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Chemo- and Diastereoselectivity in the Heterogeneous Catalytic Hydrogenation of 2,2′-Pyridoin and Its Derivatives

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The heterogeneous catalytic hydrogenations of 2,2′-pyridoin and related compounds, such as 2,2′-pyridil and *O*-acetyl-2,2′-pyridoin, were investigated over noble metal catalysts. The influence of catalytic metals, catalyst supports, solvents, acid additives, prehydrogenation, and hydrogen pressure on the chemo- and diastereoselectivity is discussed in the hydrogenation of 2,2′-pyridoin. Although hydrogenolysis and ring saturation may occur as side reactions, high chemo- (90–100%) and moderate diastereoselectivity values were achieved. Over palladium black in an acetonitrile–water solvent mixture, the hydrogenation resulted in a *meso*/*dl* ratio of 72/28, while in the hydrogenation over rhodium on carbon the *meso*/*dl* ratio was 29/71. The phenomenon of diastereoselection in the hydrogenation is explained by the stereochemistry of the hydrogen addition, considering the *cis–trans* isomerization on the catalyst surface, the possible enolization, and the competing C=C and C=O reductions.

Key Words: **heterogeneous catalytic hydrogenation; C=C and C=O double bonds; diastereoselectivity; *cis–trans* isomerization; hydrogenolysis.**

INTRODUCTION

2,2′-Pyridoin has been clearly established as being 1,2-di(2-pyridyl)-1,2-ethenediol by infrared studies (1). In neutral, acidic, or alkaline solution 2,2′-pyridoin exists to 93–98% as 1,2-di(2-pyridyl)-1,2-ethenediol, as proved by titration with Tillmann's reagent (2). As a matter of fact, in the hydrogenation of 2,2′-pyridoin mainly the saturation of C=C double bond occurs.

The stereochemistry of hydrogen addition to the C=C bond has long been of interest (3–5). The suprafacial (*syn*) addition of hydrogen is the most accepted mechanism for metal-catalyzed hydrogenations (Langmuir–Hinshelwood mechanism) (6). *Syn* addition nearly always takes place with palladium, rhodium, or ruthenium, but over platinum antarafacial (*anti*) addition of hydrogen was taken into account, too (7). Antarafacial addition can be favored by strong acids (8).

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In the hydrogenation of C=C double bonds it was observed that *cis* isomers are usually reduced more rapidly than the corresponding *trans* isomers. Rates can depend on the type of compound used, on substitution at the double bond, and on the catalyst. It was noted that unsaturated *cis* acids were more strongly adsorbed on platinum black than the *trans* acids and were also reduced more rapidly (9). The hydrogenation of symmetrical butenes over palladium on carbon gave similar results (10). During hydrogenation of the double bond *cis–trans* isomerization can also take place, which is dependent on the catalyst and reaction medium. Noble metal catalysts show marked differences in promoting olefin isomerization (11). The following decreasing isomerization activity was found: Pd ≫ Rh > Ru > Pt (12–14).

Both symmetrical and unsymmetrical pyridylglycols have great synthetic utility; several compounds of these series possess valuable and specific adrenal cortical inhibitory activity. Hence, photochemical, electrochemical, microbial, and metal reduction have been employed to prepare these diols. The reductive pinacolization of 2-pyridinecarboxaldehyde (picolinaldehyde) by titanium trichloride in acetic acid gave 78% 1,2-di(2-pyridyl)ethanediol (hydropyridoin) with a 58/42 *meso*/*dl* ratio (15). The reductive dimerization of different pyridineketones to the corresponding pinacols was investigated, in detail, since the pinacol–pinacolone-type rearrangements give as major product the pyridyl analogs of amphenone B. Microbial reduction of 2,2′-pyridil by *Cryptococcus macerans* yielded (*R*,*R*)-di(2-pyridyl)ethanediol, with a 6/94 *meso*/*dl* ratio and 81% *e.e.* (16). The absolute stereochemistry of (−)-di(2-pyridyl)ethanediol was determined by conversion in several steps to (*S*,*S*)-(+)-dimethyl diacetyltartrate. For the heterogeneous catalytic hydrogenation of 2,2′-pyridoin, only one example can be found in the literature. This hydrogenation was carried out over palladium asbestos, in ethanol with hydrochloric acid (17). The *meso* form of di(2-pyridyl)ethanediol was crystallized; the yield was poor. The heterogeneous catalytic hydrogenation of analogue compounds was investigated in detail. The hydrogenation of the ketones benzil and benzoin proceeded chemoselectively

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over a 10% Pd/C catalyst, modified with ethylenediamine (18). Hydrobenzoin was obtained in 95 and 97% yield (*meso*/*dl* = 71/29 and 76/24, respectively). The hydrogenation of benzoin and benzil over 10% Pt/C in a methanol $+PdCl_2$ solution resulted in diphenyl-ethane (19).

