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METHYLPHOSPHONIC DICHLORIDE AS REAGENT FOR THE DETERMINATION OF THE ENANTIOMERIC EXCESS OF CHIRAL THIOLS. SCOPE AND LIMITATIONS

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Abstract - Methylphosphonic dichloride, $CH_3P(=O)Cl_2$, reacts cleanly and quantitatively with thiols to form dialkylthiophosphonates, $CH_3P(=O)(SR)_2$. From the ratio of the integrations of the ^{31}P absorptions in the NMR spectra, the enantiomeric excesses of the thiols can be obtained for the cases that R is chiral. The effect of structural change in the phosphorus derivatizing reagent on the separation of peaks in the ^{31}P NMR spectra has been examined, especially the effects of variations in electronegativity and/or steric bulk. The effect of the temperature on the peak separation was also studied.

The importance of asymmetric synthesis forms the basis for the considerable interest in the development of facile and accurate methods for enantiomeric excess (e.e.)[1] determination. This has recently resulted in new chromatographic techniques using chiral stationary phases[2] and NMR techniques with chiral derivatizing agents.[3,4,5]

Our current research[6] on the synthesis and applications of chiral thiols strongly depends on reliable methods for e.e.-determination of these compounds. Feringa, Smaardijk and Wynberg reported a new method for enantiomeric excess determination of alcohols that does not require chiral auxiliary compounds.[7] The principle involved is the formation of diastereoisomeric phosphonates 1 of racemic or partly enriched alcohols by reaction with PCl_3 or the exclusive formation of one diastereoisomer of 1 when enantiomerically pure alcohol is used (eq. 1).

$$PCl_3 + R^*OH \longrightarrow \underset{1}{H-\overset{\overset{O}{\|}}{P}-(OR^*)_2} \quad \text{(eq. 1)}$$

The ratio of diastereoisomeric phosphonates 1, easily determined by ^{31}P NMR, is consequently directly related to the ratio of enantiomers of the chiral alcohol.[8] Well resolved ^{31}P NMR signals for each diastereoisomer of 1 are obtained and therefore accurate integrations are possible.

Making use of the same principle we recently described alternative phosphorus reagents for e.e. determination of chiral alcohols and extended the method to the e.e. determination of some chiral thiols.[9] We now describe the scope and limitations of the use of methylphosphonic dichloride as a new reagent for the e.e. determination of chiral thiols. Chiral alcohols and thiols are converted to diastereoisomeric (thio)phosphonates 3 via reaction with alkylphosphonic dichlorides 2 as shown in eq. 2.

$$\underset{\underline{2}}{R'-P(=O)Cl_2} + 2\,R^*XH \xrightarrow[CDCl_3]{2(C_2H_5)_3N} \underset{\underline{3}}{R'P(=O)-(XR^*)_2} \quad X=O,S \qquad \text{(eq.2)}$$

For racemic alcohols and thiols 3 is obtained as a mixture of a d,l-pair and two meso-compounds. For alcohols, the best results, i.e. the largest chemical shift differences, for the diastereoisomers of 3 (X = O), were obtained with methylphosphonic dichloride (2, $R^1 = CH_3$). Increase of the size of the alkyl substituent R^1 in 3 leads to a decrease of the chemical shift differences. Methylphosphonic dichloride has also been used for the e.e.-determination of some α-thiolcarboxylic esters.[9]

To find the best coupling reagent for chiral thiols, i.e. the one that gives the largest chemical shift differences as well as clean and quantitative reactions, a number of diastereomeric thiophosphonates of general structure 4 were prepared[10] from racemic 1-phenylethanethiol as shown in equation 3, and their ^{31}P NMR spectra were examined.

$$Y-P(=Z)Cl_2 + 2\,C_6H_5-\underset{H}{\overset{CH_3}{C}}-SH \xrightarrow[CDCl_3]{2(C_2H_5)_3N} \underset{\underline{4}}{Y-P(=Z)-(S-\underset{H}{\overset{CH_3}{C}}-C_6H_5)_2} \qquad \text{(eq.3)}$$

The effects of the substituents Y and Z on the ^{31}P NMR spectra are shown in Table I.

