Diastereoselective hydrogenation of α,β-dehydrodipeptides bearing unsaturated *N*-terminal amino acids and of their complexes with $CaCl_2$ and $MgCl_2$

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The formation of complexes of dehydrodipeptides bearing *N*-terminal *N*-benzoyl-*O*-methyl-α,β-dehydrotyrosine or *N*-benzoyl-α,β-dehydrovaline residues with Ca^{2+} and Mg^{2+} ions enhances the diastereoselectivity of their hydrogenation; *de* of 66% and 80% were achieved. This method of increasing the stereoselectivity of hydrogenation is applicable to various dehydroamino acids at both the *C*- and *N*-termini of dehydrodipeptides.

Key words: diastereoselective hydrogenation, dehydrodipeptides, complexes with alkali-earth metals.

Previously[1] we proposed a method for diastereoselective hydrogenation of dehydrodipeptides (DHDP) as their complexes with metal salts using *N*-benzoyl-α,β-dehydrophenylalanine derivatives with various amino acids at the *C*-terminus of a peptide as substrates. In a continuation of our investigations, in the present work we studied hydrogenation of DHDP bearing residues of the other unsaturated amino acids at the *N*-terminus: *N*-benzoyl-*O*-methyl-α,β-dehydrotyrosine and *N*-benzoyl-α,β-dehydrovaline. These derivatives were obtained by the azlactone method from amino acids and the corresponding azlactones, which in turn were obtained from hippuric acid and aldehyde or ketone according to the Erlenmeyer reaction[2] (Scheme 1).

Scheme 1

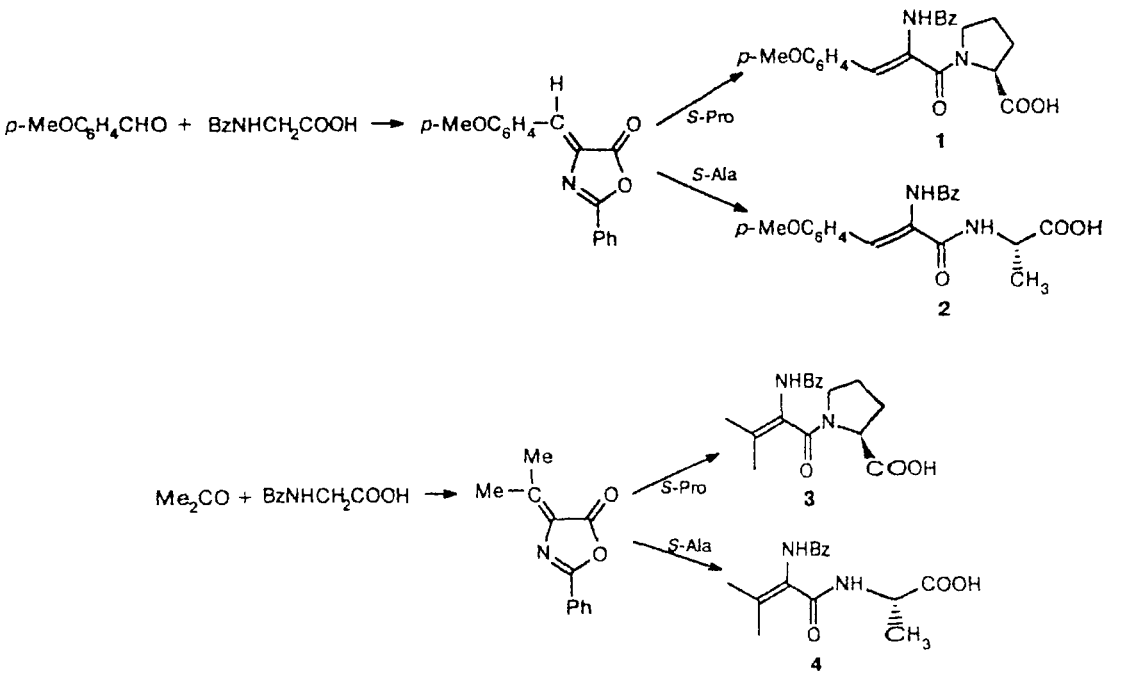

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Table 1. Parameters of ^{1}H NMR spectra (δ) of *N*-Bz-*O*-Me-ΔTyr-*S*-Pro and its complexes

