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TETRAHEDRON: *ASYMMETRY*

Determination of the enantiomeric excess of chiral carboxylic acids by ^{31}P NMR with C_2 symmetrical diamines

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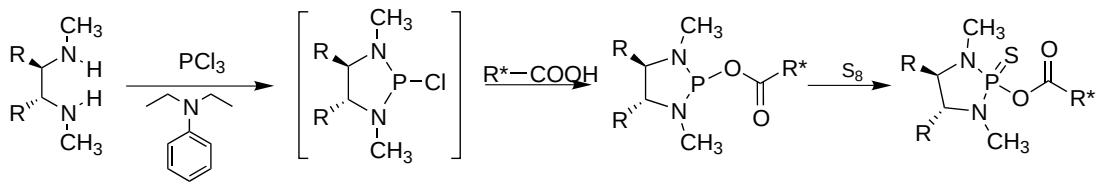
Abstract—The use of organophosphorus derivatisation agents prepared from C_2 symmetric diamines for the ^{31}P NMR determination of the enantiomeric composition of chiral carboxylic acids is described.

In contrast to the numerous methods described in the literature for NMR determination of the enantiomeric excess (e.e.) of chiral alcohols, thiols and amines[1] there have been relatively few reports of reliable analyses for chiral carboxylic acids[2] and amino acids,[3] the usual method being determination by salt formation with homochiral amines or diamines. The chiral solvating agent should possess anisotropic groups such as phenyl rings or carbonyl groups and a relatively simple ^{1}H NMR spectrum so that observation of anisochronous resonances is possible. Chiral derivatisation agents based on α-phenylethylamine or α-naphthylethylamine[4] have been developed, but in some cases the addition of an achiral shift reagent is required in order to increase the ^{1}H NMR chemical shift difference.[5] The commercial (*S*)-methyl mandelate is one of the most used chemical derivatisation agents (CDAs): the mandelate methine proton in the diastereomeric ester derivatives is typically more than 0.1 ppm anisochronous.[6] There have also been many reports of the use of 1-(9-anthryl)-2,2,2-trifluoroethanol.[7] Alternatively ^{31}P NMR spectroscopy is of considerable importance for the determination of enantiomeric purity because of the large chemical dispersion and the simplicity of the spectra.[8] Most of these organophosphorus CDAs contain a C_2 symmetric diamine moiety and have been successfully applied to the determination of the enantiomeric excess of various chiral alcohols,[2b,9] amines,[7a,9d,e,10,15] thiols[4a,8,9b,d,e,k,11] and amino acids;[9h,10b,12] however, there have been no examples reported for the e.e. determination of carboxylic acids. We recently reported the utilisation of a taddol organophosphorus derivatisation agent for the NMR determination of enantiomeric composition of chiral carboxylic acids.[13] Herein, we report the use of C_2 symmetric diamine organophosphorus derivatisation agents for ^{31}P NMR determination of the e.e. of carboxylic acids according to Scheme 1.

(*R*,*R*)-1,2-Diphenyl-1,2-bis(*N*-methylamino)ethane **1**[14] and (*R*,*R*)-1,2-bis(*N*-methylamino)cyclohexane **2**[15f] were synthesised according to procedures described in the literature. The reaction between the chiral diamine and the carboxylic acid was performed in an NMR



1 R = Ph
2 R = -$(CH_2)_4$-

Scheme 1.

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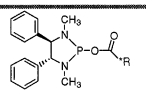
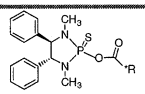
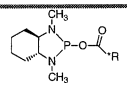
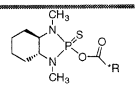
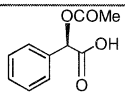
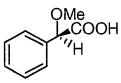
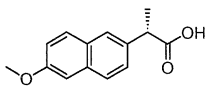
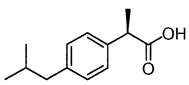
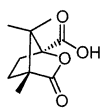
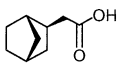
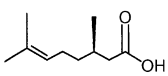
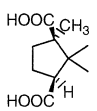
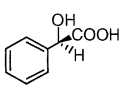
tube, according to a procedure similar to that used with secondary alcohols,[9h,j] by adding one equivalent of diamine (0.1 mmol) in solution in $CDCl_3$ with 5 equivalents of *N*,*N*-diethylaniline and one equivalent of PCl_3 and then to this solution was added the chiral carboxylic acid (0.1 mmol). ^{31}P NMR spectra could be immediately recorded after shaking the tube. Sulphur may be added directly to the NMR tube in which case the spectrum is recorded again after shaking the tube (without further purification). The carboxylic acid sample had to be anhydrous to avoid conversion of the P(III) compound to a phosphonate by-product for which no chemical shift difference can be observed between the two corresponding diastereoisomers.

A comparison of ^{31}P chemical shift differences $\Delta\delta$ (ppm) of some different C_2 symmetric diamine–P(III) and –P(V) derivatives with several carboxylic acids is presented in Table 1.