Table I

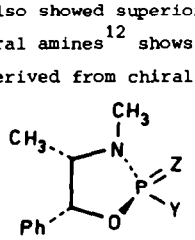
^{31}P NMR Data for $YP(=Z)[SCH(CH_3)C_6H_5]_2$

Entry	Y	Z	δ(meso)Hz	δ(meso)Hz	δ(d,l pair)Hz	Δδ(Hz)[a]
1	CH_3	O	4523	4935	4632	109.303
2	$C_6H_5CH_2$	O	4888	5100	4912	24.188
3	C_6H_5	O	4082	4127	4089	7.38[b]
4	$C_6H_5CH_2S$	O	4778	4799	4811	12.33
5	CH_3	S	6049	6208	6086	37.122
6	C_6H_5	S	6216	6233	6233	0.17[b]

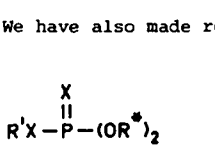
a) chemical shift differences (absolute values) between the d,l pair and the respective meso diastereomers.
b) no base line separation.

PCl_3, $POCl_3$ and $PSCl_3$ (not listed in the Table) were also tested as derivatizing reagents,[11] but the diastereoisomers derived from them were (nearly) not separated in the ^{31}P NMR spectra and the reactions were not clean.

From the data in Table I, it can be seen that the best results were obtained with methylphosphonic dichloride (entry 1). At first glance, it seems somewhat surprising that its sulfur analogue, methylthiophosphonic dichloride (entry 5), did not give larger chemical shift differences. In the work of Johnson et al.,[3] who used the chiral coupling reagent 5 (Y = Cl, Z = O,S) for the e.e. determination of chiral alcohols (Y = OR*) and amines (Y = NHR*), the thio derivatives (Z = S) in general also showed superior chemical shift differences. Our recent work on the e.e. determination of chiral amines[12] shows similar results. We have also made related observations with (thio)phosphates 6 derived from chiral alcohols R*OH.



5



X = O,S R' = H

6

Again the thio derivatives (6, X = S) gave the best (although small) chemical shift differences. The phosphates 6 (X = O, R^1 = H) gave no separation. The corresponding phosphonates (3, (X = O), on the contrary, do give well separated ^{31}P NMR spectra.[9] Like behavior is found for the benzyl thiophosphonate derived from 1-phenylethanethiol (Table I, entry 2) compared to the corresponding S-benzyl thiophosphate (Table I, entry 4). A change in substituent at phosphorus from $C_6H_5CH_2$- to $C_6H_5CH_2S$- results in a drastic fall of chemical shift difference between the diastereoisomers.

Two important conclusions can be drawn from all these observations:

1. It appears that diastereoisomeric phosphorus compounds of general structure Y-P(=Z)A,B (7) show the largest chemical shift differences in the ^{31}P NMR when a) Y ≠ Z ≠ A,B and b) the difference between Y,Z and A,B in size and/or electronegativity is maximal.
2. The thio derivatives 7 (Z = S) give in general superior chemical shift differences, except when two or more of the substituents Y, A, B are also sulfur-substituents.

7

Methylphosphonic dichloride, $CH_3P(=O)Cl_2$ is a better reagent for thiols than $CH_3P(=S)Cl_2$ because the substituents in $CH_3(P=O)(SR^*)_2$ differ more than in $CH_3P(=S)(SR^*)_2$. In the latter case, three sulfur atoms are attached to the phosphorus atom, in the former two sulfur atoms and one oxygen atom.

On the basis of these conclusions we predicted that for alcohols, however, $CH_3P(=S)(OR^*)_2$ would show larger chemical shift differences between the diastereoisomers than $CH_3P(=O)(OR^*)_2$.[9] Results for two alcohols are given in Table II. These are in agreement with the prediction. However, $CH_3P(=S)Cl_2$ is unfortunately not a suitable general reagent for alcohols, owing to byproduct formation and incomplete reactions in most cases.

