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P*-Chiral phosphapalladacycle as derivatizing agent for enantiomeric purity determination of α-amino acids by means of ^{31}P NMR spectroscopy

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Abstract

A P*-chiral cyclopalladated complex was shown to be an efficient chiral derivatizing agent for enantiomeric excess determination of α-amino acids by ^{31}P NMR technique. The main advantages of this type of reagent are discussed.

1. Introduction

The advantages of ^{31}P NMR spectroscopy for enantiomeric purity determination are well known.[1] They include: a large dispersion of chemical shifts facilitating the integration of the anisochronic signals; extremely simple spectral picture which is independent on the C,H-complexity of the molecule examined; the possibility to avoid the spectral complications caused by a presence of the reagent excess or non-phosphorus admixtures. The most universal way to provide the opportunity of ^{31}P NMR spectral analysis for any non-phosphorus substrates is the creation of a ^{31}P-containing reagent. However, until now this idea was realized only in organic chiral derivatizing agents (CDA)[2–6] with all the drawbacks caused by the necessity of substrate covalent bonding. A number of ^{31}P-containing chiral solvating agents (CSA) are also described,[7–11] although their application was limited to ^{1}H NMR spectroscopy only.

Probably, the most promising way to transform the enantiomeric mixture into diastereomers is the coordinative bonding of the substrate with a metal ion bearing an appropriate homochiral auxiliary ligand. Examples of this methodology usage were rather limited until recently,[12–16] and reagents described allow the ^{31}P NMR analysis for only phosphorus substrates to be performed.[17–19] To the best of our knowledge, the sole reported precedent of the ^{31}P NMR spectroscopy application for enantiopurity control of non-phosphorus substrates via their coordinative derivatization is

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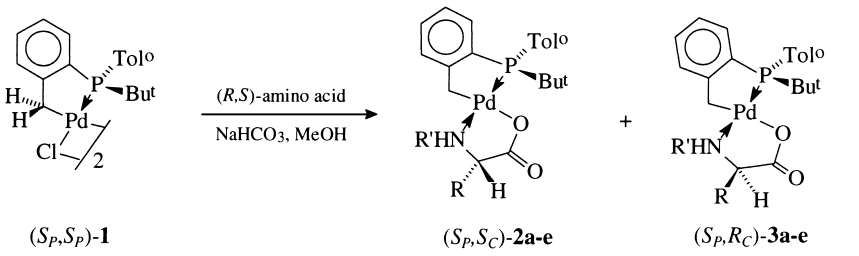
Parker's work where the (*S,S*)-Diop/Pt(0) complex was proposed for analysis of compounds such as alkenes, allenes and alkynes.[20,21]

Taking into account the advantages of ^{31}P NMR spectroscopy as an analysis method, and the excellent properties of *C,N*-type cyclopalladated complexes as organometallic chiral derivatizing agents for enantiopurity determination,[14,17–19,22] the idea of their *C,P*-analogues' examination as more universal reagents of this kind seemed to be very promising. Here we present our results of the first P*-chiral phosphapalladacycle[23] tested as a coordinative chiral derivatizing agent (CCDA) for the estimation of the enantiomeric composition of α-amino acids.

2. Results

The first P*-chiral phosphapalladacycle described recently[23] was used here in the form of μ-chloro bridged dimer (S_P,S_P)-**1** as an organometallic CCDA for a series of α-amino acids. The transformation of amino acid enantiomers into a mixture of diastereomers includes the complexation of an α-amino acidate ligand with a homochiral cyclopalladated dimer (S_P,S_P)-**1** (Scheme 1).



(S_P,S_P)-**1** (S_P,S_C)-**2a-e** (S_P,R_C)-**3a-e**

RR' = $(CH_2)_3$ (a); R' = H, R = Ph (b), Bu^i (c), Pr^i (d), Me (e)

Scheme 1.

