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Research Note

Diastereoselective hydrogenation of a tricyclic α,β-dehydrodipeptide

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Abstract

An unsaturated diketopiperazine derivative with a tricyclic α,β-dehydrodipeptide structure was isolated as a reaction intermediate in the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide). The diastereoselective hydrogenation of this dehydrodipeptide was studied using various noble metals (Pd, Pt, Rh, and Ru) supported on charcoal. The hydrogenation over Pd, Rh, and Ru catalysts proceeded with a high diastereoselectivity (71–79%), and the diastereomer with the (*S*)-configuration on both chiral carbon atoms was formed preferentially. The reaction rates and diastereoselectivities of the hydrogenation over the Pd, Rh, and Ru catalysts were similar, while the platinum catalyst was much less active and selective (48% d.e.). The obtained results were compared with those of the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide); two different pathways for the hydrogenation of this molecule were suggested. In one path, cyclization already occurs after hydrogenation to the tetrahydropyrazine molecule, and in the other path cyclization occurs after full hydrogenation of the pyrazine molecule.

Keywords: Diastereoselective hydrogenation; Diketopiperazine; Proline auxiliary; Chiral cyclic dehydrodipeptide; Nonproteinogenic amino acids; Cyclic dipeptide

1. Introduction

Diketopiperazines corresponding to cyclic dipeptides represent a large group of compounds which exhibit a wide range of biological activity [1–3]. They occur widely in nature in the *cis*-configuration because they are biosynthesized from proteinogenic L-α-amino acids. A large number of natural diketopiperazines contain a proline structure, and the diversity of biological activity of this class of diketopiperazines is very impressive [4–9].

Our study of the diastereoselective hydrogenation of pyrazine derivatives [10] revealed the stereoselective formation of a new diketopiperazine derivative (Fig. 1a). This molecule corresponds to a cyclic dipeptide and consists of one proteinogenic (L-proline) and one nonproteinogenic (piperazine-2-carboxylic acid) amino acid. The structure of this molecule is described in detail in our previous paper [10]. Moreover, we found that the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) proceeds via an unsaturated diketopiperazine intermediate, which has the structure of a cyclic α,β-dehydrodipeptide (Fig. 1b). This intermediate was formed by an intramolecular *N*-acylation of the partially hydrogenated substrate. The intramolecular *N*-acylation of various dipeptide esters, resulting in the formation of a diketopiperazine ring, is a well-known reaction [11–14]. High yields of intramolecular cyclization were obtained under hydrogenation conditions over palladium on charcoal [15,16].

The diastereoselective hydrogenation of unsaturated diketopiperazine derivatives, which correspond to the cyclic α,β-dehydrodipeptides (Fig. 1c), was studied by several authors [17–26] in order to develop a general method for the stereoselective synthesis of α-amino acids. The chiral information was usually introduced by means of a natural amino acid, which then plays the role of chiral auxiliary. (*S*)-Proline was used to advantage as a chiral auxiliary (Fig. 1d) by several authors [19,20,22,25,26]. The palladium catalyst on charcoal was used most frequently and the obtained diastereoselectivities varied from 20 to 90%. Deuteration experiments of substituted diketopiperazine (R_1 = 1-methylethyl, R_2 = phenyl, R_3 = H) with different protecting groups (R_4 and R_5) showed that the presence and type of the protecting group strongly influence the stereoselectivity of the reaction and that the diastereomeric excess can even be reversed using a different protecting group [18].

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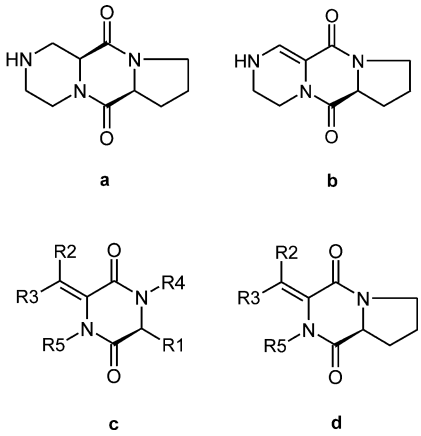

Fig. 1. Structures of diketopiperazine derivatives **a**–**d**.