The heterogeneous catalytic hydrogenation of 2,2′-pyridoin and its derivatives 2,2′-pyridil and *O*-acetyl-2,2′-pyridoin over noble metal catalysts was investigated. The effects of catalytic metals, catalyst supports, solvents, acid additives, prehydrogenation, and hydrogen pressure are discussed in the hydrogenation of 2,2′-pyridoin. The chemo- and diastereoselectivity of the hydrogenation were studied under different reaction conditions.

EXPERIMENTAL AND METHODS

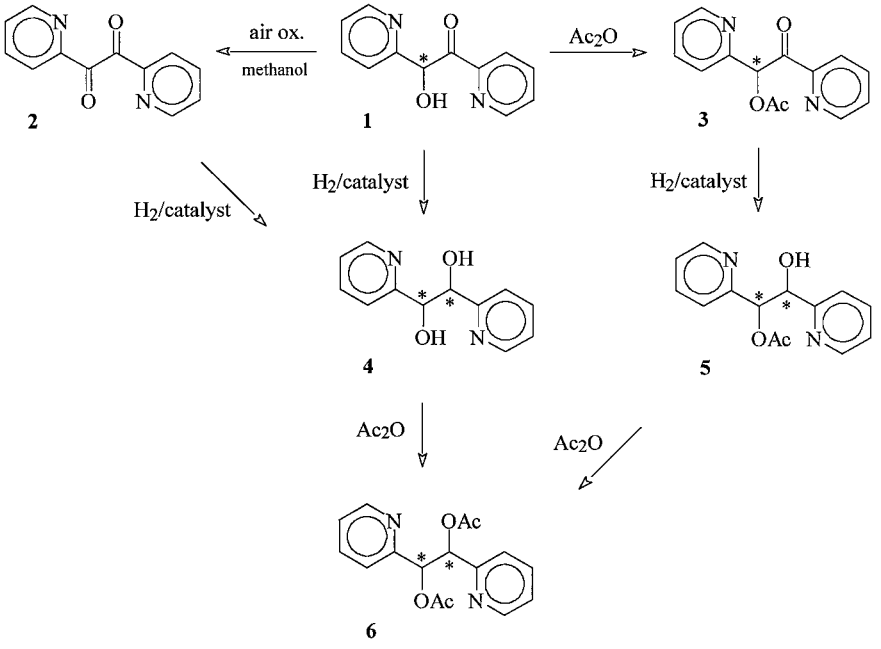
Materials

The reagent 2-pyridinecarboxaldehyde (picolinaldehyde) was supplied by Aldrich (Steinheim, Germany), while acetic anhydride was purchased from Reanal (Fine Chemicals, Budapest, Hungary). The solvents, methanol, ethyl acetate, acetonitrile, dimethyl formamide, and acetic acid, were supplied by Reanal (Fine Chemicals, Budapest, Hungary) in pro analysi grade. The inorganic chemicals used were supplied by Chemolab (Budapest, Hungary). Methanol, acetonitrile, and water (HPLC grade) were purchased from Merck (Darmstadt, Germany).

Some of the catalysts used were commercial products: 10% Pd/C Selcat ($D = 0.5$) (20) (Finomvegyszer Fine Chemicals, Budapest, Hungary), 5% Pt/C ($D = 0.36$) (Heraeus, Karlsruhe, Germany), 5% Ru/C ($D = 0.38$) (Aldrich, Steinheim, Germany), 5% Pd/Al_2O_3 (Aldrich, Milwaukee, WI), PtO_2 ($D < 0.05$) (Aldrich, Milwaukee, WI), Rh black ($D < 0.05$) (Aldrich, Milwaukee, WI), and 5% Pt/Al_2O_3 ($D = 0.2$) (Janssen, Geel, Belgium). A Pd black catalyst ($D = 0.014$) was prepared according to the following procedure: 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and reduced at boiling point with 74 mmol (5.0 g) HCOONa dissolved in 20 ml water. When the reduction was complete, the pH of the suspension was basic (pH 11). The catalyst was filtered and washed several times with distilled water. The 5% Rh/C ($D = 0.42$), 10% Pd/TiO_2 ($D = 0.41$), 10% Pd/SiO_2 ($D = 0.1$), 5% Pt/TiO_2, and 5% Pt/SiO_2 catalysts were prepared as follows. K_2PdCl_4 and $(NH_4)_2PtCl_6$ catalyst precursors were prepared from $PdCl_2$ (Reanal Fine Chemicals, Budapest, Hungary) and $PtCl_4$ (Merck, Darmstadt, Germany), respectively. The calculated amount of the catalyst precursor ($RhCl_3 \cdot 3H_2O$; Merck, Darmstadt, Germany), K_2PdCl_4, and $(NH_4)_2PtCl_6$) was added to the aqueous suspension of the support. The pH value of the solution was adjusted to 10–11 by addition of KOH. The suspension was boiled for 1 h, after which HCOONa was added to the boiling mixture. After half an hour the suspension was cooled, and the catalyst was filtered and washed with distilled water. The 5% Pt/SiO_2 catalyst was heat treated for 3 h in a hydrogen stream at 400°C in a glass reactor and cooled in nitrogen to room temperature.