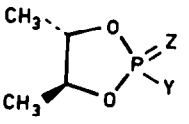
Table II

^{31}P NMR Data for $CH_3P(=Z)(OR^*)_2$

Entry	R^*OH	Z	δ(meso)Hz	δ meso(Hz)	δ(d,l pair)Hz	Δδ(Hz)
1		O	2285	2335	231	26.24
2		S	7405	7494	7451	46.43
3		O	2305	2377	2338	33.39
4		S	7477	7637	7561	84.76

The above rationale applies also to, for example, $P(SR^*)_3$, $P(OR^*)_3$ $HOP(=O)(OR^*)_2$, $(R^*S)_3P=S$, $(R^*S)_3P=O$, and $(R^*O)_3P=O$, which all exhibit no separation for their diastereoisomers in the ^{31}P NMR spectra.[13] The difference between the substituents at phosphorus is too small. The same is true for 8 (Z=O, Y=Cl). This chiral phosphorus reagent has been used for the e.e. determination of chiral alcohols.[4] Only very small separations between the diastereoisomers (0-12 Hz) are observed. We predict that the thio derivative would give better results.

On the basis of the foregoing observations, $HP(=O)Cl_2$ should be the best derivatizing reagent for chiral alcohols. This, however, is a very unstable compound, although its existence in



8

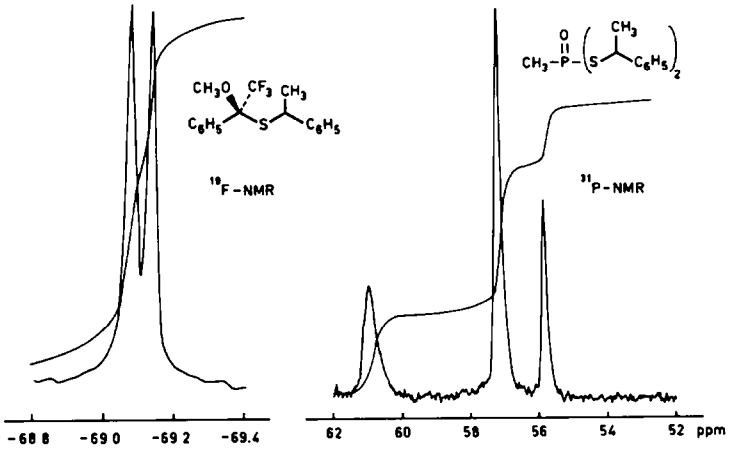
solution has been demonstrated recently by ^{31}P NMR measurements.[14] Alternative single-step syntheses of S,S-dialkylthiophosphonates, $HP(=O)(SR^*)_2$, other than from $HP(=O)Cl_2$ are not available.[15] Moreover, S,S-dialkylthiophosphonates are unstable compounds,[15] which rearrange readily to S,S,S-trialkylphosphites, $P(SR^*)_3$. $CH_3P(=O)Cl_2$ was chosen as the most suitable reagent for the e.e. determination of chiral thiols.

To test the scope and limitations of this reagent, a number of methyl-S,S dialkyl thiophosphonates (3, R = CH_3, X = S) were prepared from racemic thiols 14[16] and $CH_3P(=O)Cl_2$ as shown in equation 2. Results are summarized in Table III.

From this table it can be seen that the method is broadly applicable. It works well for α- and β-thiol carboxylic esters, α-thiolamides, secondary benzylic thiols and aliphatic thiols. Chiral self-recognition during the coupling reaction is small (entry 7) and usually negligible, as illustrated by the small deviations from the statistical 50/50 in the d,l to meso ratio.[17] Only in a few cases (entries 6, 8, 11) no baseline separation was obtained in $CDCl_3$. However, this problem could be circumvented (for entry 11) by recording the ^{31}P NMR spectrum in CD_3OD. In this solvent, (nearly) baseline separations were obtained.

Furthermore, chemical shift differences compare favorably with those obtained using chiral derivatizing reagents with 1-phenylethanethiol; separations of the meso diastereoisomers from the d,l were Δδ 1.35 and 3.74 ppm, whereas Mosher's reagent gave Δδ 0.06 ppm (see fig. 1) and Pirkle's reagent[18] a maximum separation Δδ 0.05 ppm in the ^1H NMR (no ^{19}F data were reported).

