The Solid Complex of Aminomalonic Acid with β-Alanine and Its Thermal Decomposition[1]

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For the crystallization of aminomalonic acid with several amino acids from an aqueous solution, solid complex formation was studied by means of an X-ray diffractometer. No complex formation of aminomalonic acid with α-alanine, *dl*-α-amino-*n*-butyric acid, *l*-isoleucine, *l*-leucine, *dl*-serine, *dl*-norleucine, α-amino-iso-butyric acid, *dl*-valine, *dl*-threonine, or *dl*-norvaline was observed. However, with β-alanine, the formation of a solid complex with a molar ratio of 1:1 was ascertained. When this solid complex was analyzed by the differential thermogravimetric method in air at a heating rate of 1.4°C/min, a decarboxylation reaction, accompanied by endothermic and exothermic peaks, was observed at 115—133°C. On the other hand, the decarboxylation of aminomalonic acid alone occurred in the temperature range of 112—138°C. The areas of the endothermic peak, which was attributed to the decarboxylation, and the endothermic peak, which was attributed to the crystallization energies of γ-glycine and β-alanine, were, respectively, about 3 and 3/2 times those of the peaks observed in the case of aminomalonic acid. It was also observed that the exothermic process proceeded in two steps. The X-ray analysis of the products of the decarboxylation process suggested that the complex first melted to become amorphous to X-rays, and that it was then decarboxylated to amorphous glycine and amorphous β-alanine with these subsequent crystallization. The two-step exothermic process was explained in terms of a somewhat earlier crystallization of amorphous glycine than in terms of that of the amorphous β-alanine. The activation energy of the solid complex was estimated to 119.2 kcal/mol from the thermogravimetric curve. This large value of the apparent activation energy may be considered to result because the solid complex turns to an amorphous phase much more sensitive to decarboxylation prior to decomposition, and the steep slope of the thermogravimetric curve which results from the rapid decarboxylation of the amorphous gives the large apparent activation energy.

The present authors have previously reported[2] that aminomalonic acid reacted with glycine to form a solid complex with a 1:1 molar ratio when they were crystallized from an aqueous solution, and that the complex was thermally more stable than aminomalonic aicd alone. This paper will describe the solid-complex formation of aminomalonic acid with several other amino acid, and the thermal characteristics of the complex, if formed, will be compared with those of aminomalonic acid.

Experimental

Materials. Aminomalonic acid purified by recrystallization and various amino acids (special grade chemicals) were dissolved (in a molar ratio of 1:1) into water. By then evaporating the solvent at 25°C under a pressure of 3—5 mmHg, and easily crystallizable or a highly viscous residue was obtained. When the highly viscous residue was allowed to stand in air, a crystalline powder was obtained. This crystalline powder was pulverized in an agate mortar and was then used as the sample.

Analysis. The X-ray analysis was carried out with an X-ray diffractometer, Rigaku Denki Geigerflex, using Ni filter-CuK_α radiation. The infrared absorption spectra were measured with a Nihon Bunko Grating Infrared Spectrophotometer, type DS-402G. The Nujol-mull method was adopted in the measurements. DTA-TGA was carried out by an apparatus previously reported.[3] Measurements were carried out in air, because no significant difference had been observed in air as in a nitrogen stream. Samples of 200—500 meshes were used for the measurements.

Determination of Aminomalonic Acid and β-Alanine by the X-ray Diffraction Technique. Aminomalonic acid was mixed with a solid complex, AM_1-β-AL_1 (AM: aminomalonic acid, AL: β-alanine, the subscripts refer to the molar ratio), in order to obtain samples with various weight ratios of aminomalonic acid to AM_1-β-AL_1. The mixture was triturated well in a mortar to diminish the orientation of the crystals. Then, the sample was set in a sample holder (the same sample holder was used throughout this work). The intensity [(half width) × (height)] of the diffraction peak due to aminomalonic acid at 24.1° (2θ) in these samples was measured in order to obtain a calibration curve, which was then used for the determination of the aminomalonic acid content (Fig. 3). The measuring conditions were as follows: 40 kV—1.5 mA;[4] full scale, 400 count/sec; time constant, 4: scanning speed, 0.5°(2θ)/min, and chart speed, 20 mm/min. The determination of β-alanine was carried out by the same method as that used for aminomalonic acid and under analogous condition, except for 40 kV—3 mA[4] and a chart speed of 40 mm. In this case, the height of the diffraction peak of β-alanine at 24.1° (2θ) was adopted as its intensity (Fig. 4).

