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OPTICALLY ACTIVE PERFLUORO-2-PROPOXYPROPIONIC ACID: A NEW CHIRAL REAGENT FOR ^{19}F NMR STUDY

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SUMMARY

Perfluoro-2-propoxypropionic acid, which was prepared by the anionic dimerization of hexafluoro-1,2-epoxypropane, was optically resolved via diastereomeric salt formation with chiral amines. The optically pure (+) and (-) perfluoro-2-propoxypropionic acids thus obtained were found to be a convenient chiral reagent for determining enantiomeric compositions of α-amino acids by means of ^{19}F nmr analysis.

INTRODUCTION

Nuclear magnetic resonance spectra have been widely used for the analyses of chiral compounds to determine their enantiomeric compositions or absolute configurations. The principles of the method used for the differentiation between enantiomers by means of nmr have been well established and reviewed [1].

However, in most cases, magnitudes of chemical shift differences for enantiomers in the ^{1}H nmr spectra are not satisfactory to determine the accurate values. On the other hand, as some authors pointed out [2,3,4] using fluorine resonance (^{19}F nmr) is in general a more reliable technique because the degree of nonequivalence observed in the ^{19}F nmr spectra is greater than that in the ^{1}H nmr spectra [2,3]. In addition to this, a variety of hydrogen-containing solvents can be used for the ^{19}F nmr measurements.

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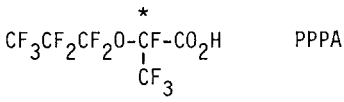
In a previous paper [5], we reported a synthetic method for optically active perfluoro-2-propoxypropionic acid (PPPA), which was the first example of an optically active perfluorocarboxylic acid.



PPPA

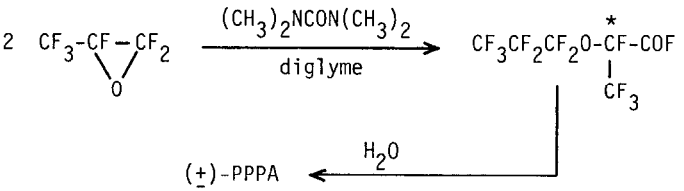
Since PPPA containes no hydrogen atom and the C-F bond at the chiral center should optically be very stable, several applications such as utilization as a chiral solvent for ^{1}H nmr analysis would be considered.

We now wish to report in this paper, as one of the useful applications of this unique perfluoro compound, the ^{19}F nmr spectral analyses of several asymmetric compounds by using PPPA as a chiral derivatizing reagent.

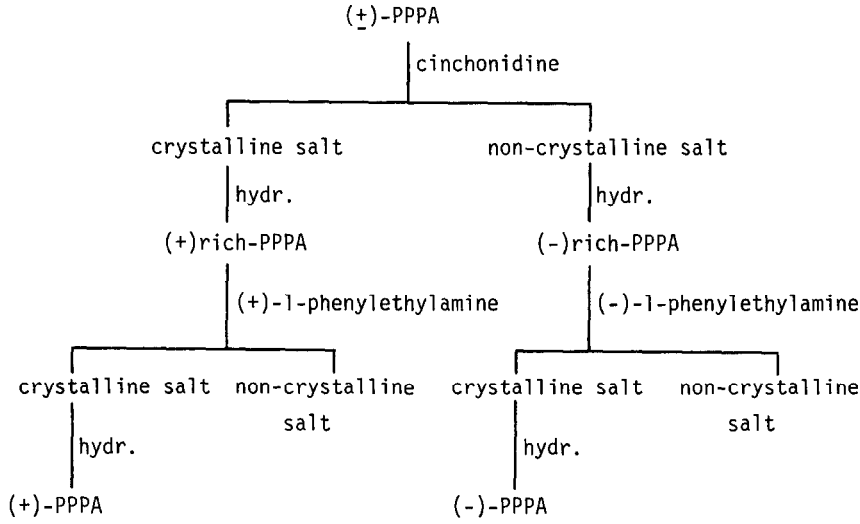
RESULTS AND DISCUSSION

Preparation of optically active PPPA

Racemic PPPA was prepared as reported [6]. Hexafluoro-1,2-epoxypropane was dimerized in the presence of tetramethylurea to give perfluoro-2-propoxypropionyl fluoride in 70% yield, which was quantitatively hydrolyzed to (±)-PPPA.