Figure 1. Comparison of Peak Separations For Derivatives of 1-Phenylethane Thiol (^{19}F Spectra Measured at 188.2 MHz and ^{31}P at 81.0 MHz)



The peak separation obtained for diethylthiomalate (entry 2) (Δδ 5.01 and 1.25 ppm) is by far the greatest ever reported in the literature for diastereomeric phosphorus compounds.

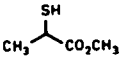
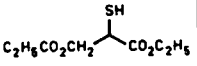
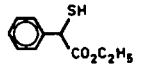
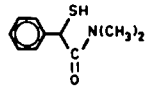
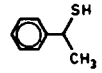
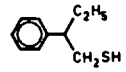
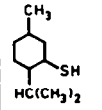
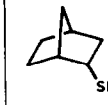
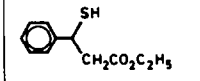
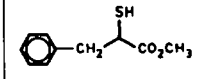
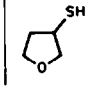
To establish the accuracy of the present method partially enriched or optically pure thiols were tested also. Results are summarized in Table IV.

As can be seen from the Table, results obtained by ^{31}P NMR are in excellent agreement with optical purity measurements. This confirms the accuracy of the method. We recommend $CH_3P(=O)Cl_2$ as a broadly applicable (non-chiral) reagent for the enantiomeric excess determination of chiral thiols.[19]

We also tested the influence of the temperature and solvent on the chemical shift differences. Results are shown in Table V for the thiophosphonate derived from 1-phenylethanethiol. From this table it can be seen that lowering the temperature causes a large increase in chemical shift difference between the diastereoisomers. This means a wider applicability of the method, because when

Table III

^{31}P NMR Data for Thiolphosphonates from Racemic Thiols and CH_3POCl_2

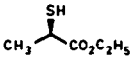
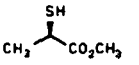
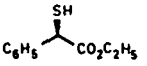
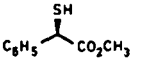
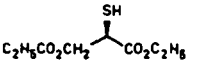
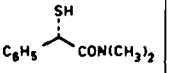
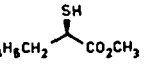
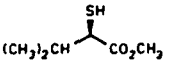
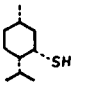
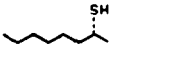
Entry	Thiol	δ(meso) Hz	δ(meso) Hz	δ(d,l pair) Hz	ratio meso, d,l
1		4660	4987	4725	49 51
2		4660	5166	4760	49 5 . 50 5
3		4641	4808	4736	49 51
4		4883	5088	5010	50 50
5		4523	4935	4632	49 5 50 5
6		4940	4977	4954	—[b]
7		4640	4707	4694	47.5 52 5
8		4805	4805	4805	—[c]
9		4590	4921	4638	48 52
10		4674	4938	4756	50 50
11		5129	5088	5050[a]	49 51

a) the reaction is carried out in $CHCl_3$, the solvent is then removed, and the ^{31}P NMR spectrum is recorded in CD_3OD.
b) no base line separation; about 50:50.
c) no separation.

peaks do not (completely) separate at room temperature this can easily be achieved by lowering the temperature. The ^{31}P NMR spectra of entries 2 and 5 are shown in Figure 2. The increase in chemical shift difference at lower temperature is clear. Similar effects were observed in d^6-DMSO although shift differences are much smaller (Table V). Another phenomenon of these spectra deserves attention, namely the remarkable form of the high field meso peak. In this case, and most cases studied, this high field meso peak is broader and lower than the low field meso peak. This may be due to a larger rotational barrier in the former molecule, as deduced from examination of molecular models and Newman projections. This should cause a sharpening of the high field signal at higher temperature but a further broadening at lower temperature. Although this is the case, as can be seen from the spectra in fig. 2 at 20 and -60°C, the effect is rather small and is not particularly convincing. This phenomenon has no detectable influence on the e.e. determination.

