Hydrogenation of complexes of diastereotopic *N*-benzoyldehydrodipeptides

I. N. Lisichkina, A. I. Vinogradova, I. B. Bachurina, L. N. Kurkovskaya, and V. M. Belikov*

Institute of Food Substances, Russian Academy of Sciences,
28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085

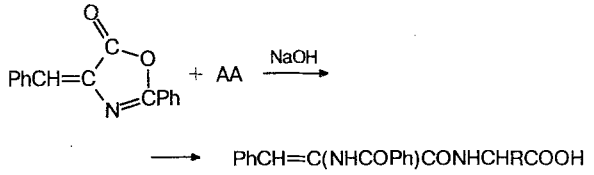
The replacement of the *N*-acetyl group by an *N*-benzoyl group in *N*-acyldehydrodipeptides results, first, in an increase in the asymmetric induction in their hydrogenation in the case of *N*-Bz-ΔPhe-(*S*)-Glu. *N*-Bz-(*S*)-Phe-(*S*)-Glu is obtained with a diastereomeric excess (*de*) of 52 %. Second, no poisoning of the Pd-catalyst by sulfur in *N*-Bz-ΔPhe-(*S*)-Met occurs, and *N*-Bz-(*R*)-Phe-(*S*)-Met is obtained with a *de* of 26 %. The formation of complexes of *N*-Bz-ΔPhe-AA with Ca^{2+} and Mg^{2+} ions does not, as a rule, affect the diastereoselectivity of the hydrogenation. The structure of the dehydrodipeptides has been determined on the basis of ^1H NMR spectra, potentiometric titration, and molecular mechanics calculations.

Key words: dipeptides, benzoyl group; diastereoselective hydrogenation; complex formation.

Recently we showed that the conformational rigidity of linear *N*-acetyldehydrodipeptides can be increased by the formation of complexes with metal salts, which results in an increase in the excess of one of the diastereomers (*de*) formed in hydrogenation with achiral catalysts.[1,2]

In the present work we have continued the search for the factors that increase the rigidity of the molecule and, consequently, the diastereoselectivity of hydrogenation. We have chosen *N*-benzoyl derivatives, instead of *N*-acetyl derivatives of dehydrodipeptides, as substrates, since these compounds contain a more bulky group near the double bond subjected to hydrogenation.

N-Benzoyl derivatives of dehydrodipeptides were synthesized by the azlactone method starting from amino acids and 4-benzylidene-2-phenyloxazolone-5, which was, in turn, prepared from hippuric acid and benzaldehyde.



AA = Tyr, Pro, Met, Glu

It should be noted first of all that the results of the hydrogenation of free *N*-acetyl- and *N*-benzoyldehydrodipeptides on a Pd/C catalyst are substantially different (Table 1).

The presence of the *N*-benzoyl group has a significant effect on the hydrogenation of methionine and glutamic peptides. In fact, in the case of the *N*-acetyl derivative of the methionine-containing dehydrodipeptide, hydrogenation does not occur at all due to poisoning of the catalyst by the S atom of the methionine moiety of the substrate,[3] whereas in the case of the *N*-benzoyl derivative this effect does not manifest itself and hydrogenation of the substrate results in a 26 % excess of one diastereomer. For the glutamic acid containing dehydrodipeptide, the *de* increases from 10 to 52 % on going from the *N*-acetyl to the *N*-benzoyl derivative.

To elucidate the nature of this effect of the benzoyl group we carried out a comparative study of *N*-acyl substrates. The parameters of the ^1H NMR spectra of *N*-acyldehydrodipeptides in various solvents are listed in Table 2.

Based on the ^1H NMR spectroscopic data the following conclusions may be drawn.

1. The variation in the chemical shifts of the protons of both amide groups (a singlet and a doublet with

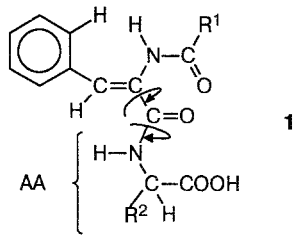
Table 1. The (*R,S*) : (*S,S*) diastereomeric ratio in the hydrogenation of *N*-acyl-ΔPhe-AA over Pd/C

N-acyl	AA			
	Tyr	Pro	Met	Glu
MeCO	53 : 47	59 : 41	*	45 : 55
PhCO	51 : 49	65 : 35	63 : 37	24 : 76

* No hydrogenation occurs.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 884—887, May, 1994.