The intramolecular cyclization and the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) were discussed simultaneously in our previous paper [10]. This research note focuses on a separate study of the diastereoselective hydrogenation of the cyclic α,β-dehydrodipeptide (Fig. 1b), which was isolated from the reaction mixture during the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide). The hydrogenation was carried out using various heterogeneous noble metal catalysts, and the influence of the nature of the catalyst on the reaction rate and the diastereoselectivity of the hydrogenation was investigated. The aim of the study was to determine the reaction rate and the diastereoselectivity of the hydrogenation step and to compare them with those of the simultaneous reaction. These results should provide us with greater insight into the mechanism of the hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide).

2. Experimental

All the organic chemicals were purchased from Fluka. The same analytical instrumentation and methods were used as in the study of the hydrogenation of pyrazine derivatives [10]. The NMR, XRD, GC-MS, and elemental analysis data of the reaction components are published ibidem [10]. The crystal structure of the prepared tricyclic α,β-dehydrodipeptide was determined on a single crystal 4-circle X-ray diffractometer (Picker) with an upgrade from Stoe. The diastereoselectivity of hydrogenation was determined by GC and the diastereomeric excess (d.e.) was defined as: d.e. $=$ ([*R*, *S*-diastereomer] $-$ [*S*, *S*-diastereomer])/([*R*, *S*-diastereomer] $+$ [*S*, *S*-diastereomer]) $\times$ 100. The enantiopurity of all the compounds and the enantioselectivity of all the reaction steps were confirmed by a chiral HPLC (Agilent 1050 Series LC system, Daicel chiral column Chiracel OD-H, mobile phase:hexane: 2-propanol with a ratio from 90:10 to 70:30 used for the analyses of different compounds).

2.1. Synthesis of the pyrazine-2-(methyl-(S)-prolinecarboxamide)—α, β-dehydrodipeptide precursor

The description of the synthesis of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) is given elsewhere [10]. There was one difference; i.e., the precursor of the carboxamide, the methyl ester of (*S*)-proline, was not purchased but prepared by esterification with thionyl chloride in methanol. Similarly, a racemic proline methyl ester was prepared. Moreover, we carried out all further reaction steps using the racemic proline auxiliary in order to prove that no racemization takes place. The racemic samples were used as chromatographic standards for chiral HPLC separation.

2.2. Preparation of tricyclic α, β-dehydrodipeptide— The substrate for the hydrogenation

The tricyclic α,β-dehydrodipeptide was prepared by partial hydrogenation of pyrazine-2-(methyl-(*S*)-prolinecarboxamide). The reaction was carried out in a 60-ml stainless-steel autoclave (Medimex AG) equipped with a sampling tube and magnetic gas-inducing impeller. In a typical experiment, 1 g of pyrazine-2-(methyl-(*S*)-prolinecarboxamide) was dissolved in 30 ml methanol, and 350 mg of 10% Pd/C was added. The reaction was carried out at 50 °C and 5 MPa hydrogen pressure. The reaction was monitored by analyzing the samples withdrawn from the reaction mixture during hydrogenation. The reaction was stopped at about the maximum concentration of the unsaturated tricyclic α,β-dehydrodipeptide intermediate. The catalyst was filtered off, the solvent evaporated, and the raw reaction mixture separated by column chromatography (methanol:chloroform, 3:1). The isolated tricyclic α,β-dehydrodipeptide was purified by recrystallization from methanol, and its crystal structure was determined by X-ray diffraction analysis.

2.3. Diastereoselective hydrogenation

The diastereoselective hydrogenation of tricyclic α,β-dehydrodipeptide was carried out using the same noble metal catalysts as in our previous work [10]. The same types of Pd/C, Pt/C, Ru/C, Rh/C, and Rh black were used. To compare the data of both studies, we used the same equipment, procedures, and reaction conditions. The substrate-to-metal molar ratio was also kept at the same level S/M $\sim$ 23.

