Solubility of 6-Aminopenicillanic Acid in Aqueous Salt Solutions from 273.15 K to 303.15 K

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The solubility of 6-aminopenicillanic acid in aqueous solutions of various concentrations of sodium sulfate and ammonium sulfate was determined from (274.15 to 303.15) K at atmospheric pressure using a synthetic method. Results showed that sodium sulfate has a salting-in effect on the solubility of 6-aminopenicillanic acid; ammonium sulfate has a salting-in effect if its concentration is below 0.5 M and a salting-out effect if its concentration is above 0.5 M. The solubility data were accurately correlated by a semiempirical equation.

Introduction

6-aminopenicillanic acid (CAS NO. 551-16-6), the nucleus of the original penicillin molecule, is 6-amino-3, 3-dimethyl-7-oxo-4-thio-1-azabicyclo [3, 2, 0] heptane-2-carboxylic acid. As can be seen from Figure 1, 6-aminopenicillanic acid has an amino group and a carboxyl group in its structure.

As an important intermediate in the production of semisynthetic antibiotics, 6-aminopenicillanic acid has normally been produced by enzymatic hydrolysis of penicillin G, and then the resulting degraded products may be subjected to an extraction process. Finally, 6-aminopenicillanic acid is crystallized from the extractive aqueous phase.[1−3] During these processes, some inorganic salts, acid, and alkali exist in the system as impurities. It has been reported that the solubilities of zwitterionic substances are affected by inorganic salts.[4−7] To design an optimized crystallization process that is pertinent to be used in a production plant, it is necessary to know the solubility in such aqueous salt solutions. Despite much interest on the solubility of the 6-aminopenicillanic acid,[8−10] no experimental solubility data in aqueous salt solutions are available. The aim of this paper was to study the effect of electrolytes on the solubility of 6-aminopenicillanic acid. The method employed in this work is classed as a synthetic method, which is much faster and convenient than the usual analytical method.[11]

Experimental Section

Materials. A white crystalline powder of 6-aminopenicillanic acid was obtained from the North China Pharmaceutical Co., Ltd. with a melting/decomposition point of 209 °C, which compares well with the literature value of 209 °C to 210 °C,[12] measured with a ETZSCH STA449C differential scanning calorimeter and was prepared by recrystallization from pure water. Its purity, determined by HPLC according to the literature,[13] is higher than 99.5 wt %. Distilled deionized water of HPLC grade obtained from the market and sodium sulfate and ammonium sulfate of analytical research grade reagent obtained from the Tianjin University KeWei Company were used as received. All solutions were prepared based on molality, and the water was weighed.

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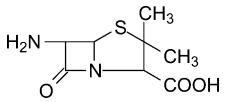

Figure 1. Chemical structure of 6-aminopenicillanic acid.

Table 1. Solubility (x_A) of 6-Aminopenicillanic Acid (A) in Different Concentrations of Aqueous Sodium Sulfate Solutions

T/K	$10^4\,x_A^{cal}$	$10^4\,x_A^{cal}$	T/K	$10^4\,x_A^{cal}$	$10^4\,x_A^{cal}$
	0.0000 M			0.0508 M	
274.15	1.3246	1.3332	274.35	1.4343	1.4465
278.15	1.4346	1.4289	278.15	1.5479	1.5517
283.15	1.5933	1.5598	283.15	1.7162	1.7031
289.15	1.7283	1.7352	288.15	1.8959	1.8708
293.15	1.8311	1.8643	293.15	2.0430	2.0564
298.15	2.0252	2.0406	298.15	2.2246	2.2618
303.15	2.2603	2.2352	303.15	2.4876	2.4888
	0.0997 M			0.2000 M	
274.35	1.5396	1.5525	274.85	1.6640	1.6920
278.97	1.6603	1.6780	278.15	1.7862	1.7800
283.15	1.8240	1.8018	283.15	1.9361	1.9245
288.15	1.9541	1.9638	288.15	2.0978	2.0834
293.75	2.2079	2.1650	293.15	2.2826	2.2581
298.15	2.3358	2.3640	298.15	2.4224	2.4498
303.15	2.5337	2.5557	303.15	2.6589	2.6603
		0.3000 M			
274.15	1.8605	1.8696	293.15	2.4353	2.3899
278.15	1.9363	1.9647	298.15	2.5534	2.5588
283.15	2.1196	2.0938	303.15	2.7187	2.7431
288.15	2.2314	2.2703			

