

CHROM. 5057

GAS CHROMATOGRAPHIC SEPARATION OF DIASTEREOISOMERIC ALKYL METHYLPHOSPHONOFUORIDATES AND RELATED COMPOUNDS

A. VERWEIJ, E. BURGHARDT AND A. W. KOONINGS

Chemical Laboratory of the National Defence Research Organization TNO, Rijswijk, Z.H. (The Netherlands)

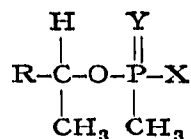
(Received August 13th, 1970)

SUMMARY

A gas chromatographic study was performed concerning the structure-separation relationship of diastereoisomeric alkyl methylphosphonofluoridates and related compounds. Relative retention values (r), determined on two stationary phases of different polarity, were used as a measure for the separation of the stereoisomeric forms. It was demonstrated that both steric and electronic interactions influence the separation. The P-O-C ester linkage and the P-F bond proved to be important in the differential interaction between the diastereoisomers and the stationary phases.

INTRODUCTION

The results of several investigations concerning the chromatographic separation of diastereoisomeric carboxylic esters¹⁻⁵, amides^{2,6} and alcohols⁷ have been published. Comparable studies dealing with organophosphorus compounds are unknown to us. We wish to report on the structure-separation relationship of diastereoisomeric alkyl methylphosphonofluoridates and related compounds with the general formula



in which R = C_nH_{2n+1}, C_nH_{2n-1}, C_nH_{2n-3} or (CH₃)₂NCH₂, Y = O or S and X = F, H or OCH₃. The gas chromatographic analyses were performed on two columns of different polarity. In order to gain insight into the factors determining the separation of the stereoisomeric forms, the effects of structural variations at both chiral centres were examined. The relative retention⁸ (r) derived from the adjusted retention times of the diastereoisomers of the respective compounds was used as a measure for their separation.

In general when two compounds are analysed under identical gas chromatographic conditions, r is a function of vapour pressures and solubilities in the stationary phase. When comparing r values obtained on columns of different polarity, used at

the same temperature, mainly solubility effects have to be considered. In this way it is possible to investigate the contribution of electronic interactions to the separation.

EXPERIMENTAL

Chromatographic procedure

The gas chromatographic data were obtained at 110° on two glass columns (2.7–3 m × 3–4 mm I.D.). The apolar column was packed with 25 % (w/w) DC-550 silicone oil, the polar one with 25 % (w/w) Triton X-305, both coated on Chromosorb W-AW, 80–100 mesh. The columns were housed in a Varian Aerograph, Model 1520-3B, equipped with two flame ionisation detectors. The carrier gas was nitrogen at a flow rate of 20 ml/min. Injection blocks and detectors were maintained at 195°. Samples ($\leq 0.1 \mu\text{l}$) were introduced by on-column injection.

Using Chromosorb as support material, a decomposition of 2,4-dimethylpentylmethylphosphinic fluoride was observed. Therefore the compound was analysed on silanised glass columns, which were packed with teflon powder (40–60 mesh) as an inert support material. The coating (5 % w/w) and packing procedures used were according to KIRKLAND⁹. This change in support material did not influence the results as was derived from control experiments.

The adjusted retention times collected in Table II were obtained from representative chromatograms. The median relative retention values given were calculated according to the statistical method of DEAN AND DIXON¹⁰. The relative standard deviation is about 0.5 %.

Materials

The methods used for the synthesis of the organophosphorus compounds and some physical constants are summarised in Table I. The purity of the compounds proved to be satisfactory as was checked by the gas chromatographic procedure described above. Infrared spectroscopy was used to identify the eluted peaks of representatives of the different types of compounds. Separate peaks ascribed to diastereoisomeric forms gave identical infrared spectra.

RESULTS AND DISCUSSION

$$R = C_nH_{2n+1}$$

As can be seen from Table II the relative retentions (r) obtained for the members of the homologous series of *sec.*-alkyl methylphosphonofluoridates (compounds 1–5) increase on lengthening the chain of the alkyl group R. The increase is observed on both the polar and apolar columns. When comparing compounds with the same carbon chain length (compounds 2, 7 and 8) an increase in the bulk size at the γ -carbon atom gave an increase in r . Another series (compounds 1, 6 and 9) shows a shorter carbon chain length but similar branching at the β -carbon atom. In this case a considerably smaller effect was found; only for compound 9 a resolution is observed. These results indicate that the resolution is determined by the length and the branching of the carbon chain R as well as the distance of the branching from the chiral carbon atom.