The chemical shift non-equivalence $\Delta\delta$ between the two diastereoisomers of diamino–P(III) derivatives can vary

Table 1. ^{31}P chemical shift δ (ppm) and chemical shift differences $\Delta\delta$ (ppm) of some carboxylic acid–P(III) and –P(V) derivatives ($CDCl_3$)

	R*COOH				
1		141.09	<u>77.66</u>	147.69	81.76
		<u>140.77</u>	77.45	146.58	81.49
		Δδ =0.32	Δδ =0.21	Δδ =1.11	Δδ =0.27
2		146.41	81.47	142.56	88.34
		145.64	80.95	<u>136.10</u>	87.01
		Δδ =0.77	Δδ =0.52	Δδ =6.46	Δδ =1.33
3		<u>136.84</u>	77.51	146.41	87.52
		136.74	<u>77.22</u>	145.64	87.13
		Δδ =0.10 [a]	Δδ =0.29	Δδ =0.77	Δδ =0.39
4		136.84	77.52	143.00	86.97
		136.74	77.22	142.76	86.23
		Δδ =0.10 [a]	Δδ =0.30	Δδ =0.24	Δδ =0.74
5		147.63	84.49	147.29	84.48
		147.42	84.36	147.07	84.36
		Δδ =0.21	Δδ =0.07	Δδ = 0.22	Δδ =0.12
6		<u>135.64</u>	/	141.52	81.25
		135,55		141.46	81.21
		Δδ =0.09 [a]		Δδ =0.06 [a]	Δδ =0.04 [a]
7		135.68	<u>77.18</u>	141.92	81.25
		135.59	77.12	141.87	81.20
		Δδ =0.09 [a]	Δδ =0.06 [a]	Δδ =0.05 [a]	Δδ =0.05 [a]
8		136.78	87.60		89.40
		136.70	86.79	/	87.57
		136.39	77.79		87.04
		136.30	77.47		83.79
9		decomposed	<u>83.01</u>	<u>141.21 (144.76 [b])</u>	88.37
			83.03	137.47 (146.72 [b])	88.07
			Δδ =0.02	Δδ =3.74 (1.96 [a])	Δδ =0.30

The underlined values are those of the major enantiomer.

[a] low resolution

[b] reaction also occurred with the alcohol moiety

between 0.05 and 6.5 ppm (and between 0.05 and 1.3 for diamino–P(V) derivatives). Despite the chemical shift difference and resolution being quite low compared to that of secondary alcohol–P(III) CDAs ($1<\Delta\delta<10$ ppm), in most cases the separation is sufficient to be able to determine e.e. by integration. Compared to ^{1}H NMR methods applied to the determination of the enantiomeric composition by salt formation, the ^{31}P NMR method can give better resolution.

Two diamines were tested in order to determine the most appropriate CDA. There is a noteworthy chemical shift difference in the case of *O*-acetyl mandelic acid between P(III)-**1** ($\Delta\delta=0.32$) and P(III)-**2** ($\Delta\delta=1.11$) (entry 1). The difference is even greater in the case of (methoxyphenyl)acetic acid derivatives (entry 2) with $\Delta\delta_{P(III)-(2)}-\Delta\delta_{P(III)-(1)}=5.7$ ppm. Such differences have already been observed in the case of alcohol derivatives, a better chemical shift difference being observed with P(III)-**2** CDAs compared with P(III)-**1** CDAs. This difference could be due to the cyclohexane skeleton which may serve to rigidify the molecule.

When comparing *O*-acetyl mandelic acid–P(V)-**1** and *O*-acetyl mandelic acid–P(III)-**1**, the $\Delta\delta$ slightly decreased but resolution is enhanced because of the