Table 2. Parameters of the ^1H NMR spectra of *N*-acyldehydrodipeptides



1

R^1	AA	Solvent	δ					
			CH=	*o*-PhCH=	>CH—	MeCO, *o*-PhCO	NHCR^1	NHCR^2
Me[a]	Met	CD_3OD	7.16	7.50	4.70	2.10	9.64	8.31, 8.49
		$CDCl_3$	7.25	7.40	4.81	2.18	7.77	7.06
		$(CD_3)_2CO$	7.14	7.55	4.71	2.11	8.83	7.74
	Met — $PdCl_2$[b]	CD_3OD	7.21, 7.25	7.50(br)	4.69	2.16	9.60	8.30
Ph	Met	CD_3OD	7.34	7.54	4.72	8.00	10.02	8.36, 8.52
	Met— $PdCl_2$[b]	CD_3OD	7.32	7.58	4.80	7.98	[c]	8.44
Me	Pro	CD_3OD	6.48, 6.23	7.51	4.50, 4.90	2.07, 2.06	9.81	—
		$CDCl_3$	6.11	7.36	4.62	2.09	8.00, 8.26	—
		$CDCl_3$ (diluted fivefold)	6.17	7.40	4.67	2.12	7.61, 7.79	—
		DMSO-d_6	6.23, 6.02	7.55	4.24, 4.70	1.97	9.80, 9.83	
Ph	Pro	CD_3OD	6.76, 6.52	7.60	4.66, 5.0	8.00	[c]	—
Me	Tyr	CD_3OD	7.06	7.49	4.74	2.10	9.57	7.74, 8.11
		DMSO-d_6	6.99	7.52	4.40	1.98	9.41	7.92, 8.30
Ph	Tyr	CD_3OD	7.32	7.52	4.70	7.92	9.99	7.9
		CD_2Cl_2	7.12	7.50	4.78	7.85	8.18	6.81
		DMSO-d_6	7.21	7.55	4.44	7.99	9.94	7.99
Me	Glu	CD_3OD	7.13	7.40	4.59	2.18	[c]	8.23
Ph	Glu	CD_3OD[d]	7.35	7.50	4.59	7.96	9.96	8.29
		$CDCl_3$	7.21	7.40	4.73	7.86	7.78	
		DMSO-d_6	7.23	7.50	4.15	7.99	9.93	8.29

[a] Literature data.[3] [b] MeS signals: for R^1 = Me, two singlets at 2.32 and 2.42 ppm, for R^1 = Ph, a singlet at 2.22 ppm. [c] Fast deuterium exchange. [d] A shifting reagent causes a downfield displacement of signals, especially of those for the vinyl proton and the *ortho*-proton of the PhCO group (0.8 and 0.5 ppm, respectively).

$J_{NH,CH}$ = 8 Hz) in various solvents and their concentration dependences in inert media indicate that these protons do not form the N—H···O type hydrogen bonds that would predetermine the formation of chelates with metals.

2. The chemical shifts of the *ortho*-protons of the phenyl ring in the ΔPhe fragment are identical for all of the derivatives and are unaffected by the anisotropy of the acyl C=O group. This suggests that the arrangement of the *N*-acyl group corresponds to that shown for the structure of compound **1**.

3. In the spectra of all of the compounds except for the proline derivatives, the chemical shifts of the vinylic protons are nearly identical (7.1 ppm for *N*-acetyl de-

rivatives and 7.34 ppm for *N*-benzoyl derivatives). This attests to fast rotation around the C—C bond, which is denoted by the arrows in formula **1**. Rotations around the single C—C bond and, especially, around the C—N peptide bond (denoted by arrows) in the system are forbidden for some AA, which can be most clearly seen for proline derivatives. The rotation around the C—N peptide bond in dipeptides derived from other amino acids is also hindered, which accounts for the two doublets of unequal intensities for the N—H groups. However, the barrier is not high: at 50 °C coalescence of these signals occurs even in the case of the proline dipeptide.

