Tetrahedron: Asymmetry Vol. 2, No. 11, pp. 1127-1132, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

THE MEASUREMENT OF ENANTIOPURITY USING PHOSPHORUS-NMR

Christopher J Welch

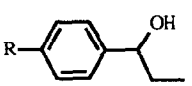
Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Centre, Uppsala University,
Box 574, S 751 23 UPPSALA, SWEDEN

(*Received* 13 *August* 1991)

Abstract: The enantiopurity of various alcohols can be determined using phosphorus-NMR by observing the signals from the trialkyl phosphites produced by the reaction of phosphorus trichloride and the alcohol. The enantiomeric excess can be determined to within 2% using this method.

Introduction: It is desirable to have a reliable method for the determination of enantiopurity of various synthetic products. Of the methods available, many involve reaction of a substrate of unknown enantiopurity with an enantiomerically pure reagent.[1,2] The resulting diastereomeric mixture may then be analysed by either physical, gc. or hplc. or spectroscopic means, most often NMR.

A method was reported where phosphorus trichloride, a non chiral reagent, reacts with chiral alcohols to form a dialkyl phosphonate.[3] Observation of the ^{31}P-NMR showed three signals close to 0 ppm, corresponding to the dialkyl phosphonates. These signals were due to an enantiomeric pair and two meso compounds.[3] The ratio between the integrals of these signals allowed for calculation of the enantiopurity of the mixtures. This method has subsequently been used[4-6] and developed[7-9] by a number of research groups.



1) R = H
2) R = CH_3-
3) R = CH_3O-

4

5

In this study the experiments of Feringa et al.[3] were investigated further using slightly different conditions. The ^{31}P-NMR signals corresponding to the phosphonates diminished in intensity while a number of signals corresponding to various phosphite derivatives could be seen in the range 140 to 180 ppm (Figure 1). These signals can be used with great ease to determine the enantiomeric distribution in mixtures of unknown

composition. The method has been tried with a number of substituted phenylpropanols (**1** - **3**) and with *endo*- and *exo*-norborneol (**4** and **5**) the results for the estimation of enantiomeric composition of the mixtures being in good agreement with the actual values as determined by weight.

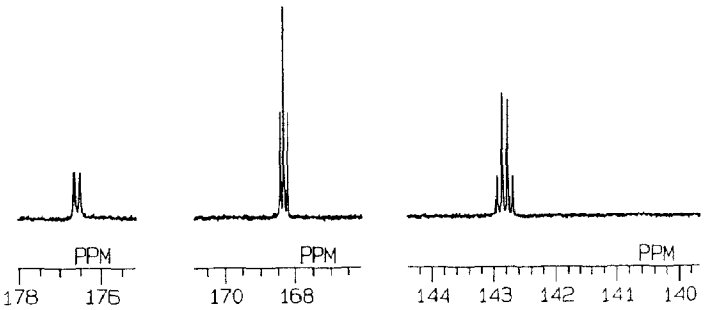


Figure 1 ^{31}P-NMR obtained for the reaction mixture of (R)-1-phenyl-1-propanol with phosphorus trichloride and pyridine

Table 1
^{31}P-NMR data for reaction mixtures

Isomer	Chemical[a] Shift (ppm)	Multiplicity	$^{3}J_{P-H}$ (Hz)	Assignment
-	220	s	-	PCl_3
R	176.6	d	14.6	$ROPCl_2$
R	168.4	t	11.3	$(RO)_2PCl$
R	142.8	q	9.7	$(RO)_3P$
S	176.6	d	14.6	$ROPCl_2$
S	168.4	t	11.3	$(RO)_2PCl$
S	142.8	q	9.7	$(RO)_3P$
Racemate	176.6	d	14.6	$ROPCl_2$[b]
Racemate	168.4	t	11.3	$(RO)_2PCl$[c]
Racemate	142.8	q	9.7	$(RO)_3P$[d]
Racemate	140.7	q	9.7	$(RO)_3P$[e]

a) Reference 80% phosphoric acid
b) Derivatives from both R and S isomers give identical signals
c) RR and SS forms are enantiomeric and give identical signals, RS and SR are indistinguishable due to rapid inversion at phosphorus
d) RRR and SSS signals
e) RRS and SSR signals

Results. The experiments of Feringa et al.[3] were repeated. Enantiomerically pure (R)-1-phenyl-1-propanol and phosphorus trichloride were reacted in the presence of a small excess of pyridine. Under normal conditions the reaction mixtures became cloudy shortly after mixing, a precipitation of biproducts occurred soon thereafter. These problems with the homogeneity of the solutions caused difficulty in obtaining ^{31}P-NMR spectra of suitable quality. The reaction was subsequently carried out under an inert atmosphere, the rate at which the solution became cloudy was greatly reduced, however the formation of the phosphonates was also much slower. The ^{31}P-NMR showed a series of multiplets in the region 140 - 180 ppm corresponding to a series of phosphite derivatives (Figure 1). These signals are characterised and assigned as mono-, di- and trialkyl phosphite esters (Table 1). The most interesting of these signals is the quartet appearing at 142.7 ppm corresponding to a trialkyl phosphite. Repeating the experiment with (S)-1-phenyl-1-propanol gave rise to an identical ^{31}P-NMR spectrum (Table 1, Figure 2). However, when racemic 1-phenyl-1-propanol was treated under the same conditions the spectrum obtained contained an extra multiplet at 140.7 ppm corresponding to a trialkyl phosphite containing both S and R alkoxy groups (Figure 2).