DHDP	CH—COOH	OCH_3	—CH=	Aromatic part
1	4.54 (t)	3.78 (s)	6.41 (s), 6.69 (s)	7.02, 7.60, 8.05
1 + 2 equiv. $MgCl_2$	4.42 (t)	3.80 (s)	6.69 (s), 6.84 (s)	6.91, 7.50, 7.96
1 + 8 equiv. $MgCl_2$	4.26 (m)	3.82 (s)	6.70 (s), 6.86 (s)	6.97, 7.57, 7.99
1 + 8 equiv. $CaCl_2$	4.28 (m)	3.84 (s)	6.69 (s), 6.86 (s)	6.94, 7.53, 7.99

Results and Discussion

The dehydrodipeptides under study and those described previously[3] form complexes with calcium and magnesium chlorides in an alcoholic solution. Complex formation can be seen in particular in the ^{1}H NMR spectra (Table 1). For all DHDP complexes with metal ions, complex formation results in the maximum changes in the chemical shifts of the signals for the vinylic protons, the proton at the chiral carbon atom, and the protons of the aromatic ring of the tyrosine fragment. As in the case of dehydrophenylalanine derivatives studied previously,[4] a probable reason for this phenomenon is the coordination of the metal ion to the carboxyl and carbonyl groups. This follows from the noticeable differences in the chemical shifts of the protons at the carbon atom that is directly linked to the carboxyl group and the changes in the chemical shift of the vinylic proton. The spectrum of **1** exhibits splitting of the signal of the proton at the vinylic carbon atom, which is typical of all analogous proline derivatives[4] and which testifies that two conformers exist in the NMR time scale due to the hindered rotation around the simple =C—C=O bond.

It can be seen from Table 2 that during hydrogenation of dehydrotyrosine derivatives **1** and **2**, unlike that of the *N*-benzoyl-α,β-dehydrophenylalanine derivatives studied previously,[3] the formation of a complex between the substrate and metal salts has a specific effect on the stereochemical outcome of hydrogenation.

To enhance the diastereoselectivity of the hydrogenation of DHDP, it is necessary to convert them into rigid complexes with a metal. Therefore, we used different ratios of DHDP and metal salts. As expected by analogy with the complexes studied previously,[5] the best results were obtained for proline derivatives at a DHDP : metal salt ratio of 1 : 8 (see Table 1). In all cases, the *RS*-diastereomer predominates.

Table 2. Excess diastereomer in the hydrogenation of *N*-Bz-*O*-Me-ΔTyr-AA and their complexes

DHDP	MeONa (equiv./equiv.)	Metal salt	Amount of salt (equiv./equiv.)	Reaction time /days	*de RS* (%)
1	—	—	—	1	38
1	1	$MgCl_2$	2	7	30
1	1	$MgCl_2$	8	7	32
1	1	$CaCl_2$	2	27	40
1	1	$CaCl_2$	8	27	66
2	—	—	—	1	18
2	1	$MgCl_2$	2	5	12
2	1	$MgCl_2$	8	9	18
2	1	$CaCl_2$	2	16	22
2	1	$CaCl_2$	8	12	34

The most interesting results were obtained for the hydrogenation of dehydrovaline derivatives **3** and **4**, which are tetrasubstituted olefins. Previously, it was demonstrated[6] that *N*-benzoyl-dehydrovalyl-*S*-amino acids, which are tetrasubstituted alkenes, are not hydrogenated on Pd/C. On Raney nickel, the double bond $Me_2C{=}C<$ is reduced to give a 4 to 56% excess of an *RS*-diastereomer. Later, hydrogenation of *N*-Bz-ΔVal-(*S* and *R*)-PheOMe was carried out on Pd/C under drastic conditions (70 °C, 2 days) with a diastereoselectivity of 20%.[7] In our case, hydrogenation of dehydrovaline derivatives on Pd/C under normal conditions also does not occur.

The hydrogenation could be performed only at an elevated pressure of H_2 (40 atm) and the process required a long time. The reaction did not go to completion even under these drastic conditions. *N*-Benzoyl-(*R* and *S*)-valyl-*S*-proline (**5**) and *N*-benzoyl-(*R* and *S*)-valyl-*S*-phenylalanine (**6**) (both with predomination of the *RS*-diastereomer) form.

As in the spectra of dehydropeptides that are alkyl-substituted at the C=C bond,[8] in the UV spectra of **3** and **4**, the absorption in the range of 280 nm typical of conjugated double bonds is shifted to 200—230 nm and overlaps the absorption of other groups. Therefore, the course of hydrogenation was monitored only by the ^{1}H NMR spectra. The ^{1}H NMR spectra of compounds **3** and **4** contain two singlets at δ ~2 corresponding to two CH_3 groups, and the spectra of compounds **5** and **6** each contain two groups of signals of the methyl protons at δ ~1. Each group belongs to one of the diastereomers.