TABLE I

PHYSICAL CONSTANTS AND METHODS OF SYNTHESIS OF DIASTEREOISOMERIC ORGANOPHOSPHORUS COMPOUNDS WITH THE GENERAL FORMULA

$$\begin{array}{c} \text{Y} \\ || \\ \text{R}-\text{CH}-\text{O}-\text{P}-\text{X} \\ | \quad | \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$$

Compound No.	R	Y	X	b.p./mm	n_D^{25}	Synthesised according to Ref.
1	CH ₃ CH ₂	O	F	47°/4.5	1.3912	II ^a
2	CH ₃ (CH ₂) ₂	O	F	73°/10	1.3966	II
3	CH ₃ (CH ₂) ₃	O	F	65°/3	1.4058	II
4	CH ₃ (CH ₂) ₄	O	F	64°/1	1.4090	II
5	CH ₃ (CH ₂) ₅	O	F	79°/0.7	1.4131	II
6	(CH ₃) ₂ CH	O	F	53°/2	1.3968	II ^a
7	(CH ₃) ₂ CHCH ₂	O	F	73°/7	1.4010	II ^a
8	(CH ₃) ₃ CCH ₂	O	F	66°/3	1.4071	II ^a
9	(CH ₃) ₃ C	O	F	57°/4	1.4045	II
10	CH ₃ (CH ₂) ₅	S	F	56°/0.3	1.4453	12
11	(CH ₃) ₂ CHCH ₂	S	F	54°/3	1.4390	12
12	CH ₃ (CH ₂) ₅	O	H	68°/0.01	—	13
13	(CH ₃) ₂ CHCH ₂	O	OCH ₃	36°/0.05	—	b
14	CH ₂ =CH	O	F	decomp.	—	II ^a
15	HC≡C	O	F	64°/4	1.4117	II ^a
16	CH ₃ C≡C	O	F	47°/0.1	1.4255	II ^a
17	(CH ₃) ₂ NCH ₂	O	F	55°/0.5	—	II ^a

^a Modified by the addition of 1 mole triethylamine to the reaction mixture.

^b Synthesised from compound No. 7 and sodium methylate.

The importance of the distance between the chiral centres was investigated by moving the alcoholic chiral centre from the α - to the β -carbon atom. 2-Methylpentyl methylphosphonofluoridate, [CH₃(CH₂)₂CH(CH₃)CH₂O]CH₃P(O)F, did not separate on both columns contrary to the obvious separations of compound 3. From this it may be concluded that the distance between the chiral centres is critical. An increase in the distance will result in a larger conformational mobility giving an unsatisfactory difference in interaction between the diastereoisomers and the stationary phase.

$R = C_nH_{2n-1}$ or C_nH_{2n-3}

An unsaturated group R is present in compounds 14–16. When comparing compounds 1, 14 and 15 having identical carbon chain lengths the increase in the ν value runs parallel with the degree of unsaturation. On lengthening the carbon chain with one carbon atom (compare compounds 15 and 16) the ν values decrease contrary to the results obtained for the saturated compounds. Nevertheless the ν values of 16 exceed those of the comparable saturated compound 2. It follows that the relatively large ν values for 15 are probably due to the influence of the C \equiv C function as well as to the presence of the acetylenic hydrogen atom.

TABLE II

RETENTION TIMES AND RELATIVE RETENTION VALUES (r) OF DIASTEREISOIMERIC ORGANOPHOSPHORUS COMPOUNDS^a WITH THE GENERAL FORMULA

$$\begin{array}{c} \text{Y} \\ \parallel \\ \text{R}-\text{CH}-\text{O}-\text{P}-\text{X} \\ | \quad | \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$$

