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Development of gas chromatographic methods for determining the enantiomeric composition of organic compounds

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Abstract

Three gas chromatographic methods for the determination of the enantiomeric composition of organic compounds are considered. The previous diastereomeric method and the method based on the use of the stationary chiral phases can be applied only when analytical reagents or sorbents are available. The proposed method consists in determining the enantiomeric composition of organic compounds with the use of achiral bifunctional reagents and does not require any optically active substances. The availability of three independent methods for determining the enantiomeric composition of organic compounds makes it possible to choose the optimum method for the solution of a particular problem.

Keywords: Gas chromatography; Achiral stationary phases; Amines; Amino acids; Enantiomers; Optical isomers

The separation of optical isomers by chromatographic methods is difficult as the antipodes have virtually identical chemical and physical properties. The difference in their three-dimensional structure can be revealed only as a result of their interaction with a third asymmetric structure that can be used as a separating reagent.

Three gas chromatographic (GC) methods for the determination of the enantiomeric composition of organic compounds were considered in this work. In addition to the traditional diastereomeric method using analytical reagents and the method based on the separation of enantiomers with the use of chiral sorbents [1–4], a method using achiral bifunctional reagents has been proposed [5,6].

The greatest success has been achieved with the first two methods when used for determining the enantiomeric composition of amino acids and peptides [1–4,7,8]. However, the determination of stereoisomers in chiral phosphorus-containing compounds has received little attention [9].

In the context of the determination of the enantiomeric composition of organophosphorus compounds, the potential of the diastereomeric method was investigated with the use of various optically pure reagents. It is known that achiral liquid stationary phases have different selectivities towards a particular class of sorbates. Moreover, achiral stationary phases retain the same properties after separating enantiomers. For the synthesis of achiral stationary phases, this paper describes the results of investigations of the separation of the enantiomers of amino acids using stationary phases of the ureide type.

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The possibilities of using a GC method for determining the enantiomeric composition without using optically pure reagents or sorbents are illustrated here by the determination of natural amino acids and amines.

EXPERIMENTAL

Obtaining diastereomers from O-alkylalkylthiophosphonium acids and esters of α-amino, α-hydroxy acids and amines

Place in a two-necked flask 4 ml of chloroform and 0.71 mmol of phosphorus pentachloride and add drop wise, under cooling (−5 °C), 0.55 mol of *O*-alkylalkylthiophosphonium acid in 1 ml of chloroform. Keep the reaction mixture at 0 °C for 10 min, filter the excess of phosphorus pentachloride and evaporate under vacuum the chloroform and phosphorus oxychloride. The undistilled *O*-alkylalkylthiophosphonium chloride (**1**) is used for further synthesis of diastereomers.

Dissolve 0.55 mmol of substance **1** in 1 ml of chloroform and add, under cooling (0 °C), 1.1 mmol of the ester of an amino acid, keep the solution at 0 °C for 5 min, filter the α-amino acid hydrochloride ester and evaporate the chloroform under vacuum. This yields 70–80% of diastereomer.

Add 5 ml of chloroform, 0.55 mmol of the α-amino acid ester and 0.55 mmol of triethylamine to 0.55 mmol of substance **1** and keep the reaction mixture at 0 °C for 5 min and then at room temperature for 60 min. Remove the triethylamine hydrochloride by filtration and wash the reaction mixture twice with water. Separate the chloroform layer and evaporate the chloroform under vacuum. This yields about 60–70% of the diastereomer.

Add 5 ml of chloroform and 1.1 mmol of an optically active amine (*S* or *R* configuration) to 0.55 mmol of substance **1**. Keep the reaction mixture at room temperature for 30 min. Wash the reaction mixture twice with water and separate the chloroform layer. Evaporate the chloroform under vacuum. Dissolve the diastereomers obtained in dichloromethan and analyse these solutions.

Obtaining diastereomers from sodium and ammonium salts of chiral phosphorus acids

In a 5-ml test-tube provided with a plug, place 1.1 mmol of α-chloropropionic acid ester and 1.3 mmol of *O*-alkylalkylphosphonium acid salt and add 1 ml of distilled water. Heat the test-tube in an oven at 100 °C for 40 min, then cool the reaction mixture, extract it with carbon tetrachloride and allow the solvent to evaporate under vacuum. This yields about 70–90% of the diastereomer.

