Molar Enthalpy of Crystallization of (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid in Aqueous Sodium Sulfate and Ammonium Sulfate Solutions†

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Molar enthalpies of crystallization of (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid in sodium sulfate and ammonium sulfate aqueous solutions were estimated based on the solubilities. A positive effect of temperature on solubility of 6-APA in both Na_2SO_4 and $(NH_4)_2SO_4$ aqueous solutions gave a result of exothermic crystallization process, and the enthalpy released was about (7 to 13) $kJ \cdot mol^{-1}$. Concentrations of the electrolytes also have influences on the enthalpy value in the 6-APA crystallization process. In the sodium sulfate aqueous system, a higher concentration of sodium sulfate resulted in a lower value of enthalpy of crystallization released; however, in the ammonium sulfate system, the enthalpy of crystallization decreased when the $(NH_4)_2SO_4$ concentration was lower than 0.5 $mol \cdot dm^{-3}$ and then increased thereafter.

Introduction

(2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid (herein after known as 6-aminopenicillin acid and given the acronym 6-APA), the precursor of all semisynthetic penicillin antibiotics, is an important intermediate in the production of semisynthetic antibiotics. As familiar to us, antibiotics such as ampicillin, oxacillin, and piperacillin are all synthesized from 6-APA by adding a side-chain group on the acyl of the 6-APA molecule.

The 6-APA crystal was traditionally produced from penicillin G crystals through enzymatic hydrolysis, extraction, and finally crystallization.[1,2] Many pharmaceutical products were produced by crystallization in the final separation step which determines the purity, crystal size distribution (CSD), morphology, and bioavailability of the medicals.

Recent process research efforts were reported in which the penicillin G crystallization step was omitted and 6-APA crystals were separated successively from the initial complex penicillin G butyl acetate solution.[3] As a result, the composition of mother liquor for crystallization has been changed, and certain kinds of inorganic salts were formed and existed as impurities.

The equilibrium state of 6-APA in aqueous salt solutions at different temperatures depicted before gave the result of higher solubility at higher temperature at all concentrations.[4] It means that this dissolution is an endothermic process. The enthalpy change that results from dissolution of a solute into a solvent is known as molar enthalpy of dissolution. By analogy, enthalpy change resulting from the crystallization is called molar enthalpy of crystallization, and it would be exothermic in the 6-APA crystallization.

The molar enthalpy of crystallization ($\Delta_{fus}H_m$) can be very significant in crystallization energy balance calculations to design an optimal crystallization process.[5] However, there are no enthalpy of crystallization data published in the literature. The aim of this work was to study the enthalpy change to support the energy balance calculation in the current 6-APA crystallization process design.

Theory

When a solute dissolves in a solvent without reaction, energy is usually absorbed from the surrounding medium. On the contrary, when a solute crystallizes out of its solution, molar enthalpy is usually liberated (molar enthalpy of fusion), and the solution temperature rises. The enthalpies of solution and of crystallization are used to calculate the energy balance in the design and operation of industrial crystallizer as significant parameters.[5,6]

The enthalpy changes associated with dissolution ($\Delta_{sol}H_m$) and crystallization ($\Delta_{fus}H_m$) are generally recorded isothermally.

The first differential enthalpy of solution (molar enthalpy of solution at infinite dilution), $\Delta_{sol}H_m^{\infty}$, may be regarded as the energy liberated when 1 mol of solute dissolves in a large amount of pure solvent at a particular temperature. This is the value most generally recorded in the data handbooks and can be used to calculate the enthalpy change that would result from making a solution of desired concentration from its components. The last differential molar enthalpy of solution ($\Delta_{sol}H_m^{d}$) is the amount of energy liberated or absorbed, when 1 mol of the solute dissolves in a large amount of virtually saturated solution. This is numerically equal to the enthalpy of crystallization $\Delta_{fus}H_m$ but of opposite sign. The relationship is given by eq 1

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$$-\Delta_{fus}H_m = \Delta_{sol}H_m^{\infty} + \Delta_{dil}H_m = \Delta_{sol}H_m^{d} \quad (1)$$

For most inorganic salts and common organic solids, the enthalpy of solution at infinite dilution is available in the handbooks.[6] So, in crystallization practice, it is usual to take the molar enthalpy of crystallization as being equal in magnitude, but opposite in sign, to the molar enthalpy of solution at infinite dilution (usually negative). As the molar enthalpy of dilution is usually only a small fraction of the molar enthalpy of solution and being a positive value for most aqueous salt solutions, the true value of the molar enthalpy of crystallization will be slightly less than that obtained by eq 2. Therefore, the calculated quantity of molar enthalpy to be removed from a crystallizing solution will be slightly greater than the true value, and this small error can serve as a factor of safety in the design of cooling molar enthalpy transfer equipment.

