Prominent Catalysis of Sodium 2- or 4-Pyridinolate in the Aminolysis of Esters[1]

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(Received May 18, 1971)

The bifunctional catalysis of 2-(1H)-pyridone (2-pyridinol) in the aminolysis of esters is a well-established phenomenon.[2–4] However, no report has been published concerning the catalytic activity of salts of pyridinols. During the course of the investigation of the catalysis in peptide synthesis,[4,5] the present author found that anhydrous sodium salts of the 2- or 4-pyridinol have a pronounced catalytic activity in the aminolysis of active esters. A preliminary kinetic study showed that the catalytic rate constant of the sodium 2-pyridinolate (I) in the reaction of *p*-nitrophenyl benzyloxycarbonyl-L-phenylalaninate (Z-L-Phe-ONp) with *t*-butyl glycinate (H-Gly-OBu^t) in anhydrous dioxane is about 20,000 (l^2/mol^2·min), whereas that of 2-pyridinol is 41 (l^2/mol^2·min).[4] Table 1 shows the results of some typical reactions.

I exhibited the catalytic activity not only for the aminolysis of "active" esters, but also for that of ordinary esters. When benzylamine (2 mmol) and methyl acetate (10 mmol) were heated for 5 hr at 78°C in dimethylacetamide (3 m*l*) in the presence of I (1 mmol), *N*-benzylacetamide (mp 60.5—62°C) was obtained in a 62% yield. In the absence of I, though, *N*-benzylacetamide could not be isolated. Moreover, when ethyl cyanoacetate (5 mmol) and thiourea (5 mmol) were refluxed for 5 hr in anhydrous methanol (3 m*l*) in the presence of I (10 mmol), 4-amino-6-hydroxy-2-mercaptopyrimidine was obtained in an 82% yield. No pyrimidine was produced in the absence of I. When triethylamine, which is similar to I in basicity, was used in place of I, only a trace amount of the pyrimidine was detected in the reaction mixture.[6] This fact suggests that the catalytic activity of I does not depend only on the basicity of the catalyst. During the course of the reaction of Z-L-Phe-ONp with *p*-nitroaniline in the presence of I, the transient formation of a compound which seems to be an active intermediate was observed on the thin-layer chromatogram.

From these facts, it may be considered that the present reactions proceed *via* a nucleophilic catalysis in which *O*-acyl pyridinol (II) or *N*-acyl pyridone (III) is formed as an active intermediate; that is, this catalysis is due to the high nucleophilicity of the pyridinolate anions and the high acylating activity of II[7] or III. Of course, the possibility that general-base catalysis is also a factor can not be disregarded. Whether the intermediate is II or III[8] is not clear at the present time.

Studies of the racemization in the presence of the catalysts are now in progress.

TABLE 1. CATALYSIS OF SODIUM 2- OR 4-PYRIDINOLATE IN THE AMINOLYSIS OF ARYL ESTERS

Acylating agent (mmol)	Amine (mmol)	2- or 4-Pyridinolate (mmol)	Solvent (m*l*)	Reaction temperarture °C	Half-life period, min	
					no catalyst	catalyst
Z-L-Val-ONp (1.0)	Benzylamine (1.0)	2 (1.0)	CH$_2$Cl$_2$ (20)	23	1440	<10
Z-L-Val-ONp (1.0)	H-L-Val-OMe (1.0)	2 (1.0)	AcOEt (5)	18	4200	<10
Z-L-Phe-ONp (2.0)	*p*-nitroaniline (2.0)	2 (2.0)	DMA[a] (5)	20	∞	50
Z-Gly-OPh (10.0)	piperidine (10.0)	2 (1.0)	AcOEt (10)	25	20	<2
Z-L-Phe-ONp (2.0)	*p*-nitroaniline (2.0)	4 (2.0)	DMA (5)	18	∞	50

a) dimethylacetamide

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6) Triethylamine also has little catalytic effect on the aminolysis of Z-L-Phe-ONp.[4]

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