Obtaining diastereomers with the aid of achiral bifunctional reagents

Phosgene and carbon disulphide have been used as achiral bifunctional reagents. With the use of phosgene diastereomers have been obtained in the following way: 0.1–0.5 g of amino acid hydrochloride was added to a mixture of 3–5 ml of dioxane or dichloromethane and 0.5–0.8 ml of triethylamine, and 0.2–0.3 ml of the phosgene in dioxane (0.4 g ml^{-1}) was slowly added to the mixture after 10–15 min. The reaction mixture was kept at room temperature for 25–30 min and then 1–2 μl of the sample was injected into the gas chromatograph.

Instrumentation

Experiments were made with a Model LHM-8MD chromatograph (USSR) provided with a flame ionization detector and a capillary glass column made of Pyrex glass and coated with the liquid stationary phase, either PMS-100 (32 m × 0.25 mm i.d. column, film thickness 0.20 μm) or XE-60 (50 m × 0.25 mm i.d. column, film thickness 0.41 μm). The stationary phases were coated on the wall with the use of the static method under high pressure. Packed glass columns (3 m × 3 mm i.d.) were used with the following sorbents: 10% polyethylene glycol succinate on Gas-Chrom Z, 10% Apiezon L on chromosorb G, 10% Dexil 300 on Celite 545, 10% methylsilicone PMS 100 on Chromaton N Super and 15% OV-225 on Chromaton N AW DMCS.

The infrared spectra were recorded using a model PE 580B spectrophotometer as carbon tetrachloride or carbon disulphide solutions in the range 500–800 cm^{-1}.

The dispersion of the optical rotation has been studied using a by Perkin-Elmer Model 141 spectropolarimeter.

Solvents and reagents

All the solvents were of analytical-reagent grade from Reakhim (USSR), the amino acids were obtained from Reanal (Budapest, Hungary) and *O*-alkylalkylthiophosphonates were synthesized in the laboratory.

RESULTS AND DISCUSSION

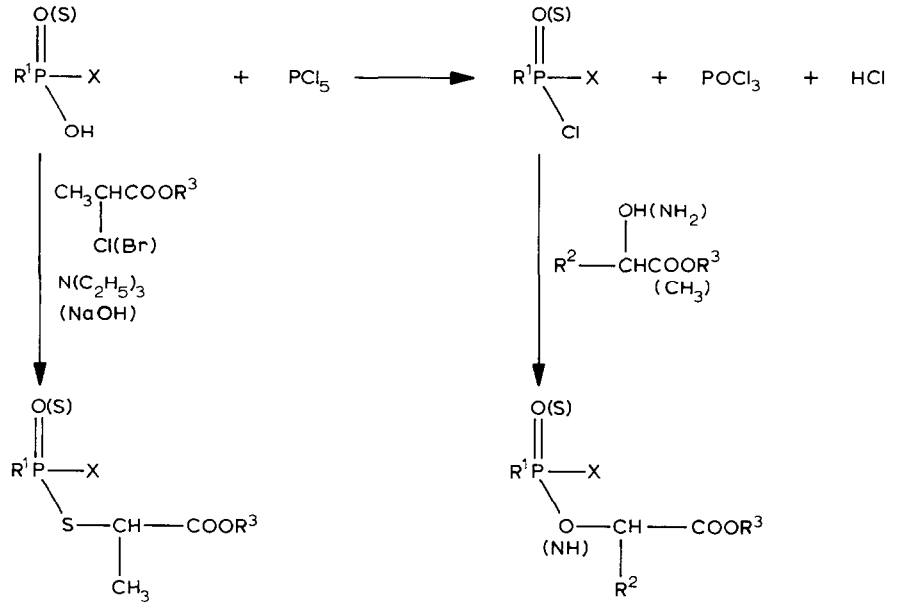
Determination of the enantiomeric composition of alkylthiophosphonium, alkylphosphonium and alkylphosphoric acids and salts in the form of diastereomers

The diastereomeric methods for the determination of the enantiomeric composition of the compounds has two steps: synthesis of diastereomers and their GC separation on achiral stationary phases.

The diastereomers were synthesized according to Scheme 1 using the esters of α-amino acids, α-hydroxy acids, α-halocarbon acids and amines.

If the esters of α-hydroxy and α-amino acids and amines (Scheme 1) are used, both stages of chlorination and amination occur with reversal of the configuration on the phosphorus atom [10,11]. When the esters of the α-halopropionic acid (Scheme 1) are used, the diastereomeric pairs are formed with reversal of the configuration on the carbon atom.