2,2′-Pyridoin (α-pyridoin) was prepared from 2-pyridinecarboxaldehyde by means of the well-known acyloin condensation, using potassium cyanide (21, 22).

2,2′-Pyridil (α-pyridil) **2** was synthesized from 2,2′-pyridoin **1** (Scheme 1) in methanol by air oxidation, according to the published procedure (17).



SCHEME 1. Preparation and heterogeneous catalytic hydrogenation of the substrates.

O-Acetyl-2,2′-pyridoin **3**, the monoacetyl derivative of 2,2′-pyridoin **1**, can be obtained with acetic anhydride (Scheme 1); the diacetyl derivative can be synthesized only from the corresponding potassium endiolate (22, 23).

Since protic acid additive was used in the hydrogenation reactions, the reaction mixture was neutralized with sodium hydroxide after the catalytic hydrogenation. The *meso* form of 1,2-di(2-pyridyl)ethanediol (hydropyridoin) **4** was crystallized from water. The *dl* form was obtained after evaporation of water *in vacuo*. The configurations of the diastereoisomers were determined by comparison of the NMR data with the published results (15) and the use of an optically active NMR shift reagent (europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], Aldrich) in the ^{1}H NMR analysis of the *dl*-diastereoisomer.

After the hydrogenation reaction the diacetyl derivative of hydropyridoin **6** was prepared in order to determine the ratio of diastereoisomers by liquid chromatographic analysis, using a reverse-phase column and the gradient elution method. After the catalyst was filtered, the reaction mixture was neutralized with sodium hydroxide and concentrated *in vacuo*; the sodium chloride, sulfate, or acetate was crystallized from methanol and filtered, and the solvent was evaporated. Acetic anhydride was added in excess. The reaction mixture was stirred for 24 h, poured onto ice, and concentrated *in vacuo*. The obtained product was dissolved in a 10% sodium hydroxide solution and extracted three times with 100-ml portions of ethyl acetate. The ethyl acetate solution was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the product was analyzed by HPLC. The retention times and response factors of *meso*- and *dl*-1,2-di(2-pyridyl)ethanediol diacetate were determined by analyzing the diacetyl derivatives of the individual diastereoisomers of 1,2-di(2-pyridyl)ethanediol.

Hydrogenation

Catalytic hydrogenation was carried out in a conventional apparatus at room temperature under atmospheric pressure or in a stainless steel autoclave (250 cm^3) (Technoclave, Budapest, Hungary) equipped with a magnetic stirrer (stirring speed, 1100 rpm) at room temperature.

The reactors containing the starting material, prehydrogenated catalyst, and solvent (and acid) were flushed with nitrogen and then hydrogen. The autoclave was charged with hydrogen to the specified pressure. After the hydrogenation was completed, the catalyst was filtered and the solvent was distilled off in a vacuum. The obtained products were analyzed by HPLC and NMR. After the completion of conversion and chemoselectivity, all the products were prepared in 97–99% yields.

Before the reactions, a 0.5-h prehydrogenation of the catalyst was carried out, the main purpose of this frequently used prereduction being to avoid corrosion of the metal catalyst and to ensure that the measured hydrogen consumption arose only from uptake by the substrate. The prehydrogenation was carried out at room temperature and atmospheric pressure in the pure solvent.

Analysis

The HPLC analyses were carried out in a Purosphere RP 18-e column (125×4 mm) using a gradient elution method. Retention data were measured on a Merck–Hitachi LiChrograph consisting of an L-6200 programmable pump, a Rheodyne 7125 injector with a 10-μl loop, and an L-4250 UV–vis detector operating at 256 nm. Data acquisition was performed using the D-7000 HPLC System Manager software. Conversion values were determined—after hydrogenation in the reaction mixture and before acetylation—under isocratic conditions using an acetonitrile–water (50 : 50) mobile phase in a SymmetryShield RP18 column (3.9×150 mm). To determine the ratio of the diastereoisomers, we developed the following separation method: the starting eluent was 3% methanol and 97% water and the gradient was $0 \rightarrow 15$% acetonitrile and $97 \rightarrow 82$% water (time of gradient, 50 min). The retention time difference of the two diacetylhydropyridoin diastereoisomers was 1.2 min at around a 50-min retention time. Their response factors were equal within the experimental error, as was expected. From the chromatograms and based on the integrated peak areas, the conversion, chemoselectivity, and *meso*/*dl* ratios were determined.

The chemoselectivity is reported as the selectivity to 1,2-di(2-pyridyl)ethanediol or its monoacetyl derivative.