$$-\Delta_{fus}H_m \approx -\Delta_{sol}H_m^{d} \quad (2)$$

However, molar enthalpy of solution data of 6-APA solid were not included in any handbook or literature. An alternative way to evaluate the molar enthalpy of crystallization, and hence to estimate the molar enthalpy of crystallization, is to consider the effect of temperature on the solubility.

$$\frac{d \ln c^*}{dT} \approx \frac{\Delta_{sol}H_m^{d}}{RT^2} \quad (3)$$

Combining eqs 1 and 3, we obtained

$$\frac{d \ln c^*}{dT} \approx -\frac{\Delta_{fus}H_m}{RT^2} \quad (4)$$

In which c^* is the solubility of the solute in solvent at a certain temperature; T is temperature; and R is the universal gas constant, equal to 8.3143 J·mol^{-1}·K^{-1}. The greater the effect of temperature on solubility, the higher the molar enthalpy of crystallization of the solute. Therefore, the molar enthalpy of crystallization of 6-APA can be deduced from eq 4.

By integration of eq 4, we obtained

$$\ln c^* = \frac{-\Delta_{fus}H_m}{RT} + M \quad (5)$$

In which M is a constant. The plot of ln c^* against $1/T$ results in a straight line. The slope is $-\Delta_{fus}H_m/R$, thus the ΔH_{crys} can be obtained from the plot. With this method, in a given crystallization system, the molar enthalpy of crystallization could be calculated by measuring solubility value in a series of temperatures.

Table 1. Enthalpy of Crystallization $\Delta_{fus}H_m$ of 6-APA in Aqueous Solutions of Sodium Sulfate in Dependence of Sodium Sulfate Concentration in the Temperature Range from (274.15 to 303.15) K

C / mol·dm^{-3}	$\Delta_{fus}H_m$ / kJ·mol^{-1}	10^2 SD
0.0000	12.147	1.34
0.0508	12.758	0.83
0.0997	11.838	1.04
0.2000	10.886	0.57
0.3000	9.131	0.86

Table 2. Enthalpy of Crystallization $\Delta_{fus}H_m$ of 6-APA in Aqueous Solutions of Ammonium Sulfate in Dependence of the Ammonium Sulfate Concentration C in the Temperature Range from (274.15 to 303.15) K

C / mol·dm^{-3}	$\Delta_{fus}H_m$ / kJ·mol^{-1}	10^2 SD
0.0000	12.133	1.40
0.2015	9.040	0.89
0.5050	7.337	0.70
1.0019	9.181	0.76
1.5000	9.604	0.80

The standard deviations (SD) of $\Delta_{fus}H_m$ are listed in Tables 1 and 2. The SD is defined as follows

$$SD = \left\{ \frac{\sum_{i=1}^{N} (\ln c^{fit} - \ln c^{exp})^2}{N} \right\}^{1/2} \quad (6)$$

where N is the number of experimental points and ln c^{exp} and ln c^{fit}, respectively, represent the experimental and the fitted values of logarithm equilibrium concentrations as shown in Figures 1 and 2.

Results and Discussion

The solubility data were published in our earlier work.[4] The relationships between the system temperatures and the equilibrium 6-APA concentration in aqueous sodium sulfate solutions and ammonium sulfate solutions according to eq 4 were shown, respectively, in Figure 1 and Figure 2, thus the molar enthalpies of crystallization in different aqueous salt solutions were calculated and listed in Table 1 and Table 2, respectively.