Apparatus and Procedure. Solubilities were measured by a synthetic method.[11] The apparatus for the solubility measurement is the same as that described in the literature.[14−16] A laser monitoring observation technique was used to determine the disappearance of the last crystal particles in the solid + liquid mixture at a known temperature. The laser-monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The equilibrium cell is a cylindrical-jacketed glass vessel (100 mL) maintained at a desired temperature by water circulated from a water bath with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ± 0.05 K of the required temperature. The cell has a perforated rubber cover plate to prevent the solvent from evaporating through which a mercury-in-glass thermometer with an uncertainty of ± 0.05 K was inserted. During the whole process, continuous stirring was performed

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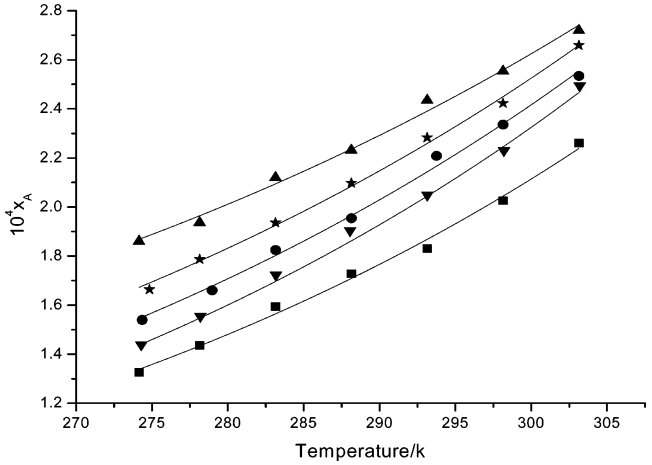

Figure 2. Experimental and calculated solubility of 6-aminopenicillanic acid in aqueous sodium sulfate solutions: square, pure water; inverted triangle, 0.0508 M; circle, 0.0997 M; asterisk, 0.2000 M; triangle, 0.3000 M.

Table 2. Solubility (x_A) of 6-Aminopenicillanic Acid (A) in Different Concentrations of Aqueous Ammonium Sulfate Solutions

T/K	$10^4\ x_A^{cal}$	$10^4\ x_A^{cal}$	T/K	$10^4\ x_A^{cal}$	$10^4\ x_A^{cal}$
	0.0000 M			0.2015 M	
274.15	1.3246	1.3332	275.3	1.9187	1.9434
278.15	1.4346	1.4289	278.15	2.0195	2.0123
283.15	1.5932	1.5598	283.15	2.1363	2.1421
289.15	1.7283	1.7352	288.15	2.2833	2.2843
293.15	1.8311	1.8643	293.15	2.4734	2.4397
298.15	2.0252	2.0406	298.15	2.6500	2.6095
303.15	2.2602	2.2352	303.15	2.7450	2.7946
	0.5050 M			1.0019 M	
275.15	2.1776	2.1992	275.35	1.849662	1.8631
278.15	2.2775	2.2640	278.15	1.942833	1.9298
283.15	2.3959	2.3807	283.15	2.044337	2.0576
288.15	2.4934	2.5087	288.15	2.208145	2.1976
293.15	2.6509	2.6488	293.15	2.34549	2.3507
298.15	2.8304	2.8016	298.15	2.550974	2.5178
303.15	2.9457	2.9682	303.15	2.67539	2.7002
		1.5000 M			
278.15	1.806437	1.7923			
288.15	2.035901	2.0613			
298.15	2.394966	2.3836			

with a magnetic stir bar. The masses of the samples and solvents were weighed using an analytical balance (Mettler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.0001 g.

The solubility was determined by the last crystal disappearance method, which is based on sequentially adding known masses of a solid to a stirred solution kept at a predetermined temperature until the last addition of the solid was not dissolved completely. The disappearance of the last crystal in the glass vessel was monitored by a laser beam. Aqueous salt solutions were prepared at different molalities of electrolyte. Predetermined excess amounts of water/solution were added in the inner chamber and then stirred continuously at the required temperature for 1 h to ensure that the temperature was constant. A known mass of 6-aminopenicillanic acid below its solubility was placed in the inner chamber of the vessel and the laser beam was blocked by the undissolved particles of solid in the solution so that the intensity of the laser beam penetrating the vessel was lower. Along with the dissolution of the particles of 6-aminopenicillanic acid, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear, and the laser intensity penetrating through the vessel reached a maximum. Then, additional solid of known mass (about 1 mg to 5 mg) was introduced into the vessel. This procedure was repeated until the maximum laser intensity could not be obtained, or in other words the last addition of solid did not dissolve completely. The interval between the addition of the solid was 60 min. The total amount of the solid consumed was recorded. The same solubility experiment was conducted three times, and the mean values were used to calculate the mole fraction solubility x_A based on the following equation:

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_W/M_W} \quad (1)$$

where m_A and m_w represent the masses of the solute and water, respectively, and M_A and M_W are the molecular weights of the solute and water, respectively. Compared to reported data, the solubility in pure water measured in this work is in good agreement with those in the literature.[17] The uncertainty of the experimental solubility values is about 0.5 %.