The presence of the ^{31}P nucleus in the reagent (S_P,S_P)-**1** offers the opportunity to employ the $^{31}P\{^1H\}$ NMR spectroscopy for the control of the diastereomeric composition of the mixtures of α-amino acidate adducts **2**/**3** formed. First of all, it was necessary to estimate the extent of diastereomeric signal dispersion by analysis of the systems with the complete set of isomers. From economic considerations the preference was given to the complexation of the racemic dimer (S_P,S_P)/(R_P,R_P)-**1** with available optically active α-amino acids bearing in mind the identity of NMR spectral pattern of enantiomeric species inside the (S_P,S_C)/(R_P,R_C)-**2** and (R_P,S_C)/(S_P,R_C)-**3** diastereomeric pairs.

At this stage, the procedure of chiral derivatization (Method 1, see Experimental) included the treatment of the racemic dimer **1** with a slight excess of optically active α-amino acid (deprotonated by sodium hydrocarbonate in situ) in a methanol solution at room temperature followed by reaction mixture evaporation and its transfer into the NMR tube with a suitable solvent (usually dichloromethane or benzene, containing 20% of $CDCl_3$ or C_6D_6, respectively). An excess of the optically active α-amino acid (ca. 10%) is necessary to guarantee the completeness of both enantiomeric phosphapalladacycle bondings.

Despite a rather simple spectral picture observed (see Fig. 1), it is complicated to some extent due to the *Z*/*E*-isomery of diastereomeric mononuclear adducts **2** and **3** caused by the similar *trans*-influences of the C- and P-donor centers of phosphapalladacycle and unsymmetric nature of

N,*O*-coordinated α-amino acidate ligands (Scheme 2). The ^{31}P NMR spectra of reaction mixtures consist of two pairs of singlet signals belonging to two diastereomers of aminoacidate derivatives (S_P,S_C)-**2a**–**e** and (R_P,S_C)-**3a**–**e**, each existing as the mixtures of *Z*/*E* geometric isomers in different ratios (Table 1). As an illustration, a complete set of signals of isomeric species observed in the ^{31}P NMR spectra for the system (S_P,R_P)-**1**/(S_C)-valine is presented in Fig. 1a.

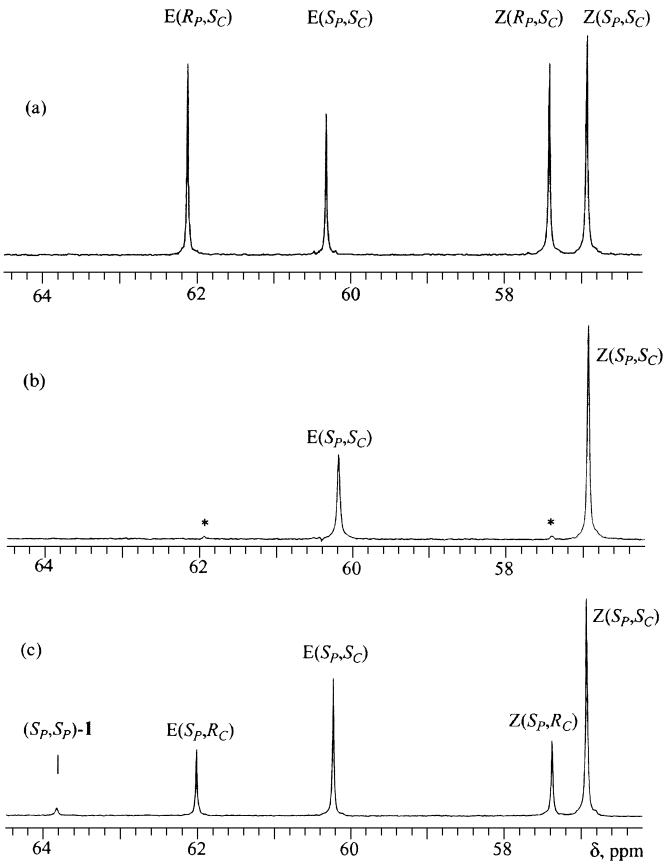
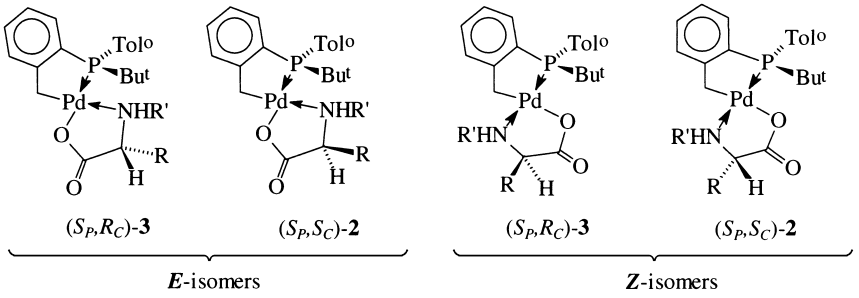