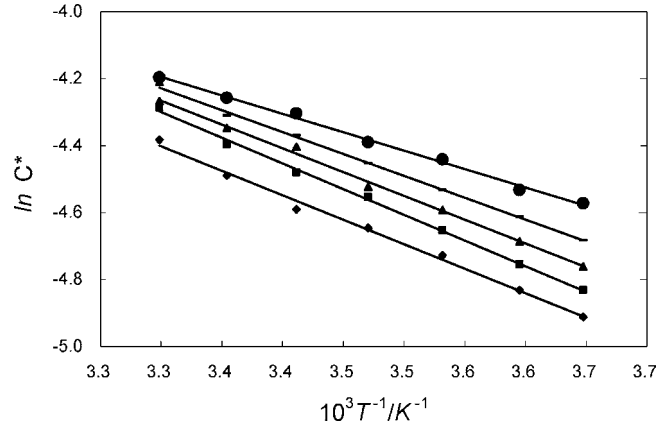

Figure 1. Relationship between logarithm equilibrium concentration, ln c^*, of 6-APA and the reciprocal of temperature T^{-1} in aqueous solutions of sodium sulfate. ◆, pure water; ■, 0.0508 mol·dm^{-3} sodium sulfate aqueous solution; ▲, 0.0997 mol·dm^{-3}; −, 0.2000 mol·dm^{-3}; ●, 0.3000 mol·dm^{-3}.

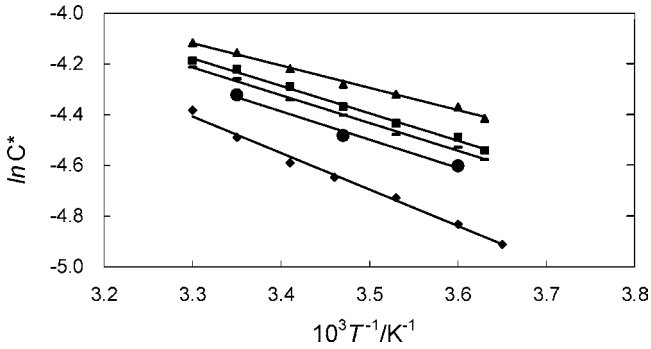

Figure 2. Relationship between the logarithm equilibrium concentration, ln c^*, of 6-APA and the reciprocal of temperature T^{-1} in aqueous solutions of ammonium sulfate. ◆, pure water; ■, 0.2015 mol·dm^{-3} ammonium sulfate aqueous solution; ▲, 0.5050 mol·dm^{-3}; −, 1.0019 mol·dm^{-3}; ●, 1.5000 mol·dm^{-3}.

The strong dependence of the molar enthalpy of crystallization on aqueous solutions of various concentrations of sodium sulfate and ammonium sulfate is shown in Tables 1 and 2.

(1) The molar enthalpy of crystallization value was positive in both sodium sulfate aqueous solutions and ammonium sulfate aqueous solutions (approximately (7 to 13)), which means the crystallization process of 6-APA was exothermic. To operate the crystallizer properly, the molar enthalpy of crystallization should be removed timely via the refrigerant, and the amount of refrigerant needed will be obtained by energy balance calculation according to the molar enthalpy of crystallization value above.

(2) In the sodium sulfate aqueous solution system, more molar enthalpy will be released when 6-APA crystallizes from the less concentrated Na_2SO_4 solution, which is in contrast to the solubility variations with temperature.

(3) As known from the previous publication concerning solubility of 6-APA in $(NH_4)_2SO_4$ aqueous solutions, the solubility value increased with the $(NH_4)_2SO_4$ concentration when the $(NH_4)_2SO_4$ concentration was from (0 to 0.5) mol·dm^{-3} ("salting-in effect"[4]) and then decreased in the $(NH_4)_2SO_4$ concentration range from (0.5 to 1.5) mol·dm^{-3} ("salting-out effect"[4]). As for molar enthalpy of crystallization discussed in this paper, its trend to $(NH_4)_2SO_4$ concentration was also divided into two stages, but opposite directions: molar enthalpy of crystallization value decreased with the concentration of ammonium sulfate in the concentration range of (0 to 0.5) mol·dm^{-3} and increased in the range of (0.5 to 1.5) mol·dm^{-3}.

Appendix

In this paper and in ref 4, different expressions for the concentration of 6-APA are used. Whereas the solubilities are given in mol·L^{-1}, the concentrations c^* are given by the mole fractions x_A.

Symbols a and b are the mole numbers of 6-APA and the solvent.

Then

$$x_A = \frac{a}{a+b} \tag{A}$$

$$c^* = \frac{1000a}{18b/\rho} \tag{B}$$

In eq B, ρ is the density of water (g·mL^{-1}), and 18 is the molar weight of water. The only unknown term (a/b) can be derived from eq A as follows

$$\frac{a}{b} = \frac{x_A}{1-x_A} \tag{C}$$

By substitution of eq B into eq C, eq D is obtained

$$c^* = \frac{1000\rho}{18}\frac{x_A}{1-x_A} \tag{D}$$

Finally, c^* can be calculated from the x_A value.

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