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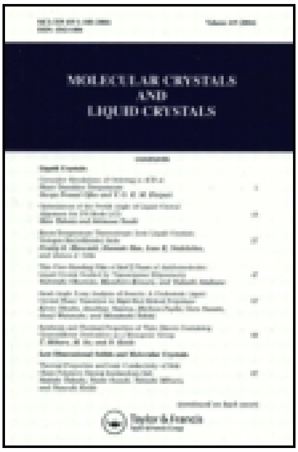

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Polymerization of N-Carboxy Anhydrides of L- and DL- Valine, and L- and DL- Phenylalanine in the Solid State

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POLYMERIZATION OF *N*-CARBOXY ANHYDRIDES OF L- AND DL- VALINE, AND L- AND DL- PHENYLALANINE IN THE SOLID STATE

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Abstract Polymerization of *N* -carboxy anhydrides (NCAs) of L-valine and DL-valine in the solid state in hexane was compared with their polymerization in the anisole solution, and the results were explained with reference to their crystal structures. Both of L-valine NCA and DL-valine NCA were less reactive in the solid state than in the solution, but the molecular weight of the polymer of L-valine NCA obtained in the solid state was much higher than that in the solution. The molecular weight of the polymer obtained in the solid state polymerization of DL-Valine NCA increased with the increase in conversion, while that in the solution decreased with the conversion. Electron microscopy, X-ray analysis and IR spectroscopy suggested that the polymerization of L-valine NCA and DL-valine NCA took place in the layer normal to the *b* axis in the crystal, which was suggested by their crystal structures. In addition, it was found that L-phenylalanine NCA and DL-phenylalanine NCA were very reactive in the solid state, while they were inactive in the solution.

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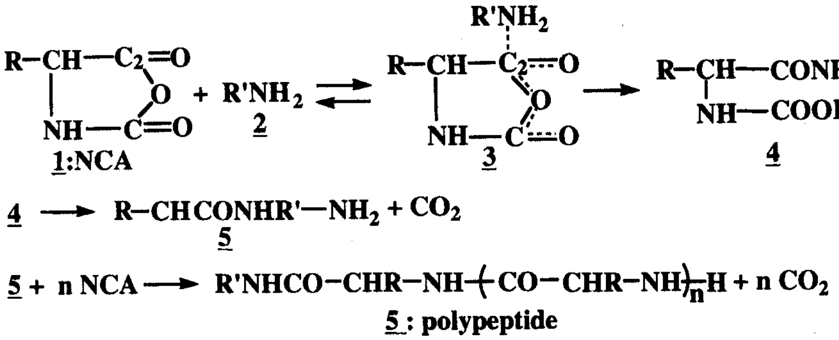
INTRODUCTION

Since the early work of *N* -Carboxy anhydride (NCA) of glycine by Leuchs in 1906,[1] much attention was payed to the investigation of amino acid NCAs many years later.[2,3] These compounds are now extensively used as monomers for the preparation of polypeptides. It has been known that some of these compounds are very sensitive to moisture in air and are polymerized or decomposed in the crystalline state. It is considered that some of the NCA on the crystal surface is converted to the corresponding amino acid by water and the amino acid can initiate the polymerization of the NCA in the solid state.[4] Similarly to this, when amino acid NCA crystals are put in hexane or decane (non-solvents for the NCAs) and butylamine is added in it, the polymerization of the NCA is initiated by the amine in the solid state. The polymerization mechanism of amino acid NCAs initiated by primary amines (R'NH_2) is believed as follows:



A primary amine attacks the carbon atom (C2) nucleophilically, and the five-membered ring of NCA opens and carbon dioxide is evolved. The product 5 reacts with the another NCA like the amine 2 and the resulting product reacts with the NCAs successively and the polypeptide 6 is formed. This mechanism seemed rather difficult to proceed in the solid state. However, we remarked that the stability of the amino acid NCA crystals depended on the kind of amino acids, and examined the solid state reactivity of various L-amino acid NCAs with reference to their crystal structures.[5,6,7] In addition, the crystallization of the NCAs of racemic amino acids has been investigated.