Figure 1. ^{31}P{^{1}H} NMR spectra of valinate derivatives **2d**/**3d** of dimer (S_P,S_P)- or (S_P,R_P)-**1**: (a) complete set of signals of *Z*- and *E*-forms of both diastereomers; (b) spectrum of (S_C)-valine chirally derivatized by the CCDA (S_P,S_P)-**1** with the signals of the trace admixture of (S_P,R_C)-diastereomer **3d** marked by asterisks; (c) spectral picture observed for the chirally derivatized artificial mixture of valine enantiomers with enantiomeric composition of 45.3% *ee*. (*S*)



Scheme 2.

Table 1
The ^{13}P NMR chemical shifts (δ) and signal separation ($\Delta\delta$) for isomeric species formed after chiral derivatizing of α-amino acids with CCDA (S_P,S_P)-**1**

Substrate	Solvent[1)]	Chemical shifts of isomeric species (δ, ppm)				Diastereomeric peak separation (ppm)	
		E-isomers		*Z*-isomers			
		(R_P,S_C) or (S_P,R_C)	(S_P,S_C) or (R_P,R_C)	(R_P,S_C) or (S_P,R_C)	(S_P,S_C) or (R_P,R_C)	$\Delta\delta_E$	$\Delta\delta_Z$
(*R,S*)-Prol[2)]	A	60.396	58.692	56.886	55.308	1.704	1.578
(*S*)-Prol	A	-	58.720	-	55.113		
(*R,S*)-Phgly[2)]	B	61.839	59.827	56.447	56.409	2.012	0.038
	C	61.980	60.564	57.743	57.496	1.416	0.247
(*S*)-Phgly[3)]	C	-	60.611	-	57.684		
(*R,S*)-Leu[2)]	C	62.418	60.739	57.103	57.001	1.679	0.102
	D	62.525	60.634	57.261	57.032	1.891	0.229
(*R*)-Leu[4)]	D	62.670	-	57.398	-		
(*R,S*)-Val[2)]	C	61.911	60.115	57.371	56.861	1.796	0.51
(*S*)-Val[5)]	C	-	60.181	-	56.915		
(*R,S*)-Ala[2)]	B	60.651	60.113	55.964	55.903	0.538	0.061
(*S*)-Ala	B	-	59.993	-	55.810		
(*R,S*)-Ala[2)]	D	61.474	60.599	56.776	56.685	0.875	0.091
(*S*)-Ala	D	-	60.738	-	57.363		

1) Notations for solvents: A – $CDCl_3$, B – benzene/d_6-benzene 4:1 mixture; C – $CH_2Cl_2/CDCl_3$ 4:1 mixture; D – benzene/$CDCl_3$ 4:1 mixture.
2) Parameters for *pseudo*-racemic mixtures were obtained from the ^{31}P NMR spectra of the racemic dimer 1, chirally derivatized by the corresponding optically active α-amino acid.
3) The signals of the trace amounts of the (S_P,R_C)-diastereomer **3b** were observed at δ 57.923 (*Z*) and 61.931 ppm (*E*) of integral intensities corresponding to the enantiomeric purity of 98% *ee*.
4) The signals of the (S_P,S_C)-diastereomer **3c** were observed at δ 56.927 (*Z*) and 60.570 ppm (*E*) of integral intensities corresponding to the enantiomeric purity of 81% *ee*.
5) The signals of the trace amounts of the (S_P,R_C)-diastereomer **3d** were observed at δ 57.371 (*Z*) and 61.911 ppm (*E*) of integral intensities corresponding to the enantiomeric purity of 98% *ee*.