As described in our previous paper [5], (±)-PPPA was optically resolved via diastereomeric amides with (-)-1-phenylethylamine by column chromatography. However, hydrolyses of the diastereomeric amides did not proceed easily and, in addition to this, the chromatographic method was not suitable for the preparation in large quantity. Hence, we tried another method which was performed by the diastereomeric salt formation. Among several chiral amines tested for the salt forming resolution [7], cinchonidine and 1-phenylethylamine were found to be excellent resolving reagents to give optically active PPPA, according to the following scheme.



The ^{19}F nmr spectra of various PPPA derivatives

The molecule of PPPA has eleven fluorine atoms and its ^{19}F nmr signals were assigned as shown in Fig 1. When PPPA was converted to diastereomeric amides or esters with several chiral amines or alcohols, their ^{19}F nmr spectra showed characteristic chemical shift differences due to the various fluoroalkyl groups. Some typical examples were shown in Fig 2. In the ^{19}F nmr spectra of diastereomeric esters with 1-phenylethylalcohol (Fig 2a), for example, spectral nonequivalences were observed on the two trifluoromethyl groups a and d with $\Delta\delta$ (nonequivalence value) of 6.5 and 7.1 Hz respectively. Meanwhile, with methyl mandelate (Fig 2b), apparently two signals due to the difluoromethylene group b appeared with $\Delta\delta$ 13.5 Hz. In the case with 1-phenylethylamine (Fig 2c), one of the trifluoromethyl groups (a) appeared nonequivalently with $\Delta\delta$ 11.3 Hz. Since PPPA had various fluoroalkyl groups which are in different environment, their chemical shift differences were strongly influenced by the counter chiral compound, i.e., amines or alcohols, and the degree of nonequivalence was large enough to calculate the accurate value of enantiomeric composition.

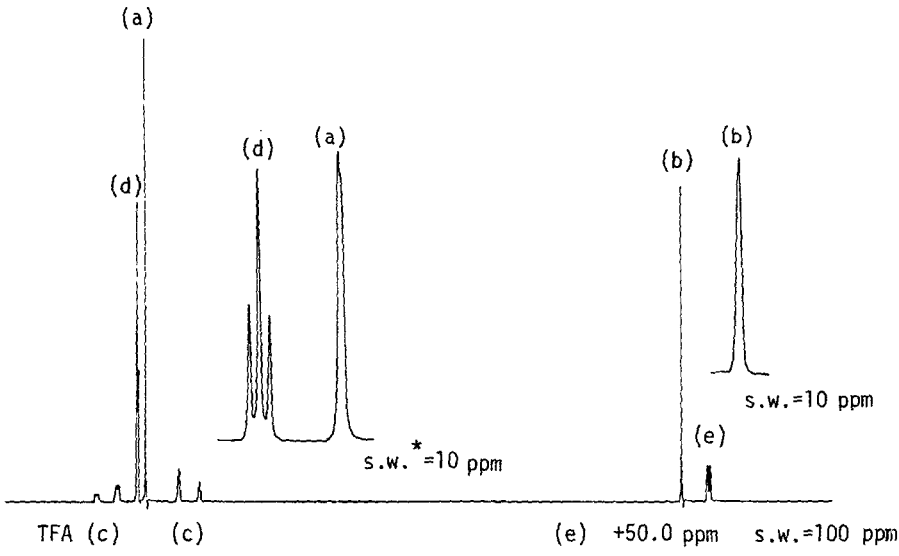


Fig. 1 ^{19}F nmr spectra for PPPA CF_3CF_2-CF_2-O-$\overset{F}{\underset{CF_3}{\overset{|}{\underset{|}{C}}}}$-$CO_2H$ (a)(b) (c) (d)

