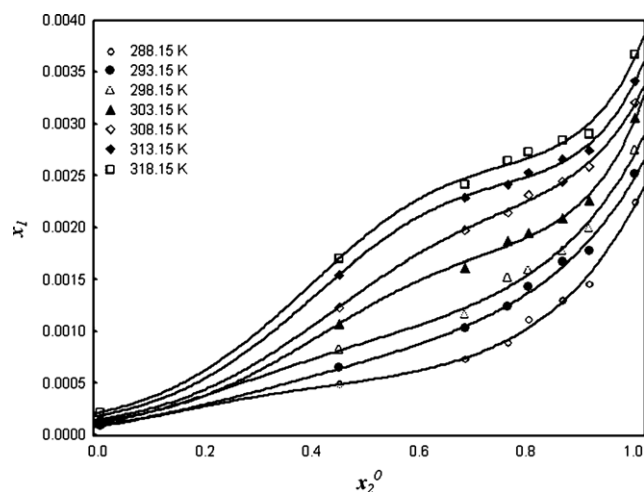
Fig. 2. Mole fraction solubility of L-phenylalanine (1) (x_1) in water (2), methanol (3) + water (2) solvent mixture at various temperatures: (○) T = 288.15 K; (●) T = 293.15 K; (△) T = 298.15 K; (▲) T = 303.15 K; (◇) T = 308.15 K; (♦) T = 313.15 K; and (□) T = 318.15 K. The points represent the experimental data, and the curves represent the results fitted by the combined nearly ideal binary solvent/Redlich–Kister model.
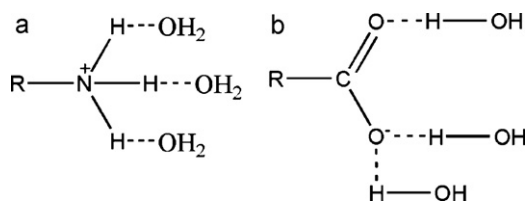
Fig. 3. Mole fraction solubility of L-phenylalanine (1) (x_1) in water (2), ethanol (3) + water (2) solvent mixture at various temperatures: (○) T = 288.15 K; (●) T = 293.15 K; (△) T = 298.15 K; (▲) T = 303.15 K; (◇) T = 308.15 K; (♦) T = 313.15 K; and (□) T = 318.15 K. The points represent the experimental data, and the curves represent the results fitted by the combined nearly ideal binary solvent/Redlich–Kister model.

Fig. 4. Structure of solvation ions for amine-group compounds (a) and carboxyl-group compounds (b) in aqueous solution.

(78.5), which make it easier to enter molecular interspaces, overcome electrostatic interaction with positive and negative ions and eventually form solvated ions [22]. Therefore, the solubility of L-phenylalanine in water is higher than in organic solvents.

Although the amino group and carboxyl group could also be associated with alcohols to form solvated ions, it was greatly weakened by the stereospecific blockade caused by the hydrophobic phenyl group exists in L-phenylalanine and the molecular configuration of methanol and ethanol (larger than water molecule). In addition, alcohols (methanol, ethanol) have weak polarity (dielectric constants are 31.2 and 25.7, respectively), which makes it difficult for them to overcome electrostatic interaction and form solvated ions [22,23]. Therefore, the solubility of L-phenylalanine was low in methanol and ethanol, and due to the longer molecular chain and weaker polarity of ethanol, the solubility of L-phenylalanine was lower in ethanol than in methanol.

However, in the mixtures, the hydroxyl group from water would associate with the alcohols via hydrogen bonds, more easily than that with L-phenylalanine. Hence, the addition of alcohols in mixture solvents decreases the water molecules available for L-phenylalanine, leading to the lower solubility of L-phenylalanine.

Therefore, water was proved to be the best solvent for L-phenylalanine among these three. Methanol and ethanol demonstrated an anti-solvent effect for L-phenylalanine, in which the solubility of L-phenylalanine had the largest change in the ethanol + water system (Fig. 3), indicating that ethanol was an effective anti-solvent for L-phenylalanine.