Com- pound No.	R	Y	X	Polar column		Apolar column		r	r
				Adj. ret. (min)		Adj. ret. (min)			
				peak 1	peak 2	peak 1	peak 2		
1	CH ₃ CH ₂	O	F	11.6	11.6	1.00	9.0	9.0	1.00
2	CH ₃ (CH ₂) ₂	O	F	20.5	20.0	1.02 ^c	15.8	15.8	1.00
3	CH ₃ (CH ₂) ₃	O	F	39.5	41.8	1.058	32.0	33.5	1.047
4	CH ₃ (CH ₂) ₄	O	F	74.5	80.7	1.083	56.6	60.4	1.068
5	CH ₃ (CH ₂) ₅	O	F	111.0	121.0	1.089	102.0	110.0	1.073
6	(CH ₃) ₂ CH	O	F	14.1	14.1	1.00	16.4	16.4	1.00
7	(CH ₃) ₂ CHCH ₂	O	F	26.9	28.9	1.074	22.6	23.8	1.055
8	(CH ₃) ₃ CCH ₂	O	F	25.2	28.4	1.131	26.3	28.4	1.087
9	(CH ₃) ₃ C	O	F	29.7	31.2	1.05 ^c	22.7	23.4	1.03 ^c
10	CH ₃ (CH ₂) ₅	S	F	84.7	92.8	1.094	116.0	125.0	1.077
11	(CH ₃) ₂ CHCH ₂	S	F	23.3	24.9	1.065	25.4	26.6	1.049
12	CH ₃ (CH ₂) ₅	O	H	359.0	378.0	1.052	231.0	239.0	1.036
13	(CH ₃) ₂ CHCH ₂	O	OCH ₃	82.9	82.9	1.00	64.3	64.3	1.00
14	CH ₂ =CH	O	F	16.2	16.7	1.03	8.5	8.5	1.00
15	HC≡C	O	F	34.5	43.7	1.262	8.8	10.3	1.174
16	CH ₃ C≡C	O	F	71.1	83.7	1.178	27.7	31.2	1.125
17	(CH ₃) ₂ NCH ₂	O	F	8.8	10.1	1.155 ^b	26.4	29.2	1.106

^a Gas chromatographic conditions as outlined in the experimental part. Compounds 1, 2, 6 and 8 were analysed on columns 2.7 m × 4 mm I.D., the other compounds on columns 3 m × 3 mm I.D.

^b For the polar column (90 cm × 3 mm I.D.) 10% liquid loading was used.

^c Because of largely overlapping peaks a curve resolver (Du Pont de Nemours 310) was used.

$R = (\text{CH}_3)_2\text{CHCH}_2$ versus $(\text{CH}_3)_2\text{NCH}_2$

Replacing an apolar CH(CH₃)₂ group by an isosteric polar N(CH₃)₂ group (compare compounds 7 and 17) an increase in the r value on both columns is observed. This result supports the forementioned conclusion concerning the importance of electronic effects.

$Y = \text{O}$ versus S

From the retention data collected in Table II (compare compounds 5 with 10 and 7 with 11), it can be seen that the retention time on the apolar column increases when P=S is substituted for P=O. On this column the vapour pressure differences will prevail showing separations which parallel molecular weights. On the polar column the reversed sequence is observed. In this case electronic interactions especially between the oxygen compounds and the stationary phase will predominate. However, the r values change very little on both columns when P=O is replaced by P=S. It follows that this substitution has only a minor effect on the separation of the diastereoisomers under consideration.

X = F versus H or OCH₃

The contribution of the P-F function to the ν values can be estimated when comparing the data of the compounds 5 with 12 and 7 with 13. Replacement of the fluorine atom by a hydrogen atom (compare 5 and 12) will result in a small change in steric requirements since the Van der Waals radii are ~ 1.4 Å and ~ 1.2 Å, respectively. As far as steric reasons are concerned comparable ν values would be expected. Nevertheless, the ν values decrease considerably on both columns when the P-H* is substituted for a P-F. The decreased difference in interactions of the diastereoisomers with the stationary phase contrasts with the increased electronic interactions as reflected by the higher retention times.

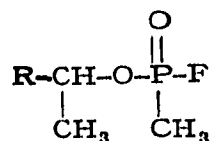
Substituting the P-OCH₃ for a P-F function (compare compounds 7 and 13) it can be seen from Table II that the separation is completely lost. This result may be ascribed to the lower polarity of the P-OCH₃ group and the presence of a second ester group at the phosphorus atom which diminishes the functional chirality.

From these results it can be concluded that the P-F function plays an essential role in the separation of the diastereoisomeric alkyl methylphosphonofluoridates.