In this paper, the polymerizations of L-valine NCA and DL-valine NCA in the solid state and in the solution are studied, and some results of L-phenylalanine NCA and DL-phenylalanine NCA are also described.

EXPERIMENTAL

Amino acid NCAs were prepared with amino acids and trichloromethyl chloroformate, and purified by the recrystallization in ethylacetate and hexane in the same manner reported previously.[8] Crystals used for the reaction were prepared in one recrystallization process at the same time. Single crystals of L- or DL-valine NCA for the X-ray work were prepared by a slow recrystallization using ethylacetate. Solvents were purified by the usual method.

Solution polymerization of the NCAs was carried out as follows ; the NCA crystals were dissolved in anisole or in acetonitrile (ACN) and butylamine was added in each of the solutions as an initiator. Solid state polymerization was made as follows ; the NCA crystals with similar sizes were put in hexane (a non-solvent for the NCA), and butylamine was added in it. The polymerization rate was checked by the amount of carbon dioxide produced in the course of the reaction. The solution viscosity of the polymer was measured in trifuluoroacetic acid (TFA) with an Ubbelohde viscometer at 25°C.

The conformation of polymers was examined by IR with a Shimadzu FTIR-8500.

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Polymerized NCA crystals were observed by a scanning electron micrograph (SEM), JSM-5310LV of JEOL (Nihon Denshi Co. Ltd.).

RESULTS AND DISCUSSION

Polymerization of L-valine NCA

Figure 1 gives the time-conversion curves of the polymerization of L-valine NCA in the solid state in hexane and in the solutions in ACN and anisole at 30 °C and 50 °C. Butylamine was added as an initiator; the molar ratio of NCA to butylamine was 200 throughout the present work. The initial stage of the reaction was observed so far in the polymerization of the NCAs in ACN, because all of the NCAs were soluble and resulting polypeptides were precipitated in ACN in the course of polymerization.[5] However, the polymerization rate of L-valine NCA was extremely low in ACN as compared with the other NCAs. The polymer chain ends were considered to be occluded in the resulting polymer crystals, which should make the successive reaction of the NCAs difficult. On the other hand, it was found that L-valine NCA and its polymer were soluble in anisole. Thus, the polymerization of L-valine NCA was carried out in the anisole solution. The reactivity of L-valine NCA in the anisole solution was higher than that in the

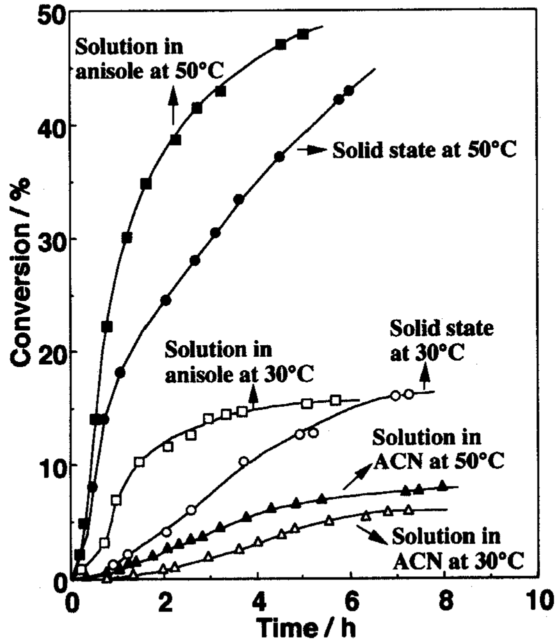

FIGURE 1 Time-conversion curves of the polymerization of L-valine NCA.

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solid state in hexane.

Figure 2 gives the relation between the intrinsic viscosity of the TFA solution of polymers obtained in the solid state and in the solution and the conversion at which each polymer was obtained. The intrinsic viscosity of the polymer is considered to be proportional to the molecular weight of the polymer. It is remarkable that the molecular weight of the polymer obtained in the solid state is much higher than that in the solution, although the reactivity in the solid state was smaller than that in the anisole solution.