The signal for the vinylic proton in the proline derivative is shifted upfield exactly by the magnitude of the anisotropy of the C=O bond, which attests to the absence of rotation (or hindered rotation) around the C—C bond. This is exhibited as a double set of signals (this fact has been discussed in detail previously[4]).

4. Hindered rotation about the C—C bond is observed as well when R^2 is a bulky substituent (for example, in the palladium complex of *N*-Ac-ΔPhe-Met formed with the participation of the S atom). This is indicated by splitting of the signal for the vinylic proton located in the neighborhood of this group.

The fact that *N*-Bz-ΔPhe-Met is hydrogenated in the presence of the palladium catalyst, while its acetyl derivative is not,[3] implies that the S atom in the former compound cannot coordinate with a Pd atom. As a consequence, the catalytic activity of Pd/C is retained (palladium is not poisoned by sulfur) and so is the ability of the substrate to undergo hydrogenation. The fact that the S atom in the Pd complex of *N*-Bz-ΔPhe-(*S*)-Met is not coordinated to palladium is supported by the absence of the downfield shift of the signal for MeS (2.22 ppm for both the Pd complex and the free molecule) in the ^{1}H NMR spectrum, whereas for the acetyl analog this downfield shift is ~0.3 ppm.[3]

Using the DESKTOP MOLECULAR MODELLER program to model the glutamic dipeptide molecule and minimize its energy showed that owing to the steric interaction of the O atom of the benzoyl group with the O atom of the peptide bond, the PhCO group is rotated with respect to the plane of the conjugated system of double bonds by ~30°. Due to this arrangement of the benzoyl group, the phenyl rings of the molecule form a "propeller". This results in an additional element of chirality, atropoisomerism, which contributes to the chiral induction and may be the cause of the difference in the diastereoselectivities of hydrogenation of the MeCO and PhCO derivatives.

The diastereoselectivity of hydrogenation of complexes derived from *N*-benzoyl derivatives with an achiral Pd/C catalyst practically does not differ from that observed for free dehydrodipeptides (Table 3), except for the proline-containing dehydrodipeptide, which, as has been shown above, exists in a form favorable for chelation.

Table 3. The (*R,S*) : (*S,S*) diastereomeric ratio in the Pd/C-catalyzed hydrogenation of complexes of *N*-Bz-ΔPhe-(*S*)-AA with salts of various metals

AA	Without a metal ion	Ca^{2+}	Mg^{2+}	Pd^{2+}
Glu	24 : 76	21 : 79	24 : 76	—
Met	63 : 37	63 : 37	—	64 : 36
Pro	65 : 35	70 : 30	75 : 25	—
Tyr	51 : 49	51 : 49	51 : 49	—

Table 4. The values of p*K* of the carboxyl group of *N*-Bz-ΔPhe-(*S*)-AA in the presence and in the absence of metal salts

Metal ion	Pro	Glu	Tyr	Met
—	8.4	8.15, 10.1	8.61	8.75
Ca^{2+}	6.95	6.85, 7.38	7.36	8.29
Mg^{2+}	8.2	7.92, 9.61	8.34	—

The formation of complexes involving the carboxyl group is typical of all of the peptides. The results of the potentiometric titration of *N*-Bz-ΔPhe-Pro and other peptides with sodium methoxide in 95 % aqueous methanol in the presence and in the absence of a metal salt are given in Table 4.

As can be seen from Table 4, in all of the cases the metal atom competes with the proton for the carboxyl group. This is especially pronounced for the Ca^{2+} ion and the proline-containing peptide. In this case, the increase in the acidity of the carboxyl group is as great as 1.45 p*K* units, like for the acetyl derivative.[4]

Thus, the diastereoselectivity of hydrogenation of the *N*-benzoyl derivatives of dehydrodipeptides studied in this work is practically unaffected by the possibility of the formation of chelate-type complexes with Ca, Mg, and even Pd ions, having a high affinity for sulfur (for the methionine-containing peptide). At the same time, in some cases the diastereoselectivity of hydrogenation increases due to induced atropoisomerism. The methyl group may be replaced by phenyl to increase the asymmetric induction in the hydrogenation of diastereotopic dehydrodipeptides.