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

RESULTS AND DISCUSSION

Effect of Catalytic Metals in the Hydrogenation of 2,2′-Pyridoin, 2,2′-Pyridil, and O-Acetyl-2,2′-pyridoin

The heterogeneous catalytic hydrogenation of 2,2′-pyridoin **1**, 2,2′-pyridil **2**, and *O*-acetyl-2,2′-pyridoin **3** was carried out over different carbon-supported precious metal catalysts; the effects of metals on chemo- and diastereoselectivity are summarized in Table 1. Using a Pd/C catalyst at atmospheric pressure, no reaction was observed in the hydrogenation of 2,2′-pyridoin in ethanol and ethyl acetate solvents without acid additive. No conversion was obtained even at 15 bar in ethyl acetate, applying a high 0.33 catalyst/reactant ratio (g g^{-1}). For that reason it was necessary to use an equivalent amount of strong acid with respect to the substrate. In hydrogenation at atmospheric pressure the reaction rate was calculated from the average hydrogen consumption in the 0–40% conversion period.

TABLE 1

Effects of Catalytic Metals in the Hydrogenation of 2,2′-Pyridoin, 2,2′-Pyridil, and *O*-Acetyl-2,2′-Pyridoin[a]

Compound	No.	Catalyst type	Reaction rate (ml H_2/g_{cat} min^{-1})	Reaction time (h)	Conversion (%)	Chemoselectivity (%)	*meso*/*dl* ratio
1	1	10% Pd/C	8	2	100	100	60/40
	2	5% Pt/C	11	2	97	95	41/59
	3	5% Rh/C	6	3	98	82	32/68
	4[b]	5% Ru/C	—	5	79	100	37/63
2	1	10% Pd/C	5	6	98	100	60/40
	2	5% Pt/C	9	4	92	96	39/61
	3	5% Rh/C	8	4	98	92	32/68
3	1[c]	10% Pd/C	5	3	100	79	49/51
	2[c]	5% Pt/C	3	6	87	82	67/33
	3[c]	5% Rh/C	4	6	90	71	65/35

[a] Conditions: 0.42 g reactant; catalyst/reactant ratio, 0.125 (g g^{-1}); equivalent HCl; 35 ml water; 0.5-h prehydrogenation; atmospheric pressure; room temperature.
[b] 13 bar.
[c] 0.058 g reactant.

The carbon-supported palladium, platinum, and rhodium (Nos. 1–3) showed good activity at atmospheric pressure, while for ruthenium (No. 4) the reaction rate was lower, even at 13 bar. Hydrogenation resulted in high chemo- and moderate diastereoselectivity for both the *meso* and *dl* isomers. In the case of rhodium, chemoselectivity was lower, but the diastereoselectivity for *dl* isomers was the highest. As the hydroxy (or acetoxy) groups are adjacent to the aromatic ring, their hydrogenolysis may be the major side reaction. On a rhodium catalyst, saturation of the aromatic ring can also take place (24). The ruthenium gave the *dl* diastereoisomers with lower diastereoselectivity but at 100% chemoselectivity.