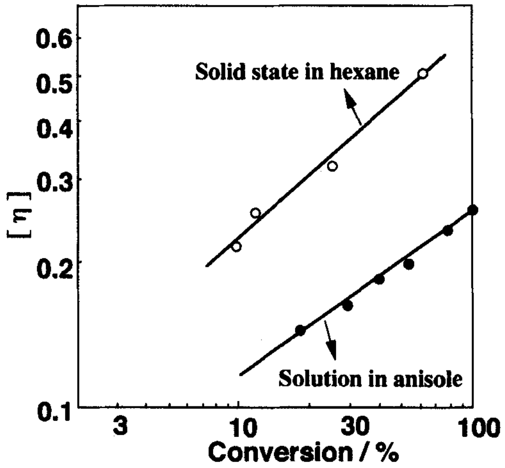

FIGURE 2 Relation between solution viscosity of polymers of L-valine NCA and conversion at which each polymer was obtained.

Figure 3 is a SEM photograph of an L-valine NCA crystal polymerized in the solid state by moisture in air. The lamellae of polymer seems to be stacked almost normal to the *b* axis. Voids are seen on the *b*-*c* and *a*-*b* planes, but not on the *a*-*c* planes.

X-ray diffraction suggested that the polymer chains were formed in the layer

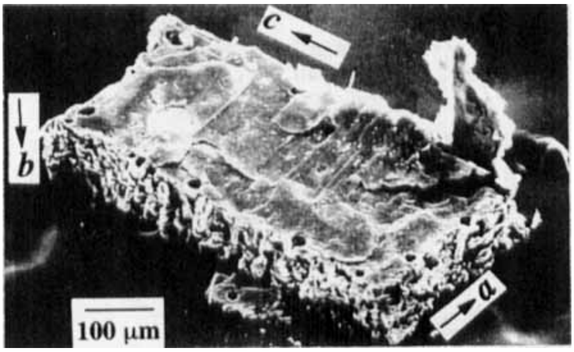

FIGURE 3 Polymerized L-valine NCA crystal in the solid state.

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normal to the *b* axis. The conformation of poly(L-valine) obtained both in the solid state and in the solution were found to be the β structure by IR.

Figure 4 gives the molecular packing in the L-valine NCA crystal. The atoms eliminated as carbon dioxide are circled by dotted lines in Fig.4 (and Figure 10). Crystal data is given in Table I.[9,10] We can see the sandwich structure; the layers of five-membered rings of NCA and the layers of the side chains of L-valine NCA are aligned alternatively. This structure was also seen in the crystal of L-leucine NCA, which was the most reactive in the solid state.[5] But, L-valine NCA is not so reactive as L-leucine NCA in the solid state. In the solid state, L-leucine NCA forms the α helix of poly(L-leucine), and the NCA molecules are arranged conveniently for the formation of

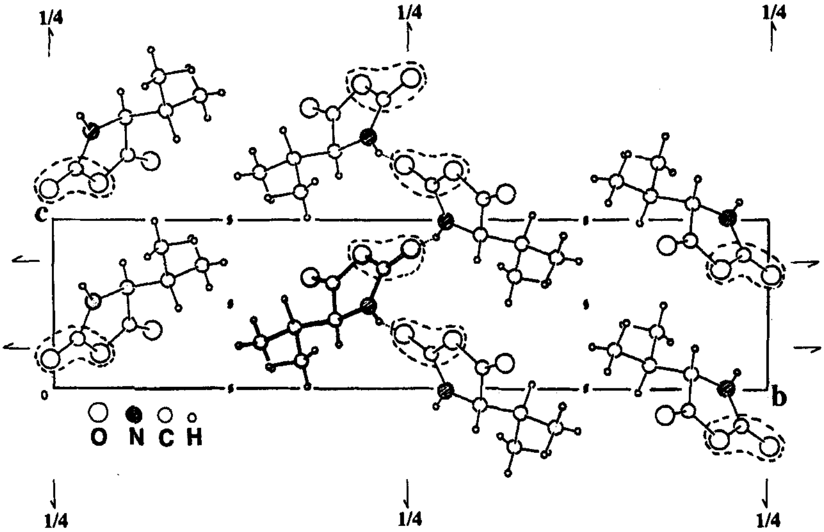

FIGURE 4 Molecular packing of L-valine NCA viewed along the *a* axis.

