CHEMISTRY LETTERS, pp. 745-748, 1982.

OPTICALLY ACTIVE F-2-ISOPROPOXYPROPIONIC ACID : A NOVEL DERIVATIZING AGENT FOR GAS CHROMATOGRAPHIC ANALYSIS

Hajimu KAWA, Fumihiko YAMAGUCHI, and Nobuo ISHIKAWA*
Department of Chemical Technology, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

F-2-Isopropoxypropionic acid (PIPA) was resolved into enantiomers via its diastereomeric (+)-1-phenylethylamide. (+)-F-2-Isopropoxypropionyl derivatives of several chiral 1-arylalkylamines and α-amino acids were effectively resolved by gas chromatography at low temperature.

The resolution of optical isomers by gas chromatography have been investigated by a number of workers for the past decade and it is now recognized as a highly efficient and versatile technique.[1-4] This procedure is accomplished by the conversion of enantiomers into diastereomers by a suitable chiral derivatizing agent which is chemically and optically stable. It is also desirable that the derivatized substance should have high volatility and thermal stability to avoid racemization during the chromatographic process. For this purpose, it is considered to be suitable to use fluorinated compounds, since, in general, they themselves are thermally stable and give volatile derivatives.

In a course of study on F-1,2-epoxypropane (hexafluoropropene oxide, HFPO), we have prepared optically active (+) and (-)-F-2-propoxypropionic acids (PPPA).[5] These carboxylic acids were revealed to be useful derivatizing agents for alcohols and amines carrying a chiral center, as the agents gave diastereomeric perfluoroacyl derivatives, of which the optical purity could be determined by the ^{19}F nmr analysis. For employing this kind of agents in gas chromatographic analysis, the more branched perfluoroacylating agent might be useful as it would give highly volatility. Hence we prepared F-2-isopropoxypropionyl fluoride (1) from F-acetone and HFPO by an improved method from patent literature.[6] The resolution of this compound was carried out by converting it into diastereomeric amides (2) of (+)-1-phenylethylamine, which were readily separated from each other by means of column chromatography. Both of the diastereomers were very resistant to hydrolysis, but by treatment with conc. H_2SO_4 they gave the corresponding unsubstituted amide, which could be hydrolyzed by aqueous alkali to free carboxylic acid (PIPA). The enantiomers of PIPA thus obtained were characterized as shown in Table 1.

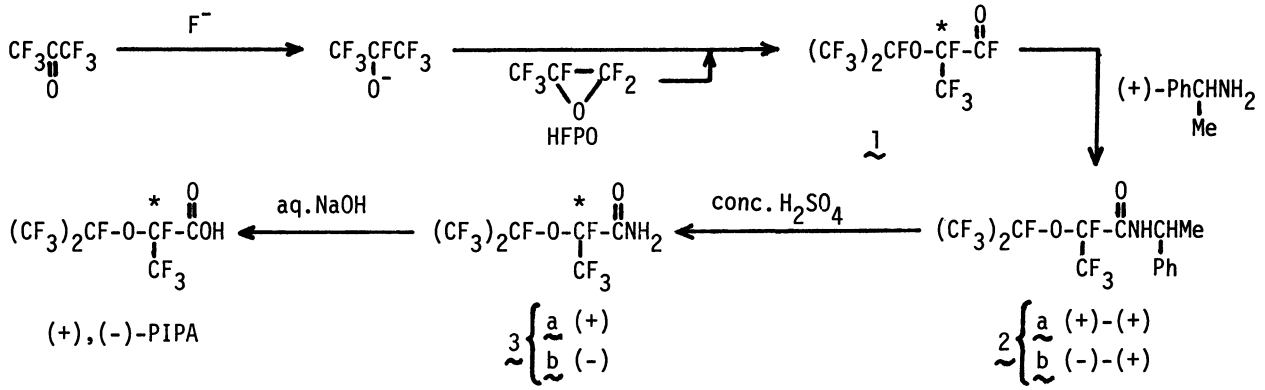


Table 1. Properties of (+) and (-)-PIPA

	(+)-PIPA	(-)-PIPA
Prepd. from	2a	2b
Yield (%)	83	80
B.p. (^{o}C/mmHg)	74 - 77/40	
α_D^{20} (neat, l = 1)	+31.10 ^{o}	-31.32 ^{o}
ir (film)(cm^{-1})	3200(OH), 1780(C=O)	
^{1}H nmr ($CDCl_3$)	δ 10.4	
^{19}F nmr (neat)	δ* 3.5(3F), 4.2(3F), 6.0(3F), 51.6(1F), 67.0(1F)	

* ppm upfield from ext. CF_3CO_2H.

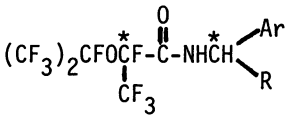
In order to compare the gas chromatographic retention times, various perfluoroacylated amino compounds, i.e., F-acetyl, F-propionyl, F-butyryl, F-2-propoxypropionyl, and F-2-isopropoxypropionyl derivatives of benzylamine and of n-dodecylamine, were prepared and subjected to glc analysis under the same conditions. It was surprising to find that F-2-propoxy- and F-2-isopropoxypropionamides, especially the latter, showed high volatilities comparable to F-acetamides and F-propionamides in spite of their high molecular weight and were more volatile than F-butyramides (Table 2).

