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Diastereoselective Hydrogenation of Substituted Aromatics on Supported Metal Catalysts

Michèle Besson,[1] Bernard Blanc, Muriel Champelet, Pierre Gallezot, Kamel Nasar, and Catherine Pinel

Institut de Recherches sur la Catalyse, CNRS, 2 Avenue Albert Einstein, 69626 Villeurbanne Cedex, France

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The purpose of this work was to hydrogenate disubstituted aromatic compounds on supported metal catalysts to produce enantiomers of the corresponding cyclohexane derivatives using a diastereoselective approach, i.e., associating the organic substrates with chiral auxiliaries. The diastereoselective catalytic hydrogenation of *N*-(2-methylbenzoyl)-(*S*)-proline methyl ester was performed on carbon-supported metal catalysts, optionally modified by the adsorption of EDCA (ethyldicyclohexylamine). The formation of *cis*-diastereoisomers predominated and a cyclohexenic compound was formed transiently. After cleavage of the proline ester auxiliary, optically active 2-methylcyclohexane carboxylic acids were obtained. The influence on reaction kinetics and diastereoselectivity of various factors were investigated on Rh/C catalysts; these factors were pressure, substrate concentration, particle size, and thermal pretreatments of the rhodium catalysts modified with an amine. The reaction rate and the diastereoisomeric excess were found to be very sensitive to these parameters as well as to the presence of water on the catalyst. The importance of the nature of the metal (Rh, Ru, Pt, Pd) was clearly demonstrated. Pt and Pd showed very low activity. Without addition of amine, unmodified rhodium catalysts were nonselective as long as the aromatic substrate was present, whereas the ruthenium catalysts produced moderate selectivity. In the latter case, the carbonyl and carboxyl groups of the molecule could interact with the surface, thus determining which face of the aromatic ring would be preferentially adsorbed. Then, because of the consecutive hydrogenation of the cyclohexenic compound, diastereoselective excesses (*d.e.*) of 17 and 32%, respectively, were observed in favor of the (1*R*,2*S*,2′*S*) isomer. In the presence of an achiral amine (e.g., EDCA) on rhodium catalysts, *d.e.* attaining ca. 50% were measured in favor of the (1*S*,2*R*,2′*S*) isomer. No inversion of configuration was observed with modified ruthenium, probably because the aromatic substrate is more strongly bonded to the surface than in the case of rhodium and thus displaces the amine. In contrast, the aromatic substrate is weakly bonded to platinum and palladium compared to the EDCA molecules which block the surface. In the absence of amine, the weaker adsorption of the aromatic substrate is responsible for the formation of *trans* products.

INTRODUCTION

Control of the enantioselectivity in the synthesis of pharmaceuticals and agrochemicals is a challenge for the forthcoming years (1). Asymmetric catalysis with soluble metal complexes has proved to be an efficient tool for the synthesis of pure enantiomers and various attempts have been made to immobilize metal complexes on a solid support to facilitate separation of reaction products from catalysts; supported aqueous phase catalysis is one of the most recent approaches of this type (2). The development of heterogeneous catalysts based on supported metals modified by chiral inductors (modifiers) has also received increasing attention and significant enantiomeric excesses (*e.e.*) were obtained for the hydrogenation of ketones and ketoesters (3–12). However, the mechanisms of chiral induction proposed for these catalytic systems are still highly speculative. It is generally accepted that the chiral modifier and the substrate should be somehow bonded together but the strength of this bonding remains a subject of dispute and every type of bond, from van der Waals interactions to pure covalent bonds, has been invoked. The final *e.e.* is also controlled by many other factors which are associated either with the catalyst (e.g., nature of the metal, metal and support morphology, presence of metal adatoms, or strongly adsorbed surface ligands) or with the reaction conditions (e.g., temperature, pressure, concentrations of substrate and of additives, nature of the solvent). Even transport processes, such as hydrogen availability on the catalyst surface controlled by diffusion, may play a role, as shown recently (12).