3.3. Temperature dependence of the mole fraction solubility of L-phenylalanine

The temperature dependence of the mole fraction solubility of L-phenylalanine (x_1) in water (2), water (2) + methanol (3) and water (2) + ethanol (3) could be correlated by using the following semiempirical Apelblat model [24].

$$\ln x_1 = \frac{a + b}{T + c \ln T} \tag{13}$$

in which a, b, and c are parameters of the Apelblat model and the percentage deviations ($\sum(\%D)$) are listed in Table 3, as is the sum of $\sum(\%D)$. The ratio of the calculated value (x_1^{cal}) from the Apelblat model and the difference between the experimental solubility value (x_1^{exp}) and the calculated value (x_1^{cal}) are listed in Table 1. The experimental solubility value of L-phenylalanine (x_1) at different temperatures and the solubility curve fitted by the Apelblat model are shown in Figs. 5 and 6. The results showed that the Apelblat model could well describe the variation in the solubility of L-phenylalanine with temperature. According to Figs. 5 and 6, it is obvious that the solubility of L-phenylalanine increased with the temperature in all systems. This may be due to the following reasons. First, as the temperature increased, the movement of molecules became more active and the stability of the crystal lattice was jeopardized, leading to the larger probability of effective collision of solvent molecules with the crystal lattice, which resulted in the formation of more hydrate molecules. Second, the
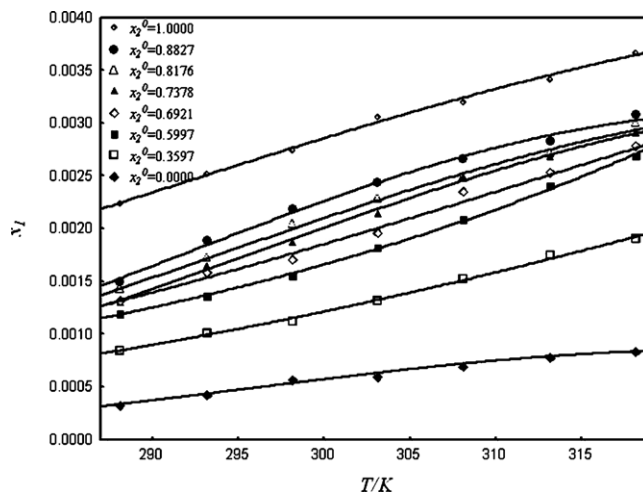

Fig. 5. Mole fraction solubility of L-phenylalanine (1) (x_1) in water (2), methanol (3) + water (2) solvent mixture correlated with different temperatures: (○) $x_2^0 = 1.0000$; (●) $x_2^0 = 0.8827$; (△) $x_2^0 = 0.8176$; (▲) $x_2^0 = 0.7378$; (◇) $x_2^0 = 0.6921$; (■) $x_2^0 = 0.5997$; (□) $x_2^0 = 0.3597$; and (◆) $x_2^0 = 0.0000$. The points represent the experimental data, and the curves represent the results fitted by the Apelblat model.

dissolving process of L-phenylalanine is endothermic, which means that higher temperature could provide more quantity of heat to promote the formation of solvated ions in the reaction.

3.4. Thermodynamic properties of solutions

From the above, it was concluded that the solution process of L-phenylalanine depended on both the solvent composition and temperature, and the results from the latter provided the basis for a thermodynamic analysis which could be used to elucidate the molecular mechanisms involved in the solution process [25]. The standard molar enthalpy change of solution could be related to the temperature and the solubility with the following equation based on the van't Hoff analysis [26].

$$\frac{\Delta H_s^{\circ}}{R} = -\frac{\partial \ln x_1}{\partial (1/T)} \tag{14}$$

