DIASTEREOSELECTIVE HYDROGENATION OF COMPLEXES OF ACE. ..DEHYDRO-PHENYLALANYLMETHIONINE AND ITS ESTERS WITH $PdCl_2$

I. N. Lisichkina, A. I. Vinogradova, M. B. Saporovskaya, V. K. Latov, and V. M. Belikov

UDC 542.941.7: 541.49:547.466

A new method, on principle, for the diastereoselective hydrogenation of dehydrodipeptides (DHDPs) and their esters entailing the utilization of the complex of the DHDP with $PdCl_2$ as the substrate was proposed. The formation of a certain conformation of the DHDP chain produced by the central atom of the metal complex-former permits the asymmetric synthesis of N-acetylphenylalanylmethionine with the optical yield up to 40%. The optical yield of the product depends both on the configuration of the methionine part of the peptide and on the bulk of the ester group.

The catalytic asymmetric hydrogenation of unsaturated precursors of amino acids and peptides is one of the promising methods for the chemical synthesis of derivatives of the natural amino acids. Effective asymmetric synthesis (the optical purity of the product up to 100%) can thereby be achieved either in the case of the use of chiral catalysts [1] or in the case of the rigidly formed DHDPs, as occurs in themixed diketopiperazines [2]. The hydrogenation of the linear DHDPs over achiral catalysts gives the usually low asymmetric yield of the product ≤ 25% [1, 3].

The present work communicates a new approach, in principle, to the diastereoselective hydrogenation of DHDPs entailing the use of the complex of the DHDP with $PdCl_2$ as the substrate. The rigidification of the peptide structure as a result of complex formation leads to the much more selective hydrogenation. At the same time, the palladium, which forms part of the composition of the complex, is also a catalyst of the hydrogenation. N-Acetyldehydrophenylalanylmethionine and its esters were chosen as the peptide complex former; their structures are shown:

$$PhCH{=}C(NHCOCH_3)CONHCH(COOR)CH_2CH_2SCH_3$$

$$R = H(I),\ CH_3,\ C_2H_5,\ i\text{-}C_3H_7,\ CH_2Ph.$$

RESULTS AND DISCUSSION

The complex of (I) with $PdCl_2$ is formed on keeping equimolar amounts of the DHDP and Na_2PdCl_4 in an alcoholic solution. It can be isolated in the solid form.

In the PMR spectrum of the complex, the CH_3 and CH_2 groups at the sulfur atom give a signal with a significant shift to low field (by 0.3 and 0.7 ppm) by comparison with the initial peptide (Table 1). The values for the proton of the α-carbon atom and the vinyl proton are practically unchanged on complex formation.

The low-field shift of the signals of the CH_3—S and —CH_2—S protons and the virtually unchanged value of $\delta^{\alpha}CH$ and δH_{vinyl} provide the basis for the proposition that the coordination of the Pd with (I) is only accomplished at the sulfur atom. Coordination at the double bond of the peptide and at the amide nitrogen is not found [4].

The IR spectral data indicate that the carboxyl group of the methionine part of the peptide is not coordinated [1719 cm^{-1} (asym. COOH)] and forms a hydrogen bond with the carboxyl group of another peptide molecule [3270 cm^{-1} (OH)] [5]. The absorption bands of the bridge Pd—Cl—Pd bonds (306 and 284 cm^{-1}) and the terminal Pd—Cl (345 cm^{-1}) are also observed.

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2828-2832, December, 1989. Original article submitted July 19, 1988.