For assignment of these signals, the $^{31}P\{^1H\}$ NMR parameters of one of diastereomers **2** or **3** were recorded using the complexation of the enantiomerically pure dimer (S_P,S_P)-**1** with 2 molar equivalents of (S_C)- or (R_C)-amino acid in situ (Method 2, see Experimental). Under these conditions, the mixture of *Z*/*E*-forms of one diastereomer was generated, and the ^{31}P NMR spectra contains two main singlet signals (Table 1, see below). For example, the spectrum for the (S_P,S_P)-**1**/(S_C)-valine system is presented in Fig. 1b. The tentative differentiation of signals of *Z*- and

E-forms for acyclic α-amino acids was based on the unambiguous assignments made previously[23] for (S_C)-prolinate derivatives of dimer **1** (inferred from an X-ray diffraction and ^{1}H NMR studies including NOE technique).

The magnitudes of the diastereomeric peak separation ($\Delta\delta$), represented as the difference in chemical shifts of diastereomeric complexes **2** and **3** $\delta(R_P,S_C)$–$\delta(S_P,S_C)$ or $\delta(S_P,R_C)$–$\delta(R_P,R_C)$ observed for the systems (S_P,R_P)-**1**/(S_C)- or (R_C)-amino acid, respectively, are given in Table 1. The $\Delta\delta$ values are generally much greater for the isomers of geometric *E*-configuration (0.88–2.01 ppm). In the case of the *Z*-isomers they are inside the range $\Delta\delta$ 0.09–0.48 ppm (with the exception of $\Delta\delta$ 1.578 ppm found for the prolinate derivative). The $\Delta\delta$ values depend on the solvent used for spectra measurement, and the separation of diastereomeric signals can be improved to some extent by means of solvent matching. Usually, aromatic solvents work better than halogenated hydrocarbons. For example, in the case of the (S_P,R_P)-**1**/(S_C)-phenylglycine system $\Delta\delta$ magnitude for the *E*-diastereomers is increased from 1.42 ppm in a dichloromethane/deuteriochloroform mixture up to $\Delta\delta$ 2.01 ppm in a benzene/d_6-benzene solution.

As an illustration of our method, Fig. 1b demonstrates an example of an enantiopurity determination of optically active (S_C)-valine chirally derivatized by enantiopure dimer (S_P,S_P)-**1** by the ^{31}P{^{1}H} NMR technique. Comparison of this spectrum with those for the complete set of diastereomers (Fig. 1a) it became evident that trace signals (marked by asterisks) may be assigned to the diastereomer (S_P,R_C)-**3d**. After signal integration in pairs of geometric isomers the enantiomeric purity of this commercial α-amino acid (purchased from 'Reanal') may be estimated in ca. 98% *ee*. (*S*). Nearly the same enantiomeric purity was found for the (S_C)-phenylglycine; in the case of (R_C)-leucine (unnatural enantiomer) it was decreased down to 81% *ee*. In contrast, the ^{31}P{^{1}H} NMR spectra of chirally derivatized (S_C)-valine from 'Reachim', (S_C)-alanine and (S_C)-proline did not reveal any signals corresponding to the admixture of (S_P,R_C)-diastereomeric adducts **3a**,**d**,**e**; thus, these amino acids may be considered as enantiomerically pure (within the accuracy of an NMR spectral method).

