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COMPLEXATION AS THE DRIVING FORCE IN DIASTEREOSELECTIVE HYDROGENATION OF DEHYDRODIPEPTIDES

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Summary. The complexation of opened dehydrodipeptides with metal ions: Pd, Ca, Fe, Ni, Cr strongly affects the diastereoselectivity in hydrogenation and permits to attain d.e. up to 88%.

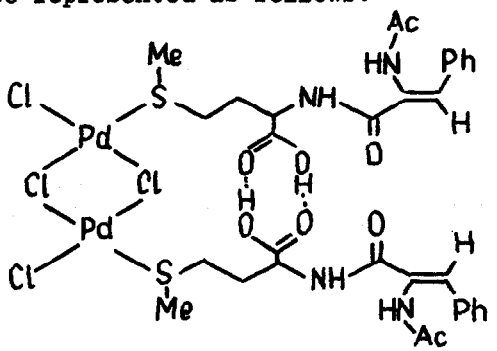
Numerous publications are devoted to asymmetric hydrogenation of dehydroamino acids, dehydrodipeptides and their derivatives. Considerable success has been achieved with the catalysis by Rh complexes of chiral phosphines. Quantitative optical yields excite in this case no surprise [1a,b]. Excellent results were also obtained by hydrogenation of cyclic dehydrodipeptides over achiral catalysts [2]. It is obvious that a rigidity of cyclic systems promotes high diastereoselectivity, whereas opened dehydrodipeptides manifest in general poor diastereoselectivity in presence of achiral catalysts[3], while chiral catalysts can lead to high stereoselectivity [4a,b].

We reasoned that complexation of opened dehydrodipeptides with metal ions may increase the rigidity of dipeptide chain and hence to improve optical yields.

The present investigation is undertaken to examine the influence of metal complex formation on the hydrogenation of dehydrodipeptides of general formula $PhCH{=}C(NHCOCH_3)CONHCH(R)COOR'$. We regarded two possibilities. First, the central ion - Pd(II) -simultaneously plays roles of complexing atom and hydrogen transfer catalyst. Second, the central atom plays only complexing role whereas the hydrogenation is performed over optically inac-

tive catalyst. In the latter case salts of Ca(II), Fe(II), Ni(II), Cr(III) were used.

We prepared methionine containing dehydrodipeptides: $PhCH{=}C(NHCOCH_3)CONHCH(CH_2CH_2SCH_3)COOR'$ (I), R'=H,Me, Et, i-Pr, Bzl and their complexes with $PdCl_2$. On the basis of well-known affinity of Pd to S, ^1H NMR and IR spectral data and elemental analysis the structure of complex (R'=H) may be represented as follows:



I·$PdCl_2$ (R'=H)

The hydrogenation of I·$PdCl_2$ was carried out either directly by H_2 (Method A), or by H_2 after preliminary reduction of Pd(II) to Pd(0) by means of $NaBH_4$ (Method B). As a result Pd-complexes of diastereomeric N-Ac-Phe-Met-OR' (2) were obtained. Experimental data are summarized in Table I.

Table I

Run	Configuration Met in (I)	R'	Taft $-E_s^o$	(RS):(SS) for (2)[a,b] Method A	Method B
1	(S)	H	-[c]	69:31	69:31
2	(R)	H	-	-	30:70 (RR):(SR)
3	(RS)	H	-	-	50:50
4	(S)	Me	0	69:31	35:65
5	(R)	Me	0	-	67:33 (RR):(SR)
6	(S)	Et	0,27	70:30	50:50
7	(S)	i-Pr	0,85	69:31	54:46
8	(S)	Bzl	0,72	68:32	

[a] 1 atm H_2, ambient temperature, EtOH. Method A 7-8 h., Method B 0,5 h. Quantitative yields.

[b] Determined from ee of Phenylalanine obtained after acid hydrolysis of (2), GLC[5].

[c] $-E_s^o$ for R'=H in the form of dimer is not available.

No reaction occured if I was treated with H_2 over Pd-black.

The most interesting feature of this reaction is the retention of Pd-S bond in the complex during the reduction of Pd(II) to Pd(0) and subsequent hydrogen transfer in the intermediate hydrido complex. This was supported by the following evidencies:

- In the ^1H NMR spectrum of (2) CH_3S- group gives a strong downfield shifted signal of about 0,3 ppm towards the free (I);
- In the course of reaction no precipitate of metallic Pd was formed;
- When (S)-Met in (I) was replaced by (R)-Met the enantiomeric reaction occured: see runs 1-2 and 4-5 in Table I.

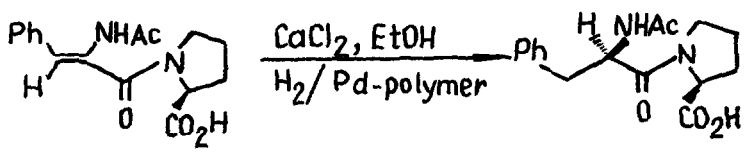
Although structure of hydrido complex is unknown we suppose that in an intermediate where chiral discrimination occures carboxy group of methionine residue is placed in close proximity to Pd. It follows from dependance of the direction of diastereomeric hydrogenation on the volume of R' [6].

In the framework of the idea of complexation we further investigated the hydrogenation of dehydrodipeptides N-Ac-Δ-Phe-AA-OH (3), where AA were the residues of Glu, Tyr, Leu and Pro over homogeneous catalyst [7] in the presence of $CaCl_2$, $FeSO_4$, $Ni(NO_3)_2$ or $Cr(OAc)_3$. Labile complexes which probably are formed in this case were not isolated. Nevertheless these salts sometimes drastically affect the stereochemistry of reaction. The ratios (RS):(SS) for diastereomeric peptides N-Ac-Phe-AA-OH (4) produced are presented in table II.

Table II

(S)-AA	no salt	$CaCl_2$	$FeSO_4$	$Ni(NO_3)_2$	$Cr(OAc)_3$
Glu	55:45	46:54	49:51	52:48	48:52
Tyr	60:40	68:32	45:55	62:38	72:28
Leu	45:55	44:56	49:51	39:61	58:42
Pro	70:30	94: 6	65:35	89:11	72:28

(3):salt 1:1 (mol), (3):catalyst 30:1 (wt), 1 atm. H_2, EtOH, 2-10 h. Quantitative chemical yields [8]. The ratios determined from ee of Phenylalanine obtained after acid hydrolysis of (4), GLC [5].



94%

High diastereoselectivity up to 88% d.e. was achieved for opened dehydrodipeptide. The investigation of other factors influencing the stereochemistry of this reaction (character of complex, solvent, counterion) is now in progress.

Thus dehydrodipeptide-metal complexation represent a novel approach to the regulation of diastereoselective hydrogenation.

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6. When R'=H we consider that the volume of R' is not that of hydrogen atom but the volume of the second molecule of peptide in dimer.
7. Complex of $PdCl_2$ with copolymer of styrene and glycine maleimide; Latov V.K., Belikov V.M., Belyaeva T.A., Vinogradova A.I., Soinov S.D.; Izv. AN SSSR, Ser. khim. 1977, 2481.
8. Estimated by ^1H NMR and UV spectra of produced complexes. Free acetyldipeptides could be isolated on Helex column in a yield of about 95%.