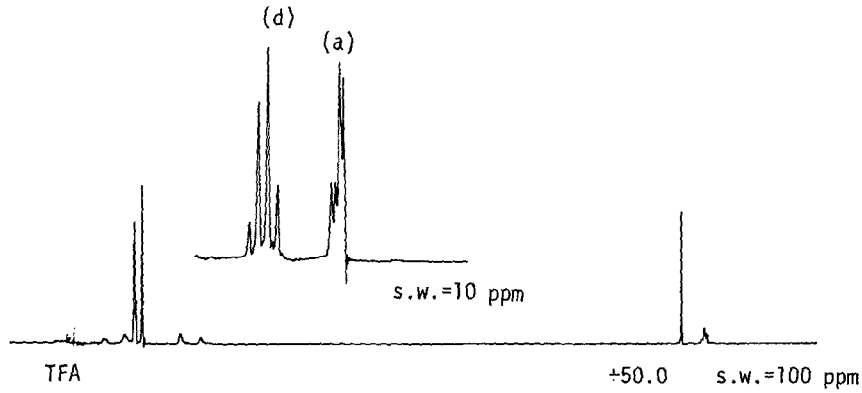


Fig. 2a ^{19}F nmr spectra for $CF_3\overset{(a)}{CF_2}CF_2O$-$\overset{*}{\underset{(d)}{\overset{|}{\underset{|}{CF}}}}$-CO-O-$\overset{*}{\underset{CH_3}{\overset{|}{\underset{|}{CH}}}}$-Ph [8]

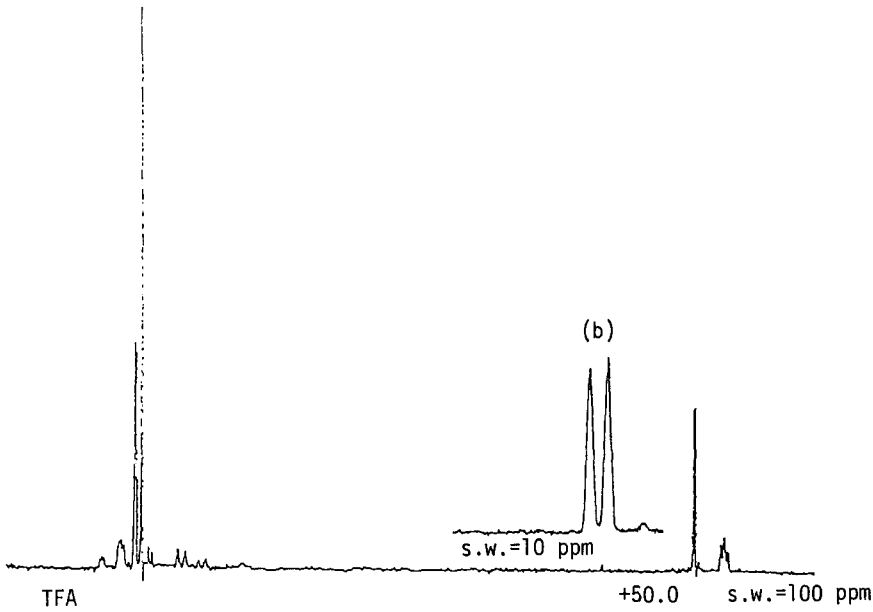


Fig. 2b ^{19}F nmr spectra for $CF_3CF_2CF_2O-\overset{*}{C}F(CF_3)-CO-O-\overset{*}{C}H(CO_2CH_3)-Ph$ (b)

