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Ternary phase diagram and the formation mechanism of two distinct solid solutions of amino acid systems: L-Valine/L-norvaline and L-valine/L-alanine

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ABSTRACT

The ternary phase diagram of L-valine (L-Val)/L-norvaline (L-Nva)/water system was determined at 293.15 K, in which the tie lines clearly indicate the formation of complete solid solution and X-ray powder diffraction (XRPD) analysis of the solid phases further confirms complete miscibility of L-Val and L-Nva molecules in the solid state. Further, homogeneous solid solution can be obtained via mechanochemical method of non-solution system and via anti-solvent method. Similar composition analysis of solid and liquid phase suggests that L-Val and L-alanine (L-Ala) is partially miscible with only a narrow scope of component substitution. The similarity degree of the three amino acids in cell dimensions and supramolecular organization determines the miscibility of L-Val and L-Nva or L-Val and L-Ala, and the investigation in molecular incorporation of L-Val/L-Nva system was developed. Applying the experimental solid-liquid equilibrium data, fractional crystallization is verified as an effective purification method.

1. Introduction

As the main components of protein and enzymes, amino acids play an important role in all forms of life served a variety of functions, which are widely used in the fields of cosmetics, food additives, pharmaceuticals, organic synthetic intermediate, et al. [1,2]. Usually, they can be obtained via hydrolyzation of protein-containing materials (such as hairs, wool, *etc.*) or fermentation and chemical synthesis [3]. Among these projects, microbial fermentation is the major promising process to produce amino acids [4]. However, during the process, it produced many other amino acid by-products as well as the undesired materials. Therefore the quality of the desired amino acid, such as crystal shape, purity, *etc.*, is significantly influenced by the presence of certain impurities [5,6]. For example, the presence of glutamic acid can induce significant agglomeration of L-Val according to the study of Hiromu Yoshiura et al. [7]. BBCAs are reported readily incorporating each other because of the similar crystal structures [8–10]. And the incorporation mechanism of the impurity and host amino acids was researched by Toshimichi Kamei [11], stating that lattice changes of solid solution result from the substitution of molecule in the unit lattice.

On this basis, to avoid undesired side effects from the impurities presenting in the resulting solution, crystallization is commonly used for further purification purposes. However, the maximum extent of purification is thermodynamically limited by miscibility of the target compound and the impurity in the solid state. Two components can be completely immiscible in the solid state forming a simple eutectic. Beyond that, they can also be miscible in forming solid solution which is a kind of multi-component and single-phase solid phase. According to the degree of miscibility, the solid solution can be divided into complete and partial solid solution corresponding to entire composition of the mixtures (completely miscible) and just covering a limited part (partially miscible), respectively. The crucial distinction of different types of solid solution is the incorporation ability for different molecules and the conditions for forming complete solid solution are more limited. The ternary phase diagrams representing different solid solution are depicted in Fig. 1. For partial solid solution, Fig. 1(a) having a simple eutectic is only one type of systems with the solid solution being isomorphic to B in crystal structure. And for

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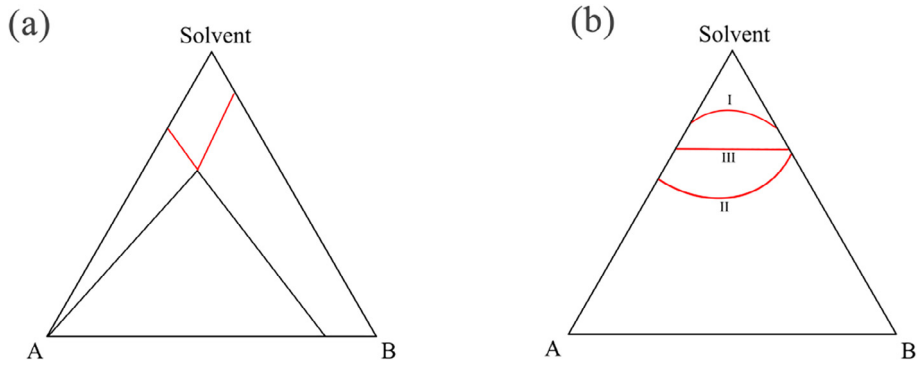

Fig. 1. Ternary phase diagrams for: (a) partial solid solution of A and B; (b) complete solution of A and B (I, II, III corresponding to three different types in solubility).

complete solid solution, Fig. 1(b), the ternary phase diagram may be displayed with minimum (I), maximum (II) or without extremum (III) in solubility isotherms [12]. The recent research on solid solution is mainly gathered for purification and design of materials [13,14]. For separation purpose in such solid solution systems, it is difficult to separate the pure components through a simple recrystallization. Therefore, it is necessary to study the amino acid solid solution.

