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Correlation between the Configurational Structure and the Asymmetric Hydrogenation of Δ^1-, Δ^2-, and Δ^3-Dehydrotripeptides

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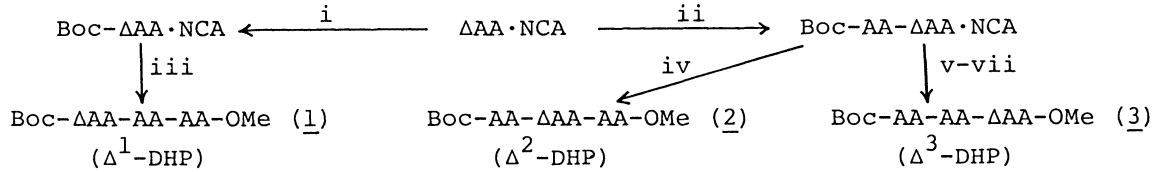
The heterogeneous catalytic hydrogenation of Δ^1-dehydrotripeptides (Δ^1-DHP), which have a β-turn structure, was carried out to give the corresponding tripeptides indicative of the very large diastereomeric excess, comparing with those from Δ^2- and Δ^3-DHPs. The efficient differences of the chiral inductions were found to be closely correlated to the configuration of the respective DHPs.

Recently, the many studies on the heterogenous catalytic hydrogenation of α-dehydroamino acids (DHA, ΔAA) and dehydropeptides, inclusive of cyclic dehydrodipeptides, have been reported, indicating that the hydrogenation gave sometimes rise to comparatively large asymmetric induction.[1-4] At present, however, it is not yet clear the reason why some of the linear dehydropeptides cause the large diastereomeric excess (d. e., %), i. e., chiral induction, except for the cyclic dehydrodipeptides.[4]

In this paper, we wish to report regarding the similar catalytic hydrogenation of N-t-butoxycarbonyl (Boc)-Δ^1-, Δ^2-, and Δ^3-dehydrotripeptide methyl esters (DHP: 1, 2, and 3) and the correlation among the separation facors (α-value) of diastereomeric mixture,[5,6] the d. e. of the hydrogenated tripeptides, and the configurational structures of the respective DHPs. The starting materials, 1, 2, and 3, were synthesized from ΔPhe·NCA and ΔLeu·NCA by the so-called ΔNCA (N-carboxy-α-dehydroamino acid anhydride) method reported earlier,[5,7] according to Scheme 1.



i) $(Boc)_2O$/pyridine. ii) Boc-AA-OH/DCC/pyridine. iii) H-AA-AA-OMe/MeOH
iv) H-AA-OMe/MeOH. v) MeOH. vi) HCl/MeOH. vii) Boc-AA-OH/DCC.

Sequence: a) Leu∿Ala, ΔPhe b) Ala∿Leu, ΔPhe
c) Leu∿Ala, ΔLeu d) Ala∿Leu, ΔLeu

Scheme 1.

In the preceding paper,[5] we have reported the convenient separation of

diastereomeric mixtures of various kinds of 1, 2, and 3 on high performance liquid chromatography (HPLC). As was already reported[5] and summarized briefly in Table 1, the total twenty four variations of dehydrotripeptides (1, 2, and 3) were synthesized and subjected to the HPLC separation, according to the following manner. The diastereomers of an appropriate DHP, which were derived from exactly equimolar mixture of (L)-(L) and (D)-(L) or (L)-(D) sequential structures, were separated on an HPLC column (4 Ø x 250 mm) packed Lichrosorb RP-18 (Merck) using a mixture of MeOH and H_2O (60 : 40 v/v) as the eluent. As the result, Δ^1-DHP (1) containing a DHA residue at the N-terminus was found to show considerably large α-value.

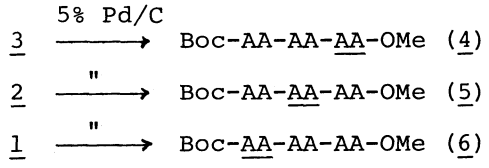
Table 1. Separation of Boc-(AA, AA, ΔAA)-OMe Containing a Racemic Alanine or Leucine Residue by HPLC

No.	Substrate, diastereomer mixture (DL)-Ala or Leu (Z)-ΔAA[a]	Separation factor (α)
3a, 3c	-Leu-Ala-ΔAA-	1.00
3b, 3d	-Ala-Leu-ΔAA-	1.00
2a, 2c	-Leu-ΔAA-Ala-	1.04
2b, 2d	-Ala-ΔAA-Leu-	1.04
1a, 1c	-ΔAA-Leu-Ala-	1.11
1b, 1d	-ΔAA-Ala-Leu-	1.26

a) ΔAA: a, c=ΔPhe, b, d=ΔLeu residue.

From the above results, it has became apparent that the differences of diastereomer separation of DHPs were closely related to their configurational structures. Consequently, we have concluded that the fairly large α-value of diastereomeric Δ^1-DHP, comparing with those of Δ^2- and Δ^3-DHPs, was due to the formation of the ten membered ring structure by the appreciably stable intramolecular hydrogen bonding between N-protecting acyl carbonyl group and the amide hydrogen atom of the C-terminal peptide bond (Fig. 1).

Subsequently, the twelve kinds of optically active DHPs (1, 2, and 3), prepared by the combinations of (L)-Ala, (L)-Leu, and (Z)-configurational ΔPhe or ΔLeu, were submitted to the following catalitic hydrogenation, according to Scheme 2. A solution of an appropriate DHP (10 mmol) in MeOH (30 ml) was hydrogenated catalytically with 5% Pd/C (50 mg) at 1.5 atmosphere and at room temperature for 6 h. After removing the catalyst, the reaction solution was then concentrated under reduced pressure at the temperature as lower as possible. The residual colorless syrup or crystals were dissolved in a small amount of MeOH and the resulting solution was sub-



AA=Hydrogenated AA from ΔAA residue.