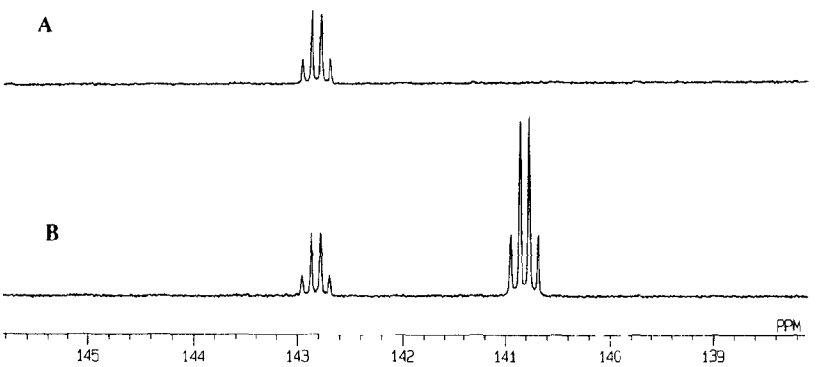


Figure 2 ^{31}P-NMR obtained for the reaction of an alcohol with phosphorus trichloride and pyridine. A: (R)-1-phenyl-1-propanol. B: racemic 1-phenyl-1-propanol.

By measuring the ratio of the signals at 140.7 and 142.7 it is possible to calculate the enantiomeric composition of the mixture. Calculating the probability of forming the homogeneous, RRR or SSS, and heterogeneous, RRS and SSR, trialkyl phosphites the quadratic relationship (1) can be derived, where Q represents the integral of the signal at 140.7 ppm expressed as a fraction of the total integral for the trialkyl phosphites, and a is the molar fraction of one isomer.

$$Q = 3a(1-a) \qquad (1)$$

The enantiomeric excess may then be calculated by solving Equation (1) for a and substituting into equation (2)

$$\% \text{ e.e.} = (2a\text{-}1) \times 100 \qquad (2)$$

The usefulness of this method has been demonstrated through two series of experiments. In the first series a set of mixtures of (R)- and (S)-1-phenyl-1-propanol of known composition from pure (R) to pure (S) were reacted with phosphorus trichloride and examined by ^{31}P-NMR. The data obtained are displayed in Table 2. The observed values for the enantiomeric excesses were found to be in very good agreement with the actual values, the difference not exceeding 2%.

Table 2.
Measurement of enantiomeric in mixtures of (R) and (S)-1-phenyl-1-propanol

% e.e. actual[a]	Ratio of multiplets A and B		% e.e. observed
	theoretical	observed	
100.0 (R)	b	b	100.0
87.4 (R)	4.65:1	3.99:1	85.6
64.2 (R)	1.27:1	1.30:1	64.8
49.0 (R)	1:1.33	1:1 31	49.5
0.0	1:3.00	1:2.98	2.0
32.4 (S)	1:2.03	1:1.93	34.8
64.0 (S)	1.26:1	1.32:1	65.2
100.0 (S)	b	b	100.0

a) Measured by weight
b) Only one multiplet observed

The second series of results were obtained for a set of racemic alcohols, **1** - **5**. The results are shown in table 3. In all cases the enantiomeric excess was estimated to be less than 2%. It is worth noting that whilst neither *endo* nor *exo* norborneol gave signals sufficiently well separated for evaluation in the proton coupled spectra, the signals were sufficiently well separated in the decoupled spectra allowing reliable integrals to be measured. The signals which correspond to the dialkyl phosphonates for norborneol are reported to be too close to each other to allow for accurate integration [3]

Table 3.
Integral ratios and estimated enantiomeric composition of racemic alcohols **1** - **5**

Alcohol	Ratio of peaks A : B	Chemical Shift A	Chemical Shift B	Isomeric Ratio	% e.e.
1	1 : 2.97	142.7	140.7	49.0 : 51.0	2
2	1 : 2.96	142.7	140.7	49.0 : 51.0	2
3	1 : 3.01	142.7	140.7	49.5 : 50.5	1
4	1 : 3.03	142.7	140.7	49.0 : 51.0	2
5	1 : 2.95	142.7	140.7	49.0 : 51.0	2

Discussion. The method presented herein allows for the simple estimation of enantiopurity of chiral alcohols using ^{31}P-NMR spectroscopy. The reaction uses readily available, inexpensive reagents, can be carried out fairly quickly, less than 30 min for sample preparation and spectroscopic analysis, requires only a small sample of the alcohol and no special equipment. The limitations imposed on this method lie in the accuracy of integration of the NMR signals. It is therefore of the utmost importance that good quality spectra, with high signal / noise ratios, are obtained.