Table 2. Glc retention time of F-acylated amines

R_f	Relative retention time[a] of	
	R_f-CONHCH$_2$Ph (80 ^{o}C)	R_f-CONH-(CH$_2$)$_{11}$-Me (130 ^{o}C)
CF_3	0.74	0.84
C_2F_5	0.73	0.82
n-C_3F_7	1.00	1.00
n-$C_3F_7OCF(CF_3)$	0.97	0.90
i-$C_3F_7OCF(CF_3)$	0.87	0.85

a) OV-1 (1%) on chromosorb W (80 - 100 mesh) was used as the stationary phase. Retention times are relative to that of F-butyryl derivative.

These results indicated that chiral amines could be analyzed under mild conditions by gas chromatography when (+) or (-)-PIPA was used as the chiral derivatizing agent. Practically, (+)-F-2-isopropoxypropionyl chloride, prepared by the chlorination of PIPA with PCl_5, was used as the agent, and several derivatives of 1-arylalkylamines (4) were subjected to the analysis. The results showed (Table 3) that the diastereomers in all cases were well resolved with large r(-)/r(+) values even at comparatively low temperatures. It was also noticeable that the first glc peak was always due to the (+)-PIPA derivative of (-)-amines, and the second one was due to that of (+)-amines. The results obtained here, therefore, would be related to the absolute configurations of analogous 1-arylalkylamines. Subsequently, we extended the application of the chiral PIPA agent to the analysis of α-amino acid enantiomers. Thus a mixture of several amino acid esters was derivatized to the corresponding (-)-F-2-isopropoxypropionamides and subjected to gas chromatographic analysis. The result, Fig. 1, shows that the enantiomers of all amino acids examined except methionin were well distinguished from each other at relatively low temperature and within a short period.



4

Table 3. Glc resolution[a] of (+)-PIPA derivatives of 1-arylalkylamines (4)

R	Ar	Column Temp.(°C)	Uncorrected retention time (min) r(-)	r(+)	r(-)/r(+)
Me	Ph	90	9.62	10.95	1.138
Et	Ph	90	14.66	16.53	1.128
i-Pr	Ph	90	18.30	21.38	1.176
Me	p-MeC_6H_4	90	17.40	20.46	1.176
Me	p-ClC_6H_4	120	5.80	6.62	1.141
Me	p-BrC_6H_4	120	9.02	10.37	1.150
Me	α-$C_{10}H_7$	140	9.98	11.45	1.147

a) OV-1 (1%) on chromosorb W (80 - 100 mesh) as the stationary phase and nitrogen (30 ml/min) as carrier gas were used.

In this way, the sterically designed and optically active PIPA was found to be a useful derivatizing agent for the resolution of chiral amines or α-amino acids by glc analysis.

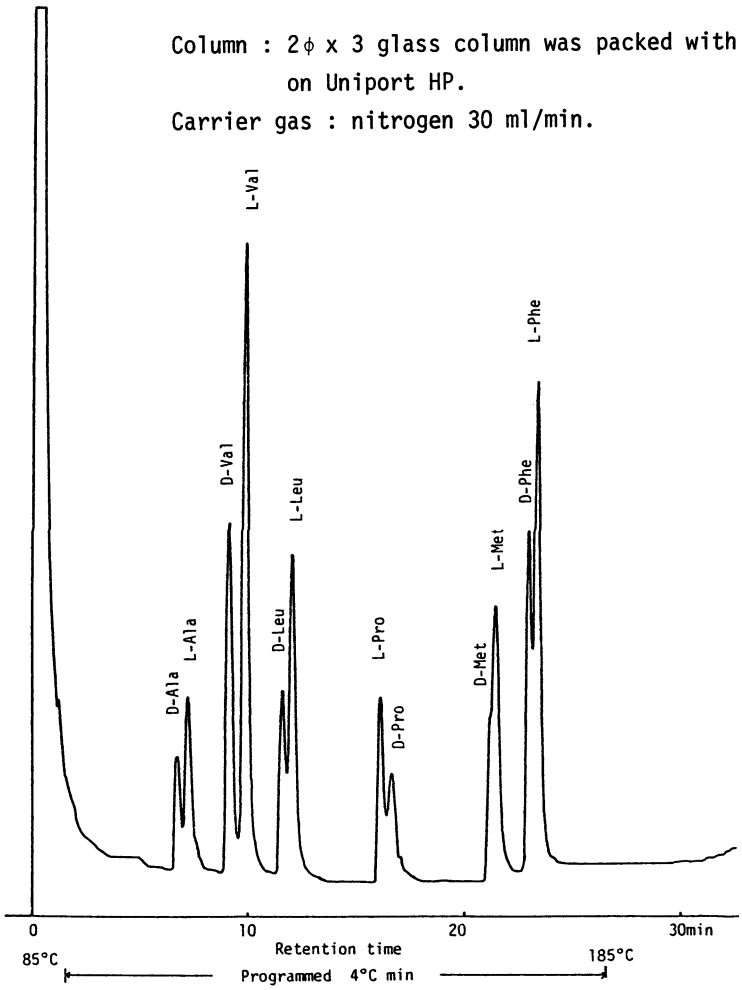


Fig. 1 Gas chromatogram of N-(-)-perfluoro-2-isopropoxypropionyl amino acid methyl esters