TABLE I Crystal data.

NCA	L-Valine	DL-Valine
Molecular Formula	$C_6H_9NO_3$	$C_6H_9NO_3$
Molecular Weight	143.1	143.1
Crystal Color	colorless	colorless
Crystal System	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$Pca2_1$
a (Å)	5.787(1)	8.938(1)
b (Å)	22.740(3)	10.207(2)
c (Å)	5.395(1)	7.788(1)
V(Å^3)	709.1(1)	710.6(2)
Z	4	4
Dcalc (Mg m^{-3})	1.33	1.34

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the α helix. In the present case, L-valine NCA molecules have to transfer some distance to form the β structure, which does not seem easy in the crystal. Thus, the polymerization rate of L-valine NCA is considered to be lower in the solid state than that in the anisole solution. On the other hand, the five-membered rings of NCA to react with each other are in the same layer, which should be an important requirement for the polymerization and produces the high-molecular-weight polymer in the solid state. A model of the polymerization in the L-valine NCA is shown in Figure 5. The polymerization is considered to take place in the layer normal to th *b* axis. Black arrows mean the direction of the reaction, and white arrows the going out of carbon dioxides.

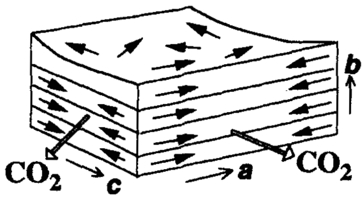

FIGURE 5 Model of the polymerization in L-valine NCA crystal.

Polymerization of DL-valine NCA

Time-conversion curves for the polymerization of DL-valine NCA at 30°C, 40°C and 50°C in the solid state in hexane and in the solution in anisole are given in Figures 6 and7,

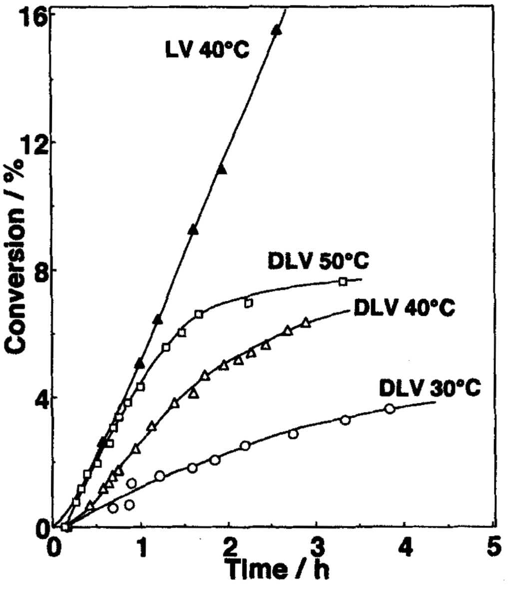

FIGURE 6 Time-conversion curves of the polymerization of DL-valine NCA in the solid state.

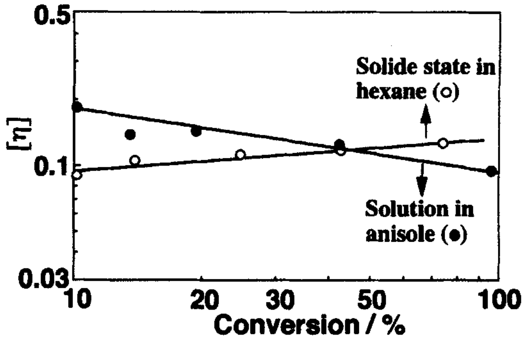

FIGURE 8 Relation between solution viscosity of polymer of DL-valine NCA and conversion at which each polymer was obtained.