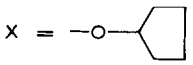
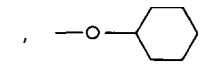
The optimum conditions for the stereoselective synthesis of diastereomers were found for a model substance (*O*-cyclohexyl ester of methylthiophosphonium acid) with the use of the simplex method [12]. The six parameters with variable values taken



$R^1 = CH_3, C_2H_5, OCH_3, OC_2H_5$

$R^2 = CH_3, C_6H_5, CH(CH_3)_2, CH_2CH(CH_3)_2$

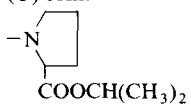
$R^3 = C_2H_5, CH_3, i\text{-}C_3H_7,$ 

X =  ,  , $OC(CH_3)_3$, F

Scheme 1.

TABLE 1

Effect of nature of the solvent on stereospecificity of obtaining diastereomeric pairs [a]

Solvent	Antipode content (R) when used as separating reagent (%)		
	(S) conf. 	(S) conf. $CH_3CHCOOCH(CH_3)_2$ | OH	(S) conf. $H_2N-CHC_6H_5$ | CH_3
Diethyl ether	19.3	20.2	19.8
Acetonitrile	15.3	14.9	20.1
Dimethylformamide	40.2	38.2	36.3
Carbon tetrachloride	5.2	5.9	6.3
Benzene	6.6	6.0	6.6
Chloroform	2.4	2.5	2.4

[a] Test substance = (S)-O-cyclohexyl ester of methylthiophosphonium acid of optical purity 97.6%.

into consideration were reaction temperature, proportions of amount of reagent, amount of solvent, duration of reaction, rate of addition of reagents and amount of moisture in the solvent. The response to this was the amount of enantiomer (R) in the enriched sample (S) of the O-cyclohexyl ester of methylthiophosphonium acid.

The data demonstrating the effect of the nature of the solvent on the stereospecificity of formation of the diastereomeric pairs under the optimum conditions are given in Table 1. It is clear that the racemization of O-cyclohexylmethylphosphonium chloride may amount to 40% in the course of obtaining diastereomers (Scheme 1). The latter indicates that the solvent has a significant effect on the stereochemistry of the process of obtaining diastereomers of the organophosphorus compounds. At the same time there are common regularities in the substitution reactions for the asymmetric atom [13].

In addition to the chromatographic data (on the enriched samples of opposite configuration),

TABLE 2

Effect of nature of the solvent on stereospecificity of synthesis of diastereomeric pairs [a]

Solvent	Antipode content (R) when used as separating reagent (%)		Degree of conversion (%) [b]
	$CH_3CHCOOCH(CH_3)_2$ | Cl	$CH_3CHCOOC_2H_5$ | Cl	
Methanol	4.5	4.8	37
Ethanol	4.7	4.3	42
Water	1.5	1.5	100
Dimethylformamide	25.0	24.5	63
Dimethyl sulphoxide	26.1	27.0	50
Acetonitrile	29.8	21.0	42
Benzene	1.6	1.7	11
Chloroform	1.6	1.6	11
Methylene chloride	1.6	1.4	12
Pyridine	29.5	30.0	100

[a] Test substance is sodium or ammonium salt of (S)-O-cyclohexylmethylphosphonium acid of optical purity 98.5%. [b] Degree of conversion is the ratio of heights of the peaks of the diastereomeric pairs on the chromatograms of the solutions in organic solvent and water.