Results and Discussion

Solid Complex-formation Ability. The solid complex-formation abilities of aminomalonic acid with several amino acids, studied by X-ray analysis, are shown in Table 1. The absence of any solid-complex formation is shown by the sign ×. In these cases, only the diffraction patterns of aminomalonic acid were observed. In the cases shown with the sign ○, a new diffraction pattern, different from those of the component amino acids, was observed, indicating a complex

1) Presented at the 91st Annual meeting of the Pharmaceutical Society of Japan, April, 1971.

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2) T. Kinugasa, J. Nishijo, and G. Hashizume, and I. Imanishi, This Bulletin, **44**, 2035 (1971).

3) T. Kinugasa, J. Nishijo, and G. Hashizume, *Nippon Kagaku Zasshi*, **90**, 584 (1969).

4) Each constant X-ray intensity was ascertained by measuring the height of the diffraction peak of γ-glycine at 21.8° (2θ).

Table 1. Solid complex-formation ability of aminomalonic acid with amino acids

α-Alanine	△
dl-α-Amino-*n*-butyric acid	△
l-Isoleucine	△
l-Leucine	×
dl-Serine	×
dl-Norleucine	×
α-Aminoisobutyric acid	△
dl-Valine	△
dl-Threonine	△
dl-Norvaline	×
β-Alanine	○
Glycine	○

formation. In the cases shown with the sign △, diffraction pattern consisted of the peaks due to unknown species and those of the component amino acid, (aminomalonic acid or added amino acid). The former were found to correspond to the diffraction peaks of the hydrate of aminomalonic acid or the added amino acid. Thus, we concluded that no complex is formed in these cases.

The fact that aminomalonic acid can form solid complexes with β-alanine and glycine, but not with α-substituted amino acids, seems to suggest that steric factors in the neighborhood of amino and carboxyl groups of amino acids have a bearing on the complex-formation ability of aminomalonic acid with other amino acids.

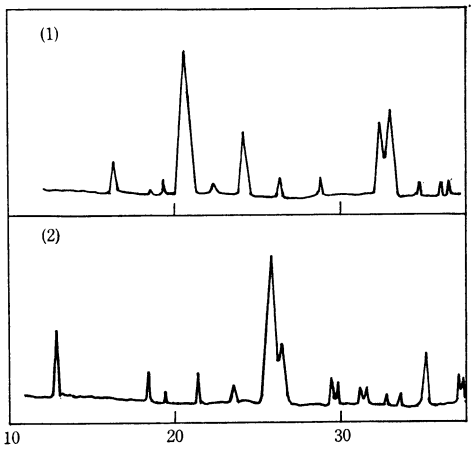

Fig. 1. X-ray diffraction patterns of aminomalonic acid (1) and β-alanine (2).

Solid Complex of Aminomalonic Acid with β-Alanine. The X-ray diffraction patterns of aminomalonic acid and β-alanine are shown in Fig. 1, while those of the samples, whose molar ratios of aminomalonic acid to β-alanine are 1 : 1, 2 : 1, and 1 : 2, are shown in Fig. 2. In the case of AM_1-β-AL_1, a new diffraction pattern, different from those of the components, aminomalonic acid and β-alanine, was obtained, while in the cases of AM_2-β-AL_1 and AM_1-β-AL_2, diffraction patterns of AM_1-β-AL_1 with those of aminomalonic acid or β-alanine respectively were observed. Also, AM_3-β-AL_2 and AM_4-β-AL_3 gave patterns of AM_1-β-AL_1 and