The enantiopurity is calculated from Equation 1, given above. A plot of the integral, Q, against the mole fraction, a, (Figure 3) shows that small errors in the measurement of the integral lead to larger inaccuracies in the calculated e.e. for mixtures which are close to racemic, and smaller inaccuracies for mixtures approaching 100 % enantiopurity. This is due to the gradient of the curve being large at the extremes of enantiopurity and zero for racemic mixtures. The reliability of the method increases with the enantiopurity of the alcohol. With such a method there is a risk for enantioselectivity in the formation of the trialkyl phosphite products.[10,11] The results obtained suggest, however, that the reaction occurs on a random basis.

A comparison of the curve obtained by the observation of the integrals of the phosphite triesters with the curve obtained by observation of the phosphonates, which can be described by the Equation 3, shows that the former has a larger gradient over the entire range of measurement. A consequence of this observation is that the method presented here, i.e. observation of the signals from phosphite triesters, gives greater accuracy in the measurement of enantiopurity.

$$Q = 2a(1-a) \qquad (3)$$

The method presented herein has subsequently been used for the determination of enantiopurity of alcohols from synthetic sources.[11]

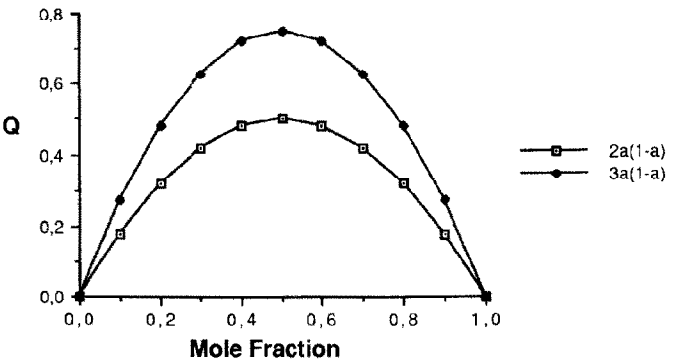


Figure 3 Relationship between partial integral Q and mole fraction of one enantiomer

Experimental section: (R)-1-phenyl-1-propanol, (S)-1-phenyl-1-propanol and racemic 1-phenyl-1-propanol, were purchased from Fluka. 1-(4-methylphenyl)-1-propanol and 1-(4-methoxyphenyl)-1-propanol were prepared from the corresponding aryl bromides via grignard reactions. *Endo*- and *exo*-norborneol were purchased from Aldrich. Phosphorus trichloride was of reagent grade and used without further purification. ^{31}P-NMR were recorded at 25 °C using a JEOL EX270 NMR spectrometer equipped with a 5 mm tunable probe operating at 109.25 MHz. Spectra were recorded both with and without proton decoupling. Phosphoric acid (80 %) was used as external reference, with deutero chloroform as solvent.

General method for sample preparation. An NMR tube was charged with 0.1 mmol of the alcohol. To this was added deutero chloroform 0.5 ml and dry pyridine and the tube shaken to ensure thorough mixing. The tube was flushed with nitrogen Phosphorus trichloride, 0.04 mmol, was added and the tube again flushed with nitrogen. After shaking the sample was ready for spectroscopic analysis.

References.

1. Dale, J. A ; Dull, D. L.; Mosher, H S. *J. Org. Chem.* **1969**, *34*, 2453.
2. Tokles, M.; Snyder, J.K. *Tetrahedron Letts.* **1988**, *29*, 6063.
3. Feringa, B.L.; Smaardijk, A. A.; Wynberg, H. J. Am. Chem. Soc. **1985**, *107*, 4798.
4. Chaloner, P. A.; Renuka Perera, S. A. *Tetrahedron Letts* **1987**, *28*, 3013.
5. Basile, T.; Tagliavini, E.; Trombini. C.; Umani Ronchi, A. *J. Chem. Soc. Chem. Commun.* **1989**, 596.
6. Chaloner, P A.; Langadianou, E. *Terahedron Letts.* **1990**, *31*, 5185.
7. Feringa, B.L.; Strijtveen, B.; Kellogg, R. M.*J Org. Chem.* **1986**, *51*, 5486.
8. Feringa, B.L.; Smaardijk, A. A.; Wynberg, H.; Strijtveen, B., Kellogg, R. M.*Tetrahedron Letts.* **1986**, *27*, 997.
9. Strijtveen, B.; Feringa, B.L.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 123.
10. Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.
11. Werner, M.; Pasquier, M.L.; Gampp, H. *Helv Chim Acta* **1987**, *70*, 1774.
12. Näslund, J.; Welch, C. J. *Accompanying manuscript.*