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Diastereoselective and enantioselective heterogeneous catalytic hydrogenation of aminocinnamic acid derivatives

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Abstract

Various kinds of aminocinnamic acid derivatives were hydrogenated with different stereoselectivities. In the presence of cinchonidine or (−)-dihydroapovincaminic acid ethyl ester modifiers, the enantioselective hydrogenations resulted in very low enantiomeric excesses (ee). Moderate diastereomeric excesses (de, 5–68%) were achieved in the diastereoselective hydrogenations. The highest de (68%) was obtained in the hydrogenation of *N*-acetyldehydrophenylalanyl-(*S*)-prolinanilide due to a 10-member intermediate stabilized by hydrogen bond.

Keywords: Asymmetric; Diastereoselective; Heterogeneous catalytic hydrogenation; Aminocinnamic acid

1. Introduction

Stereoselective hydrogenations can be divided into two main groups: enantioselective and diastereoselective reactions. In few cases, the enantioselective route is more effective, but more examples can be found for diastereoselective reductions.

Cinchonidine was used as a chiral auxiliary in the saturation of C=C bond of (*E*)-α-phenylcinnamic acid. The reported optical yield of (*S*)-(+)-2,3-diphenylpropionic acid was 30.5% [1]. In the hydrogenation of the same molecule with cinchonidine modified 5% Pd/TiO_2, in the mixture of dimethylformamide and water, the highest optical yield was 72% [2].

A newly found modifier is the (−)-dihydroapovincaminic acid ethyl ester. Using Pd black catalyst in the hydrogenation of C=C bond of isophorone, the highest enantiomeric excess (ee) was 55% [3,4].

In diastereoselective reactions, the starting molecule should contain an asymmetric carbon atom. A review was published recently about

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the synthesis of chiral amino acids and amines over solid catalysts. Several examples can be found here concerning the diastereoselective hydrogenation of C=C bonds [5]. Didehydrodipeptides containing prolinamides were hydrogenated with high diastereoselectivity [6]. The preferred didehydrodipeptides were prepared from 4-benzylidene-2-phenyl-5(4*H*)-oxazolone and proline methyl amide. The observed diastereomeric excess (de) values were over 75% under various reaction conditions.

Relatively high optical purities were obtained in the hydrogenations of chiral α- and β-methylcinnamates over different types of catalysts. Platinum catalysts provided ca. 40% optical purity, palladium ones 50%, whilst Raney-Ni 60–70% [7].

In the present study, we compared the diastereoselective hydrogenations of some *N*-acylaminocinnamic acid derivatives with the enantioselective hydrogenation of *N*-acyldehydrophenylalanines in order to find out which is the more effective stereoselective preparation method of phenylalanine derivatives.

In the enantioselective reactions, the effect of different modifiers, solvents, catalyst supports and pressure on ee was investigated. On the basis of the diastereoselective hydrogenation results, structural considerations were made.

2. Experimental

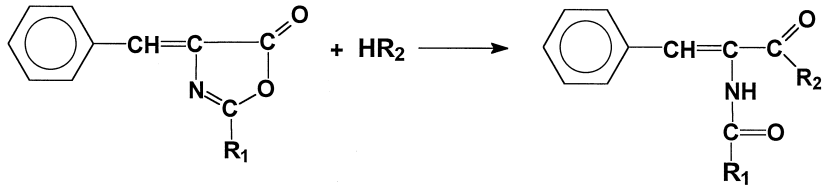
2.1. Materials

The starting materials for the enantioselective hydrogenations were prepared from azlactones, such as 4-benzylidene-2-methyl-5(4*H*)-oxazolone and 4-benzylidene-2-phenyl-5(4*H*)-oxazolone. The oxazolones were made by the classical Erlenmeyer method [8]. To obtain the 2-acetylaminocinnamic acid (**1**) and the 2-benzoylaminocinnamic acid (**2**), the azlactone ring was opened by heating the corresponding oxazolone in a stirred, 1 M sodium hydroxide solution. The oxazolone ring was hydrolyzed at 80°C, the solution was cooled to room temperature and its pH value was adjusted to 2–3 by addition of conc. HCl. The precipitated cinnamic acid derivatives were filtered, washed with distilled water and dried.

The substrates for the diastereoselective hydrogenations were prepared in the following way (Scheme 1).