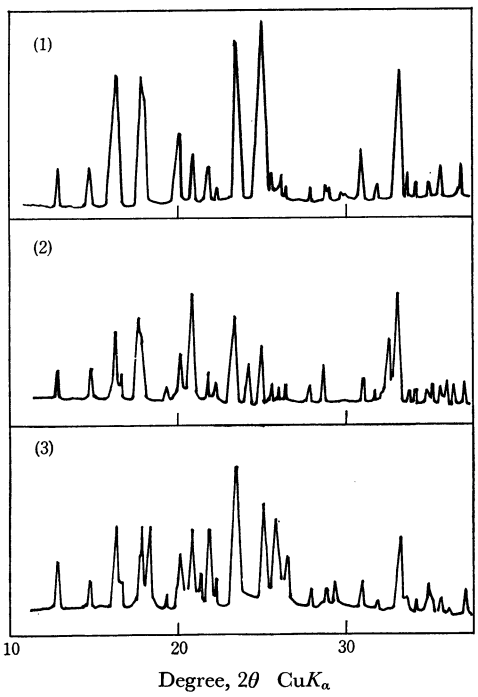

Fig. 2. X-ray diffraction patterns of AM_1-β-AL_1 (1), AM_2-β-AL_1 (2) and AM_1-β-AL_2 (3).

aminomalonic acid, while AM_2-β-AL_3 and AM_3-β-AL_4 gave patterns of AM_1-β-AL_1 and β-alanine. To determine the molar ratio of aminomalonic acid to β-alanine in the complex, the content of aminomalonic acid in AM_2-β-AL_1, AM_3-β-AL_2, and AM_4-β-AL_3, and that of β-alanine in AM_1-β-AL_2, AM_2-β-AL_3, AM_3-β-AL_4, were estimated by using the calibration curves (Figs. 3, 4). The contents of aminomalonic acid and β-alanine, which exist excessively in these samples, were calculated by assuming that the crystals corresponding to the diffraction pattern of AM_1-β-AL_1 were composed of aminomalonic acid and β-alanine in a molar ratio of 1 : 1. These calculated values agreed fairly well with the found values, as shown in Table 2. It was concluded

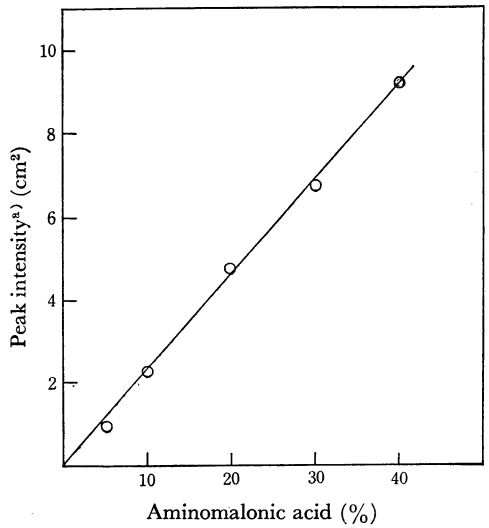

Fig. 3. Calibration Curve for Aminomalonic Acid in AM_x-β-AL_y($x>y$)
[a] [(half width) × (height)] of diffraction peak

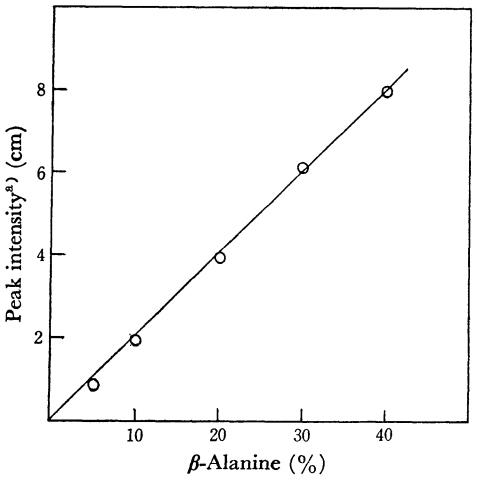

Fig. 4. Calibration Curve for β-Alanine in AM_x-β-AL_y ($x<y$)
[a] height of diffraction peak

Table 2. Quantitative determination of excess aminomalonic aicd in AM_2-β-AL_1, AM_3-β-AL_2 and AM_4-β-AL_3 and excess β-alanine in AM_1-β-AL_2, AM_2-β-AL_3 and AM_3-β-AL_4 by X-ray analysis