Experimental

^{1}H NMR spectra were recorded on a Bruker WP-200 spectrometer with respect to TMS. Potentiometric measurements were carried out as described previously.[4]

***N*-Benzoyl derivatives of dehydrodipeptides** were prepared by the azlactone method, starting from hippuric acid and the corresponding amino acid according to the previously described procedure.[5]

***N*-Bz-ΔPhe-(*S*)-Met**, yield 68 %, m.p. 115 °C (from 10 % ethanol). Found (%): C, 61.21; H, 5.65; N, 6.72. $C_{21}H_{22}N_2O_4S \cdot H_2O$. Calculated (%): C, 60.60; H, 5.70; N, 6.73.

***N*-Bz-ΔPhe-(*S*)-Pro**, yield 57 %, m.p. 110 °C (from 10 % acetone). Found (%): C, 65.52; H, 5.41; N, 6.87. $C_{21}H_{20}N_2O_4 \cdot H_2O$. Calculated (%): C, 65.97; H, 5.75; N, 7.32.

***N*-Bz-ΔPhe-(*S*)-Glu**, yield 72 %, m.p. 111 °C (from 10 % acetone). Found (%): C, 60.86; H, 5.05; N, 6.63. $C_{21}H_{20}N_2O_6 \cdot H_2O$. Calculated (%): C, 60.87; H, 5.31; N, 6.76.

***N*-Bz-ΔPhe-(*S*)-Tyr**, yield 70 %, m.p. 125—127 °C (from 10 % ethanol). Found (%): C, 67.06; H, 5.15; N, 6.34. $C_{25}H_{22}N_2O_5 \cdot H_2O$. Calculated (%): C, 66.96; H, 4.91; N, 6.25.

Hydrogenation. 0.1 mmol of a metal salt was added to a solution of 0.1 mmol of dehydrodipeptide in 5 mL of abs. ethanol. The mixture was stirred for 1 h and 0.1 mmol of MeONa was added to it (except for the complex of *N*-Bz-ΔPhe-Met with $PdCl_2$). Then hydrogenation was carried out according to the previously described procedure.[2]

The diastereomeric composition of the hydrogenation products was determined as described in the literature[6] and from the ^1H NMR spectra. In the case of the methionine-containing dipeptide both signals for the CH_3S groups of diastereomers occur at 1.9 ppm; the assignment was carried out using enantiomeric GLC analysis.[6]

This work was carried out with the financial support of the Russian Foundation for Basic Research (Project 93-03-4646).

References

1. I. N. Lisichkina, A. I. Vinogradova, B. O. Tserevitinov, M. B. Saporovskaya, V. K. Latov, and V. M. Belikov, *Tetrahedron: Asymmetry*, 1990, **1**, 567.
2. I. N. Lisichkina, A. I. Vinogradova, N. B. Sukhorukova, E. V. Tselyapina, M. B. Saporovskaya, and V. M. Belikov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 601 [*Russ. Chem. Bull.*, 1993, **42**, 569 (Engl. Transl.)].
3. I. N. Lisichkina, A. I. Vinogradova, M. B. Saporovskaya, V. K. Latov, and V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2828 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 2592 (Engl. Transl.)].
4. I. N. Lisichkina, A. I. Vinogradova, N. B. Sukhorukova, M. B. Saporovskaya, and V. M. Belikov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1667 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1293 (Engl. Transl.)].
5. J. Grinstein and M. Vinits, in *Khimiya aminokislot i peptidov* [*Chemistry of Amino Acids and Peptides*], Mir, Moscow, 1965, 346 (Russ. Transl.).
6. M. B. Saporovskaya, L. M. Volkova, and V. A. Pavlov, *Zh. Anal. Khim*, 1989, **44**, 525 [*J. Anal. Chem.*, 1989, **44** (Engl. Transl.)].

Received December 12, 1993