3. Results and discussion

3.1. Preparation of the tricyclic α, β-dehydrodipeptide

The first step in the synthesis of the substrate to study the diastereoselective hydrogenation was the preparation of a chiral auxiliary, the methylester of (*S*)-proline (**1**). A simple esterification with thionyl chloride and methanol provided a

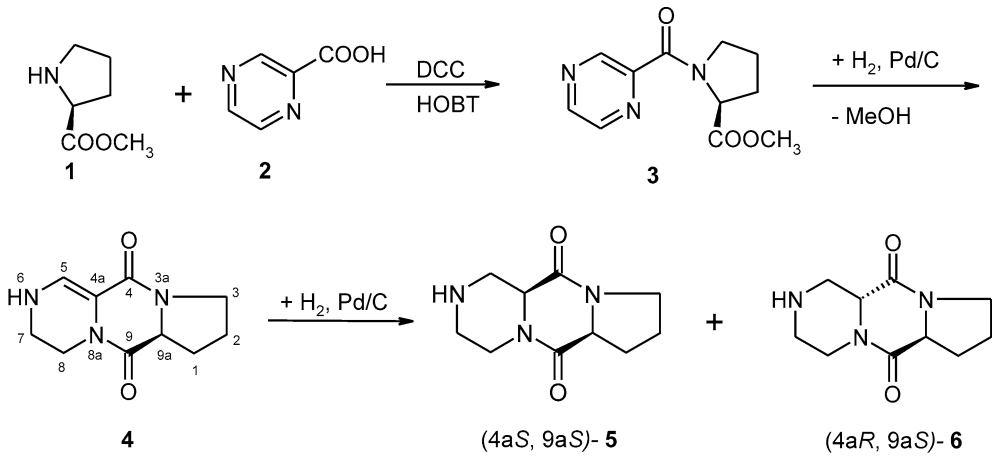

Fig. 2. Reaction scheme of the synthesis of the cyclic α,β-dehydrodipeptide and its diastereoselective hydrogenation.

95% yield. The second step was the coupling of pyrazine-2-carboxylic acid (**2**) with the (*S*)-proline methyl ester (**1**) to form pyrazine-2-(methyl-(*S*)-prolinecarboxamide) (**3**) (Fig. 2). This reaction also gave a very high yield of 85%. The products of the esterification as well as of the coupling were subjected to a chiral HPLC. The comparison with their corresponding racemic mixtures proved that both reactions proceeded without racemization and that the enantiopurity of (**1**) and (**3**) was higher than 99%. The tricyclic α,β-dehydrodipeptide (**4**) was then obtained by partial hydrogenation of (**3**) followed by intramolecular cyclization. At the same time, a methanol molecule was formed as the product of splitting the ester group of the proline auxiliary. The intramolecular cyclization was probably fast, because we did not observe the formation of a partially hydrogenated substrate or of a noncyclic saturated product. The main by-product of this reaction had a similar mass spectrum as the cyclic dehydrodipeptide (**4**), but the molecular weight was lower by two masses. Therefore, we assume that it has the same tricyclic dehydrodipeptide structure (**4**) but with an additional double bond, between N(6)–C(7) or C(7)–C(8), in the tetrahydropyrazine ring. The concentration of this by-product in the reaction mixture was below 10%. The reaction was carried out under milder reaction conditions than the diastereoselective hydrogenation of (**1**) to (**5**) and (**6**) in order to stop the reaction close to the maximum concentration of the dehydrodipeptide (**4**). After the separation and recrystallization of (**4**), its structure was confirmed by ^{13}C and ^{1}H NMR measurements. The chiral HPLC proved that this reaction, too, proceeded without racemization. Moreover, an X-ray diffraction analysis of a prepared single crystal was carried out. The structure is almost flat and very similar to the structure of the final hydrogenation product [10].