0568-5230/89/3812-2592$12.50

TABLE 1. PMR Parameters of N-Ac-ΔPhe-MetOR, Their Complexes with $PdCl_2$, and the Products of Hydrogenation (CD_3OD, δ, ppm)

Compound	CH_3S	CH_3CO	$-CH_2-S$	$-CH_2-$	α-CH	CH vinyl	Ph	OCH_3
(I)	2,13 s	2,13 s	2,20 m	2,62 m	4,71 q	7,13 s	7,39 m	
(I)·$PdCl_2$	2,42 s 2,32 s	2,18 s	3,01 m	2,61 m	4,71 q	7,20 s 7,24 s	7,46 m	
(I)·$PdCl_2$+$NaBH_4$	2,43 s	2,18 s	3,01 m	2,61 m	4,72 q	7,13 s	7,43 m	
N-Ac-Phe-MetOH·$PdCl_2$	2,30 d	1,94 d	2,95 m 3,14 m *	2,62 m	4,71 m 4,46 m*	–	7,29 m	
N-Ac-Phe-MetOH	2,05 d	1,91 d	2,97 m 3,10 m *	2,51 m	4,70 m 4,51 m *	–	7,29 m	
N-Ac-ΔPhe-$MetOCH_3$	2,11 s	2,11 s	2,15 m	2,63 m	4,72 q	7,11 s	7,39 m	3,77 s
N-Ac-ΔPhe-$MetOCH_3$·$PdCl_2$	2,42 s 2,32 s	2,16 s	3,01 m	2,57 m	4,70 q	7,22 s 7,25 s	7,46 m	3,82 s
N-Ac-Phe-$MetOCH_3$	2,04 d	1,91 d	3,01 m 3,10 m *	2,56 m	4,66 m 4,53 m*	–	7,26 m	3,73 d

*The signal of the corresponding protons of the Phe fragment of the product.

TABLE 2. Hydrogenation of N-Ac-ΔPhe-S(R)-MetOR·$PdCl_2$*

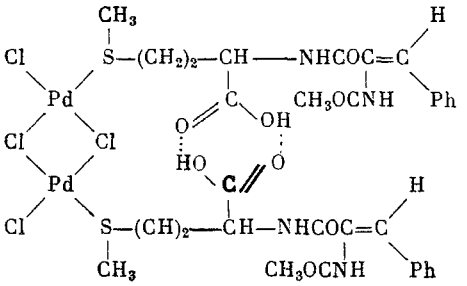
Configuration of MetOR	Radical R	Optical yield of Phe, %	
		without $NaBH_4$**	in the presence of of $NaBH_4$**
S	H	38(*R*)	38(*R*)
R	H	–	38(*S*)
R,S	H	–	Racemate
S	CH_3	36(*R*), 37(*R*)	30(*S*)
R	CH_3	–	30(*R*), 33(*R*)
S	C_2H_5	40(*R*), 36(*R*)	Racemate
S	*i*-C_3H_7	37(*R*), 39(*R*)	5(*R*), 8(*R*)
S	$CH_2C_6H_5$	36(*R*)	27(*R*), 26(*R*)

*The reaction time was 7-8 h without $NaBH_4$ and 0.5 h with $NaBH_4$.
**Determined by the GLC according to [8] for Phe, obtained by the acid hydrolysis of the complex.

TABLE 3. Constants of the Obtained N-Ac-ΔPhe-(R)S-MetOR

R	Yield, %	Mp, °C	Empirical formula	Found/ Calculated, %			$[\alpha]_D^{20}$ (c 0.5, methanol)
				C	H	N	
CH_3	76,4	165–167	$C_{17}H_{22}N_2O_4S$	58,01 / 58,27	6,33 / 6,33	7,90 / 7,99	–39,80
CH_3(R)	73,0	165–167					
C_2H_5	80,5	144–146	$C_{18}H_{22}N_2O_4S$	59,33 / 59,32	6,37 / 6,64	7,68 / 7,68	–11,94
i-C_3H_7	42,8	143–145	$C_{19}H_{26}N_2O_4S$	60,21 / 60,29	7,13 / 6,92	7,36 / 7,40	+8,91
CH_2Ph	33,0	139–141	$C_{23}H_{26}N_2O_4S$	64,39 / 64,77	6,01 / 6,14	6,46 / 6,57	+3,88

All these data as well as the data of the elemental analysis permit the proposition of the following structure for the complex



This complex, which is obtained in situ or isolated in the solid form, is readily hydrogenated by H_2 at atmospheric pressure in an alcoholic solution both in the presence of $NaBH_4$ and without it. As a result of the hydrogenation, the mixture of the diastereomeric complexes in which the coordination of the Pd at the sulfur atom is also preserved is obtained; the signal of the protons of the CH_3S group appears in the form of a doublet and the chemical shift comprises 2.3 ppm (2.05 ppm in the uncoordinated peptide, Table 1).

