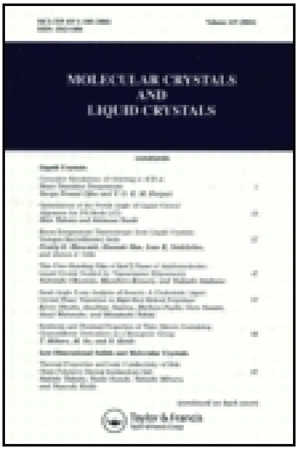

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Amino Acid N-Carboxy Anhydrides with High Polymerizability in the Solid State

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Amino Acid *N*-Carboxy Anhydrides with High Polymerizability in the Solid State

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Solid-state polymerization of amino acid *N* -carboxy anhydrides was carried out in hexane with butylamine. L-Leucine NCA, L-phenylalanine NCA, β-benzyl-L-aspartate NCA and DL-phenylalanine NCA gave high polymerizability in the solid state, compared with the reaction in the solution. L-Leucine NCA and L-phenylalanine NCA were found to polymerize mainly along a definite direction in the crystal. The crystal structure to determine the high reactivity in the solid state were considered; a sandwich structure: the alternative alignment of the five-membered ring layers and the side chain layers, and the molecular arrangement preferable for the formation of the polymer conformation.

Keywords: amino acid NCA; solid-state polymerization; crystal structure;

INTRODUCTION

The geometrical arrangement of monomers in the crystal is expected to affect the reaction products or reaction rates in the solid state polymerization[1-6].

Amino acid *N* -Carboxy anhydrides (amino acid NCAs) have been extensively used for the preparation of polypeptides though they were not payed attention for a long time since the early report of glycine NCA by Leuchs[7]. The NCAs are generally polymerized in solutions with bases as the initiator. The polymerization mechanism of the NCAs seems unfavorable for the solid state reaction[8, 9]. Miller and Kovacs et. al. studied the solid state polymerization of some NCAs by heating or exposure to water vapor[10,11]. The NCAs were polymerized in the solid state in hexane with triethylamine[12]. But, their crystal structures were not determined. We studied the polymerization of the NCAs in hexane with butylamine and confirmed that the polymerization took place in the solid state[13], and determined the crystal structure of several NCAs[14-20]. Moisture in air is considered to initiate the solid-state polymerization of the NCA similarly to amines in hexane[21]. In this paper, the crystal structure favorable for the high reactivity in the solid state is reconsidered.

EXPERIMENTAL

The NCAs were prepared by the same manner reported previously[13]. Solid state reaction: the NCA crystals were put in hexane, and butylamine was added in it as an initiator. Solution reaction: the NCA crystals were dissolved in acetonitrile, dioxane or nitrobenzene, and butylamine was added in the solution. The reaction rate was estimated from the amount of carbon dioxide. The IR of polymers was observed by a Shimadzu FTIR-8500.

RESULTS AND DISCUSSION

Polymerization rate

The reactivity of nine amino acid NCAs was examined in the solid state and in the solution. Solvents for all of the NCAs could not be found. In acetonitrile, all NCAs dissolve but the resulting polymer precipitates and the polymerization takes place between the precipitated polymer and the NCA in the solution. The maximum polymerization rate for each reaction system is listed in Table1 (used solvents are given in it). L-Leucine NCA, L- and DL- phenylalanine NCAs and BLA NCA gave much higher re activity in the solid state than in the solution.

L-Alanine NCA was the most reactive in the solution among the examined NCAs and its reactivity was not high in the solid state. L-Leucine NCA seemed to have a contrast property to L-alanine NCA. The molecular weight of poly(L-leucine) obtained in the solid state was much higher than that in the solution, on the other hand, that of poly(L-alanine) obtained in the solution was much higher than that in the solid state. The X-ray and electron microscopy suggested that the polymerization of L-leucine NCA proceeds mainly along the c axis in the crystal, but L-alanine NCA reacts at random in the crystal [16].