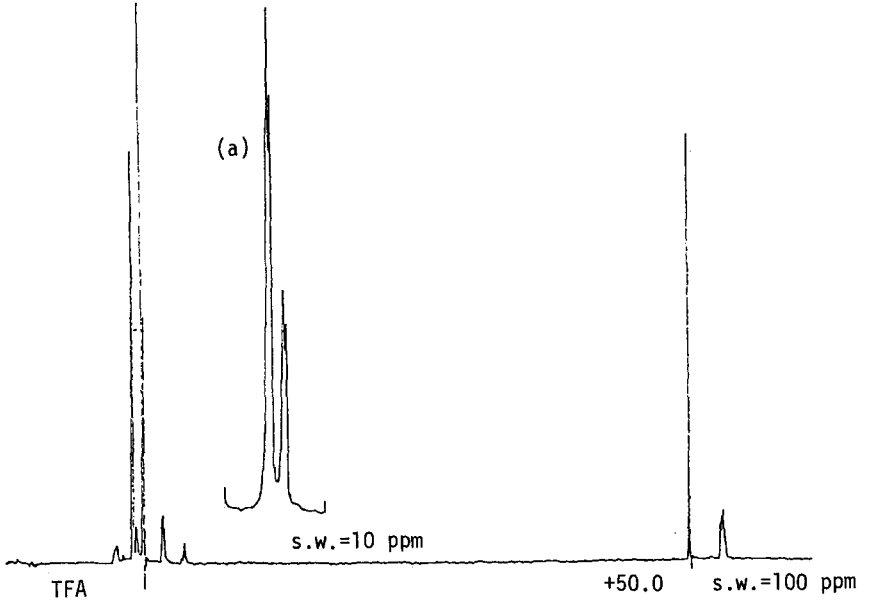
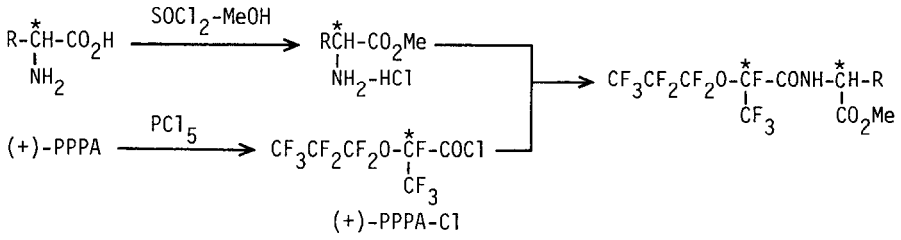


Fig. 2c ^{19}F nmr spectra for $CF_3CF_2CF_2O-\overset{*}{C}F(CF_3)-CO-NH-\overset{*}{C}H(CH_3)-Ph$ [8] (a)

Determination of enantiomeric composition of α-amino acids

The facts obtained heretofore were applied to the determination of enantiomeric composition of α-amino acids. Several methods, such as a chiral solvent [9] or a lanthanide shift reagent [10], have been already reported for this purpose by using ^{1}H nmr. However, it is difficult to obtain accurate values by these methods for two reasons: 1) To use a chiral solvent or a shift reagent, the amino acid must be converted to its amino ester by an optically risky procedure. 2) The structures of complicated amino acids make their nmr spectra very intricate. Then, we converted α-amino acids to their stable PPPA derivatives and determined their enantiomeric compositions by ^{19}F nmr spectra.

α-Amino acids were converted to their methyl ester hydrochlorides by treating them with a large excess of a methanol-thionyl chloride mixture [11], then esters were made to react with (+)-perfluoro-2-propoxypropionyl chloride (PPPA-Cl), prepared by the reaction of (+)-PPPA with phosphorous pentachloride. The formed diastereomeric mixture was subjected to resolving.



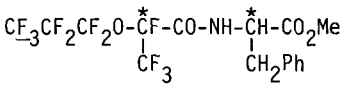
Solvent effect

Chemical shift differences of diastereoisomers observed in the ^{1}H nmr spectra are known to be sparingly affected by the employed solvent [12], while no studies on the solvent effect in the ^{19}F nmr have been reported. Since any non-deuterated solvents can be employed in the ^{19}F nmr study, we first tested the effect of nine solvents with different polarity on the chemical shift differences of a PPPA derivative of amino acid (Table 1). As in the case of 1-phenylethylamine, two signals due to the trifluoromethyl group ($CF_3CF_2CF_2O$-) appeared separately in the nmr spectra of

N-(+)-perfluoro-2-propoxypropionyl phenylalanine methyl ester and the value of chemical shift differences ($\Delta\delta$) was found to be strongly affected by the solvent. Polar solvents gave good results on the separation of signals of diastereoisomers, and in particular, dimethyl sulfoxide gave the best effect. Since nonequivalent trifluoromethyl groups ($C\underline{F}_3CF_2CF_2O$-) appeared as two sets of small doublets (less than 2 Hz), the determination of enantiomeric compositions was easily accomplished by calculating each signal intensity.