The results of the hydrogenation of the complexes are presented in Table 2. It can be seen that the diastereomeric composition of the complexes formed both in the presence of $NaBH_4$ and without it only depend on the configuration of the methionine part of the peptide: the S-Met leads to the 40% excess of the R,S-isomer, and the R-Met leads to the same excess of the S,R-isomer. The mirror reaction therefore takes place. It is natural that the R,S-Met leads to the achiral peptide. It was shown in a special experiment that (I) is not hydrogenated over Pd-black, obtained under analogous conditions by the reduction of Na_2PdCl_4 with sodium borohydride.

Therefore, the formation of the complex of the DHDP with palladium, which leads to the establishment of a form of the peptide molecule fixed in relation to the catalytic center in a certain way, is a determining factor for the successful asymmetric hydrogenation of DHDPs.

We also extended such an approach to the diastereoselective hydrogenation of the DHDPs to their esters.† In this case as well, the complexes with $PdCl_2$ having the coordination at the sulfur atom are formed (Table 1). The results of the hydrogenation of these complexes are also presented in Table 2, from which it follows that there is a difference in the hydrogenation of the complexes of the esters in the presence of $NaBH_4$ and without it. The hydrogenation without $NaBH_4$ leads to the mixture of the diastereomers in which the excess of one of them is only determined by the configuration of the methionine part of the peptide as in the case of the DHDPs: the S-MetOR gives an excess of the R,S-isomer. The optical yield of the product does not depend on the radical of the peptide ester group and comprises 36-40%, i.e., it has practically the same value as that of the complex of the peptide itself.

The hydrogenation of the complexes of the esters proceeds differently in the presence of $NaBH_4$. If the result of the asymmetric hydrogenation of N-Ac-ΔPhe-S-MetOR·$PdCl_2$ is expressed as the yield of the R,S-isomer, the direct dependence of this value on the steric constant of the substituent R of the ester group [6] of the methionine residue is observed.

$-E_S^0$, R	CH_3	C_2H_5	i-C_3H_7	CH_2Ph	H (dimer)
Yield of R,S-isomer, %	35	50	54	63	70

In the light of the facts stated, the result of the hydrogenation of (I) (R = H) in the presence of $NaBH_4$ becomes apparent. The carboxyl groups of the complex (I)·$PdCl_2$ are also evidently associated with the hydrogen bond in solution; this leads to the significant increase in their effective volume. The high yield of the R,S-isomer is also a consequence of this.

EXPERIMENTAL

The PMR spectra were measured on a "Bruker WP-200" spectrometer relative to TMS. The UV spectra were taken on a "Specord UV-VIS" spectrometer. The optical rotation was measured on a "Perkin-Elmer-241" polarimeter.

N-Acetyldehydrophenylalanyl-S-methionine. This compound was obtained according to [7]. The yield was 80%; it had the mp 171-172°C (from ethyl acetate) and the $[\alpha]_D^{20}$ +3.8° (c 1, methanol). Found: C, 56.96; H, 6.43; N, 8.10%. $C_{16}H_{20}N_2O_4S$. Calculated: C, 57.03; H, 6.18; N, 8.34%. The N-acetyldehydrophenylalanyl-R-methionine was obtained analogously.

Esters of N-Acetyldehydrophenylalanylmethionine. To 5 ml of absolute alcohol cooled to −15- −30°C were added 2 mmoles of thionyl chloride and then 1.5 mmoles of (I) with stirring. The solution was maintained with cooling for 10 min and was then gradually heated to 20°C. After 2-3 h, the excess of the alcohol and thionyl chloride was distilled in vacuo at 20°C. The remaining oil was triturated with 1 N NH_4OH until a colorless powder was formed; the powder was washed with ether and recrystallized from 2:1 aqueous alcohol. The properties of the esters thereby obtained are presented in Table 3.