	Calcd (%)		Found (%)	
	AM	β-AL	AM	β-AL
AM_2-β-AL_1	36.4		34.8	
AM_3-β-AL_2	22.2		19.0	
AM_4-β-AL_3	16.0		16.5	
AM_1-β-AL_2		30.0		33.5
AM_2-β-AL_3		17.6		16.8
AM_3-β-AL_4		12.5		13.1

that aminomalonic acid reacts with β-alanine in a 1:1 molar ratio to produce a solid complex which gives the diffraction pattern of AM_1-β-AL_1.

The infrared absorption spectra of aminomalonic acid, β-alanine, and AM_1-β-AL_1 are shown in Fig. 5. In the spectrum of AM_1-β-AL_1, absorption bands observed in the neighborhood of 820, 910, and 1100 cm^{-1} were especially different from those of aminomalonic acid or β-alanine. In addition, the band at 1710 cm^{-1},

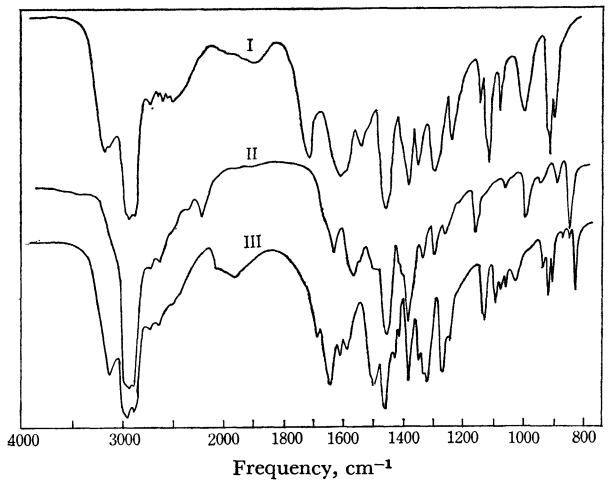

Fig. 5. Infrared absorption spectra of aminomalonic acid (I), β-alanine (II) and AM_1-β-AL_1 (III) in Nujol

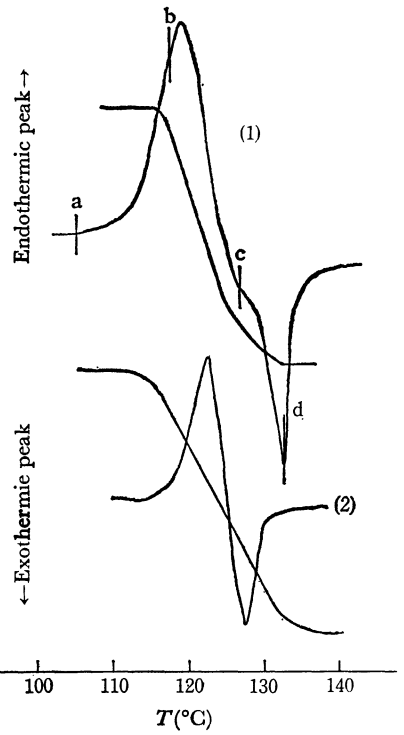

Fig. 6. DTA-TGA curves of AM_1-β-AL_1(1) and aminomalonic acid (2), in air. heating rate: 1,4/min.
Sensibility: ± 50 μv reference: silica powder