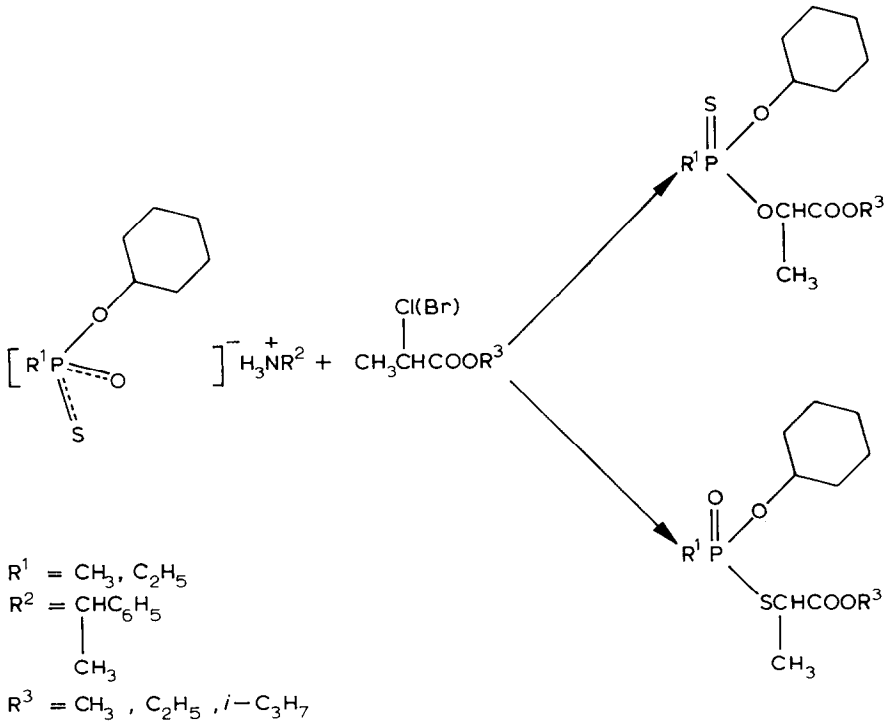
the inversion of the configuration of the phosphorus atom was demonstrated by the polarimetric method in which the dispersions of the optical rotation were obtained.

The effect of the nature of the solvent on the stereochemistry of the synthesis of diastereomers from the sodium and ammonium salts of the chiral organophosphorus compounds and esters of the α-halopropionic acid (Scheme 1) is shown by the data in Table 2, which indicate that the mechanism of the process of forming diastereomeric pairs for various solvents is very complicated. However, the very high stereospecificity of reaction [13] in benzene, chloroform and methylene chloride and the dispersion curves of the optical rotation indicate that the interaction of alkyl esters of α-chloropropionic acid takes place according to the S_N2 mechanism with reversal of configuration of the carbon atom. It should be noted that the salts of the alkylthiophosphoric and phosphonium acids exist in the form of an ambient ion [14] and in the case of alkylation two substances, A and B, can be formed according to Scheme 2.

With the aid of IR spectrometry and chromatography it has been demonstrated that as a result of alkylation of the sodium and ammonium salts of the alkylthiophosphoric acids with the esters of the α-halopropionic acids a compound is formed which corresponds to the structural formula B. Thus, in the IR spectra absorbtion bands are observed that are specific to P–S (530 cm^{-1}), P–OC (980 cm^{-1}), P = 0 (1220 cm^{-1}), CH_3P (1300 cm^{-1}) and C = 0 (1740 cm^{-1}) stretching vibrations and a multiplet is seen in the region of 2800–300 cm^{-1} which corresponds to CH stretching vibrations. In addition, Fig. 1 shows a chromatogram of diastereomers from racemic *O*-cyclohexylmethylphosphonium acid and its sodium salt treated (Scheme 1) with the ester of α-hydroxy- and α-halopropionic acid.

Figure 1 provides additional proof of the results obtained with IR spectrometry and shows the salts of the alkylthiophosphoric acids interact with the esters of the α-halopropionic acid to give substance B (Scheme 2).

When the salt of the racemic cyclohex-



Scheme 2.