Complex of (I) with $PdCl_2$. The solution of 75 mg (0.2 mmole) of (I) and 60 mg (0.21 mmole) of Na_2PdCl_4 in 10 ml of absolute ethanol was held for 3 h at 20°C. The NaCl was filtered off and the solution was concentrated in vacuo to a low volume prior to treatment with absolute ether. The yield of 100 mg of the complex (I)·$PdCl_2$ (97%) was obtained; it had the decomposition temperature 159°C (from alcohol). Found: C, 37.41; H, 3.82; N, 5.32; Pd, 20.50%. $C_{16}H_{20}N_2O_4SCl_2Pd$. Calculated: C, 37.43; H, 3.90; N, 5.46; Pd, 20.66%.

Hydrogenation in the Presence of $NaBH_4$. To 102 mg (0.2 mmole) of the complex (I)·$PdCl_2$ in 10 ml of absolute ethanol were added 8 mg (0.4 mmole) of $NaBH_4$. The color of the solution changes from yellow to dark brown. The hydrogenation was then performed in H_2 at atmospheric pressure according to [8]. The reaction is completed after 20-30 min; it is monitored by the disappearance of the absorption band at 280 nm in the UV spectrum of the sample pertaining to the $\pi \rightarrow \pi^*$ transition of the C=C bond of the complex. To the homogeneous solution of brown coloration was added 0.1 ml of 5 N HCl; the solution was passed

†The esters of the DHDPs were obtained from the corresponding peptides by the treatment of their solutions in alcohols with $SOCl_2$ at −15 to −30°C. Under these conditions, virtually no decomposition of the methionine part of the peptide is observed. The constants of the esters obtained are presented in Table 3.

through a column with Al_2O_3, concentrated to dryness, and recrystallized from absolute alcohol. A yield of 63 mg (92%) of N-Ac-Phe-MetOH was obtained; it had the mp 155°C. Found: C, 56.60; H, 6.45; and N, 8.08%. $C_{16}H_{22}N_2O_4S$. Calculated: C, 56.80; H, 6.51; N, 8.28%.

Hydrogenation without $NaBH_4$. The solution of 75 mg (0.2 mmole) of (I) and 60 mg (0.21 mmole) of Na_2PdCl_4 was maintained for 3 h at 20°C prior to the hydrogenation with H_2 at atmospheric pressure. The formation of Pd-black was observed after 10 min. The hydrogenation was completed after 8 h. After filtering off the black material, the solution was concentrated to dryness in vacuo; the residue was recrystallized from absolute alcohol. The yield of 74 mg (98%) of N-Ac-Phe-MetOH was obtained; it had the mp 155°C.

The hydrogenation of the complexes of the esters of (I) was performed analogously. The enantiomeric composition of the Phe, forming part of the dipeptide, was evaluated using GLC analysis of the amino acids separated after the acid hydrolysis of the complexes of the peptide on a column with Dowex-50 with 3 N NH_4OH according to [9].

LITERATURE CITED

1. M. Jatagai, T. Jamagihi, and M. Higa, Bull. Chem. Soc. Jpn., 57, No. 3, 823 (1984).
2. I. Ojima and T. Suzuki, Tetrahedron Lett., 21, No. 13, 1239 (1980).
3. I. N. Lisichkina, A. I. Vinogradova, M. B. Saporovskaya, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 1170 (1988).
4. B. Jezowska-Trzebiatowska, T. Kowalik, and H. Koslowski, Bull. Acad. Pol. Sci., 26, No. 3, 223 (1978).
5. S. E. Livingstone and J. D. Nolan, Inorg. Chem., 7, No. 7, 1447 (1968).
6. V. A. Pal'm, Basis of the Quantitative Theory of Organic Reactions [in Russian], Khimiya, Leningrad (1977), p. 319.
7. J. P. Greenstein and M. Winitz, Chemistry of the Amino Acids, Wiley, New York (1961).
8. V. K. Latov, V. M. Belikov, T. A. Belyaeva, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 11, 2481 (1977).
9. Yu. N. Belokon', N. I. Chernoglazova, K. A. Kochetkov, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 804 (1984).