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SIMPLE ³ ¹P NMR METHOD FOR THE DETERMINATION OF THE ENANTIOMERIC PURITY OF CHIRAL O-ALKYLALKYLTHIOPHOSPHONIC ACIDS

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The ${}^{31}P-({}^{1}H)$ NMR spectra of bis(alkylalkoxythiophosphoryloxy)phosphonites may be utilized to determine the enantiomeric purity (p) of <u>O-alkylalkylthioph</u>osphonic acids with the application of the Oro equation, $p = \sqrt{(Q - Q')/(Q + Q')}$, where Q is the integral intensity of the d, *l*-form, and Q' is the integral intensity of the meso forms.

We recently showed [1] that compounds with a pseudochiral P atom - bis(ethylethoxythiophosphoryloxy)phosphonites (phosphonates, thiophosphonates), obtained from racemic Oethylethylthiophosphonic acid, are the mixture of three diastereomers - the two nonequivalent meso forms and the racemic d, *l*-form.

The present work presents the results of the study of the stereoisomeric composition of bis(alkylalkoxythiophosphoryloxy)phosphonites and bis(alkylalkoxythiophosphoryloxy)phosphonates (I)-(IV) by the ^{31}P NMR method depending on the enantiomeric composition of the optically active O-alkylalkylthiophosphonic acids (ATPAs) utilized in their synthesis, and the possible utilization of the spectra of compounds with a pseudochiral P atom for the determination of the enantiomeric purity of chiral thioacids of P.



R = Ph, R', R'' = Et, X = UEP (I); R = Ph, R' = Me, R'' = i-PrO, X = UEP (II); R = Me, R', R'' = Et, X = O (III); R = Ph, R' = Et, R'' = i-PrO, X = UEP (IV). UEP - unshared electron pair.

The compounds (1)-(IV) were obtained from the dichlorides of P acids and 2 equivalents of the ATPA in the presence of an organic base according to the method of [1].

The synthesis of the compounds (I)-(IV) from the optically pure ATPAs should lead to one of the enantiomers of the d, ℓ -form. In the gradual transition from the racemic to the optically pure thioacid, the share of the two meso forms in the mixture of the four stereoisomers of the compounds (I)-(IV) should decrease from 0.5 (in the case of the racemic thioacid) to 0 (in the case of the optically pure thioacid).

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TABLE 1. Refractive Index and the Angle of Rotation of the Compounds (Ia-e) of O-Ethylethylthiophosphonic Acid

Fig. 1. ³¹P-(¹H) NMR spectrum of the bis(ethylethoxythiophosphoryloxy)phenylphosphonites (Ia-d).

The region of the ${}^{31}P-({}^{1}H)$ NMR spectrum of 150 ppm is presented in Fig. 1 for the bis (ethylethoxythiophosphoryloxy)phenylphosphonites (Ia-e) obtained from O-ethylethylthiophosphonic acid (ETPA) of a varying degree of optical purity. The refractive indexes and the angles of rotation of the compounds (Ia-e), as well as the angles of rotation of the initial ETPA are presented in Table 1.

TABLE 2. Optical Purity p of O-Ethylethylthiophosphonic Acid and the A:B:C Diastereomer Ratio of the Compounds (Ib-e)

Compound	p, %		
	$[\alpha]_D^{20}/14,4.100$	$V^{\overline{Q-Q'}}_{\overline{Q+Q'}}$.100	A:B:C
(Ib) (Ic) (Id) (Ie)	26,4 55,2 83,2 88,3	27,1 56,1 85,6 90,3	1,02 : 2,34 : 1 1 : 4,14 : 1,16 1,37 : 15,39 : 1 1,18 : 21,42 : 1

TABLE 3. Refractive Index and Rotational Angle of the Compounds (IIIa-d) and O-Ethylethylthiophosphonic Acid

Compound	n ²⁰ D	$[\alpha]_D^{20}(C, C_{\mathbf{s}}\mathbf{H}_{\mathbf{s}})$	$\begin{bmatrix} [\alpha]_D^{20} \text{ (without solvent)} \\ (Et) (EtO) P(S) OH \end{bmatrix}$
		degree	
(IIIa) (IIIb) (IIIc) (IIId)	1,4983 1,4978 1,4990 1,4970	$\begin{array}{r} 0 \\ -9,68 \ (C \ 9,9) \\ +24,75 \ (C \ 9,8) \\ -33,75 \ (C \ 9,1) \end{array}$	$0 \\ +3,80 \\ -7,27 \\ +11,98$

It follows from Fig. 1 that the intensity of the triplets A and C, corresponding to the two meso forms, decreases with the increase in the absolute value of the rotational angle of the initial ETPA in the ${}^{31}P-({}^{1}H)$ NMR spectrum of the compounds (Ia-e); the intensity of the multiplet B (doublet of a doublet), corresponding to the enantiomers of the d, &-form, increases. The ratios of the integral intensities A:B:C are presented in Table 2 (column 4).