P-O-C versus P-C-C

In order to examine the contribution of the ester linkage to the separation, the P-O-C group was replaced by the isosteric P-C-C group (compare 7 with 2,4-dimethylpentylmethylphosphinic fluoride**). The introduction of the P-C-C group causes a diminished functional chirality in analogy with the forementioned reasoning concerning the P-OCH₃ substitution for P-F. On both columns the phosphinic fluoride gave no perceptible separation. It follows that the P-O-C ester linkage is important for the separation of diastereoisomeric phosphonofluoridates. A similar result was found by KARGER *et al.*¹ for diastereoisomeric carboxylic esters. They regarded the ester function as an important zone in the differential interaction with the stationary phase.

The forementioned results concerning the structure-separation relationship of diastereoisomeric alkyl methylphosphonofluoridates with the general formula



on polar and apolar gas chromatographic columns can be summarised as follows:
The relative retention ν

- (a) increases on lengthening as well as on branching of the carbon chain R;
- (b) increases considerably by replacement of the alkyl group R by a function of increased polarity such as a vinyl, an acetylenic or dialkylamino group;
- (c) decreases to $\nu = 1.00$ by moving the chiral centre from the α -carbon to the β -carbon atom in the alkoxy group;

* Infrared vapour spectra of compound 12 did not indicate the presence of a P-OH bond.

** $[(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2]\text{CH}_2\text{P}(\text{O})\text{F}$. Gas chromatographic conditions were changed as outlined in the experimental part. Synthesis according to Ref. 14.

- (d) shows a small change when substituting P=S for P=O;
 (e) decreases to $r = 1.00$ when the P-O-C ester linkage is replaced by a P-C-C grouping;
 (f) decreases when the P-F function is replaced by a P-H or P-O-CH₃ group;
 (g) increases when substituting a polar column for an apolar column.
 It may be concluded that both steric and electronic interactions are important for the separation of diastereoisomeric alkyl methylphosphonofluoridates.

ACKNOWLEDGEMENT

Thanks are due to the Central Laboratory TNO (Delft) for permitting use of the curve resolver (Du Pont de Nemours 310).

REFERENCES

- 1 B. L. KARGER, R. L. STERN, H. C. ROSE AND W. KEANE, in A. B. LITTLEWOOD (Editor), *Gas Chromatography 1966*, Institute of Petroleum, London, 1967, p. 240.
- 2 J. W. WESTLEY, B. HALPERN AND B. L. KARGER, *Anal. Chem.*, 40 (1968) 2046.
- 3 E. GIL-AV, R. CHARLES-SIGLER, G. FISCHER AND D. NUROK, *J. Gas Chromatog.*, 4 (1966) 51.
- 4 D. NUROK, G. L. TAYLOR AND A. M. STEPHEN, *J. Chem. Soc.*, B (1968) 291.
- 5 G. E. POLLOCK AND V. I. OYAMA, *J. Gas Chromatog.*, 4 (1966) 126.
- 6 B. L. KARGER, R. L. STERN, W. KEANE, B. HALPERN AND J. W. WESTLEY, *Anal. Chem.*, 39 (1967) 228.
- 7 Y. GAULT AND H. FELKIN, *Bull. Soc. Chim. France*, 1965, 742.
- 8 Nomenclature in accordance with *Chromatographia*, 1 (1968) 153.
- 9 J. J. KIRKLAND, *Anal. Chem.*, 35 (1963) 2003.
- 10 R. D. DEAN AND W. J. DIXON, *Anal. Chem.*, 23 (1951) 636.
- 11 C. MONARD AND J. QUINCHON, *Bull. Soc. Chim. France*, (1961) 1084.
- 12 H. L. BOTER AND A. J. J. OOMS, *Rec. Trav. Chim.*, 85 (1966) 21.
- 13 K. APETROV, N. K. BLIZNYUK, YU. N. STUDNEV AND A. F. KOLOMIETS, *Z. Obshch. Khim.*, 31 (1961) 179.
- 14 L. MAIER, *Chem. Ber.*, 94 (1961) 3056; A. H. FORD-MOORE, L. J. LERMIT AND C. STRATFORD, *J. Chem. Soc.*, (1953) 1776.

J. Chromatog., 54 (1971) 151-156