Preparation and Properties of N-(Pentafluoropropionyl)amino Acid

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Synopsis. N-(Pentafluoropropionyl)amino acids, which were prepared by treating amino acids with hexafluoro-1,2-epoxypropane in diglyme, were found to be a versatile derivative of amino acids in gas chromatographic analysis.

N-Trifluoroacetylated α -amino acids are known to be useful derivatives for detection and separation of the parent amino acids.¹⁻⁷⁾ Various esters of N-(trifluoroacetyl)-, N-(pentafluoropropionyl)- and N-(heptafluorobutyryl)-amino acids, which were prepared by perfluoroacylation with the corresponding perfluorocarboxylic anhydrides, were also reported to be useful in gas chromatographic resolution of the amino acids.⁸⁾ N-perfluoroacyl-L- α -amino acid chlorides are claimed to be resolving agents for asymmetric amines, as the gas chromatography of the complexes of these compounds provides a rapid, sensitive, and effective method for separating enantiomers.⁹⁾

In the course of our studies on the reactivities of hexafluoro-1,2-epoxypropane, it was revealed that this perfluoro epoxide can be used as a versatile pentafluoro-propionylating agent for alcohols, thiols and amines.¹⁰⁾ On extention of this reaction, the perfluoroacylation was applied for the preparation of pentafluoropropionylated amino acids, which are expected to be more volatile and more sensitive to gas chromatography than trifluoroacetyl derivatives.

Our previous method of pentafluoropropionylation of usual amines and alcohols using a hexafluoro-1,2-epoxypropane-triethylamine system in acetonitrile was not applicable to amino acids, as it gave only tarry material. Then we allowed amino acids to react with hexafluoro-1,2-epoxypropane without any amines using diglyme as a solvent. The reaction proceeded smoothly even at room temperature and after 2 or 3 h pentafluoropropionylamino acids were obtained in good yields (Table 1).

Thus by the aid of a fluorine ion hexafluoro-1,2-epoxypropane isomerized to pentafluoropropionyl fluoride, which reacted then with the amine to give pen-

tafluoropropionyl derivative. 10)

$$\begin{array}{c} \operatorname{CF_3CF-CF_2} \xrightarrow{\operatorname{F^-}} \operatorname{CF_3CF_2CF} \\ \stackrel{\circ}{\operatorname{O}} & \stackrel{\circ}{\operatorname{O}} \end{array} \xrightarrow{\operatorname{diglyme}} \begin{array}{c} \operatorname{CF_3CF_2CF} \\ \stackrel{\circ}{\operatorname{O}} \end{array}$$

$$\begin{array}{c} \operatorname{CF_3CF_2CF} + \operatorname{H_2N-CHCO_2H} \rightarrow \\ \stackrel{\circ}{\operatorname{O}} & \stackrel{\circ}{\operatorname{R}} \end{array}$$

$$\begin{array}{c} \operatorname{CF_3CF_2CNH-CHCO_2H} + \operatorname{HF} \\ \stackrel{\circ}{\operatorname{O}} & \stackrel{\circ}{\operatorname{R}} \end{array}$$

Though pentafluoropropionylamino acids have relatively higher melting points than the corresponding trifluoroacetyl derivatives, they are vaporized more rapidly on gas chromatography as expected (Table 2). It was also found that the pentafluoropropionyl group can be easily removed under mild alkaline conditions without racemization.

Experimental

Pentafluoropropionylation of Amino Acids. A mixture of L-phenylalanine (1.65 g, 10 mmol) and diglyme (10 ml) was placed in a glass pressure vessel and cooled to ≈ -70 °C. Liquefied hexafluoro-1,2-epoxypropane (bp -27 °C, 1.80 g, 10.9 mmol) was then introduced into the vessel and the whole was brought to room temperature with stirring. The mixture gradually became a clear solution, and the stirring was continued additional one hour. The reaction mixture was then poured into dilute aqueous hydrochloric acid, and the product was extracted with diethyl ether. The extract was dried over magnesium sulfate and the solvent was evaporated to give solid material. This crude product was subjected to column chromatography on silica gel using chloroform as an eluent. Pure N-(pentafluoropropionyl)-Lphenylalanine (2.18 g) was obtained in a yield of 70%.

Hydrolysis of Pentafluoropropionylamino Acid. A pentafluoropropionyl group was easliy removed under similar conditions to those reported in the case of a trifluoroacetyl group.¹¹⁾ For example, N-(pentafluoropropionyl)-L-phenylalanine (0.62 g, 2 mmol) was added to an ethanol-water solution containing 5% sodium hydroxide, and the mixture was stirred for 1 h at room temperature. After neutraliza-

Table 1. Pentafluoropropionylamino acids and their derivatives (PFP= CF_3CF_2CO)

N-PFP-amino acida)	Yield ^{b)}	$\frac{\mathbf{Mp}}{^{\circ}\mathbf{C}}$	¹⁹ F NMR (ppm)		Γ. 720
	%		$\widetilde{\mathrm{CF_3}}$	$\widetilde{\mathrm{CF}_2}$	$[\alpha]_D^{20}$
N-PFP-glycine	75	122—123	+6.2	+45.3	**************************************
N-PFP-DL-phenylglycine	70	124—125	+6.0	+45.2	
N-PFP-L-alanine	60	86.5-87.5	+6.2	+45.3	-39° (c=0.4, Et ₂ O)
N-PFP-L-proline benzylamine salt	70	150—151	+6.3	+45.5	$-315^{\circ} (c=1, \text{ Me}_2\text{CO})$
N-PFP-L-isoleucine benzylamine salt	65	98—98.5	+6.3	+45.3	$+55^{\circ}$ ($c=1$, EtOH)
N-PFP-DL-phenylalanine	63	128—129	+6.0	+45.1	
N-PFP-L-phenylalanine	72	122.5—123.5	+6.1	+45.3	$+545 (c=1, Et_2O)$

a) The microanalyses of these new compounds were in satisfactory agreement with calculated values ($C\pm0.34\%$, $H\pm0.14\%$, $N\pm0.23\%$). b) Yield of isolated product. c) Upfield from external CF₃COOH in acetone.

Table 2. Gas chromatographic properties of perfluoroacylated amino ${\it acids}^{a)}$

Amino acid	CF ₃ CO-derivative		CF ₃ CF ₂ CO-derivative		Retention time
	$\frac{\mathbf{Mp}}{\ ^{\circ}\mathbf{C}}$	Retention time min	$\frac{\mathbf{Mp}}{\mathbf{^{\circ}C}}$	Retention time min	${\rm ratio} \\ {\rm C_2F_5CO/CF_3CO}$
Glycine	118	7.11 ^{b)}	122—123	5.93 ^{b)}	0.83
L-Alanine	6567	5.37b)	85.5-87.5	4.98 ^{b)}	0.92
L-Phenylalanine	120—121	4.50c)	122.5—123.5	4.13c)	0.91

a) G. L. C. analysis were carried out on a Shimadzu GC-3BT apparatus equipped with a TCD. The $4\phi \times 3$ steel column was packed with 10% Silicone GE-SE 30 on Chromosorb W. b) Helium gas was flowed at the rate of 19 ml/min, while the column was kept at 140 °C. c) The column was kept at 190 °C.

tion with aqueous hydrochloric acid, the solvent was removed. Residual solid was washed with water and recrystallized from water giving pure L-phenylalanine (0.16 g, 48%).

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