TABLE 1

The solvent effect on chemical shift difference of



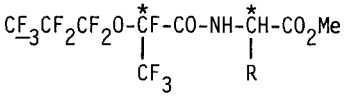
Solvent	$\Delta\delta$ (Hz)
benzene	5.5
diethyl ether	2.0
chloroform	6.3
methylene chloride	8.2
acetone	7.8
methanol	8.1
N,N-dimethylformamide	7.5
dimethyl sulfoxide	13.5

Enantiomeric compositions of partially resolved eight α-amino acids [13] were determined by ^{19}F nmr spectra as their PPPA derivatives (Table 2). In all cases, observed values well agreed with calculated values and $\Delta\delta$ values were large enough to obtain the accurate values. From these results, the presence of an aromatic group in the amino acid is not prerequisite for the nonequivalence phenomenon to obtain. The steric factor seems to be more important to influence a $\Delta\delta$ value than the anisotropic factor as leucine showed a very large $\Delta\delta$ value. In addition, a signal due to L-form of amino acid always appeared in higher field than that due to D-form of amino acid. These facts reveal that our method using optically active PPPA and ^{19}F nmr should be a versatile analytical method for chiral compounds. However, some problems remain unsolved, for example, why the

fluoroalkyl group which is far from the chiral center appears nonequivalently, and why the degree of nonequivalence observed in the ^{19}F nmr spectra is larger and is influenced more strongly by the solvent than those in the ^{1}H nmr spectra. Studies on these problems are now underway.

TABLE 2

Determination of optical purities of several α-amino acids derivative



Amino acid	R	Optical purity (%)		Δδ (Hz)
		Calcd.	Obsd.	
PheGly	C_6H_5	33.3	32.6	10.9
Ala	CH_3	47.8	44.2	12.2
Val	$(CH_3)_2CH$	20.0	21.2	12.3
Leu	$(CH_3)_2CHCH_2$	50.0	48.0	21.2
Ile	$CH_3CH_2CH(CH_3)$	47.8	45.0	14.9
Phe	$C_6H_5CH_2$	50.0	49.0	13.0
Met	$CH_3SCH_2CH_2$	70.4	68.5	15.4
Glu	$CH_3OCOCH_2CH_2$	48.6	49.8	15.2

EXPERIMENTAL

Perfluoro-2-propoxypropionic acid (PPPA)

A mixture of tetramethylurea (3.00 g) and diglyme (50 ml) was placed in a glass pressure vessel and cooled to -70 °C. Liquefied hexafluoro-1,2-epoxypropane (64.0 g, 385 mmol) was then introduced into the vessel and the whole was brought to room temperature. After stirring for 3 h at this temperature, gaseous pentafluoropropionyl fluoride CF_3CF_2COF was removed and the resulting two oily phases were separated. The upper layer was diglyme containing the catalyst which can be used again for the repeated oligomerization reaction. The lower layer was distilled and

the fraction of bp 50 - 54 °C was collected (44.8 g, 70%). Redistillation gave pure perfluoro-2-propoxypropionyl fluoride, bp 52 - 54 °C (lit [6], 55 - 57 °C).

Perfluoro-2-propoxypropionyl fluoride (89.5 g, 270 mmol) was added to water (300 ml) and the mixture was stirred for 1 h at room temperature. The resulting oily layer was separated and water layer was extracted with three portions of diethyl ether (50 ml). The combined organic solution was dried over magnesium sulfate and then the solvent was removed. Concentrated sulfuric acid (20 g) was carefully added to the remained oil and distilled under reduced pressure to give pure (±)-PPPA (82.9 g, 93%), bp 70 - 71 °C (27 mmHg) (Lit [6], 143 - 144.5 °C).

Optical resolution of PPPA

(±)-PPPA (33.00 g, 100 mmol) and cinchonidine (Wako Pure Chemical Industries. Ltd., 29.40 g, 100 mmol) were mixed in methanol (200 ml). After 0.5 h, methanol was evaporated under reduced pressure to give a crude salt. The crude product was recrystallized three times from a diisopropyl ether-ethyl acetate (4 : 1) mixture (600 ml) to give less soluble salt (31.2 g), mp 142 - 143 °C (dec), $[\alpha]_D^{20}$ -53.8 ° (c 1.00, $CHCl_3$), which was then decomposed with 2N aqueous sodium hydroxide solution, and precipitated cinchonidine was removed by filtration. The filtrate was acidified with 6N hydrochloric acid and the regenerated perfluorocarboxylic acid was extracted with diethyl ether. The extract was dried ($MgSO_4$) and the solvent was evaporated to give a crude acid (16.00 g) which was identified with (+)-rich-PPPA (73% ee) by the gas chromatography [14].