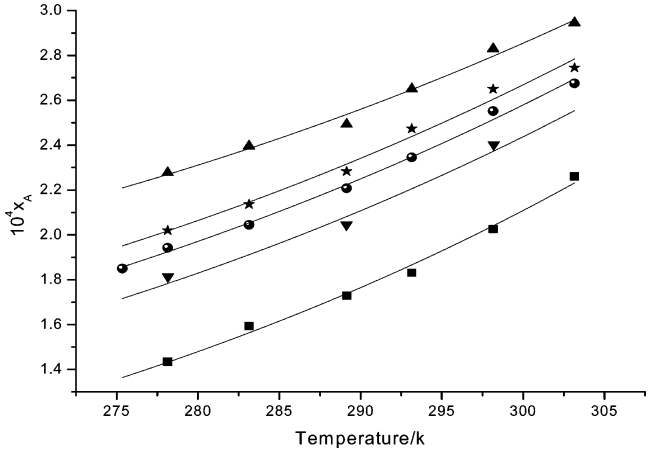

Figure 3. Experimental and calculated solubility of 6-aminopenicillanic acid in aqueous ammonium sulfate solutions: square, pure water; asterisk, 0.2015 M; triangle, 0.5050 M; circle, 1.0019 M; inverted triangle, 1.5000 M.

Table 3. Parameters of Equation 2 for 6-Aminopenicillanic Acid in Aqueous Sodium Sulfate Solution of Different Molalities

molality	A	B	C	10^2 RMSD
0.0000	−84.52	2422	13.53	2.14
0.0508	−83.00	2286	13.36	2.05
0.0997	−83.20	2405	13.34	1.33
0.2000	−83.24	2503	13.29	2.05
0.3000	−84.73	2767	13.41	2.26

Table 4. Parameters of Equation 2 for 6-Aminopenicillanic Acid in Aqueous Ammonium Sulfate Solution of Different Molalities

molality	A	B	C	10^2 RMSD
0.0000	−84.52	2422	13.53	2.15
0.2015	−84.05	2753	13.30	2.91
0.5050	−84.39	2936	13.26	1.87
1.0019	−84.19	2735	13.32	1.84
1.5000	−84.12	2662	13.35	1.18

Results and Discussion

The solubilities of 6-aminopenicillanic acid in a series of concentrations of aqueous solutions are presented in Tables 1 and 2 and visually in Figures 2 and 3.

The temperature dependence of 6-aminopenicillanic acid solubility in aqueous solutions was described by the modified empirical equation[18]

$$\ln x_A = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \quad (2)$$

where x_A is the mole fraction solubility of 6-aminopenicillanic acid in water, T is the absolute temperature, and A, B, and C are the empirical parameters.

The calculated solubility values of 6-aminopenicillanic acid (x_A^{cal}) in aqueous solutions are also given in Tables 1 and 2. The values of the parameters A, B, and C and the root-mean-square deviations (RMSD) are listed in Tables 3 and 4. The RMSD is defined as follows:

$$\mathrm{RMSD} = \left\{ \frac{\sum_{i=1}^{N} (x_i^{cal} - x_i^{exp})^2}{N} \right\}^{1/2} \quad (3)$$

where N is the number of experimental points, and $x_i^{cal}$and x_i^{exp}represent the solubilities calculated from eq 2 and the experimental values, respectively.

From Tables 1 through 4 and Figures 2 and 3, we can draw the following conclusions: (1) the solubility of 6-aminopenicillanic acid in aqueous solutions increases with temperature; (2) sodium sulfate has a salting-in effect on the solubility of 6-aminopenicillanic acid; with increasing concentrations of sodium sulfate in water, the mass of 6-aminopenicillanic acid dissolved in water increases; (3) the effect of ammonium sulfate on the solubility of 6-aminopenicillanic acid can be divided into two stages: a salting-in effect if the concentration of ammonium sulfate is below 0.5 M and a salting-out effect if it is between 0.5 M and 1.5 M; (4) the calculated solubilities of 6-aminopenicillanic acid in aqueous solutions show good agreement with the experimental values, and the experimental solubility and correlation equation in this work can be used as essential data and models in the practical purification process of 6-aminopenicillanic acid.

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