Three compounds, the *N*-acetyldehydrophenylalanyl(*S*)prolinedimethylamide [**3**, R_1 = methyl, HR_2 = (*S*)prolinedimethylamide], the *N*-acetyldehydrophenylalanyl-(*S*)-prolinanilide [**4**, R_1 = methyl, HR_2 = (*S*)-prolinanilide] and the *N*-benzoyldehydro-phenylalanyl-(*S*)-prolinanilide [**5**, R_1 = phenyl, HR_2 = (*S*)-prolinanilide) were prepared as follows. The corresponding oxazolone (0.01 mol) was dissolved in 20 ml dioxane and the HR_2 reactant (0.01 mol) was added gradually. The solution was stirred for 24 h at room temperature and for additional 2 h under reflux. The dioxane was distilled off in vacuum. The product crystallized from the retained oily material during a few days. The (*S*)-proline dimethyl amide and (*S*)-prolinanilide were prepared as described in Ref. [9].

Three additional compounds were also prepared. *N*-Acetyldehydrophenylalanyl-α-methylbenzylamide [**6**, R_1 = methyl, HR_2 = (*S*)-α-methylbenzylamine], *N*-acetyldehydropheny-



Scheme 1. Preparation of substrates for the diastereoselective hydrogenations.

lalanyl-1-hydroxy-2-butylamide [**7**, R_1 = methyl, HR_2 = (*S*)-1-hydroxy-2-butylamine] and *N*-acetyldehydrophenylalanyl ethyl lactate ester [**8**, R_1 = methyl, HR_2 = (*S*)-ethyl lactate]. An amount of 0.1 mol 4-benzylidene-2-methyl-5(4*H*)-oxazolone was dissolved in 150 ml dioxane and 0.1 mol corresponding HR_2 reactant was added gradually while stirring. In the preparation of **6**, the product was precipitated after stirring for 20 min, then filtered and dried. When **7** was prepared, the reaction solution was stirred for 24 h, the dioxane was distilled off in vacuum and the product was recrystallized from ethyl acetate. During the preparation of **8**, a small amount of sodium methylate was added to the reaction mixture, which was stirred for 24 h. The dioxane was distilled off in vacuum and the product was recrystallized from *n*-hexane.

The catalysts used were partly commercial products: 10% Pd/C Selcat [10] (Fine Chemical, Budapest, Hungary), 5% Pd/Al_2O_3 and 5% $Pd/BaSO_4$ (Aldrich, Steinheim, Germany). The 5% Pd/TiO_2 catalyst was prepared by the same method as Pd/C Selcat type catalysts [10].

2.2. Hydrogenations

The hydrogenations were carried out in a conventional apparatus under atmospheric pressure or in a Büchi BEP 280 autoclave equipped with a magnetically driven turbine stirrer and a gas-flow controlling and measuring unit. In the hydrogenation of **1** and **2**, the reaction mixtures were worked up as follows. The catalyst was filtered, the solvent was distilled off in vacuum. The residue was dissolved in dichloromethane then extracted with 10% HCl solution and distilled water in order to remove the remainder of chiral modifiers. The organic phase was separated and dried over Na_2SO_4. After the removal of the solvent, the afforded crude product was analyzed.

The ee values were calculated from the optical rotational data based on the value of $[\alpha]_D^{20} = 40.1°$ for optically pure *N*-acetyl-(*S*)-phenylalanine and that of $[\alpha]_D^{20} = -41.4°$ for optically pure *N*-benzoyl-(*S*)-phenylalanine, respectively.

During working-up procedure of the reaction mixtures in the diastereoselective hydrogenations, the catalyst was filtered and the solvent was removed in vacuum. The retained products were analyzed and the de values were either determined by HPLC [in case of **3**, **4**, **5**] or from the nuclear magnetic resonance (NMR) spectra [in case of **6**, **7**, **8**].

2.3. Analysis

The HPLC analyses were carried out on a Purosphere® RP 18-e column (125 mm × 4 mm) using gradient elution method. The starting eluent was 10% acetonitrile and 90% water and the gradient was 10 → 100% in 15 min (with respect to acetonitrile). The UV absorbance was measured at 220 nm.

The NMR spectra were recorded on a Bruker DRX500 spectrometer, in $CDCl_3$.

Optical rotational data were measured with a Perkin-Elmer 241 automatic polarimeter ($c = 5$, MeOH).