Table IV

Determination of Enantiomeric Excesses of Chiral Thiols

Entry	Thiol	% e.e. by rotation	% e.e. by ^{31}P-NMR
1	(R) 	91	92
2	(R) 	92	93
3	(S) 	88	90
4	(S) 	91	93
5	(R) 	92	93
6	(S) 	(48)[a]	47
7	(R) 	—[b]	93
8	(R) 	—[b]	≥ 98
9	(+) 	—[b]	≥ 98
10	(S) 	100	≥ 98

a) the corresponding thioacetate had an e.e. of 48%.[6]
b) rotation higher than reported in the literature (see ref. 6 and references cited therein).

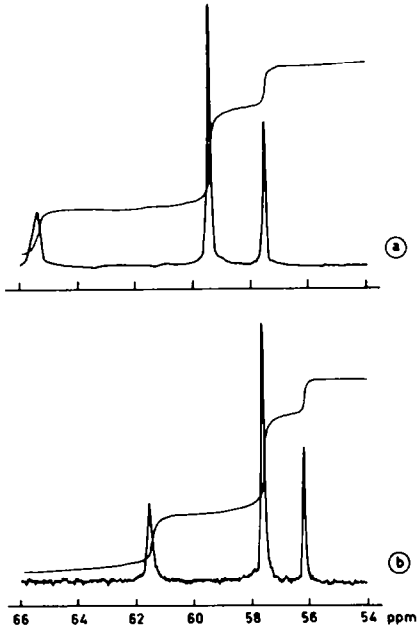
Table V

^{31}P NMR Data for $CH_3P(=O)[SCH(CH_3)C_6H_5]_2$

Entry	temp (°C)	solvent	δ(d,l pair)Hz	Δδ(Hz)[a]
1	60	$CDCl_3$	4601	255, 98
2	20	"	4663	329, 115
3	-20	"	4731	394, 134
4	-40	"	4765	436, 143
5	-60	"	4809	484, 155
6	-80	"	4854	537, 166
7	80	DMSO-d^6	4588	148, 78
8	40	"	4618	175, 82
9	20	"	4644	188, 90

a) chemical shift differences (absolute values) between the d,l pair and the respective meso diastereomer.

Figure 2. ^{31}P NMR Spectrum of $CH_3P(=S)[SCH(CH_3)C_6H_5]_2$ at (a) - 60°C and (b) 20°C



Experimental Section

^{31}P NMR spectra were recorded on a Nicolet NT-200 (at 81.0 MHz) spectrometer with 85% H_3PO_4 (δ 0.0 ppm) as an external standard. If necessary, line-broadening programs were used to obtain better peak separations without influencing the ratio of the peak areas.

The phosphorus coupling reagents were prepared according to literature procedures, see ref. 8. A typical experiment for the preparation of the thiophosphonates follows:

To a stirred solution of 1 mmol thiol and 1 mmol triethylamine in 1 mL $CDCl_3$ was added at 0°C a solution of 0.5 mmol $Y-P(=Z)Cl_2$ in 1 mL $CDCl_3$ (excess base should be avoided to prevent racemization). After stirring for 10 minutes, the reaction mixture was transferred into an NMR tube and the ^{31}P NMR spectrum recorded.

References and Footnotes

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10. The starting materials $Y-P(=Z)Cl_2$ were commercially available (entries 3,6) or prepared according to literature procedures.
entry 1, see ref. 6; entry 2, Kinnear, A.M. and Perren, E.A., J. Chem. Soc., 1952, 3437; entry 4: Houben-Weyl, "Methoden der Organischen Chemie, Georg Thieme Verlag Stuttgart, Band E_2, p. 526, 1982; entry 5: Ibid, Band XII/1, p. 555.
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16. Racemic and partially enriched thiols were prepared from the corresponding alcohols or bromides by S_N2 substitution with cesiumthioacetate or cesiumthiobenzoate in DMF and subsequent hydrolysis.
17. For most of the examples studied the ratio of the two meso compounds deviates from the statistical one to one ratio, but this had no detectable influence on the determination.
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19. In principle, it should also be possible to determine the enantiomeric excess of chiral thiols by separation of the diastereomeric thiophosphonates by GLC or HPLC.