3.2. Diastereoselective hydrogenation

The diastereoselective hydrogenation of the α,β-dehydrodipeptide (**4**) proceeds to a mixture of two saturated diastereomers, (4a*S*, 9a*S*)- and (4a*R*, 9a*S*)-octahydro-3a,6,8a-triazacyclopenta[*b*]naphthalene-4,9-dione (**5** and **6**) (Fig. 2). One of the diastereomers prevails in the reaction mixture. This diastereomer was isolated and its configuration on the chiral carbon atoms C-4a and C-9a was assigned to (4a*S*, 9a*S*) in our previous work [10]. Furthermore, we carried out the chiral separation of the final diastereomers, which confirmed that no racemization of the proline moiety took place during the diastereoselective hydrogenation.

Table 1 presents the effect of different noble metal catalysts (Pd, Rh, Pt, and Ru) on the hydrogenation of the dehydrodipeptide (**4**). The experiments were carried out under the same reaction conditions as during the hydrogenation of the pyrazine derivative (**3**) in order to facilitate a comparison of the results of both studies. The activities of the catalysts are reported as integral turnover frequency at 50% conversion of the substrate. It is important to remember that, while the reaction of the pyrazine derivative is a complex reaction and includes hydrogenation as well as ring formation, the hydrogenation of the dehydrodipeptide (**4**) is a simple one-step reaction. The reaction time, defined as the time at which 100% conversion of (**4**) was reached, is also presented. The main by-products consist of two saturated diastereomers with the same structure as the product but methylated at the secondary nitrogen atom (N-6). Their ratio corresponds roughly to the ratio of the diastereomers (**5** and **6**), and they were formed by the reaction of the products with the solvent [10].

Table 1
Hydrogenation of α,β-dihydrodipeptide (**4**) in methanol at 80 °C and 8 MPa over different noble metal catalysts

Catalyst	TOF at 50% conversion (h^{-1})	Reaction time (h)	By-products (%)	d.e. (%)
Pd/C	36.0	1.1	< 3	79
Pd/C[a]	41.6	0.8	< 1	83
Rh/C	43.4	0.7	< 2	77
Pt/C	11.7	7.8	13	48
Ru/C	39.4	0.8	< 2	71
Rh-black	16.3	2.8	< 5	75

[a] Water as solvent.

Table 1 shows that the activity and the diastereoselectivity of Pd/C, Rh/C, and Ru/C were similar during the hydrogenation of the dehydrodipeptide (**4**). The highest TOF as well as the shortest reaction time were obtained with the rhodium catalyst; diastereoselectivity decreased slightly in the following order: Pd/C > Rh/C > Ru/C. The lowest activity as well as the lowest diatereoselectivity were obtained with the platinum catalyst. The highest content of by-products was also observed with the platinum. The difference between the rhodium catalyst supported on charcoal and unsupported rhodium black consisted mainly of a lower reaction rate obtained with unsupported rhodium. The content of by-products increased slightly and the diastereoselectivity remained almost the same with the rhodium black.

The diastereoselectivity obtained during the hydrogenation of the dehydrodipeptide (**4**) was significantly higher over all the catalysts than that obtained during the hydrogenation of the pyrazine derivative (**3**). This is probably because the reaction does not proceed 100% via the dehydrodipeptide intermediate (**4**). The pyrazine derivative may be hydrogenated first to the tetrahydropyrazine derivative. Part of this will undergo cyclization to (**4**), while the other part will be fully hydrogenated before cyclization takes place. The stereoselectivity of the C(4)–C(4a) bond will depend on the conformational freedom of the intermediate that precedes the final hydrogenation step. The stereoselectivity will be higher when the final hydrogenation occurs in the rigid dehydrodipeptide (**4**) structure. This dehydrodipeptide will preferentially adsorb with one of its two diastereotopic faces on the catalyst and, thus, the formation of only one diastereomer is favored. As a consequence, the final diastereoselectivity in the hydrogenation of the pyrazine derivative (**3**) will depend on the rate of further hydrogenation versus the rate of cyclization of the tetrahydropyrazine derivative. This is also supported by our former results [10], which show that there is a relationship between the final diastereoselectivity and the maximum concentration of the dehydrodipeptide intermediate. Moreover, the diastereoselectivity was increasing at the beginning of the hydrogenation of the pyrazine derivative [10]. This may also indicate that the pyrazine substrate (**3**) was fully hydrogenated before cyclization could occur. On the other hand, the diastereoselectivity remained constant during the hydrogenation of the dehydrodipeptide (**4**). Therefore, the explanation that an increased d.e. results from the modification of the catalyst surface with the chiral reaction intermediates or products, which are strongly adsorbed on the surface and influence the mode of adsorption of the substrate, seems unlikely.