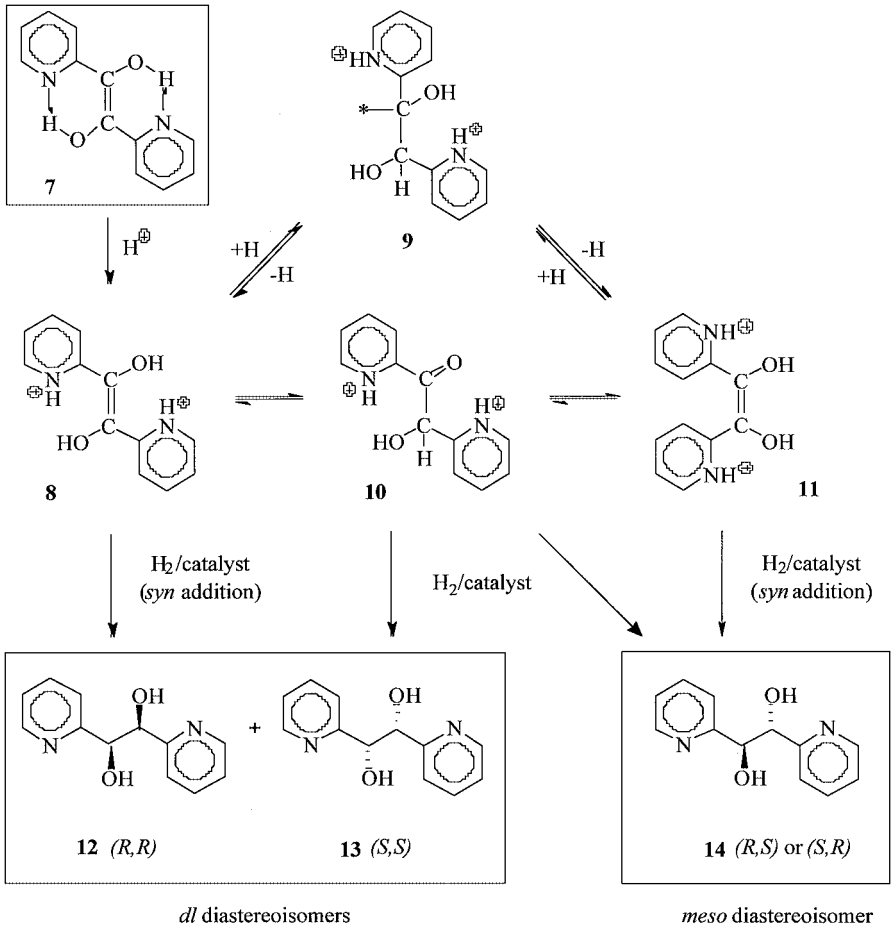
In 1,2-di(2-pyridyl)-1,2-ethenediol, an intramolecular hydrogen bond can be formed. The downfield shift (δ 12.95) of the hydroxylic proton resonance shows the effect of the hydrogen bond; hydropyridoin also shows the effect of intramolecular bonding but to a lesser degree (*meso*, δ 5.58; *dl*, δ 5.24). The lack of the singlet of an aliphatic proton proves the existence of the enediol structure. The *trans*, double six-membered ring structure **7** (Scheme 2) has been proposed to be the most reasonable hydrogen-bonded form (1). This chelated structure is highly conjugated and forms a quasiaromatic system. Maximum stability is achieved when the conjugated system is planar. The *cis* form can not be planar and chelation, if possible at all, would be extremely difficult. The chelated enediols—possessing a conjugated, four-ring system—absorb in the visible region and are thus intensely colored. The conjugated system was also proved by determining the dipole moment (25). The factors contribute to the stability of enediols on the one hand and block the catalytic hydrogenation on the other. This is why the use of a protic acid is necessary to open the chelated structure and to eliminate the poisoning of the metal catalysts by the nitrogen of the pyridine ring. This explains why the chelated enediols such as 1,2-di(2-quinolyl)-1,2-ethenediol were not affected under low-pressure hydrogenation conditions (26).

Using a protic acid additive, the chelated structure can break, which, in solution, gives the *trans* form of the enediol **8**. After the transfer of the first hydrogen atom from the Pd catalyst surface to the chemisorbed *trans* enediol **8**, *cis–trans* isomerization may occur, if it is assumed that the reaction to the half-hydrogenated state **9** is reversible. Geometric isomerization occurs readily in the presence of hydrogen. The configuration of the hydrogenation product is also the result of other competing reactions. There is a pyridoin–enediol equilibrium, where the *trans* form **8** can be changed into the *cis* form **11** via enolization. In the ketol form **10**, saturation of C=O can also occur.

Assuming the *syn* addition of hydrogen atoms, the hydrogenation of *trans* enediol **8** results in the **12**, **13** *dl*-hydropyridoins, while the *cis* form **11** gives the **14** *meso* diastereoisomer.

In the hydrogenation of 2,2′-pyridoin, palladium can cause extensive isomerization via the *cis*-enediol, which reacts faster, the main hydrogenation product being the *meso* diastereoisomer. On platinum, rhodium, and ruthenium, which have much lower isomerization activity, the hydrogenation of the *trans*-enediol resulted in an excess of the *dl*-hydropyridoin.

The reduction of the keto-compound benzil and its derivatives over platinum catalysts has been widely investigated; it takes place via 1,4-addition (1). The first product is usually the *cis* form, but in the absence of acids (27), and particularly in the presence of a base such as piperidine, the *cis* form is converted to the *trans* form. The effective conformation of 2,2′-pyridil is a skew structure in which the



SCHEME 2. Hydrogenation mechanism of 2,2′-pyridoin on the surface of metal catalysts.

dihedral angle between the C_5H_4N–CO planes is 80–83°. Each C_5H_4N–CO moiety is assumed to adopt a flat *s–trans* arrangement (28); this structure promotes the formation of *trans*-enediol during the catalytic hydrogenation.

Concerning both the chemo- and diastereoselectivity, the hydrogenation of 2,2′-pyridil over palladium, platinum, and rhodium catalysts (Table 1) gave similar or almost the same results as the hydrogenation of 2,2′-pyridoin. This means that the catalytic hydrogenation of 2,2′-pyridil occurs via the *trans*-enediol form of 2,2′-pyridoin, according to the same hydrogenation mechanism.

In the hydrogenation of *O*-acetyl-2,2′-pyridoin, not only the saturation of the C=O double bond but also deacetoxylation can occur. Although the acetoxy functionality on the benzylic position can be easily hydrogenolyzed, 80% chemoselectivity was achieved over palladium and platinum, while for the rhodium on carbon catalyst the chemoselectivity was 71% (Table 1). The hydrogenation over palladium (No. 1) was not diastereoselective. Platinum and rhodium (Nos. 2 and 3) were less active, and the thermodynamically preferred *meso* product was obtained in excess.