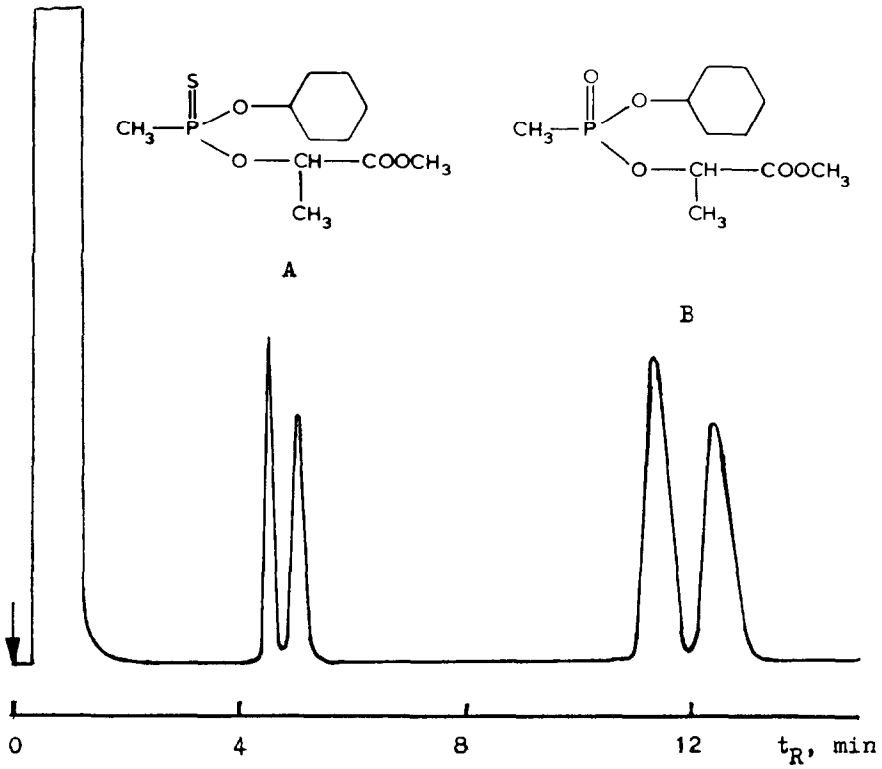


Fig. 1. Chromatogram of diastereomeric pairs of structures A and B. Glass column: 4 m × 3 mm i.d.; 10% SE-30 on Gas-Chrom Z; column temperature, 140 °C; carrier gas, nitrogen at 80 ml min^{-1}; flame ionization detection.

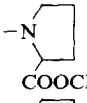
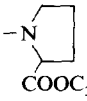
ylmethylphosphonium acid is treated with the ester of the α-bromopropionic acid, in contrast to α-chloropropionic acid the chromatogram shows two peaks of different areas which correspond to B in Fig. 1. The inequality of the areas of the peaks may be explained by the existence of a kinetic factor, which has been confirmed experimentally in the following way. When taking samples (at intervals of 10 min) from the reaction mixture (racemic salt and ester of α-bromopropionic acid in chloroform at 80 °C), it was found that the equality of areas of the chromatographic peaks of diastereomeric pairs (*SS* or *RR* and *SR* or *RS* configurations) is observed in 80 min. Also, there was no equality of the chromatographic peaks in the experiments when 10 min after the beginning of heating the racemic salt that does not take part in the reaction was removed by washing the reaction mixture with water. Subsequently the reaction mixture was heated at 80 °C for 120 min, and in this instance in the same relationship of the peak areas was observed on the chromatogram as after heating the reaction mixture for 10 min.

The occurrence of the kinetic factor makes it difficult to use α-bromopropionic acid derivatives as separating reagents in determining enantiomeric compositions using the diastereomeric method. The degree of kinetic enrichment depends on the temperature of the alkylating reaction (the isomers of the same configuration interact at a higher rate). Thus, for instance, at 20 °C it amounts to 40%, which can be used for stereodirectional synthesis.

Thus, using the test substance and different separating reagents, it was possible to establish the possibility of the GC determination of the enantiomeric composition of chiral phosphoric acids and their salts.

Table 3 shows the results of the separation of the diastereomeric pairs of the organophosphorus

TABLE 3
Results of chromatographic separation of organophosphorus diastereomers: $R^1P(R^2)(OR^3)R^4$

No.	R^1	R^2	R^3 [a]	R^4	Column [b]	$\alpha = \frac{t_R(SR)}{t_R(SS)}$	$\Delta(\Delta G)$ (J mol^{-1})
1	CH_3	S	CP	$-NH-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HC_6H_5$	A	1.01	43
					B	1.02	87
					C	1.06	209
2	C_2H_5	S	CH	$-NH-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HC_6H_5$	A	1.03	111
					B	1.05	184
					C	1.06	209
3	CH_3	S	CH	$-NH-\underset{\displaystyle (CH_2)_5CH_3}{\overset{\displaystyle |}{C}}HCH_3$	A	1.01	43
					B	1.00	0
					C	1.00	0
4	CH_3	S	CP		A	1.06	223
					B	1.06	223
					C	1.07	257
5	CH_3	S	CH		A	1.07	257
					B	1.07	257
					C	1.08	292
6	CH_3	O	CP	$-SCH(CH_3)COOCH_3$	C	0.96	142
					E	0.94	205
					D	0.93	237
7	CH_3	O	CH	$-SCH(CH_3)COOC_2H_5$	C	0.95	180
					E	0.93	237
					D	0.92	270
8	CH_3O	S	CP	$-OCH(CH_3)COOCH_3$	D	1.04	
9	F	O	CH	$-OCH(CH_3)COOCH_3$	D	1.09	330