3. Results and discussion

3.1. Enantioselective hydrogenations

In the presence of cinchonidine or (−)-dihydroapovincaminic acid ethyl ester chiral modifiers, the enantioselective hydrogenations of **1** and **2** resulted in very low enantiomeric excesses. The reductions were carried out over

Table 1
Diastereoselective hydrogenation of **6**, **7** and **8**

Number	Substrates	Reaction time (h)	Conversion (%)	de (%)
1	**6**	1.5	90	10.9
2	**7**	1.5	95	12.6
3	**8**	1.0	95	5.4

Conditions: 0.01 mol substrate, 50 ml methanol, 10% Pd/C (Selcat), catalyst/substrate ratio: 0.1, atmospheric pressure.

Table 2
Hydrogenation of **6** over different supported palladium catalysts

Number	Catalyst type	Pressure (bar)	Reaction time (h)	de (%)
1	10% Pd/C	1.0	1.5	10.9
2	5% $Pd/BaSO_4$	5.5	1.2	10.9
3	5% Pd/Al_2O_3	5.6	1.0	11.1

Conditions: 0.01 mol substrate, 50 ml methanol, catalyst/substrate ratio: 0.1.

Table 3
Diastereoselective hydrogenation of **3**, **4** and **5**

Number	Substrates	Reaction time (h)	Conversion (%)	de (%)
1	**3**	7	75	36
2	**4**	8	80	68
3	**5**	8	70	50

Conditions: 1.0 g substrate, 0.2 g 10% Pd/C (Selcat), 50 ml toluene, 10 bar.

different supported palladium catalysts (Pd/C and Pd/TiO_2), either in dimethylformamide/water mixture or in methanol and under various hydrogen pressure (1–50 bar), respectively.

Despite the systematic changing of reaction conditions (catalyst, solvent, pressure and chiral modifier) the ee values have never exceeded 2%, i.e., the asymmetric induction was very small in these substrate–modifier–catalyst systems.

3.2. Diastereoselective hydrogenations

The results of the diastereoselective hydrogenation of **6**, **7** and **8** are shown in Table 1. These reductions resulted in low diastereomeric excesses (5.4–12.6%). In these compounds, the chiral carbon atom is located relatively far from the prochiral carbon one and the molecules are quite flexible; therefore, the asymmetric induction is moderate.

The effect of the catalyst support on de was also investigated. The results are summarized in Table 2. As seen, almost similar de values (10.9–11.1%) were achieved in the hydrogenation of **6** over palladium on carbon, $BaSO_4$ or Al_2O_3, i.e., the catalyst support has no influence on the diastereoselectivity.

Contrary to the previous low diastereomeric excesses, relatively high de values were obtained in the hydrogenation of **3**, **4** and **5** (Table 3). The highest de was 68%, which was observed in the reduction of **4** over 10% Pd/C catalyst, in toluene. These significant differences between the de values can be attributed to structural causes, which will be discussed in Section 3.3 in detail.

3.3. Structural considerations

According to the NMR spectra, compounds **6**, **7** and **8** are pure *Z* isomers. Substances **4** and **5** are also pure *Z* isomers but the detailed NMR

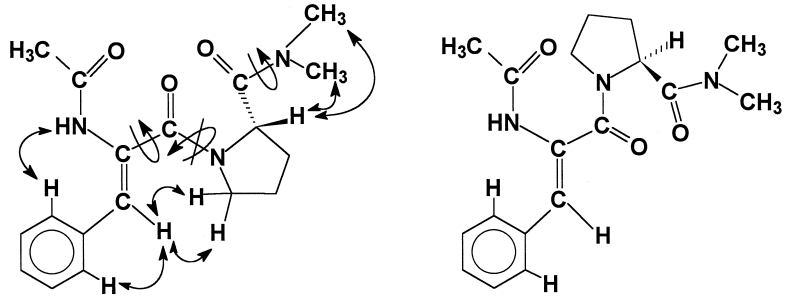


Fig. 1. The two rotational isomers of **3**. Double-headed arrow curving from left to right: hydrogen–hydrogen interaction. Curved arrow pointing upward: rotation.