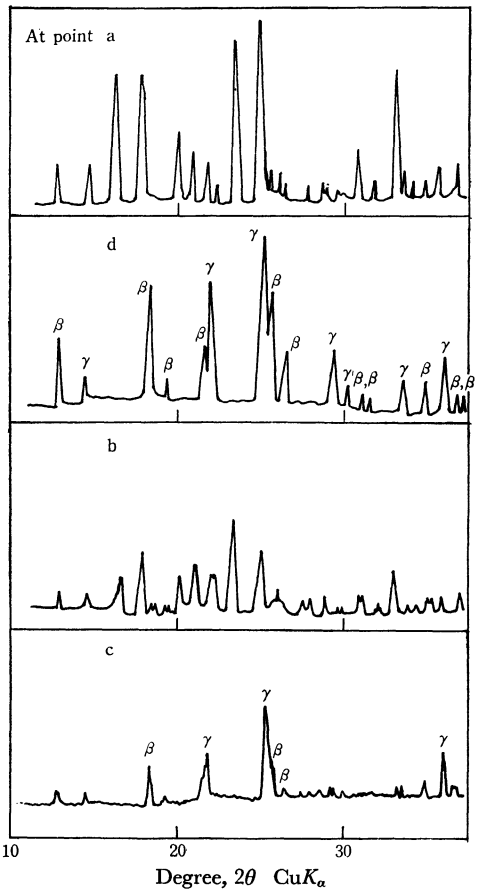

Fig. 7. X-ray diffraction patterns of samples taken out rapidly at point a, d, b and c in DTA curve in Fig. 4.
γ: γ-glycine β: β-alanine

attributed to the carboxyl group of aminomalonic acid, was shifted to about 1685 cm^{-1}. On the contrary,when no complex was formed, only superimposed absorption bands of aminomalonic acid were observed.

Differential Thermal Analysis and Thermogravimetric Analysis. The DTA–TGA curve of AM_1-β-AL_1 in air, using 87.4 mg of the sample at a heating rate of 1.4°C/min, is shown in Fig. 6, together with the corresponding curve of aminomalonic acid. These curves show that the beginning temperature of the decarboxylation of AM_1-β-AL_1 is slightly higher than that of aminomalonic acid, while the completion temperature of the former was about 5°C lower than that of the latter and that, consequently, the rate of decomposition of the former was larger than that of the latter. On the other hand, it is confirmed that, in the case of AM_1-β-AL_1, the endothermic process slightly precedes a decrease in weight, and the peak area is about 3 times that of aminomalonic acid. It is also found that the exothermic process proceeds in two steps. The peak area was about 3/2 times that of aminomalonic acid. To study the decarboxylation process of AM_1-β-AL_1, the samples were taken out rapidly at the a, b, c, and d points in the DTA curve shown in Fig. 6 and these samples were subjected to X-ray analysis. The results are shown in Fig. 7. Figure 7 shows that, at the a point, diffraction pattern is identical with that of AM_1-β-AL_1. This means that no change in AM_1-β-AL_1 occurs untill the decarboxylation begins. The diffraction patterns of the sample at the d point, where the decarboxylation is almost completed, were identical with those of γ-glycine and β-alanine. The sample rapidly taken out at the b point, where the decarboxylation proceeds about 15%, gives only a diffraction pattern identical with that of AM_1-β-AL_1. The sample at the c point, where the differencial thermal curve tends to a large second exothermic peak and where the decomposition fraction is about 70%, gives diffraction patterns of γ-glycine and β-alanine. These samples were allowed to stand in air in the sample holder for an X-ray diffractometer, and an X-ray analysis of the samples was carried out under the same conditions. The results are shown in Fig. 8. With the sample at the b point, the intensity of the diffraction pattern of AM_1-β-AL_1 increases and the diffraction peaks of γ-glycine and β-alanine appear. With the sample at the c point, the intensities of the diffraction peaks due to γ-glycine and β-alanine increase, but the increasing rate of intensity in β-alanine is larger than that in γ-glycine. Moreover, the diffraction peaks of AM_1-β-AL_1 appear, they can not be observed in the sample rapidly taken out. As it takes 7—10 min to transfer the sample from the DTA-TGA apparatus to the sample holder for X-ray analysis and to measure its diffraction pattern, the following decarboxylation process may be suggested. At first, AM_1-β-AL_1 may melt as a complex amorphous to X-ray analysis, and the amorphous complex may decarboxylate to amorphous glycine and amorphous β-alanine, which then soon crystallize to γ-glycine and β-alanine. The crystallization of amorphous glycine to γ-glycine may take place slightly earlier than that of β-alanine. Therefore, it can be considered that the endothermic peak corresponds to the heat required for the decarboxylation with melting, while the exothermic peak corresponds to the energy of crystallization to γ-glycine and β-alanine from their amorphous forms. The two-step change from the endothermic to the exothermic process can be interpreted in terms of a slight difference in crystallization velocity between the two compounds.