[a] CP = cyclopentyl; CH = cyclohexyl. [b] Glass columns: (A) 3 m × 3 mm i.d., 10% polyethylene glycol succinate on Gas-Chrom Z; (B) 3 m × 3 mm i.d., 10% Apiezon L on Chromosorb G; (C) 3 m × 3 mm i.d., 10% Dexil 300 on Celite 545; (D) 4 m × 3 mm i.d., 10% methylsilicone PMS 100 on Chromaton N Super; (E) 3 m × 3 mm i.d., 15% OV-225 on Chromaton N AW DMCS.

compounds on different liquid stationary phases. The selectivity coefficients (α) for separation of diastereomers listed in Table 3 show that not all diastereomers can be separated because of the small difference in the physical and chemical properties of the diastereomeric pair. This is shown by small values of $\Delta(\Delta G)$, which amount to a few J mol^{-1}. At the same time, the general differential molar free energy of solution of the diastereomers amounts to kJ mol^{-1}, which is connected with the nature and volume of the substituents both in the central fragment of the enantiomer and in the increments forming a separating reagent.

Determination of enantiomeric composition with the use of chiral stationary phases

The function of the chiral stationary phases can be fulfilled by various compounds, which may be subdivided into the following main groups: low-molecular-weight stationary phases [15], metal complexes [16], cyclodextrins [17] and polymeric stationary phases [18]. Certain regularities in the separation of enantiomers for the practical synthesis of chiral phases have been obtained with the use of the low-molecular-weight stationary phases of the ureide type according to:

$$2R^1NH_2 + COCl_2 \xrightarrow{(C_2H_5)_3N} R^1NHC(=O)NHR^2 + 2HCl$$
$$(R^2)$$

where $R^1 = R^2$ = valyl, prolyl, α-phenylethyl; $R^1 \neq R^2$, R^1 = prolyl, R^2 = α-phenylethyl.

During investigation of the chiral phases of the ureide type, the racemic ethyl esters of α-(trifluoroacetic)amino acids and α-phenylethyl(tri-

fluoroacetic)amine were used as the test sorbates. The results of the investigations are given in Table 4.

Table 4 indicates that the separation of the enantiomers (sorbates) does not take place only as a result of the different stabilities of the complexes of the diastereomeric pairs formed between the chiral stationary phase and the enantiomers which are coupled through the hydrogen links. The relative stability of the diastereomeric complexes is determined by the mutual positions of the fragments of the chiral phase and the enantiomers to be separated, and depends especially on the presence of the fragment corresponding to one of the splitting enantiomers in the structure of the chiral phase. On the basis of these conclusions we have synthesized a high-temperature chiral phase from the polymer NPS-50 DF (a nitrile–polymethylsiloxane fluid) and optically pure α-amino acids and α-phenylethylamine.

Figure 2 shows a chromatogram demonstrating the successful separation of the enantiomers of amino acids and amines on the chiral stationary phase obtained, which substantiates the present suggestions.

TABLE 4

Selectivity of chiral stationary phases of ureide type: $R^1NHC(O)NHR^2$

R^1	R^2	Selectivity in separation of enantiomer		
		Proline	Valine	α-Phenylethylamine
Prolyl	Prolyl	1.83	1.44	1.18
Valyl	Valyl	1.30	1.55	1.16
Prolyl	α-Phenylethyl	1.60	1.15	1.40

Determination of enantiomeric composition of compounds without using chiral reagents or sorbents

During interaction (see below) of a chiral compound (in the general case of a non-racemic mix-