As follows from Table 3, the diastereoselectivity of hydrogenation of magnesium complexes **3** and **4** leading to *N*-benzoyl-*R*-valyl-*S*-proline and *N*-benzoyl-*R*-valyl-*S*-phenylalanine is considerably higher (80 and 66%, respectively) than that of free compounds **3** and **4** and that reported in an earlier work.[7]

Thus, the increase in the rigidity of dehydrodipeptides due to the formation of complexes with metals and, as a consequence, the increase in the diastereoselectivity of hydrogenation of these complexes are of general character for various amino acids incorporated in dipeptides at both the *C*- and *N*-termini of the peptides. Steric hindrances in the dehydrovalylproline molecule are an ad-

Table 3. Excess diastereomer in the hydrogenation of N-Bz-ΔVal-AA and their complexes

DHDP	MeONa, (equiv./equiv.)	Metal salt	Amount of salt (equiv./equiv.)	Reaction time /days	Pressure of H_2 /atm	Conversion (%)	*de RS* (%)
3	—	—	—	5	40	76	48
3	1	$MgCl_2$	8	7	40	76	80
4	—	—	—	4	21	50	12
4	1	$MgCl_2$	2	4	40	77	66

ditional factor that increases the rigidity of the system to be hydrogenated and results in a considerable increase in *de*.

Experimental

^1H NMR spectra were measured on a Bruker WP-200 instrument in CD_3OD using Me_4Si as the internal standard.

Compounds **1** and **2** and their complexes were hydrogenated in an ethanolic solution under hydrogen at atmospheric pressure over Pd/C. The course of hydrogenation was monitored by UV spectroscopy. The end of the hydrogenation was determined by the disappearance of the absorption at 280 nm assigned to the system of conjugated double bonds. According to the data from UV and ^1H NMR spectra, the yield of the hydrogenation product is almost quantitative. The data on *de* in *N*-benzoyl-*O*-methyltyrosyl-*S*-proline and *N*-benzoyl-*O*-methyltyrosyl-*S*-alanine formed were obtained from the ^1H NMR spectra, in which two signals (or two groups of signals) of protons belonging to two diastereomers are clearly observed. This is especially noticeable for the signals of the OCH_3 (at δ 3.72) and CH_3 groups (at δ 1.4). For assignment of signals and in the case when a signal could not unambiguously be assigned to one or another diastereomer, the product of hydrogenation was subjected to hydrolysis with 2*M* HCl for 10 h. The mixture of amino acids obtained was isolated in the free form on a cation-exchange resin and analyzed by GLC on a column with a chiral phase.

***N*-Benzoyl-*O*-methyl-α,β-dehydrotyrosyl-*S*-proline (1)** was obtained by the azlactone method from 2-phenyl-4-*p*-methoxybenzylideneoxazolone-5 [9] and *S*-proline in 50% yield, m.p. 110 °C (from aqueous ethanol, 1 : 1). Found (%): C, 66.27; H, 5.93; N, 7.0. $C_{21}H_{22}N_2O_5$. Calculated (%): C, 65.95; H, 5.81; N, 7.33.

***N*-Benzoyl-*O*-methyl-α,β-dehydrotyrosyl-*S*-alanine (2)** was obtained by the azlactone method from 2-phenyl-4-*p*-methoxybenzylideneoxazolone-5 and *S*-alanine in 71% yield, m.p. 165 °C (from aqueous ethanol, 1 : 1). Found (%): C, 63.77; H, 5.32; N, 7.40. $C_{20}H_{20}N_2O_5 \cdot 0{,}5H_2O$. Calculated (%): C, 63.64; H, 5.61; N, 7.42.

***N*-Benzoyl-α,β-dehydrovalyl-*S*-proline (3)** was obtained by the azlactone method from 2-phenyl-4-isopropylideneoxazolone-5 [9] and *S*-proline in 50% yield, m.p. 165—166 °C. Found (%): C, 64.72; H, 6.56; N, 8.70. $C_{17}H_{20}N_2O_4$. Calculated (%): C, 64.54; H, 6.37; N, 8.86.

***N*-Benzoyl-α,β-dehydrovalyl-*S*-phenylalanine (4)** was obtained by the azlactone method from 2-phenyl-4-isopropylideneoxazolone-5 and *S*-phenylalanine in 61% yield, m.p. 200 °C. Found (%): C, 68.55; H, 6.08; N, 7.55. $C_{21}H_{22}N_2O_4$. Calculated (%): C, 68.85; H, 6.05; N, 7.65.

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