The Steric Hindrance of the Stepwise Reaction of *N*-Carboxy α-Amino Acid Anhydride with the α-Amino Acid Ester

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The mechanisms of the reactions of 4-alkyloxazolidinediones (**1**) (*N*-carboxy α-amino acid anhydrides(NCAs)) with α-amino acid benzyl ester *p*-toluenesulfonates (**2**) were investigated in acetonitrile containing triethylamine at low and room temperatures. Two types of reactions were observed: (1) the polymerization of NCAs was initiated with a small amount of **2** to produce polypeptides (**6**), and (2) the dipeptide benzyl esters (**4**) were produced by the stepwise reaction of NCAs with the esters. Both the polymerization and the dipeptide formation (**1**+**2**) seemed to be initiated by the nucleophilic attack of the amino group of the ester on the C-5 carbon of NCAs. The polymerization proceeded when the side chains of the amino acid esters (R^2) were more bulky than those of the NCAs (R^1). On the contrary, dipeptide esters were produced when the side chains of the NCAs (R^1) were more bulky than those of the esters (R^2).

The mechanisms of the polymerization of *N*-carboxy α-amino acid anhydrides (NCAs) are extensively studied. The mechanisms involve the initiation of the polymerizations of the NCAs with amines, sodium alcoholates, inorganic salts such as lithium chloride, and organometallic compounds, followed by propagation reactions.[1-4] In comparison, there is little information on the stepwise reaction of NCAs with compounds having an α-amino group to produce α-amino acid amides or their derivatives. The mechanism of the reaction of the glycine ethyl ester with the NCAs derived from other α-amino acids to produce dipeptide-ethyl esters is regarded as the stepwise reaction of an α-amino group with NCAs.[5] This stepwise reaction does not occur for any α-amino acid esters except for the glycine ester (with NCAs) in anhydrous media, because the polymerization reaction of NCAs occur.[6]

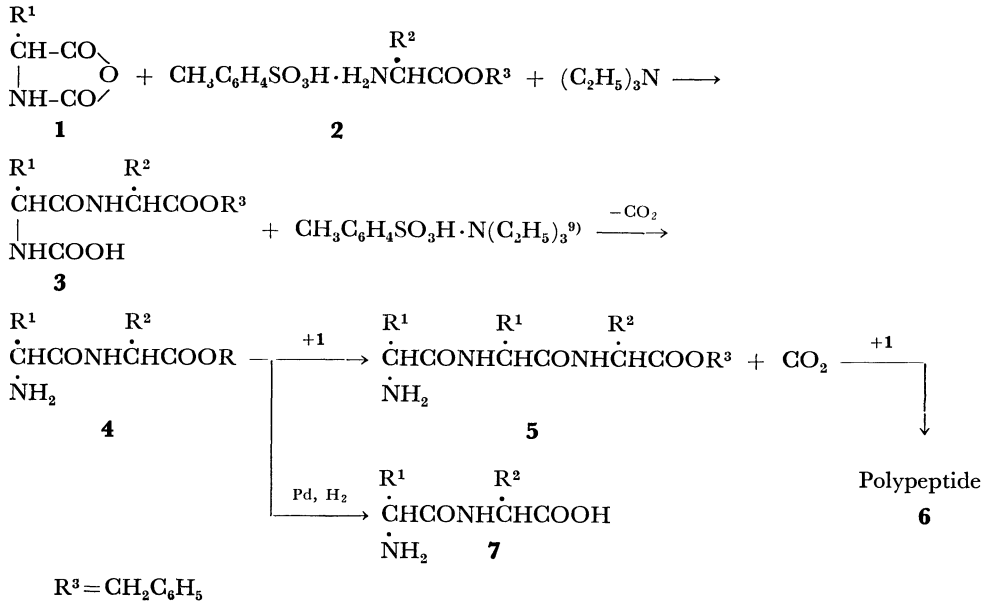
We previously synthesized oligopeptides with regular sequences by the stepwise reaction of α-amino acid sodium salts with NCAs in a water–acetonitrile system.[7] In another previous study, we synthesized dipeptides and cyclodipeptides by the stepwise reaction of α-amino acid benzyl ester *p*-toluenesulfonates with NCAs in anhydrous acetonitrile in the precence of triethylamine.[8] No mechanism of the reaction was discussed in detail, however.

In this paper, the mechanisms of the reactions are discussed with regard to the steric hindrance of the side chains of both α-amino acid esters and NCAs.

Results and Discussion

The reactions of NCAs (**1**) with α-amino acid benzyl-ester *p*-toluenesulfonates (**2**) were carried out in acetonitrile containing triethylamine at low and room temperatures (Eq. 1). The reactions which occured may be classified as the following types: (1) polypeptides were obtained by the polymerization of NCAs initiated with a small amount of the amino acid esters, (2) dipeptide esters were produced by the stepwise reaction of NCAs with the amino acid esters, and (3) both the polypeptides and dipeptide esters were produced by the polymerizations and the stepwise reactions. The results are shown in Table 1.