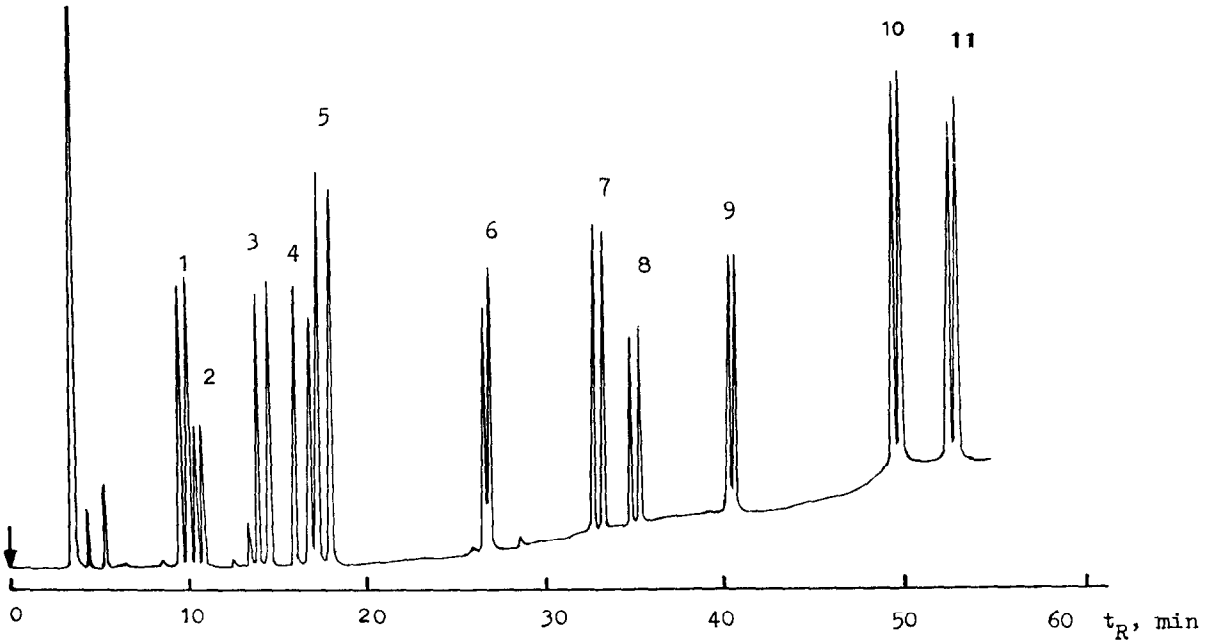
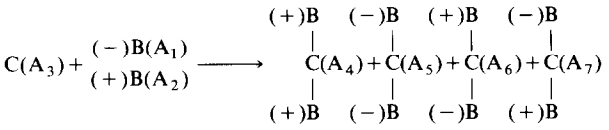


Fig. 2. Separation of enantiomers of *N*-TFA isopropyl esters of amino acids and acylated derivatives of α-phenylethylamine on a capillary column (25 m × 0.25 mm i.d.) with chiral liquid phase synthesized from NPS-50 DF, (*S*)-valine and (*S*)-α-phenylethylamine. Injection, flow split 1 : 100; column temperature program, from 100 °C to 230 °C at a rate of 3 °C min^{-1}; carrier gas, nitrogen at 0.5 ml min^{-1}; flame ionization detection. 1, Alanine; 2, valine; 3, norvaline; 4, leucine; 5, norleucine; 6, aspartic acid; 7, methionine; 8, α-phenyl-β-alanine; 9, α-phenylethylamine; 10, ornithine; 11, lysine.

ture of enantiomers) with a bifunctional achiral reagent, two pairs of diastereomers were obtained: racemic form (A_4 and A_5) and *meso* form (A_6 and A_7).

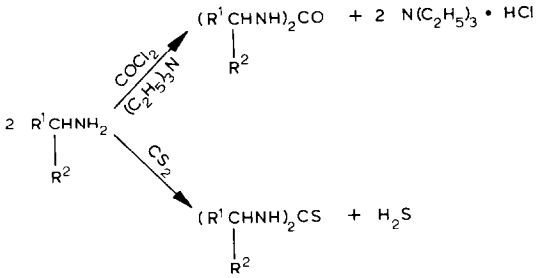


where B is the chiral reagent and C the bifunctional achiral reagent.

The racemic and *meso* forms differ from each other not only in the possibility of optical rotation but also in other physical and chemical properties, which makes it possible to separate them chromatographically on achiral stationary phases.

Thus, the determination of the enantiomeric composition of the chiral compounds consists in determining the relationship between the known composition of the obtained four-component system of two pairs of diastereomers and the composition of the initial mixture of enantiomers. Such a problem may be solved in principle with the use of the deterministic approach [12] based on the study of the kinetics of the reactions being investigated [19]. However, it should be taken into consideration that the composition of the kinetic model of the chemical transformations of the enantiomeric mixture is connected with very lengthy and difficult experimental and theoretical work.