As for the accuracy of the method proposed here, it seems to be compatible with the usual precision level of integration in the NMR spectroscopy.[1] The following experimental data may be presented in support of this assertion. First of all, the ratios of integral intensities of diastereomeric signals **2**:**3** (combined for the both geometric isomers, see Experimental) in the spectra of the chirally derivatized racemates are close to the naturally expected 1:1 ratio. For example, in the case of the racemic dimer **1** chirally derivatized by the (S_C)-valine (see Fig. 1a) this ratio of diastereomers was found with accuracy to $<1\%$.

Furthermore, to demonstrate a practical applicability of our method, we have prepared artificial mixtures of known enantiomeric composition using racemic and optically active valine in strictly fixed ratio (Table 2). The latter was established from the samples weighting with an accuracy of 0.001 mg and taking into account the actual enantiomeric purity of this α-amino acid (98% *ee*.) determined by our method. The comparison of the magnitudes of the enantiomeric excess determined by means of ^{31}P{^{1}H} NMR spectroscopy with the values based on the weighting method has shown that the deviation did not exceed 2% that is the natural limit of NMR spectroscopy possibilities.

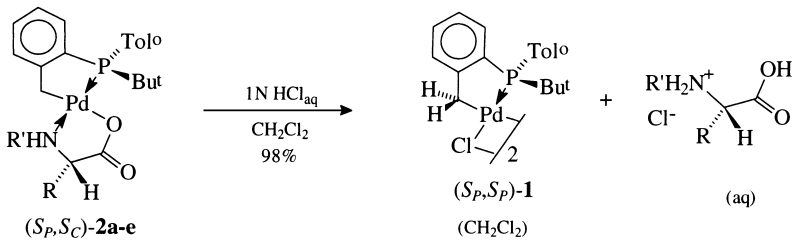
From the comparison of the ^{31}P{^{1}H} NMR parameters for the five substrates studied (Table 1) it becomes evident that in all cases the signals of (S_P,S_C) or (R_P,R_C) diastereomers (**2a**–**e**) are shifted upfield relative to that for the (S_P,R_C) or (R_P,S_C) diastereomers (**3a**–**e**). Thus, this trend in the chemical shift values of diastereomeric derivatives of this P*-chiral phosphapalladacycle can be useful for the tentative estimation of the absolute configuration of amino acids.

Table 2
Determination of enantiomeric composition of artificial mixtures of valine enantiomers by ^{31}P NMR method with dimer (S_P,S_P)-**1** as chiral derivatizing agent

Run	Enantiomer ratio (S_C) / (R_C)		Enantiomeric excess (% *ee*)		Error of determination (%)
	calculated[1)]	found by NMR	calculated[1)]	found by NMR	
1	2.659	2.64	45.33	45.1	0.5
2	7.718	7.24	77.06	75.7	1.7

[1)]the values were calculated taking into account an actual enantiomeric purity (98 %*ee*) of commercial *L*-valine determined by ^{31}P NMR method.

It is very important that the CCDA proposed here may be easily recovered in the form of μ-chloro-bridged dimer (S_P,S_P)-**1** in nearly quantitative yield and with complete retaining of its enantiomeric purity by means of the simplest procedure of the protonolytic elimination of amino-acidate ligand from adducts **2**/**3** (Scheme 3).

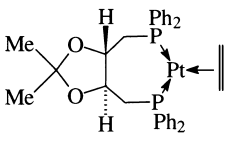


Scheme 3.

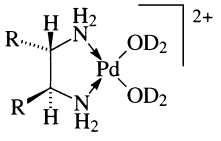
Moreover, the amino acidate ligand may also be, in principle, recovered as its hydrochloride from the aqueous phase.

3. Discussion

The only reported previous method designed for $^{31}P\{^1H\}$ NMR spectroscopy using non-phosphorus substrates to estimate the enantiomeric composition of η^2-donor ligands (alkenes, alkynes and allenes) using the (*S*,*S*)-*Diop* platinum(0) complex (**A**) as chiral derivatizing agent is by Parker.[20,21] However, this approach suffers from a number of drawbacks: (i) oxidative instability of this organometallic reagent requires special care during manipulation and storage; (ii) the necessity of excess substrate used to achieve the complete ethene displacement creates the conditions for its kinetic resolution; as a consequence, this method's applicability is only limited by compounds not capable of selective coordination with reagent **A**; and (iii) the spectral analysis of diastereomeric complex mixtures is complicated by the presence of two ^{31}P nuclei and ^{195}Pt nucleus in the reagent **A** resulting in spin–spin coupling between them.