As the mole fraction solubility is temperature dependent, Eq. (13) could be put into Eq. (14). The heat capacity change of
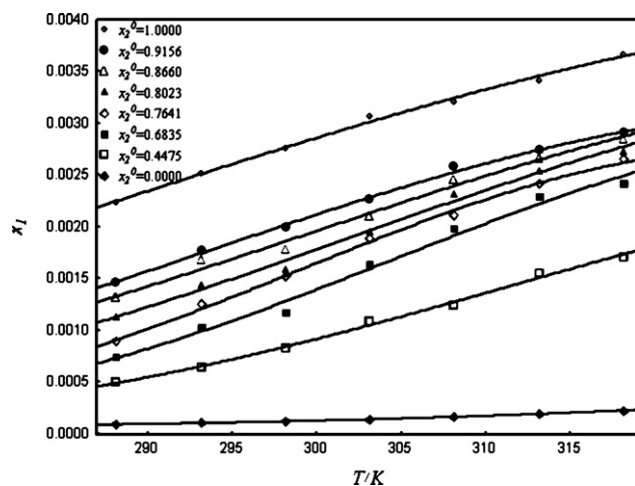

Fig. 6. Solubility of L-phenylalanine (1) (m_1) in water (2), ethanol (3) + water (2) solvent mixture correlated with different temperatures: (○) $x_2^0 = 1.0000$; (●) $x_2^0 = 0.9156$; (△) $x_2^0 = 0.8660$; (▲) $x_2^0 = 0.8023$; (◇) $x_2^0 = 0.7641$; (■) $x_2^0 = 0.6835$; (□) $x_2^0 = 0.4475$; and (◆) $x_2^0 = 0.0000$. The points represent the experimental data, and the curves represent the results fitted by the Apelblat model.

Table 3
Fitted parameters of Apelblat model for L-phenylalanine for different temperature at various contents of organic solvent (x_2^0).

x_2^0(mole fraction)	a	b	c	$\sum(\%D)$
Water (2) + methanol (3)				
1.0000	212.1827	−11089.2307	−31.7472	0.8457
0.8827	593.2957	−28790.3658	−88.2607	1.6247
0.8176	461.2417	−22930.8150	−68.5458	1.3941
0.7378	495.1208	−24637.6181	-73.4963	1.3125
0.6921	123.6992	−7819.1763	−18.2207	2.0364
0.5997	−57.0506	141.4455	8.7974	0.8372
0.3597	100.3076	−6961.6025	−14.6946	1.3465
0.0000	861.3524	−41535.0837	−128.0545	2.9292
				$\sum\sum(\%D)/n = 1.5408$
Water (2) + ethanol (3)				
1.0000	212.1827	−11089.2307	−31.7472	0.8457
0.9156	445.2782	−22134.7330	−66.2107	1.0712
0.8660	375.6429	−19221.1132	−55.7192	2.3885
0.8023	449.4992	−22887.3484	−66.5421	1.8933
0.7641	890.1547	−43185.1989	−131.9493	1.6913
0.6835	763.0755	−37896.8211	−112.7898	3.5326
0.4475	566.2419	−29150.6569	−83.4662	1.9719
0.0000	−248.7317	8308.7767	37.1693	0.9476
				$\sum\sum(\%D)/n = 1.7928$

solution could be assumed to be constant in the temperature interval of 288.15–298.15 K, so that the values of the molar enthalpy change for solution process could be considered as valid for the mean temperature (303.15 K) [27]. Therefore the standard molar enthalpy change of the solution ($\triangle H_s^\circ$) can be calculated by Eq. (15).

$$\Delta H_s^\circ = -R\left(\frac{\partial \ln x_1}{\partial(1/T)}\right) = -R(b - cT_{mean}) \tag{15}$$

The standard molar Gibbs energy change for the solution process can be calculated by the following equation [27]:

$$\Delta G_s^\circ = -RT_{mean} \times \text{intercept} = \Delta H_s^\circ + T_{mean}\Delta S_s^\circ \tag{16}$$

where the intercept could be obtained from the line of $\ln x_1$ vs. $(1/T - 1/T_{mean})$ [28] (partially shown in Fig. 7). The standard molar entropy change for solution process could be calculated by the equation above. These standard thermodynamic parameters for the solution process for different mixture systems have been calculated and presented in Table 4.