In the polymerization of γ-benzyl L-glutamate NCA with a primary amine in dioxane, it has been reported that 70% of the initiator (the amine) was involved



(1)

Table 1. Reaction of NCA with amino acid benzyl ester in acetonitrile

Reactant[a]		Product yield/%			
		Dipeptide (**7**)[b]		Polypeptide (**6**)[c]	
NCA/R^1	Ester/R^2	−20 °C	20 °C	−20 °C	20 °C
H	H	0	0	90	85
	CH_3	0	0	97	97
	$(CH_3)_2CH$	0	0	92	95
	$(CH_3)_2CHCH_2$	0	0	98	99
	$C_6H_5CH_2$	0	0	90	95
CH_3	H	80	80	0	0
	CH_3	20[d]	20[d]	50	55
	$(CH_3)_2CH$	0	0	92	94
	$(CH_3)_2CHCH_2$	0	0	97	98
	$C_6H_5CH_2$	15	15	75	80
$(CH_3)_2CH$	H	80	80	5	0
	CH_3	70	70	8	7
	$(CH_3)_2CH$	80	75	5	5
	$(CH_3)_2CHCH_2$	80	80	10	10
	$C_6H_5CH_2$	0	0	96	90
$(CH_3)_2CHCH_2$	H	75	75	5	0
	CH_3	75	80	5	5
	$(CH_3)_2CH$	10	10	90	90
	$(CH_3)_2CHCH_2$	70	75	5	5
	$C_6H_5CH_2$	0	0	90	90
$C_6H_5CH_2$	H	90	90	0	0
	CH_3	90	90	0	0
	$(CH_3)_2CH$	90	90	0	0
	$(CH_3)_2CHCH_2$	90	90	0	0
	$C_6H_5CH_2$	90	90	0	0

a) L-Amino acid (except for glycine) was used. b) Isolated yields. c) Isolated yields; near reaction yields. d) Isolated yields of mixtures of dipeptides and amino acids.

in the attack on the C-5 carbonyl carbon of the NCA, while the remaining 30% of the amine was involved in the abstraction of the proton attached to the nitrogen of NCA.[3-4] When the polymerization of NCAs was initiated by the proton abstraction, the propagation could not be controlled because of the fast polymerization.

It has been concluded that the reactions of NCAs with amino groups are initiated only by the C-5 attack in acetonitrile.[10] As is shown in Eq. 1, the polymerization of NCAs should not proceed when the reaction of **1** with **2** is faster than that of **4** with **1**. The following mechanism are assumed. (1) Since the carbamic acid (**3**) is stable, the reaction from **3** to **4** should be very slow. (2) The basicity of the amino group of the amino acid ester (**2**) may be stronger than that of the dipeptide and tripeptide esters, so that the reaction of **1** with **2** is predominant compared to that of **1** with **4** or **5**. (3) An unknown mechanism other than (1) and (2) proceeds. As is shown in Table 1, glycine NCA is polymerized by all amino acid esters. Alanine NCA ($R^2=CH_3$) was usually polymerized with amino acid esters, but it produced the alanylglycine benzyl ester in 80% yield when reacted with the glycine ester ($R^2=H$). Valine and leucine NCAs were polymerized when the reactions were carried out with the amino acid esters having side chains more bulky than those of NCAs. Phenylalanine NCA produced the dipeptide esters without the polymerization of NCAs, even when the NCAs were allowed to react with the phenylalanine benzyl ester having the same side chain as that of the NCA.

It is known that a carbamic acid is stable in a basic medium at a low temperature.[5] The decarboxylation reaction from the carbamic acid occurs through the zwitter ion as the temperature increases.[11] If the decarboxylation reactions (**3**→**4**) were influenced by the temperature in Eq. 1, the yields of the polypeptides would also be influenced by the temperature. Table 1 shows, however, that the yields of the polypeptides and dipeptides were not influenced by the rise in temperature from −20 °C to 20 °C. Therefore, the decarboxylation reactions (**3**→**4**) can not be considered to have been influenced by the temperature and has to be the rate-determining step in the reactions.

It has generally been considered that the basicity of the amino group on dipeptides is slightly stronger than that of the corresponding amino acid.[12] This

may be also the case with the basicity of the dipeptide benzyl ester and the corresponding amino acid benzyl esters. If such a consideration could be applied to Eq. 1, the polymerization would proceed in all cases. The polymerization, however, proceeds only when the side chains of the esters are more bulky than that of NCAs. From these results, it is concluded that the steric hindrance of the side chains of both NCAs and esters affected whether the polymerization of NCAs proceeds or whether the stepwise reaction proceeds to produce the dipeptide esters.

Experimental

The α-amino acid benzyl esters[13] and NCAs[10,14] were prepared by the methods reported previously.

*Reaction of NCAs (**1**) with α-Amino Acid Benzyl Esters (**2**). General Procedure*: To the α-amino acid benzyl ester *p*-toluenesulfonate (**2**) (10 mmol) was added NCA (**1**) (10 mmol) in acetonitrile (25 cm^3) containing triethylamine (10 mmol). The mixture was thus stirred for 4 h. When the polypeptide formed by the polymerization of NCA was precipitated, it was separated by filtration and dried *in vacuo* to determine the extent of polymerization. The clear solution of the resulting mixture or the filtrate was distilled *in vacuo* to remove the solvent. The residual oily product was washed with ethyl ether and hydrogenated with palladium black in a mixture of acetic acid, *t*-butyl alcohol, and water. Dipeptide was thus obtained (**7**). When the NCA was partly polymerized, the final product was mixture of amino acid and dipeptide. The isolated polypeptides, dipeptides, and these mixtures, when analyzed on C, H, N, and by means of the NMR and IR spectra, proved identical with independently synthesized authentic specimens.[7,8]

Valylalanine ($R^1=(CH_3)_2CH$, $R^2=CH_3$): ^{1}H-NMR (CF_3COOH): δ 1.2—1.3(d, 6H), 1.6—1.7(d, 3H), 2.1—2.6(m, H), 4.1—4.4(q, H), 4.8—4.9(t, H), 7.3(s, H), 7.7—7.8(d, H). Found: C, 50.77; H, 8.59; N, 14.68%. Calcd for $C_8H_{16}O_3N_2$: C, 51.06; H, 8.51; N, 14.87%.

Further, the polypeptides were analyzed by means of X-ray diffraction measurement.[15]

The residual NCA after finishing the reaction was analyzed by the method of Berger.[16]

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