(A)



(B)

To the best of our knowledge, the only precedent of coordinative chiral derivatizing of amino acids is the Buddrus's method[15] based on the use of the palladium(II) coordination complexes of type **B**; however, this approach also cannot be recognized as an ideal one because: (i) the main drawback of the reagents **B** is that they may be used only with the ^{1}H or ^{13}C NMR spectroscopy as a method for enantiopurity control; (ii) the advantage of the C_2 symmetry of chiral auxiliaries in CCDAs of type **B** is partly lost due to the unsymmetric nature of amino acidate ligands: the diamine part in the NMR spectra is presented by doubled sets of signals for each diastereomer; under these conditions using this method for the substrates with a complicated C,H-skeleton may be difficult; (iii) the preparation of the reagents **B** requires the use of an additional expensive reagent $AgNO_3$ and it can be generated in a solution only; and (iv) the possibility of recovery of the CCDA was not discussed and seems to be a rather problematic one.

It is evident from our data presented here that P*-chiral cyclopalladated dimer (S_P,S_P)-**1** reveals several advantages as compared to the Parker's platinum(0) complex **A** and Buddrus' palladium(II) coordination complexes of type **B**:

(i) The reagent (S_P,S_P)-**1** is a very stable compound which is convenient for the performance of all manipulations in air;[23]
(ii) the preparation of dimer (S_P,S_P)-**1** in an enantiopure state is a rather simple procedure, and both enantiomers are available from fractional recrystallization of its diastereomeric L-prolinate derivatives;[23,24]
(iii) the quantitative bonding of the amino acidate substrate with the palladium of reagent **1** does not require Ag^+ ions as a dehalogenating agent or substrate excess; moreover, some excess of reagent may be used to avoid any danger of kinetic resolution without serious complications of the total spectral picture because the signal of the reagent **1** (δ ca. 64 ppm) is outside the signal range of its amino acidate derivatives (δ 55–63 ppm);
(iv) the reagent proposed here contains only one phosphorus atom and the ^{31}P NMR spectra of its derivatives with either non-phosphorus substrates consists of only narrow singlet signals that facilitate the interpretation of the spectral picture and integration procedure (even despite the presence of Z/E isomeric species);
(v) a dispersion of diastereomeric signals in the ^{31}P NMR spectra is rather large (up to 2 ppm) to provide an accurate signal integration;
(vi) one of the most important advantages of the method proposed is the opportunity to recover cyclopalladated reagent (S_P,S_P)-**1** using the simplest procedure of the protolysis.

The main drawback of the method proposed here is the formation of amino acidate derivatives of dimer (S_P,S_P)-**1** as a mixture of *Z*- and *E*-geometric isomers. However, our recent studies[25] have shown that the ferrocene-derived phosphapalladacycles are free of this shortcoming. The estimation of their potential as CCDA and possibilities of the method expanding onto other *N*,*O*- and *N*,*N*-donor substrates is now under investigation.

4. Conclusion

The method of enantiomeric purity determination and the reagent described here satisfies all general requirements for CDA:[1] (i) the chiral derivatizing agent (S_P,S_P)-**1** is stable and easily available in the enantiopure state; (ii) its diastereomeric derivatives **2**/**3** may be prepared under mild conditions and without any racemization or kinetic resolution; (iii) the use of a CDA excess does not result in any spectral complications due to the choice of ^{31}P NMR spectroscopy as a method of analysis; (iv) the methodology used does not require the isolation of diastereomeric complexes **2**/**3** before ^{31}P NMR spectra measurement; and (v) the valuable enantiopure CCDA (S_P,S_P)-**1** can be quantitatively recovered from its α-amino acidate adduct by a simple protonation procedure in the form of the dimer suitable for further use.