From Table 4, it can be seen that the standard molar enthalpy of solution for all system was positive, which indicates the process was endothermic. In the binary mixtures, the values of $\triangle H_s^\circ$ increased with the decline in the molar fraction of water and attained a maximum at $x_2^0 = 0.4475$ in the (water + ethanol) mixture, which was the same as the entropy $\triangle S_s^\circ$. But it was complicated in the (water + methanol) mixture (Table 4), although the maximal values of enthalpy and entropy were still obtained at the same point, $x_2^0 = 0.5997$. In the pure solvent, the value of $\triangle H_s^\circ$ in methanol is lower than that in ethanol, and the value in water is the lowest. The value of the enthalpy for the solution process is the integration of several kinds of interactions, thus the higher values of the enthalpy indicated that more energy was needed to overcome the cohesive force of the solute and the solvent in the dissolution process, which also signified the stronger dependence between the temperature and the solubility [26]. Therefore the lowest value of $\triangle H_s^\circ$ in pure water implied that the dissolution in water is easier than in the organic solvents.

For all cases, the values of the standard molar Gibbs energy change of solution were positive, which indicated that the process was not spontaneous. However, the value of entropy was negative in pure water and positive in the other mixtures, which demonstrated that the entropy was driving the solution process [29]. Eqs. (17) and (18) were used to compare the relative contribution to
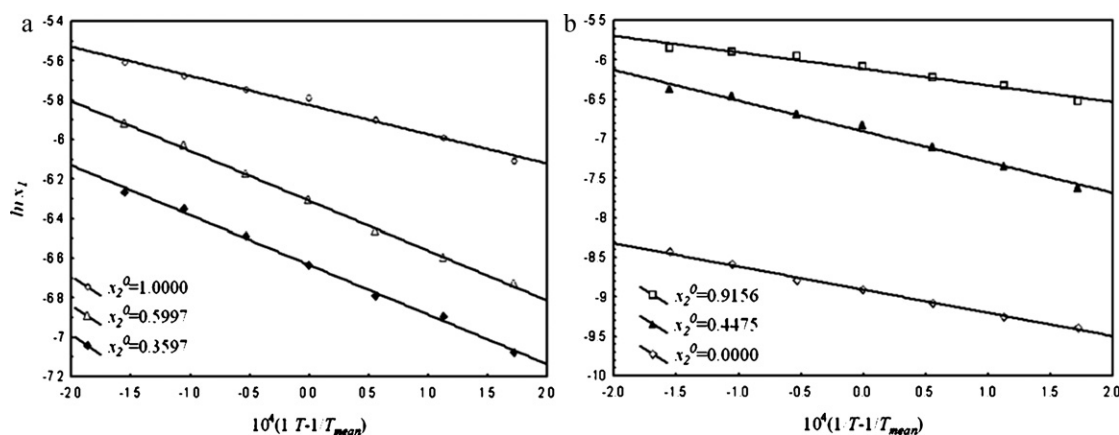

Fig. 7. Temperature dependence of solubility of L-phenylalanine in water, some of methanol + water (a), and ethanol + water (b) solvent mixture. (a) (○) x_2^0 = 1.0000; (△) x_2^0 = 0.5997; and (♦) x_2^0 = 0.3597; (b): (□), x_2^0 = 0.9156; (▲) x_2^0 = 0.4475; and (◊) x_2^0 = 0.0000. The points represent the experimental data, and the curves represent the results based on linear fitting.