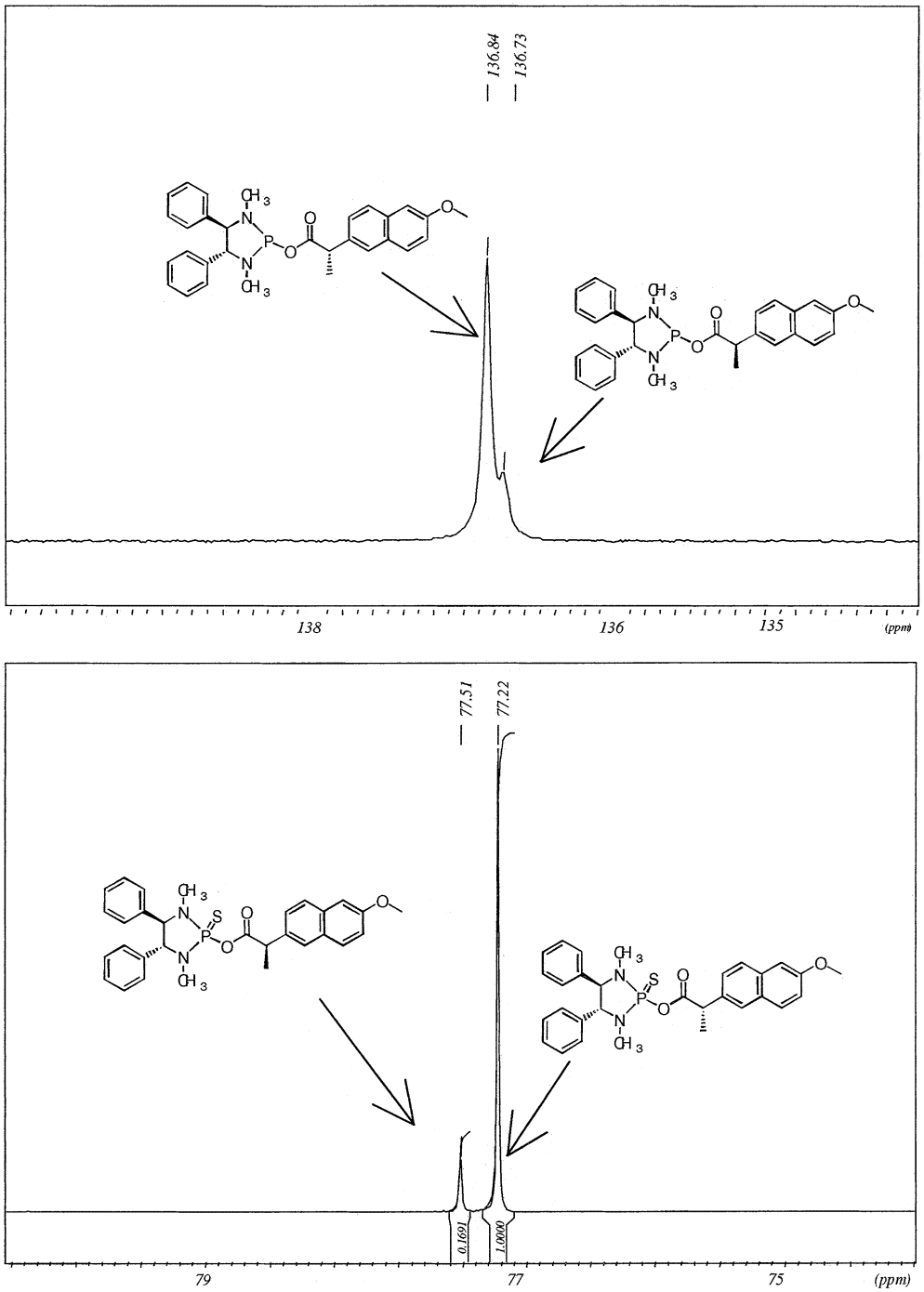


Figure 1.

narrowed peaks, as already observed in the case of alcohols.[9d,e] Direct addition of sulphur in the NMR tube can then be a powerful tool to determine enantiomeric composition. A representative example is given in the case of naproxen with a low baseline separation in the case of naproxen–P(III)-**1** and a high one with naproxen–P(V)-**1** (Fig. 1). The same phenomenon is even greater in the case of ibuprofen, for which there is low resolution in the case of P(III) derivative (entry 4). These compounds are used in medicinal chemistry and this method provides both a convenient and accurate way to determine the enantiomeric composition and absolute configuration of the chiral carboxylic acid in enantiomerically enriched samples (Fig. 1).

When the stereogenic centre is in the β-position to the carboxylate moiety, as is the case with 2-norbornacetic acid (entry 6) and citronellic acid (entry 7), there is very little resolution and enantiomeric excess could not be determined using this method. When using (1*R*,3*S*)-(+)-camphoric acid (entry 8), two singlets were observed because of the non-equivalent carboxylic moieties. Similarly, in the case of malic acid (entry 9) there is a competition between the carboxylic and the alcohol moiety: for this reason two signals are observed for one single diastereoisomer, the major one being observed with the reaction between PCl_3 and the carboxylic moiety. A better chemical shift non-equivalence is observed with these P(III) derivatives compared to the ones provided by reaction between P(III) CDAs and the alcohol moiety. With P(III)-**1** derivatives, decomposition occurred so that sulphur had to be added in the NMR tube prior to the addition of the carboxylic acid. Only two phosphorus singlets were then observed, corresponding to reactivity with the carboxylic moiety.

In conclusion, ^{31}P NMR can be a useful tool to determine the e.e. of chiral carboxylic acids when the stereogenic centre is α to the carboxylate moiety. Accurate determination of enantiomeric purity could be achieved with both P(III) and P(V) CDAs and, in some cases, sulphurated compounds gave better chemical shift non-equivalence than non-sulphurated ones, as demonstrated with naproxen and ibuprofen derivatives. In most cases, a larger chemical shift separation was achieved with (*R*,*R*)-1,2-bis(*N*-methylamino)cyclohexane **2** CDAs compared with those based on (*R*,*R*)-1,2-diphenyl-1,2-bis(*N*-methylamino)ethane **1**.

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