5. Experimental

5.1. General

^{31}P NMR spectra were recorded on a Varian VXR-400 instrument at 161.9 MHz. The measurements were carried out at ambient temperature; chemical shifts are reported in parts per million (ppm) relative to H_3PO_4 as external reference. The precision of signal integration was improved by means of a standard line fitting procedure. The weighting experiments were performed using the analytical weigher 'Sartorius 4503/Micro' providing the precision of 0.001 mg.

Deuterated chloroform was purchased from Aldrich. Amino acids L- and D,L-valine, L-proline (from 'Reanal', Hungary), L-alanine (from 'VEB Berlin-Chemie', Germany), D-leucine and L-phenylglycine (from 'Reachim', Russia) were used as received. For L-valine the measurement of the specific rotation gave a value $[\alpha]_D = +26.4$ (*c* 1, 5 M HCl) compared to $[\alpha]_D = +26.5$ (*c* 0.5–2, 5 M HCl) reported for the enantiopure amino acid.[26]

Methanol was dried by a two-fold distillation from MeONa; benzene was kept over $CaCl_2$, refluxed over Na and distilled from Na under argon; dichloromethane was purified by passing through a column of Al_2O_3 and distillation under argon.

Cyclopalladated dimer (S_P,S_P)-**1** was obtained in an enantiopure state as described previously[23] with $[\alpha]_D^{20} = +45$ (*c* 0.2, dichloromethane).

5.2. Generation of a complete set of Z/E and diastereomer mixtures (Method 1)

A slight excess of solid L-valine (0.0149 g, 0.127 mmol) and sodium hydrocarbonate (0.0107 g, 0.127 mmol) was added to a suspension of the racemic dimer **1** (0.0500 g, 0.0607 mmol) in anhydrous methanol (5 mL). After stirring for 4 h at room temperature, the homogeneous reaction mixture was evaporated to dryness, the residue was dissolved in dichloromethane (3 mL) and washed with water (2×3 mL). The aqueous layer was extracted with dichloromethane (2×2 mL); combined organic layers were evaporated to dryness, dried in vacuo over $CaCl_2$, then dissolved in the 4:1 mixture of CH_2Cl_2:$CDCl_3$, transferred into the NMR tube and the $^{31}P\{^1H\}$ NMR spectra of the reaction mixture was recorded at room temperature. Other isomer mixtures were generated by the same manner; the parameters of their ^{31}P NMR spectra are given in Table 1.

5.3. Procedure of enantiomeric purity determination of optically active amino acids (Method 2)

Equimolar amounts of solid L-valine (0.0063 g, 0.054 mmol) and sodium hydrocarbonate (0.0045 g, 0.054 mmol) were added to a suspension of the calculated amount of the enantiopure dimer (S_P,S_P)-**1** (0.0222 g, 0.0269 mmol) in anhydrous methanol (2 mL). After stirring for 2 h at room temperature the homogeneous reaction mixture was evaporated to dryness, the residue was dried in vacuo over $CaCl_2$, and then transferred into a NMR tube by the 4:1 mixture of CH_2Cl_2:$CDCl_3$ for a subsequent measurement of the $^{31}P\{^1H\}$ NMR spectra. The chiral derivatizing of other amino acids was performed in the same manner; the ^{31}P chemical shifts for one of the diastereomers are presented in Table 1.