Applying the probability–statistical approach to the mathematical description of the investigated



R^1 = valyl, leucyl, prolyl, methyl
R^2 = $C(O)OR^3$, C_6H_5
R^3 = CH_3, C_2H_5, i-C_3H_7

Scheme 3.

chemical–chromatographic method of analysis, the difficulties with the deterministic approach can be avoided. At the same time, it should be borne in mind that the results obtained with the aid of the probability–statistical approach are of a probabilistic nature, as distinct from the conclusions drawn on the basis of the solution of the problems of chemical kinetics.

The material balance in the terms of the theory of chance is as follows:

$$p^2 + 2p(1-p) + (1-p)^2 = 1$$

where p, $(1-p)$ are the amounts of the initial and obtained substances in terms of the theory of chance.

From the equation of the material balance the probability–mathematical models corresponding

TABLE 5

Separation of diastereomers of general formula $XC(NHCHR^2)_2$ on a glass column (50 m × 0.25 mm i.d.)

R^1

R^1	R^2	X	t_R (min)		α		$\Delta(\Delta G)$ (J mol^{-1})	
			Racemic form	*Meso* form	XE-60	PMS 100	XE-60	PMS 100
Valyl	$C(O)OCH_3$	O	13.90	14.95	1.07	1.10	277.2	390.1
Valyl	$C(O)OC_2H_5$	O	16.73	17.50	1.05	1.08	199.9	312.3
Valyl	$C(O)OC_3H_7$-i	O	26.76	27.42	1.02	1.06	81.3	238.7
Leucyl	$C(O)OCH_3$	O	18.50	19.40	1.05	1.08	199.9	315.3
Leucyl	$C(O)OC_2H_5$	O	25.80	26.40	1.02	1.04	81.3	160.7
Prolyl	$C(O)OCH_3$	O	32.60	39.12	1.20	1.23	746.9	1043.2
Prolyl	$C(O)OCH_3$	S	40.80	51.80	1.27	1.36	979.2	1259.7
Methyl [a]	C_6H_5	S	14.60	15.20	1.06	1.09	260.4	318.8

[a] Diastereomers were analysed with use of a 7 m × 0.25 mm i.d. glass column.

TABLE 6

Results of determination of enantiomeric composition of artificial mixtures of (*S*)- and (*R*)- amino acids

(*S*)-Valine			(*R*)-Valine			(*S*)-Leucine			(*R*)-Leucine		
Taken (%)	Obtained (%)	Relative error (%)	Taken (%)	Obtained (%)	Relative error (%)	Taken (%)	Obtained (%)	Relative error (%)	Taken (%)	Obtained (%)	Relative error (%)
46.9	43.0	6.5	53.1	57.0	7.3	48.4	43.7	9.7	51.6	56.3	9.1
26.3	26.7	1.8	73.7	73.7	0.5	76.0	77.1	1.4	24.0	22.9	4.5
17.3	18.2	5.2	82.7	81.8	1.3	21.2	18.6	12.3	78.8	81.4	3.3
9.9	10.7	8.1	90.1	89.3	0.9	15.8	15.7	5.7	84.2	84.3	0.2
0.25	0.23	8.0	99.75	99.77	0.02	0.40	0.45	12.5	99.60	99.55	0.1

to different cases of the experimental measurements can be obtained and they can be presented in the form of inverted quadratic functions which make it possible to express the unknown value by means of the experimental parameters measured chromatographically.

Thus, the content (x) of enantiomers in the sample mixture can be calculated according to the following equation:

$$X(\%) = \frac{(1+Z) \pm \sqrt{1-Z^2}}{2(1+Z)} \times 100$$

where Z is the ratio of areas of the chromatographic peaks of the *meso* and racemic forms. In this case $Z \leqslant 1$.

This method has been used in determining the enantiomeric composition of certain α-amino acids and amines. The dichloroanhydride of carbonic acid (phosgene) and carbon disulphide have been used as bifunctional reagents. The diastereomeric pairs were obtained according to Scheme 3.

The results of the investigations are given in Tables 5 and 6.

The application of achiral bifunctional reagents, owing to their variety and accessibility, makes it possible to develop the methods for determining the enantiomeric composition of almost any class of organic compound.

Conclusion

The experimental evidence indicates that the enantiomeric composition of a mixture of organic compounds can be determined by using the differences in the spatial structure of enantiomers not only with the aid of a third asymmetric structure but also with the use of an achiral bifunctional reagent.

The diastereomeric method and the method based on the use of chiral stationary phases are labour consuming and require optically pure reagents. The proposed method involving achiral bifunctional reagents is simpler but requires effective capillary columns for separating diastereomeric pairs.

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