Scheme 2.

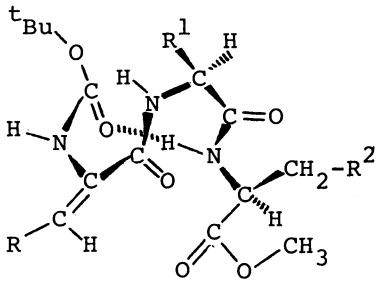
sequently subjected to the HPLC (Hitachi 438-50). The separations of the diastereomers of the obtained N-Boc-tripeptide methyl esters (4, 5, and 6) from 3, 2, and 1, respectively, were carried out on an HPLC column (4ø x 250 mm) packed Lichrosorb RP-18 using a mixture of MeOH and H_2O (60 : 40 v/v) as the eluent. The eluent was made to flow the column at rate of 0.1 ml/min at column temperature of 25 °C. The yields and d. e. of 4, 5, and 6 were summarized in Table 2.

Table 2. Asymmetric Hydrogenation of 1, 2, and 3

No.	Product Boc-(AA, AA, AA)-OMe[a)]	Yield %	Config. of AA residue	d.e./%
4	-Leu-Ala-Phe-	82	R	5.2
	-Ala-Leu-Phe-	90	R	4.1
	-Leu-Ala-Leu-	93	R	6.4
	-Ala-Leu-Leu-	95	S	2.4
5	-Leu-Phe-Ala-	80	S	16.2
	-Ala-Phe-Leu-	88	S	17.8
	-Leu-Leu-Ala-	90	S	16.8
	-Ala-Leu-Leu-	92	S	15.0
6	-Phe-Leu-Ala-	91	R	65.7
	-Phe-Ala-Leu-	85	R	81.5
	-Leu-Leu-Ala-	95	R	60.1
	-Leu-Ala-Leu-	98	R	80.1

a) AA=α-Amino acid residue derived by the hydrogenation.

As Table 2 shows, the hydrogenation proceeded very smoothly and the yields of the obtained tripeptides (4, 5, and 6) were fairly high to reach ca. 90%. Furthermore, very interestingly, it can be seen that there are very pronounced differences among the magnitude of d. e. of the respective tripeptides, thus obtained, according to the sequential position of DHA residue in the DHPs. Particularly, in the case of 6 from Δ^1-DHP (1), the d. e. was found to be extremely large to reach 60.1-81.5%, indicating the configuration of the hydrogenated AA residue to have R (D), whereas the d. e. and configuration of 5 from Δ^2-DHP (2) and 4 from Δ^3-DHP (3) show 15.0-17.8% [S (L)] and only 2.4-6.4% [R (D) or S (L)], respectively. In addition, surprisingly, it was found that the α-value of successive Δ^3-, Δ^2- and Δ^1-DHPs are closely proportional to the d. e., that is to say, to the degree of the asymmetric inductions, of 4, 5, and 6 respectively. Consequently, from the above results and fact reported



R=i-C_3H_7, C_6H_5.
R^1=CH_3, i-C_4H_9.
R^2=H, i-C_3H_7

Fig. 1.

previously,[5] it is clear that the high asymmetric induction by the hydrogenation of Δ^1-DHP is also intimately connected with its configurational structure, for example, cyclic structure. In fact, as was reported by Izumiya and collaborators,[4] in order to induce the high chirality to an arbitrary small dehydropeptide by the similar heterogenous hydrogenation, it is effective and essential to take rigidly cyclized structure having reasonably planar ΔAA moiety such as 3-alkylidene-2,5-piperazinedione.

The configuration of Δ^1-DHP was already proposed as β-turn structure,[5] as illustrated in Fig. 1. Even though the relative rigidity of the ring-structure of 1 caused by the intramolecular hydrogen bonding is naturally weaker than that of the cyclic dehydrodipeptides, in the case of Δ^1-DHP too, the moiety of C=C bond in DHA residue is thought to have come into contact effectively on the catalyst surface and caused higher chiral induction, compared with the cases of 2 and 3. Furthermore, then it can be seen that the bulkier the C-terminal AA residue is, the more the chiral induction increases. This reason is tentatively postulated that the bulkiness of the moiety on the α-carbon atom of the C-terminal AA residue has compelled the ring configurational structure to further flatten.

Moreover, in order to clarify the necessity of the ten membered ring structure mentioned above for the asymmetric hydrogenation, Boc-ΔPhe-Leu-Pro-OMe {mp 146-148 °C, $[\alpha]_D^{25}$ -80.6° (c 1.00 in MeOH)}, which has no hydrogen atom in C-terminal peptide bond, was chosen, followed by the similar hydrogenation. As a result, according to the expectation, the d. e. of the obtained tripeptide was found to be only an 18.4%, indicating the S (L) configuration. However, in the case of Boc-ΔPhe-Leu-Gly-OMe (syrup, $[\alpha]_D^{25}$ -25.7°), though the hydrogen atom was present in C-terminus, the d. e. by the asymmetric induction showed a fairly small to be only a 5.8%. From these results, it can be seen that the asymmetry of tripeptides derived from Δ^1-DHP were induced by the influence of the chirality of the C-terminal AA residue as well as the rigid ring-structure.

In conclusion, it is remarkable that the first systematic study regarding the heterogeneous catalytic hydrogenation of the linear dehydrooligopeptides could be accomplished resulting in the important and useful tendency for the relationship between the hydrogenation and the configurational structure.

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