5.4. Procedure of enantiomeric purity determination of scalemic amino acids (Method 3)

A mixture of the racemic (0.004568 g, 0.03899 mmol) and L-valine (0.003932 g, 0.03356 mmol) [total weight of 0.008500 g (0.07256 mmol) and specific rotation $[\alpha]_D = +11.9$ (*c* 1.0, 5 M HCl)] and sodium hydrocarbonate (0.0061 g, 0.073 mmol) were added to a suspension of a slight excess of the enantiopure dimer (S_P,S_P)-**1** (0.0310 g, 0.0377 mmol) in anhydrous methanol (15 mL). After stirring for 7 h at room temperature the homogeneous colorless reaction mixture was evaporated to dryness, a solid residue was dried in vacuo over $CaCl_2$ and extracted by dichloromethane (5×4 mL). The combined organic extracts were evaporated to dryness, and transferred into a NMR tube by the 4:1 mixture of CH_2Cl_2:$CDCl_3$. $^{31}P\{^1H\}$ NMR (δ, ppm; integral intensities are given in the non-normalizated state): δ 56.862 (s, 4.71 *P*, *Z*(S_P,S_C)-isomer), 57.312 (s, 1.45 *P*, *Z*(S_P,R_C)-isomer), 60.168 (s, 2.39 *P*, *E*(S_P,S_C)-*isomer*), *61.970 (s, 1.24 P, E*(S_P,R_C)-*isomer*), *63.769 (br s, 0.28 P*, dimer **1**).

Another testing experiment was performed in the same manner using a mixture of the racemic (0.001820 g, 0.01554 mmol) and L-valine (0.006697 g, 0.05717 mmol) of specific rotation $[\alpha]_D = +20.0$ (*c* 1.0, 5 M HCl). $^{31}P\{^1H\}$ NMR (CH_2Cl_2:$CDCl_3$ mixture in 4:1 ratio; δ, ppm; integral intensities are given in the non-normalized state): δ 56.924 (s, 5.62 *P*, *Z*(S_P,S_C)-isomer), 57.361 (s, 0.62 *P*, *Z*(S_P,R_C)-isomer), 60.185 (s, 3.07 *P*, *E*(S_P,S_C)-isomer), 61.956 (s, 0.58 *P*, *E*(S_P,R_C)-isomer), 63.771 (br s, 0.25 *P*, dimer **1**).

The calculation of enantiomeric composition of the samples of L-valine in the terms of enantiomeric ratio (*er*.) and enantiomeric excess (*ee*.) were performed using the following simple equations, Eq. (1) and Eq. (2), respectively:

$$er = \frac{I_{Z(S,S)} + I_{E(S,S)}}{I_{Z(S,R)} + I_{E(S,R)}} \tag{1}$$

$$ee = \frac{[I_{Z(S,S)} + I_{E(S,S)}] - [I_{Z(S,R)} + I_{E(S,R)}]}{I_{Z(S,S)} + I_{E(S,S)} + I_{Z(S,R)} + I_{E(S,R)}} \times 100\% \tag{2}$$

where $\boldsymbol{I}_{Z(S,S)}$, $\boldsymbol{I}_{Z(S,R)}$, $\boldsymbol{I}_{E(S,S)}$, and $\boldsymbol{I}_{E(S,R)}$ designate the integral intensities of the signals assigned to the isomers *Z*(S_P,S_C), *Z*(S_P,R_C), *E*(S_P,S_C) and *E*(S_P,R_C), respectively.

The results of the enantiomeric purity estimation for artificial mixtures are given in Table 2.

5.5. Regeneration of the starting dimer (S_P,S_P)-**1**

A solution of (*S*)-prolinate derivative (S_P,S_C,S_N)-**2a** (0.1090 g, 0.223 mmol) in dichloromethane (8 mL) was vigorously shaken with 1N HCl solution (8 mL) for 3 min. The organic layer was separated, washed with water (5 mL), dried over sodium sulfate and then evaporated to dryness. After drying the residue in vacuo (10^{-2} mm Hg) over P_2O_5 dimer (S_P,S_P)-**1** was obtained as an amorphous powder in the yield of 98% (0.0898 g, 0.109 mmol) and enantiomeric purity of >98% *ee*. (according to the ^{31}P NMR data for (*S*)-prolinate derivative). M.p. (dec) 308–310°C, R_f 0.77 (Silufol, ether:hexane, 4:1); $[\alpha]_D^{20} = +45$ (*c* 0.2, dichloromethane).

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