Effect of Catalyst Supports in the Hydrogenation of 2,2′-Pyridoin

The catalyst support has a strong effect on the hydrogenation and isomerization activity of catalysts and, thus, on the stereoselectivity of the hydrogenation reactions. In the hydrogenation of 2,2′-pyridoin, palladium and platinum catalysts with different supports were screened (Table 2). All palladium catalysts (Nos. 1–4) gave the *meso* diastereoisomer with different activity and diastereoselectivity. The hydrogenation over palladium black (No. 5) resulted in the highest diastereoselectivity.

Carbon-supported platinum (No. 6) gave the *dl* diastereoisomer in excess, but Adams Pt (No. 7) and other supported platinum catalysts (Nos. 8–10) mainly gave the *meso* isomer. The hydrogenation of the ketol form **7** has to be taken into account, too, even though it is present in the reaction mixture only in small concentrations because of the pyridoin–enediol equilibrium. This contributes to the formation of the thermodynamically more stable *meso*-hydropyridoin.

TABLE 2

Effects of Catalyst Supports in the Hydrogenation of 2,2′-Pyridoin[a]

No.	Catalyst type	Reaction rate (ml H_2/g_{cat} min^{-1})	Reaction time (h)	Conversion (%)	Chemoselectivity (%)	*meso*/*dl* ratio
1	10% Pd/TiO_2	12	2	84	99	54/46
2	5% Pd/Al_2O_3	2	8	96	100	57/43
3	10% Pd/C	8	2	100	100	60/40
4	10% Pd/SiO_2	9	2	98	96	62/38
5	Pd black	2	8	94	96	66/34
6	5% Pt/C	11	2	97	95	41/59
7	PtO_2	8	2	99	94	60/40
8[b]	5% Pt/SiO_2	—	5	94	98	60/40
9	5% Pt/TiO_2	3	6	84	95	63/37
10	5% Pt/Al_2O_3	9	2	94	97	64/36
11	5% Rh/C	6	3	98	82	32/68
12	Rh black	14	8	98	>5	—

[a] Conditions: 0.42 g reactant; catalyst/reactant ratio, 0.125 (g g^{-1}); equivalent HCl; 35 ml water; 0.5-h prehydrogenation; atmospheric pressure; room temperature.
[b] 13 bar.

Rhodium black (No. 12) showed high activity, and saturation of the aromatic rings was observed. The value of the *meso*/*dl* ratio is unclear because of the very low chemoselectivity.

Effect of Solvents and Acid Additives in the Hydrogenation of 2,2′-Pyridoin

Equivalent protic acid in alcohol or acetic acid as a solvent is frequently used for the selective saturation of the C=C double bond in the presence of a pyridine ring (29, 30). A stochiometric amount of acid does not promote the hydrogenolysis of the hydroxyl group in pyridoin, and C=C bond saturation occurs readily in neutral medium. Furthermore, it was found that a small amount of pyridine might be enough to inhibit hydrogenolysis (31).

The hydrogenation of 2,2′-pyridoin was carried out over palladium on carbon in water, in acetic acid, and in different solvent–water mixtures (Nos. 1–5, Table 3). The highest diastereoselectivity for the *meso* isomer was achieved in the acetonitrile–water (1 : 1) mixture (No. 5). Over palladium black in an acetonitrile–water solvent mixture (No. 6), somewhat more *meso* product was obtained. The acetonitrile–water mixture favors the formation of the *meso* isomer, which has been also clearly shown in the hydrogenation over rhodium on carbon (No. 7) (Table 1).

The use of half-equivalent hydrochloric acid (No. 8) had no effect on the chemo- and diastereoselectivity of

TABLE 3

Effects of Solvents and Acid Additives in the Hydrogenation of 2,2′-Pyridoin[a]

No.	Solvent	Catalyst type	Reaction rate (ml H_2/g_{cat} min^{-1})	Reaction time (h)	Conversion (%)	Chemoselectivity (%)	*meso*/*dl* ratio
1	H_2O	10% Pd/C	8	2	100	100	60/40
2	AcOH	10% Pd/C	9	2	100	95	54/46
3	MeOH–H_2O (1 : 1)	10% Pd/C	12	2	99	97	54/46
4	DMF–H_2O (1 : 1)	10% Pd/C	6	3	98	94	64/36
5	MeCN–H_2O (1 : 1)	10% Pd/C	9	2	100	93	71/29
6	MeCN–H_2O (1 : 1)	Pd black	3	6	99	99	72/28
7	MeCN–H_2O (1 : 1)	5% Rh/C	3	6	84	70	37/63
8[b]	H_2O	5% Rh/C	6	3	100	84	32/68
9[c]	H_2O	5% Rh/C	6	3	100	89	30/70
10[b]	MeOH–H_2O (1 : 1)	5% Rh/C	3	6	98	94	33/67
11[d]	MeOH	10% Pd/C	—	5	100	27	75/25

[a] Conditions: 0.42 g reactant; catalyst/reactant ratio, 0.125 (g g^{-1}); equivalent HCl (except AcOH is the solvent); 35 ml solvent; 0.5-h prehydrogenation; atmospheric pressure; room temperature.
[b] 0.5 equivalent HCl.
[c] 0.5 equivalent H_2SO_4.
[d] 0.80 g reactant; catalyst/reactant ratio, 0.375 (g g^{-1}); 40 ml solvent; 8 equivalent AcOH; 12 bar.