L-Phenylalanine NCA, DL-phenylalanine NCA and BLA NCA are very reactive in the solid state while very stable in the solution. As a fact, highly purified L-phenylalanine NCA crystals are too reactive to estimate the exact reaction rate. BLA NCA gave the maximum reaction rate in the solid state. The time-conversion curves of the polymerization are given in Fig.1.

TABLE I Maximum polymerization rate (%/h) at 30°C.

NCA	Solid State	Solution	
	in hexane	acetonitrile	other solvent
Gly	0.90	4.52	
L-Ala	3.60	17.4	
L-Val	3.57	1.38	10.7 in anisol
L-Leu	21.8	4.37	
L-Phe	131	0-1*	0-1 * in dioxane, 10 in nitrobenzene
BLG	2.40	5.72	
BLA	140	1.08	
DL-Val	1.45		3.50 in anisol
DL-Phe	38.5	0-1*	

Ala:alanine, val;valine, leu:leucine, phe:phenylalanine, BLG:γ-benzyl-L-glutamate, and BLA: β-benzyl-L-aspartate.
* : very small reactivity.

Polymer Conformation

Wavenumbers at the absorptions, amide I, amide II and amide V in the IR spectra of the resulting polymer are listed in Table 2 (all polymers except marked two were obtained in the solid state). It is known that amide I for the α helix and that for the β structure are seen at around 1635 cm^{-1} and at around 1650 cm^{-1}, respectively, and that amide II gives ambiguous information. Amide V at around 700 cm^{-1} is due to the N-H out-of-plane deformation vibration in the β structure[22]. Thus, poly(glycine) and poly(L-valine) are apparently the β structure. Poly(L-leucine) is the α helix. Poly(L-alanine) obtained in the solid state seems mainly the α helix and that obtained in the acetonitrile solution

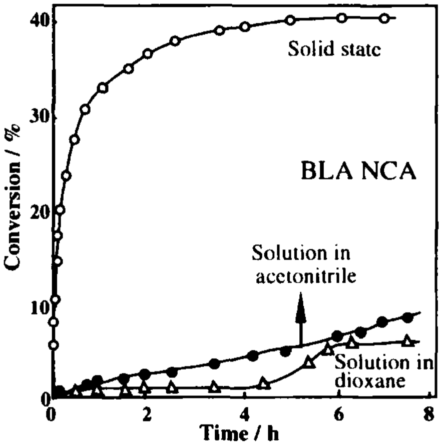

FIGURE 1 Time-conversion curves.

seems mainly the β structure. Poly(L-phenylalanine) obtained in the solid state seems mainly the β structure and the shoulder at around 1652 cm^{-1} suggests the existence of the α helix. Poly(L-phenylalanine) obtained in the solution in nitrobenzene seems to be the α helix. Poly(BLA) is considered to be the α helix. X-ray powder patterns were not useful for the judgement of the conformation.

TABLE II Wave numbers of typical absorptions in IR spectra

Polypeptide	AmideI	AmideII	AmideV
Gly	1634	1523	706, 600
L-Ala	1652, sh. at 1625	1540	-
L-Ala/soln^{*1}	1635, sh. at 1650	1549	703, 591
L-Val	1635	1544	716, 700
L-Leu	1654	1543	703, 667
L-Phe	1639/1641, sh. at 1652	1535-1536	563-569
L-Phe/soln^{*2}	1648/1650	1527-1535	581
BLA	1649	1539	582
BLG	1655	1546	584

^{*1} polymer obtained in acetonitrile and^{*2} polymer obtained in nitrrobenzene.