A comparison of the TOF data obtained during the hydrogenation of the pyrazine derivative [10] with the TOF data of the hydrogenation of the cyclic α,β-dehydrodipeptide over Pd/C, Rh/C, and Pt/C (Table 1) shows that the latter TOF data are lower. This was expected, because the hydrogenation of a double bond conjugated with a carbonyl group is more difficult than the partial hydrogenation of a pyrazine ring [27]. The lowest TOF, obtained with Pt/C, was approximately four times lower than the TOF during the hydrogenation of the pyrazine derivative; the reaction time was almost double.

In contrast, the TOFs of the hydrogenation of the dihydrodipeptide over Ru/C and Rh black were higher than during the hydrogenation of the pyrazine derivative. For these catalysts, the hydrogenation of the pyrazine derivative seems to be inhibited by the substrate itself or by partially hydrogenated intermediates. A possible explanation is that the cyclization reaction is slower with these catalysts and that the hydrogenation of a noncyclic partially hydrogenated pyrazine derivative is more difficult to achieve than the hydrogenation of the dehydrodipeptide.

In the previous study we found that water as a solvent has a beneficial influence on the reaction rate as well as on the diastereoselectivity. Therefore, we tested water as a solvent also during the hydrogenation of the dehydrodipeptide over the palladium catalyst. The TOF of the reaction increased slightly, and the reaction time was shorter when water was used as a solvent (Table 1). The diastereoselectivity was also somewhat higher than with methanol and almost no by-products were formed. The slight difference in TOF compared with the large change during the hydrogenation of the pyrazine derivative indicates that the solvent mainly influences the cyclization reaction and that its influence on the hydrogenation is much weaker.

4. Conclusion

The study of the diastereoselective hydrogenation of the cyclic α,β-dehydrodipeptide showed that high diastereoselectivity can be obtained over noble metal catalysts. Pd/C, Rh/C, and Ru/C were the most active as well as the most selective catalysts for this reaction. The activity of Pt/C and Rh black catalysts was much lower. The lowest d.e. as well as the largest amount of by-products were obtained with the Pt/C catalyst. This corresponds to our former results of the hydrogenation of the pyrazine derivative. The reaction rates and the diastereoselectivities obtained during the hydrogenation of the pyrazine derivative over Pd/C were considerably higher than over the other catalysts. On the other hand, similar reaction rates and diastereoselectivities were obtained with Pd/C, Rh/C, and Ru/C during the hydrogenation of dehydrodipeptide. The main reason for this might be that the cyclization reaction on palladium was much faster than on the other catalysts and that a greater molecular rigidity of the dehydrodipeptide facilitates the differentiation of the two diastereotopic faces on the metal surface of the catalyst and thus increases diastereoselectivity.

A comparison of the results of both studies suggests that the hydrogenation of the pyrazine derivative only partly proceeds via the dehydrodipeptide and that the ratio between the reaction rates of cyclization and hydrogenation influences the final diastereoselectivity.

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Appendix

Supplementary crystallographic data are available at the Cambridge Crystallographic Data Centre (CCDC) (reference number CCDC 195739). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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