L-Val, L-Nva and L-Ala are the three L-amino acids we studied. L-Nva and L-Val are isomeric compounds both extensively applied in pharmaceuticals [15,16]. L-Ala is one of the smallest chiral molecules used in medicine and veterinary drug industry [17]. The difference of the three L-amino acids is displayed in the hydrophobic side chains, and the molecular structures of them are presented in Fig. 2. Jan-Bernd Grosse Daldrup et al. [18] determined the solubility of L-Val/L-Ala/water system at 303 K and 323 K. However only the *liquidus* had been studied, and there was no analysis of the composition of solid products. Toshimichi Kamei *etc.* [19] illustrated that the incorporation of L-Nva doesn't affect the lattice length of L-Val when the content of the L-Nva within 4% (on L-Val wt% basis). Considering that the composition range of the system in their study is relatively narrow for the incorporation research and the related research for entire composition range has not yet been further carried out, therefore the scope of the study can be further broadened.

In this paper, we will give a detailed analysis about the systems of the L-Val with L-Nva and L-Ala. The main content of the article is divided into the following several points. In the first section, the solid-liquid phase analysis of L-Val/L-Nva/water and L-Val/L-Ala/water is reported and discussed. Then by comparing the difference of the three amino acids of L-Val, L-Nva and L-Ala, we highlight that the crystal structure similarity plays an important role in the formation of different solid solution. Finally, based on the ternary phase diagram and tie lines, fractional crystallization was exemplarily discussed to obtain more purified amino acids.

2. Experimental

2.1. Materials

L-Val and L-Ala were obtained from Shanghai Macklin Biochemical Co., Ltd. and L-Nva is provided by Adamas Reagent Co., Ltd.

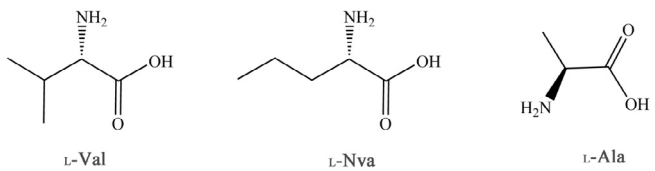

Fig. 2. Molecular structure of the L-amino acid.

with the mass purity > 0.990. They are all used as received without further purification. The HPLC-grade water was made in our own lab, which was used to prepare solutions of the amino acids, as well as the mobile phases for high-performance liquid chromatography (HPLC) analysis. The detailed information about the materials is listed in Table 1.

2.2. Methods

2.2.1. Isothermal method

Distilled water was added to the mixture of weighted batches of amino acids. The amount of water and reactants prepared to form a saturated solution at 323.15 K was determined in our preliminary experiments. And the preparation procedure was referred to the practice of Anton I. Isakov for L-Val/L-isoleucine system [20]. The particular process is as follows: (a) The vessel containing the solution was sealed and heated to 343.15 K under permanent mixing via magnetic stirrer until dissolution was completely. (b) The solution was then cooled to 268.15 K to form a mixture of ice and precipitated crystals, and kept this state for several hours. (c) The mixtures were heated to 293.15 K, and the suspension obtained was maintained at this temperature for 3 days to achieve solid-liquid equilibrium. There was no solid phase appearing if the solution was cooled down to 293.15 K directly. (d) The supernatant was withdrawn by syringe equipped with a filter and the wet residue was obtained and dissolved into water, then both of them were analysed by HPLC for determination of the composition. While for binary system (L-Val + water, L-Ala + water, L-Nva + water), the solubility of the pure L-amino acid at 293.15 K was determined by the analysis of gravimetric method. The equilibrated solid phase was obtained by filtering the suspension. The experimental procedure for liquid phase or wet residue analysis and the comparisons of the solubility data with the literatures were presented in Supporting Information in detail.

The samples of liquid phase were analysed by HPLC to get the ternary phase diagram and the solid phase was subjected to XRPD analysis.

2.2.2. Liquid assisted grinding method

200 mg of amino acid mixture containing both L-Val and L-Nva were transferred to a 15 mL stainless steel grinding jar with a grinding ball of 7 mm, and the mass fraction of L-Val ranged from 10% to 90%. A drop of water, approximately 30 μL, was added into the 200 mg of reactants. The solvent-drop grinding was executed on a Retsch MM 200 grinding mill for 30 min at 30 Hz. The samples after grinding were analysed via XRPD.

2.2.3. Anti-solvent method

Predetermined quantities of L-Val and L-Nva were added into beakers. Then a specific amount of deionized water was applied