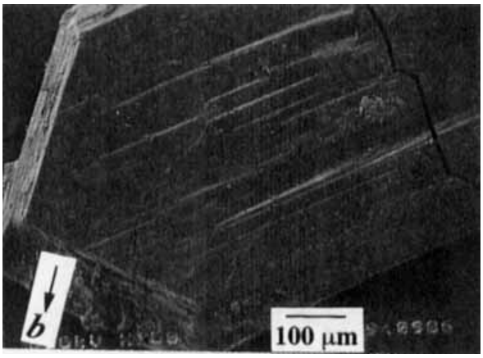

FIGURE 9 SEM photograph of polymerized DL-valine NCA crystal.

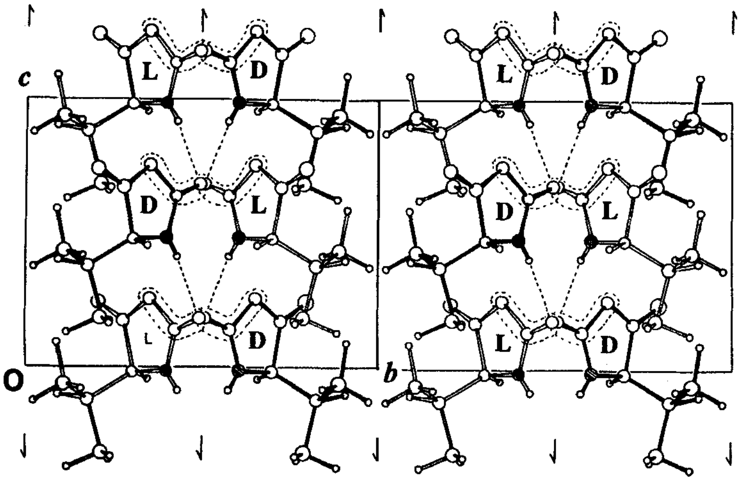

FIGURE 10 Molecular packing of DL-valine NCA viewed along the *a* axis.

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respectively. As a reference, the results of L-valine NCA at 40°C are shown in the Figs. The reactivity of DL-valine NCA is lower than that of L-valine NCA both in the solid and solution states. In addition, the polymerization rate of DL-valine NCA is smaller in the solid state than that in the solution.

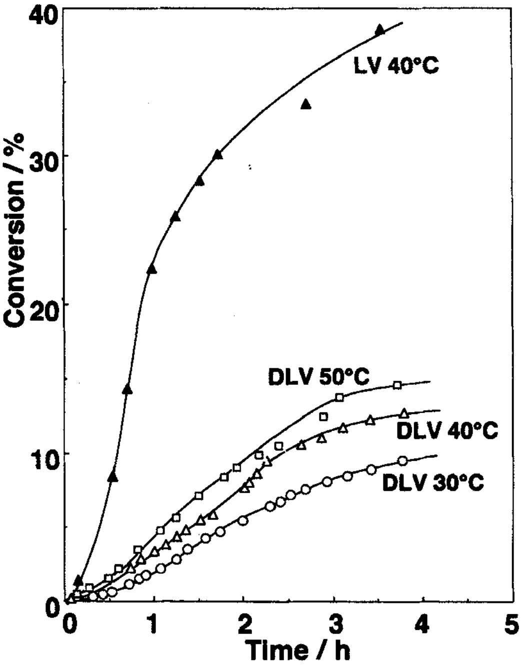

FIGURE 7 Time-conversion curves of the polymerization of DL-valine NCA in the solution in anisole.

Figure 8 gives logarithmic plots between the solution viscosity of the polymers formed in the solid state and in the solution and the conversion at which each polymer was obtained. The molecular weight of the polymer of DL-valine NCA obtained in the solid state increased linearly with the increase in the conversion, while that in the solution decreased with the conversion.

Figure 9 is a SEM photograph of a DL-valine NCA crystal polymerized in the solid state. The *a-c* plane seems rather smooth as compared with the other planes. The polymers obtained in the polymerization of DL-valine NCA both in the solid state and in the solution were found to contain the conformation of random coil by IR.