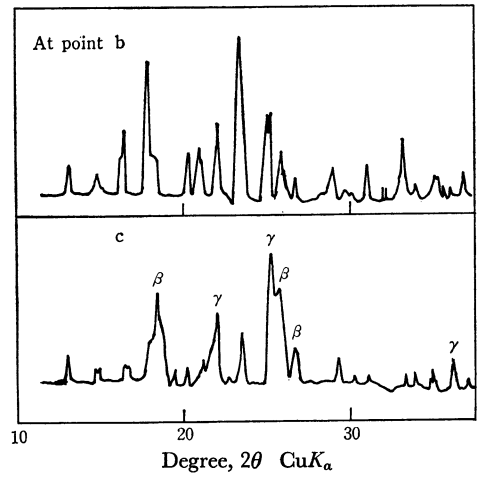

Fig. 8. X-ray diffraction patterns of samples at point b, c, left overngiht at room temperature.
γ:γ-glycine β:β-alanine

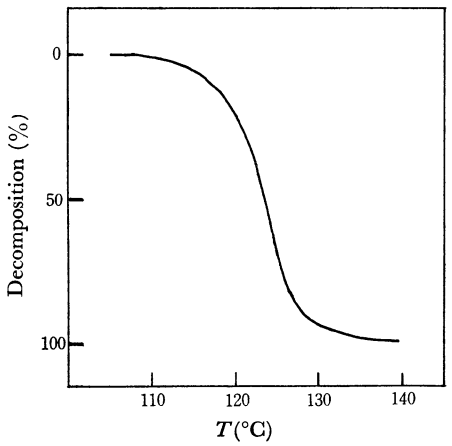

Fig. 9. Thermogravimetric curve of AM_1-β-AL_1 in air. heating rate: 1.0°C/min. sample amount: 50 mg.

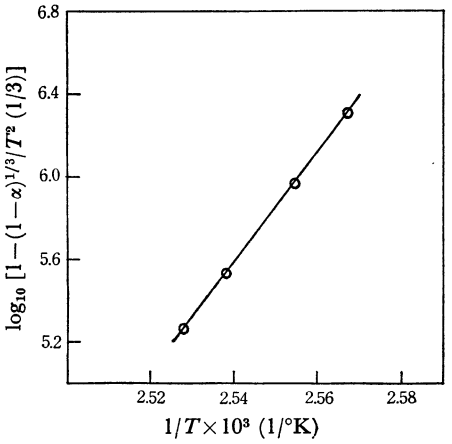

Fig. 10. Decarboxylation from AM_1-β-AL_1. n=2/3

5) A. W. Coats and J. P. Redfern, *Nature*, **201**, 68 (1968).

Activated Energy. By applying the equation previously proposed by Coats and Redfern[5] for the determination of the activation energy of a solid state reaction accompanied by a weight decrease, the activation energies of the decarboxylation of aminomalonic acid and AM_1-G_1 were calculated as 69.4 kcal/mol and 20.3 kcal/mol respectively. The determination of the activation energy of the decarboxylation of AM_1-β-AL_1 from its thermogravimetric curve with a heating rate of 1°C/min (Fig. 9) was attempted using the same equation. In the decomposition range from 10 to 63%.

$$\log_{10}\{1-(1-\alpha)^{1-n}/T^2(1-n)\} \text{ or } \log_{10}\{-\log(1-\alpha)/T^2\}$$

was plotted against $1/T$, assuming $n=0$, 1/2, 2/3, or 1. The best linearity was found with $n=2/3$ (Fig. 10). From the slope, the activation energy was calculated as 119.2 kcal/mol. This very large value may be explained as follows, amorphous AM_1-β-AL_1, to which the complex has melted prior to its decomposition, is so active in the decarboxylation that the reaction proceeds very rapidly; consequently, the slope of the thermogravimetric curve may be so steep that a very large apparent activation energy can be obtained.

It was concluded from these experimental results that a solid complex of aminomalonic acid with β-alanine was formed, but unlike the complex of aminomalonic acid with glycine, thermal stabilization can be obtained in this complex.