TABLE 4

Effects of Prehydrogenation and Hydrogen Pressure in the Hydrogenation of 2,2′-Pyridoin[a]

No.	Catalyst type	Prehydrogenation	Reaction rate (ml H_2/g_{cat} min^{-1})	Reaction time (h)	Conversion (%)	Chemoselectivity (%)	*meso*/*dl* ratio
1[b]	5% Rh/C	+	6	3	100	89	30/70
2[b]	5% Rh/C		6	3	100	94	29/71
3[c]	Pd black	+	3	6	99	99	72/28
4[c]	Pd black		4	6	100	96	66/34
5	5% Pt/C	+	11	2	97	95	41/59
6[d]	5% Pt/C		—	1	100	46	48/52
7[e]	5% Pt/C		—	2	100	95	46/54

[a] Conditions: 0.42 g reactant; catalyst/reactant ratio, 0.125 (g g^{-1}); equivalent HCl; 35 ml water; atmospheric pressure; room temperature.
[b] 0.5 equivalent H_2SO_4.
[c] MeCN–H_2O (1 : 1) solvent.
[d] 14 bar.
[e] 14 bar; catalyst/reactant ratio, 0.05 (g g^{-1}).

rhodium on carbon. Using sulfuric acid, however, both chemo- and diastereoselectivity increased (No. 9). Over rhodium on carbon in a methanol–water mixture (No. 10), a similar stereoselectivity but higher chemoselectivity were observed. Simultaneously applied high pressure and acidic medium (No. 11) resulted in extensive hydrogenolysis and ring saturation.

Effect of Prehydrogenation and Hydrogen Pressure in the Hydrogenation of 2,2′-Pyridoin

It was assumed that the prehydrogenation of the catalysts and the hydrogen pressure can both affect the ratio of reaction rates of hydrogenation and isomerization and may, therefore, have an effect on the stereoselectivity as well. The two systems that afforded the highest diastereoselectivity were chosen and tested to determine whether the preliminary saturation of the catalysts with hydrogen and the higher hydrogen pressure improved the stereoselectivity.

The hydrogenation over rhodium on carbon, with or without prehydrogenation (Nos. 1 and 2; Table 4), gave similar stereoselectivity; without prehydrogenation the chemoselectivity was higher.

In the hydrogenation over palladium black, without prehydrogenation (No. 4), the *meso*/*dl* ratio was smaller and the reaction rate somewhat higher. This is in accordance with the former observation that Pd catalysts reduced *in situ* have higher activity for hydrogenation, and consequently lower activity for isomerization.

Over platinum on carbon (Nos. 5–7), increasing the pressure at the same catalyst/reactant ratio (g g^{-1}) decreased the chemoselectivity; however, with a lower catalyst/reactant ratio chemoselectivity was preserved.

CONCLUSION

The purpose of this work was to explore the effects of reaction conditions on the stereoselectivity in the hydrogenation of 2,2′-pyridoin; it is, thus, a preliminary study for chirally modified systems. With palladium, the main hydrogenation product is the *meso* diastereoisomer because of extensive isomerization and the difference in hydrogenation rates for the *trans*- and *cis*-enediols. Platinum, rhodium, and ruthenium possess much lower isomerization activity; consequently, in the hydrogenation via the *trans*-enediol the *dl*-hydropyridoin was formed in excess. The supported platinum catalysts gave both the *meso* and the *dl* products with different *meso*/*dl* ratios, which was explained by competing enolization and C=O reduction. Solvents showed a marked effect on the diastereoselectivity. Hydrogenations without prehydrogenation and at higher pressure did not improve the stereoselectivity. The hydrogenation of 2,2′-pyridil occurs via the 2,2′-pyridoin intermediate; we assume that the hydrogenation mechanism is the same, because chemo- and diastereoselectivity are the same. The hydrogenation of *O*-acetyl-2,2′-pyridoin resulted only in the thermodynamically more stable *meso* product. In the hydrogenation of 2,2′-pyridoin, the best catalyst for producing *meso*-hydropyridoin was palladium black and that for the *dl* isomer was rhodium on carbon.