Figure 10 gives the crystal structure of DL-valine NCA, in which the sandwich structure is also seen and D and L enantiomers which are represented by L and D are aligned alternatively along the *c* direction. The polymerization should take place in the

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layer of the NCA rings in the sandwich, which should increase the molecular weight of the polymer as seen in Fig.8. On the other hand, the steric hindrance between the D and L enantiomers is considered to decrease the reaction rate in the crystal. The difference in the reactivity between L-valine NCA and DL- valine NCA in the solid state and in the solution should be also caused by this steric effect. The exact structure of the polymer formed in the polymerization of DL-valine NCA has not been clarified.

3. Polymerization of L- and DL-phenylalanine NCAs

Table II gives the maximum reaction rates in the polymerization of amino acid NCAs determined so far. It is remarkable that L-phenylalanine NCA and DL-phenylalanine are very reactive in the solid state, but their reactivity in the solutions are very small. Especially, L-phenylalanine NCA was found to polymerize regularly along the long dimension of needle crystals in the solid state; voids through which carbon dioxides passed in the course of polymerization were seen on one side of the original NCA crystal. Figure 11 gives a photograph of polymerized L-phenylalanine NCA crystal.

TABLE II Maximum polymerization rates (%/h) at 30°C.

NCA	Solution[*a]	Solid State[*b]
Glycine	4.52	0.90
L-Alanine	17.4	3.61
L-Leucine	3.87	21.8
BLG[*c]	5.72	2.40
L-Valine	10.7[*d]	3.57
DL-Valine	3.50[*d]	1.45
L-Phenylalanine	0-1[*e]	91.9
DL-Phenylalanine	0-1[*e]	38.5

[*a] In acetonitrile; [*b] in hexane; [*c] benzyl-L-glutamate; [*d] in anisole; [*e] to mean very small reactivity both in ACN and in anisole.

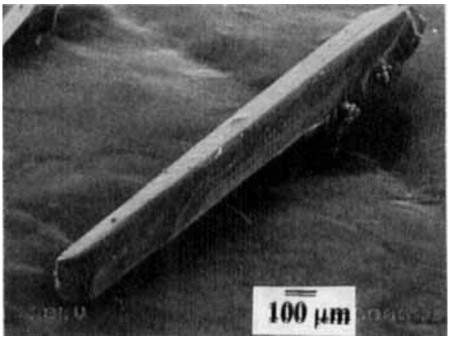

FIGURE 11 Polymerized L-phenylalanine NCA crystal.

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CONCLUSIONS

The investigation of the polymerizations of L-valine NCA and DL-valine NCA gave new requirements to determine the reactivity in the solid state; the sandwich structure composed of the five-membered rings of NCA and the side chains of amino acids and the molecular packing preferable for the conformation of the resulting polymer in the crystal.

On the other hand, L-phenylalanine NCA and DL-phenylalanine NCA gave a high reactivity in the solid state, while they were very stable in the solution. Some new aspects for the solid state polymerization will be given by more detailed studies.

REFERENCES

1. H. Leuchs, Berihit, 39, 857 (1906).
2. C. H. Bamford, A. Elliot, and W. E. Hanby, Synthetic Polypeptides (Academic Press, New work, 1956) , p.62.
3. Y. Imanishi, Kobunshi, 32, 92, 21 (1972).
4. M. Szwarc, Adv. Polym. Sci., 4, 1 (1965).
5. H. Kanazawa, Polymer, 33, 2557 (1992).
6. H. Kanazawa, Gendai Kagaku (translated in Chemistry Today, Tokyo Kagaku Dojin, Tokyo), No.259, 28 (1992).
7. H. Kanazawa, Kagaku (translated in Chemistry, Kagaku Dojin, Kyoto), 47, 692 (1992).
8. H. Kanazawa and T. Kawai, J. Polym. Sci., Polym. Chem. Ed., 18, 629 (1980).
9. H. Kanazawa, Y. Ohashi and Y Sasada, Acta Cryst., C40, 1094 (1984).
10. Y. Takenaka, Y. Ohashi and H. Kanazawa, Acta Cryst., C50, 1950 (1994).