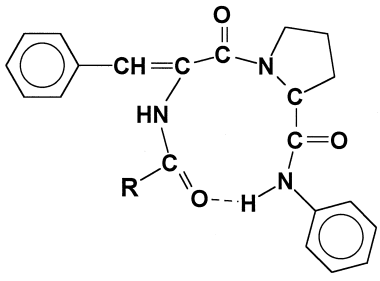


Fig. 2. The presumed 10-member ring of **4** and **5**.

studies showed that **3** contains two rotational isomers in 73–27% ratio (Fig. 1.). In this molecule, the rotation is hindered around the bond between the proline nitrogen atom and the acid carbon atom of the cinnamic acid. On the basis of the nuclear Overhauser effect (NOE) measurements, the hydrogen–hydrogen interactions are also depicted. In case of compounds **4** and **5**, only one rotational isomer can be detected, presumably due to the more bulkier anilide group.

The de values of **4** and **5** are higher than that of the prolinedimethylamide derivative. This can be interpreted by the 10-member ring hypothesis [6]: there is a possibility in molecule **4** or **5** to form a 10-member ring where hydrogen bond exists between the amide nitrogen and the carbonyl group of the *N*-acyl part of the didehydroamino acid (Fig. 2).

In consequence of the stabilized conformation of this ring, the adsorption on the catalyst surface is more uniform. Therefore, the diastereomeric excess is higher (68%) than in the hydrogenation of molecules without possible ring formation. Since in molecule **3** no hydrogen is attached to the amide nitrogen, the ring cannot be formed; thus, in adsorption state, the conformation is not uniform and the diastereomeric excess is lower (36%).

4. Conclusions

In the stereoselective heterogeneous catalytic hydrogenation of some aminocinnamic acid derivatives, different ee and de values were obtained over various supported palladium catalysts. Comparing the stereoselectivities in these hydrogenations, the asymmetric induction, as usual, was much higher in the diastereoselective hydrogenations than in the enantioselective ones.

As known, the enantioselective hydrogenation of phenylcinnamic acid resulted in good optical yield. The molecular models of phenylcinnamic acid and *N*-acetylaminocinnamic acid demonstrate that the structure of the former is much more rigid (Fig. 3). This can be responsible for the much larger asymmetric induction in the enantioselective hydrogenation of it.

In the diastereoselective hydrogenations, the presence of rigid, ring-forming substituents (e.g., proline) in the substrates are preferred and such

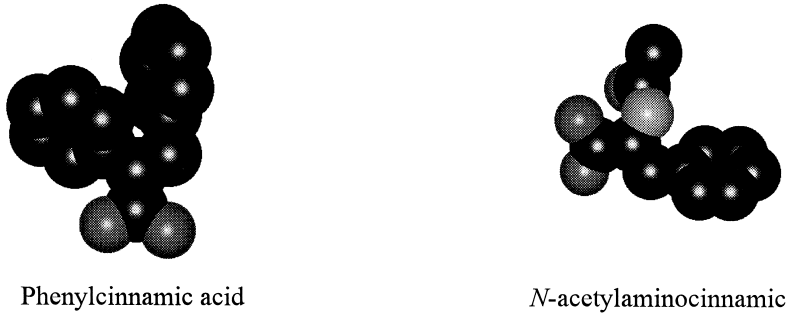


Fig. 3. Molecular models of two cinnamic acid derivatives.

intermediates are advantageous which can form a stabilized ring (via hydrogen bond).

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References

[1] J.R.G. Perez, J. Malthete, J. Jacques, C.R. Acad. Sci. Paris, Ser. II 5 (1985) 169.
[2] Y. Nitta, K. Kobiro, Chem. Lett. (1996) 897.
[3] T. Tarnai, A. Tungler, T. Máthé, J. Petró, R.A. Sheldon, G. Tóth, J. Mol. Catal. A 102 (1995) 41.
[4] A. Tungler, K. Fodor, T. Máthé, R.A. Sheldon, Stud. Surf. Sci. Catal. 108 (1997) 157.
[5] A. Tungler, K. Fodor, Catal. Today 37 (1997) 191.
[6] U. Schmidt, S. Kumpf, K. Neumann, J. Chem. Soc., Chem. Comm. (1994) 1915.
[7] L. Horner, H. Ziegler, H.D. Ruprecht, Liebigs Ann. Chem. (1979) 341.
[8] Org. Synth. Coll., Vol. II, Wiley, New York, 1943, p. 11.
[9] E. Öhler, E. Prantz, U. Schmidt, Chem. Ber. 111 (1978) 1069.
[10] T. Máthé, A. Tungler, J. Petró, U.S. Patent 4-361-500, 1982.