The ³¹P-(¹H) NMR spectrum of the P(III) atom of bis(methylisopropyloxythiophosphoryloxy) phenylphosphonite (IIa), obtained from the racemic O-isopropylmethylthiophosphonic acid, is similar to the spectrum of the P(III) atom of the compound (Ia). In the spectrum of (IIb), obtained from the optically active (-)(S)-O-isopropylmethylthiophosphonic acid with the $[\alpha]_D^{2^0}$ -l3.85°, only the multiplet corresponding to the RR-enantiomer of the d, *l*-form is observed in the region of \sim 150 ppm.

The analogous dependence of the integral intensities of the corresponding stereoisomeric forms on the optical purity of the ETPA is observed in the ${}^{31}P-({}^{1}H)$ NMR spectra of the compounds (IIIa-d).

The refractive indexes and the rotational angles of the compounds (IIIa-d) as well as the rotational angles of the initial EPTA are presented in Table 3.

It was shown in [2] that the ³¹P NMR spectra of compounds with a pseudochiral P atom of the type ROPH(=0)OR (R is the residue of the chiral alcohol) may be utilized for the determination of the enantiomeric purity p of the chiral alcohols utilizing the Oro equation, $p = \sqrt{(Q - Q')/(Q + Q')}$ [3], where Q is the integral intensity of the d, *l*-form, and Q' is the total of the integral intensities of the two meso forms.

It follows from Table 2 that the values of the enantiomeric purity of ETPA found from the ${}^{31}P-({}^{1}H)$ NMR spectra of the compounds (Ib-e) are close to those determined polarimetrically.* In the case of the compounds (IIIa-d), the precise values of the integral intensities of the signals in the ${}^{31}P-({}^{1}H)$ NMR spectra could not be determined due to their partial overlapping.

The known method for the determination of the enantiomeric purity of the chiral thioacids of P by the NMR method, developed in [5], was based on their ability to form diastereomeric

*The maximal value of the rotational angle of ETPA was taken to be 14.4° [4].

salts with optically active amines. However, a disadvantage of this method is the requirement to utilize an auxiliary chiral reagent.

In this connection, there is interest in the comparison of the results of the determination of the enantiomeric purity of the chiral ATPAs by the method of Mikolaijczyk [5] and the method with the application of the Oro equation.

With this objective, we converted O-isopropylethylthiophosphonic acid with the rotational angle $[\alpha]_D^{20}$ -4.38° to two compounds: bis(ethylisopropyloxythiophosphoryloxy)phenylphosphonite (IV) and (α -phenylethylammonium) ethylisopropyloxythiophosphonate (V).



As in the case of the compounds (I) and (II), the ${}^{31}P-({}^{1}H)$ NMR spectrum of the compound (IV) contains two triplets A' and C' corresponding to the meso forms, and the multiplet B' (doublet of a doublet) corresponding to the d, ℓ -form; the A':B':C' ratio is 1:2.57:1. Hence, the enantiomeric purity of O-isopropylethylthiophosphonic acid is 35.3%, The ${}^{31}P-({}^{1}H)$ NMR spectrum of the compound (V) consists of two signals in the ratio of 2.03:1; this corresponds to the enantiomeric purity of 34.0% for O-isopropylethylthiophosphonic acid.

Therefore, the ${}^{31}P-({}^{1}H)$ NMR spectra of the compounds with a pseudochiral P atom may be utilized for the determination of the enantiomeric purity of O-alkylalkylthiophosphonic acids.

EXPERIMENTAL

The ${}^{31}P-({}^{1}H)$ NMR spectra were recorded on the "Bruker WM-250" instrument at the frequency of 101.27 MHz, using the external standard of 85% H₃PO₄. The concentration of the dissolved substance was ${}^{\circ}O.4$ M; the temperature of the solution was 308 K. The rotational angles of the optically active compounds were determined on the Polamat automatic polarimeter (Carl Zeiss, Jena).

The compounds (I)-(IV) were obtained according to the method of [1] in quantitative yield. The refractive indexes n_D^{20} were as follows: 1.5410 for (IIa), 1.5395 for (IIb), and 1.5245 for (IV).

(<u>a-Phenylethylammonium)ethylisopropyloxythiophosphonate (V)</u>. To the solution of 0.97 g (0.006 mole) of O-isopropylethylthiophosphonic acid with the $[\alpha]_D^{20}$ -4.38° (without a solvent) in 15 ml of ether at 0°C was added 0.7 g (0.006 mole) of α -phenylethylamine with the $[\alpha]_D^{20}$ -40.3° (without a solvent). After 1 h, the ether was evaporated in a vacuum, and the precipitated crystals were washed with ether. The yield of 1.51 g (90%) of (V) was obtained; it had the mp 144-148°C. Found: P 11.12% and S 10.73%. C₁₃H₂₄NO₂PS. Calculated: P 10.73% and S 11.07%.

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