APPENDIX

2,2′-Pyridoin

NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.20$ (t, $J = 5.9$ Hz, 2H, Ar–H), 7.85 (t, $J = 7.9$ Hz, 2H, Ar–H), 7.92 (d, $J = 8.1$ Hz, 2H, Ar–H), 8.49 (d, $J = 4.8$ Hz, 2H, Ar–H), 12.95 (brs, 2H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 119.7$ (Ar–CH), 121.3 (Ar–CH), 136.1 (C), 137.7 (Ar–CH), 145.8 (Ar–CH), 156.8 (Ar–C).

Mp 156°C (17).

2,2′-Pyridil

NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.51$ (t, $J = 6.2$ Hz, 2H, Ar–H), 7.95 (t, $J = 7.6$ Hz, 2H, Ar–H),

8.24 (d, $J = 7.8$ Hz, 2H, Ar–H), 8.61 (d, $J = 4.5$ Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDC1_3$): $\delta = 122.8$ (Ar–CH), 128.3 (Ar–CH), 137.6 (Ar–CH), 149.9 (Ar–CH), 152.2 (Ar–C), 197.3 (CO).

Mp 154–155°C (17).

O-Acetyl-2,2′-pyridoin

NMR data: ^{1}H NMR (500 MHz, $CDC1_3$): $\delta = 2.17$ (s, 3H, CH_3), 5.25 (s, 1H, CH), 7.26 (t, $J = 6.1$ Hz, 1H, Ar–H), 7.32 (d, $J = 7.9$ Hz, 1H, Ar–H), 7.37 (d, $J = 7.8$ Hz, 1H, Ar–H), 7.56 (t, $J = 6.1$ Hz, 1H, Ar–H), 7.73 (t, $J = 7.6$ Hz, 1H, Ar–H), 7.93 (t, $J = 7.7$ Hz, 1H, Ar–H), 8.24 (d, $J = 7.3$ Hz, 1H, Ar–H), 8.62 (d, $J = 4.7$ Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDC1_3$): $\delta = 21.1$ (CH_3), 66.9 (CH), 122.1 (Ar–CH), 122.7 (Ar–CH), 123.1 (Ar–CH), 124.4 (Ar–CH), 137.1 (Ar–CH), 138.2 (Ar–CH), 148.7 (Ar–CH), 149.5 (Ar–CH), 155.9 (Ar–C), 155.9 (Ar–C), 170.9 (COO), 194.2 (CO).

Mp 122–123°C (22).

meso-1,2-Di(2-pyridyl)ethanediol

NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.92$ (s, 2H, CH), 5.58 (brs, 2H, OH), 7.26 (t, $J = 6.1$ Hz, 2H, Ar–H), 7.51 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.73 (t, $J = 7.1$ Hz, 2H, Ar–H), 8.55 (d, $J = 4.5$ Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 75.4$ (CH), 122.3 (Ar–CH), 122.9 (Ar–CH), 137.2 (Ar–CH), 147.9 (Ar–CH), 160.6 (Ar–C).

Mp 156–157°C (32).

dl-1,2-Di(2-pyridyl)ethanediol

NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.18$ (s, 2H, CH), 5.24 (brs, 2H, OH), 7.17 (t, $J = 6.1$ Hz, 2H, Ar–H), 7.50 (d, $J = 7.9$ Hz, 2H, Ar–H), 7.67 (t, $J = 7.7$ Hz, 2H, Ar–H), 8.44 (d, $J = 4.7$ Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 75.2$ (CH), 121.7 (Ar–CH), 122.7 (Ar–CH), 137.2 (Ar–CH), 147.9 (Ar–CH), 160.7 (Ar–C).

Mp 92–3°C (16).

meso-1,2-Di(2-pyridyl)ethanediol diacetate

NMR data: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.96$ (s, 6H, CH_3), 6.36 (s, 2H, CH), 7.22 (t, $J = 6.2$ Hz, 2H, Ar–H), 7.34 (d, $J = 7.8$ Hz, 2H, Ar–H), 7.65 (t, $J = 7.7$ Hz, 2H, Ar–H), 8.60 (d, $J = 4.4$ Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$ (CH_3), 76.3 (CH), 123.2 (Ar–CH), 123.4 (Ar–CH), 136.5 (Ar–CH), 149.7 (Ar–CH), 155.9 (Ar–C), 169.6 (COO).

dl-1,2-Di(2-pyridyl)ethanediol diacetate

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.07$ (s, 6H, CH_3), 6.46 (s, 2H, CH), 7.14 (t, $J = 6.0$ Hz, 2H, Ar–H), 7.25 (d, $J = 7.9$ Hz, 2H, Ar–H), 7.57 (t, $J = 7.7$ Hz, 2H, Ar–H), 8.55 (d, $J = 4.5$ Hz, 2H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$ (CH_3), 76.9 (CH), 122.8 (Ar–CH), 123.6 (Ar–CH), 136.5 (Ar–CH), 149.6 (Ar–CH), 155.9 (Ar–C), 170.0 (COO).

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