Consideration of the Reaction with Reference to Crystal Structures

The low reactivity of glycine NCA is explained by the dimer structure with hydrogen bonds in the crystal.[14] The L-leucine NCA crystal gave the typical sandwich structure; a layer of isobutyl groups and that of five-membered NCA rings are aligned alternatively. L-Leucine NCA polymerizes along the c axis to form the α helix in the five-membered ring layer. The molecular arrangement in the crystal and a model of the α helix of poly(L-leucine) is given in Fig. 2. The sandwich structure was also seen in the crystal of L-valine NCA. But, L-valine NCA gave low reactivity in the solid state among the examined NCAs. This NCA was seen to polymerize along random directions in the plane perpendicular to the c axis by the X-ray analysis and electron microscopy[28]. The formation of the β structure seemed difficult in the crystal of L-valine NCA, because the molecules must transfer considerably long distance to the axis of the β structure in the crystal (see a model shown in Fig.3). The crystal structures of L-phenylalaine NCA gives an apparent sandwich structure as shown in Figure 4. In the figure, hydrogen bonds are given by broken lines. Crystal data of L-phenylalanine NCA; space group: $p2_12_12_1$, Z=4,a=5.499(1)Å,

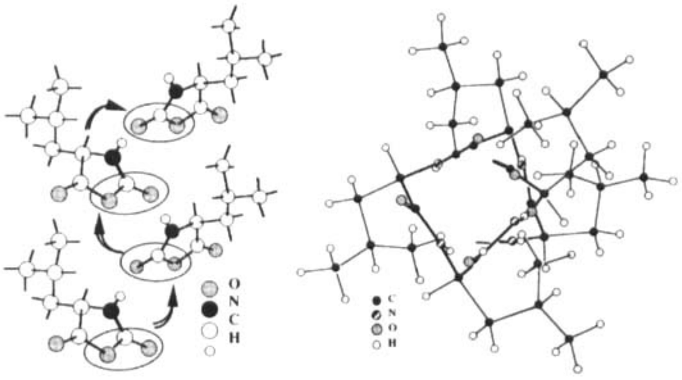

FIGURE 2 Arrangement of L-leu NCA molecules in the crystal (left) and a mdel of the α helix of poly(L-leu).

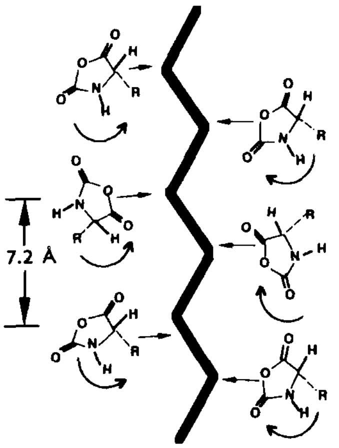

FIGURE 3 Transfer of L-val NCA for the formation of the β structure.

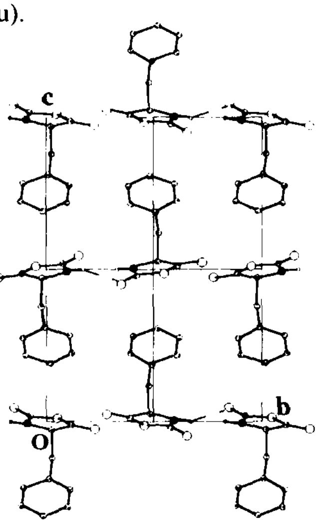

FIGURE 4 Crystal of L-phe NCA.

p$2_12_12_1$, Z=4,a=5.499(1)Å, b= 11.013(1)Å and c=15.806(2) Å. Electron microscopy of a polymerized crystal by moisture in air suggested that L-phenylalanine NCA polymerizes along the a axis in the crystal. The IR suggests that poly(L-phenylalanine) obtained in the solid state is mainly the β structure. In general, the α helix of poly(L-phenylalanine) is considered to be a stable conformation. The formation of the conformation of polypeptides in the crystal will be studied in detail hereafter.

The crystal structure of BLA NCA was determined; crystal data, space group:P2_1, Z=4, a=8.110(1)Å, b=5.2782(7)Å, c=13.490(2)Å, β=100.500(4)°. The sandwich structure was also seen in this crystal. The detailed crystal structure will be reported. BLA seemed to form the α helix of polymer. This seems reasonable for the high reactivity in the solid state. The problem of the formation of polymer conformation in the crystal will be investigated in detail.

CONCLUSION

The two factors in the crystal structure favorable for the high reactivity are proposed; (1) the sandwich structure and (2) the molecular arrangement favorable for the formation of the α helix or the β structure.

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