Experimental

F-2-Isopropoxypropionyl fluoride (1) The reported procedure[6] was improved by using a small amount of KF instead of CsF to give a much higher yield. Anhydrous KF (0.60 g, 10 mmol) suspended in diglyme (20 ml) was placed in a glass pressure vessel and liquefied F-acetone (17.8 g, 107 mmol) was introduced at -70 °C. The mixture was brought to room temperature with stirring. After the crystals of KF disappeared (~1 h), liquefied HFPO (15.8 g, 95 mmol) was introduced at -70 °C and the whole was brought again to room temperature with stirring. After 1 h of stirring, volatile substance at 30 mmHg was trapped in a dry ice-acetone bath, giving 1 (29.3 g, 93% from HFPO), b.p. 50 - 52 °C (lit.[6] 57 °C).

(+) and (-)-PIPA 1 (10 g, 30 mmol) was added to a mixture of (+)-1-phenylethylamine (3.6 g, 30 mmol) and triethylamine (3.0 g, 30 mmol) in acetonitrile (20 ml). After 0.5 h of stirring, the mixture was poured into water, and an oily material was extracted with diethyl ether. Removing the solvent from the extract, 2 (12 g, 92%) was obtained. The diastereomeric mixture was subjected to a silica-gel column chromatography using hexane-benzene (3 : 1) as a solvent and diluent. The first fraction gave 2a (4.1 g, 63%), m.p. 50 - 51 °C, α +74.4 ° (c 1.00, $CHCl_3$), while the second fraction afforded 2b (4.0 g, 61%), m.p. 75 - 76 °C, α +85.8 ° (c 1.00, $CHCl_3$).[7]

The hydrolysis of these amides was carried out as follows. Conc. H_2SO_4 (2.2 ml) was added to 2a (1.5 g), and the mixture was stirred for 1 h at room temperature then thrown into ice water. An oily material was extracted with diethyl ether and the solvent was evaporated. The residue was refluxed for 3 h with aq. NaOH (7N, 4 ml) and acidified with aq. HCl. (+)-PIPA was extracted with diethyl ether, and 10% aq. NaOH was added to the extract. Evaporation of the solvent gave (+)-PIPA sodium salt, which were acidified with conc. H_2SO_4 and subjected to distillation, giving a pure (+)-PIPA (0.96 g, 83%). (+)-PIPA chloride (b.p. 76 - 78 °C) was prepared in 93% yield by distillation of a mixture of (+)-PIPA and PCl_5.

Glc analysis of 1-arylalkylamine enantiomers Into a mixture of 1-arylalkylamine (0.2 mmol), triethylamine (0.3 mmol) and dichloromethane (10 ml), (+)-PIPA chloride (0.3 mmol) was added and stirred for 10 min at room temperature. The dichloromethane solution was washed with water and 1 μl of this substance was subjected to glc analysis.

Glc resolution of α-amino acid enantiomers Thionyl chloride (2 ml) was added to a methanol solution (20 ml) containing a mixture of α-amino acids (20 mg) at -70 °C. The mixture was warmed up to 40 °C and stirred for 2 h at this temperature. The solvent and excess agent were evaporated in vacuo, then dichloromethane (10 ml) and triethylamine (10 μl) were added. (-)-PIPA chloride (40 μl) was added and the mixture was stirred for 1 h at room temperature. After the solvent was removed, water (10 ml) was added and the products were extracted twice with diethyl ether (10 ml). The extract was washed with 5% aq. $NaHCO_3$ (10 ml) and dried over $MgSO_4$. The solvent was removed and the residue was dissolved in dichloromethane (3 ml), and subjected to glc analysis.

References

1) E. Gil-Av and D. Nurok, Adv. Chromatogr., 10, 99 (1974).
2) C. H. Lockmuller and R. W. Souter, J. Chromatogr., 113, 288 (1975).
3) B. Halpern, "Handbook of Derivatives for Chromatography," ed. by K. Blau & G. King, Heyden, London, 1977, p. 457.
4) D. R. Knapp, "Handbook of Analytical Derivatization Reactions," John Wiley, 1979, p. 405.
5) H. Kawa and N. Ishikawa, Chem. Lett., 1980, 843.
6) Du Pont, U.S.P. 3,274,239 (1966).
7) Found: C, 39.09; H, 2.36; N, 3.25%. Calcd for $C_{14}H_{10}NO_2F_{11}$: C, 38.81; H, 2.33; N, 3.23%.

(Received April 3, 1982)