Table 4
Thermodynamic functions relative to solution process of L-phenylalanine in various contents of organic solvent (x_2^0) at 303.15 K.

x_2^0(mole fraction)	$\triangle H°$ (kJ/mol)	$\triangle G°$ (kJ/mol)	$\triangle S°$ (J/mol/K)	%ς_H	%ς_{TS}
Water (2) + methanol (3)					
1.0000	12.18 ± 0.03	14.68 ± 0.06	−8.25 ± 0.03	82.96	17.04
0.8827	16.91 ± 0.02	15.28 ± 0.03	5.37 ± 0.02	91.22	8.78
0.8176	17.88 ± 0.04	15.43 ± 0.05	8.08 ± 0.05	87.95	12.05
0.7378	19.59 ± 0.06	15.54 ± 0.07	13.35 ± 0.07	85.15	14.85
0.6921	19.09 ± 0.08	15.68 ± 0.06	11.23 ± 0.06	84.86	15.14
0.5997	21.00 ± 0.08	15.90 ± 0.03	16.81 ± 0.08	80.47	19.53
0.3597	20.84 ± 0.05	16.72 ± 0.03	13.61 ± 0.04	83.48	16.52
0.0000	22.58 ± 0.11	17.97 ± 0.07	15.19 ± 0.05	83.06	16.94
Water (2) + ethanol (3)					
1.0000	12.18 ± 0.05	14.68 ± 0.07	−8.25 ± 0.04	82.96	17.04
0.9156	17.15 ± 0.06	15.42 ± 0.03	5.72 ± 0.05	90.81	9.19
0.8660	19.37 ± 0.03	15.59 ± 0.05	12.48 ± 0.07	83.66	16.34
0.8023	22.57 ± 0.07	15.81 ± 0.08	22.32 ± 0.11	76.94	23.06
0.7641	26.48 ± 0.12	16.03 ± 0.06	34.46 ± 0.15	71.71	28.29
0.6835	30.80 ± 0.09	16.39 ± 0.02	47.54 ± ± 0.16	68.13	31.87
0.4475	31.99 ± 0.03	17.41 ± 0.04	48.10 ± 0.12	68.69	31.31
0.0000	24.60 ± 0.05	22.46 ± 0.03	7.08 ± 0.06	91.97	8.03

the standard Gibbs energy by enthalpy and entropy in the solution process [30].

$$\%\varsigma_H = 100 \frac{\left|\Delta H_s°\right|}{\left|\Delta H_s°\right| + \left|T_{\mathrm{mean}}\Delta S_s°\right|} \qquad (17)$$

$$\%\varsigma_{TS} = 100 \frac{\left|T_{\mathrm{mean}}\Delta S_s°\right|}{\left|\Delta H_s°\right| + \left|T_{\mathrm{mean}}\Delta S_s°\right|} \qquad (18)$$

The values of %ς_H and %ς_{TS} were calculated and listed in Table 4. The values of %ς_H were greater than 60%, which indicated that the main contributing force to the standard Gibbs energy was the enthalpy during the dissolution of L-phenylalanine in all the mixtures studied.

4. Conclusion

The solubility of L-phenylalanine in mixed systems was investigated from 288.15 to 318.15 K. The solubility data were fitted to the CNIBS/Redlich–Kister model and the semiempirical Apelblat model, and the dimensionless parameters for each fitting equation at each system were determined. The values of the sum of deviation ($\Sigma\Sigma(\%D)/n$) for the CNIBS/Redlich–Kister model are 1.0953 (water + methanol) and 1.7627 (water + ethanol), while these values for Apelblat model are 1.5408 (water + methanol) and 1.7928 (water + ethanol). This result indicated that the experimental data agreed well with the calculated results from the two models, and the CNIBS/Redlich–Kister model provided a more reasonable prediction according to its lower value of the sum of deviation ($\sum\sum(\%D)$).

The experimental results showed that the solubility of L-phenylalanine in binary solvent mixtures increased with the molar fraction of water and the temperature. Water was a better solvent for L-phenylalanine than the others. Methanol and ethanol could be used as effective anti-solvents in the crystallization process, and furthermore ethanol showed a more prominent anti-solvent effect than methanol.

In addition, the thermodynamic properties for the solution process including Gibbs energy, enthalpy, and entropy were obtained by the van't Hoff equation and the Gibbs equation. For all the cases studied, both of the values of standard molar enthalpy change and standard molar Gibbs energy change of solution were positive, which indicated that the process was endothermic and not spontaneous. Entropy-driving was found overall to be the solution process for almost all the mixtures.

Acknowledgements

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