The more soluble salt was collected from the previous filtrate, and was decomposed with an alkali and worked up as above, giving (-)rich-PPPA (15.40 g), 74% ee.

The (+)rich-PPPA (16.00 g, 50 mmol) and (+)-1-phenylethylamine (Tokyo Kasei Kogyo Co., Ltd., α_D^{25} +37.45 °, neat, l = 1, 6.05 g, 50 mmol) were mixed in diethyl ether (100 ml), and the resulting salt obtained by evaporation of the solvent was recrystallized twice from hexane (500 ml). The pure salt (15.79 g), mp 99 - 100 °C, $[\alpha]_D^{20}$ +19.00 ° (c 1.00, $CHCl_3$), thus obtained was decomposed again with dilute hydrochloric acid and the perfluorocarboxylic acid was extracted with diethyl ether and was dried ($MgSO_4$). After evaporating the solvent, the residue was distilled to

give (+)-PPPA (10.74 g, 65%), bp 69 - 70 °C (25 mmHg), α_D^{20} +26.50 ° (neat, l = 1), with optical purity >98% (glc).

Optically pure (-)-PPPA (9.90 g, 60%, α_D^{20} -26.30 °, neat, l = 1) was obtained similarly by treating the (-)rich-PPPA with (-)-1-phenylethylamine (α_D^{25}-37.50 °, neat, l = 1).

(+)-Perfluoro-2-propoxypropionyl chloride (PPPA-Cl)

(+)-PPPA (3.30 g, 10 mmol) was added to phosphorus pentachloride (2.50 g, 12 mmol) in an ice bath. The mixture was stirred for 10 min at room temperature and distilled carefully to give (+)-PPPA-Cl (3.24 g, 93%), bp 73 - 74 °C, α_D^{20} +8.66 ° (neat, l = 1).

^{19}F nmr analysis of N-(+)-perfluoro-2-propoxypropionyl-α-amino acid methyl ester

Typical procedure: Thionyl chloride (2 ml) was added to a dry methanol solution (20 ml) containing α-amino acid (0.5 mmol) at -70 °C. The mixture was warmed to 40 °C and stirred for 2 h at this temperature with a $CaCl_2$-drying tube. The solvent and an excess reagent were evaporated under reduced pressure, then was added dichloromethane (10 ml) and triethylamine (1 mmol). (+)-PPPA-Cl (0.6 mmol) was added and the mixture was stirred for 1 h at room temperature. After evaporating the solvent under vacuum, water (10 ml) was added to the residue and the product was extracted twice with diethyl ether (10 ml). The ethereal solution was washed with 5% aqueous sodium bicarbonate (10 ml) and dried over magnesium sulfate. The solvent was evaporated under vacuum and dimethyl sulfoxide (0.4 ml) was added to the residual oily materials. Benzotrifluoride $PhCF_3$ (0.5 mmol) was added as an internal standard and subjected to the ^{19}F nmr analysis. The spectra were measured by Varian EM-360 (84.67 MHz) spectrometer and the determinations of diastereomer ratios were based on signal intensity intergrals using sweep widths of 10 ppm.

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13 All of the amino acids used in this study are commertially available and were used without further purification. Partially resolved amino acids were prepared by mixing weighed portions of racemic and optically active components, and the calculated optical purities are given in Table 2.
14 Optical purity of partially resolved PPPA was determined as follows (see also reference [5]): Partially resolved PPPA (10 mg) was quantitatively converted to diastereomers with (-)-1-phenylethylamine by using 2-chloro-1-methylpyridinum iodide [15] as a coupling reagent. Resulting two diastereoisomers were characterized from the different glc retention times of (+)-(-)isomer and (-)-(-)isomer. Optical purity was determined by calculating their peak area.
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