To reach a better understanding of the role of these factors, especially those controlling the geometry of adsorption on the metal surface, the study of metal-based catalytic systems can be greatly simplified by establishing, in a well-controlled manner, covalent bonds between the chiral auxiliaries and prochiral substrates, thus solving the question of the substrate–inductor association. This diastereoselective approach was not applied to the hydrogenation of prochiral C═O or C═C bonds, since these reactions are successfully achieved enantioselectively with metal complexes, but it has been used successfully for the hydrogenation

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[1] To whom correspondence should be addressed.

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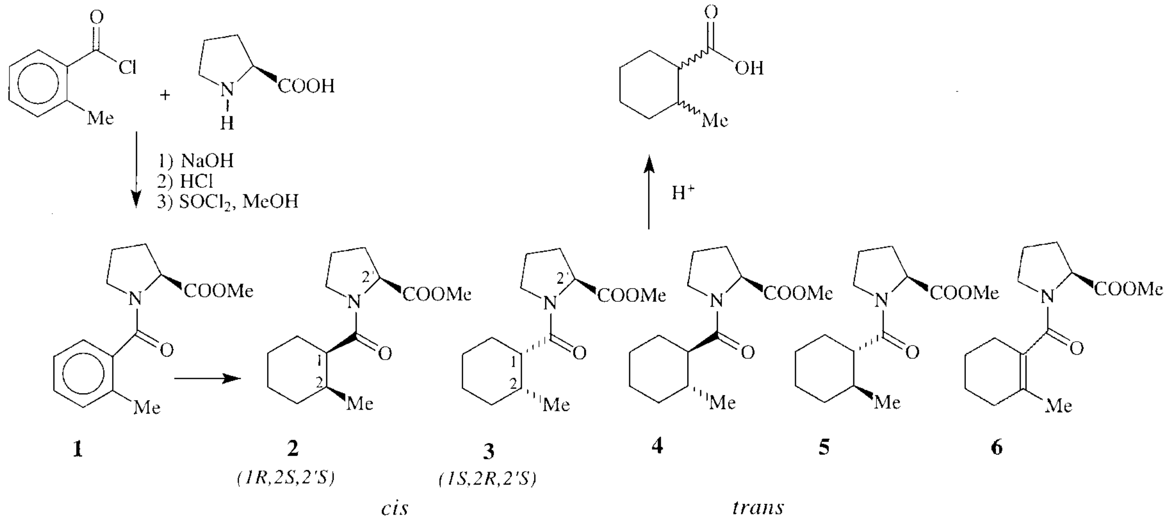


FIG. 1. Diastereoselective hydrogenation of *N*-(2-methylbenzoyl)-(*S*)-proline methyl ester.

of disubstituted aromatics into the corresponding cyclohexyl derivatives (13, 14). These intermediates are often used as "chirons" or optically active building blocks (15). This type of reaction had never been accomplished by homogeneous or heterogeneous catalysis. Figure 1 shows the strategy which consisted of coupling a prochiral substrate (*o*-toluic acid) with chiral auxiliaries (proline esters) to obtain *N*-(2-methylbenzoyl)-(*S*)-proline esters whose aromatic rings were hydrogenated on a carbon-supported rhodium catalyst. We already described the diastereoselective catalytic hydrogenation of the aromatic ring on a commercial rhodium catalyst supported on active carbon (13, 14). This study illustrated the interest of the diastereoselective approach for identifying and evaluating the importance of the different factors involved in asymmetric catalysis on metal surfaces. Since the aromatic moiety and the chiral auxiliary are associated in a well-defined molecular entity, the effects of other parameters on the final diastereoselectivity can be studied in a reproducible manner. The kinetics and diastereoselectivity of the hydrogenation reactions were studied as a function of various factors such as the configuration of the proline auxiliary and the steric hindrance of the ester group, the structure and amount of various amines added to the reaction medium, and the nature of the solvent. Hydrogenation of the methyl ester **1** yielded essentially the *cis*-diastereoisomers **2** and **3** and variable amounts, less than 30%, of the cyclohexenic compound **6** (Fig. 1). It was shown that the configuration of the hydrogenation product could be inverted by changing the configuration of the chiral auxiliary, which confirms the overwhelming effect of the configuration of the asymmetric center. More surprisingly, it was shown that the diastereoselectivity of the reaction can be controlled by the addition of achiral amines to the reaction medium. Thus, in the absence of amines, a negligible selectivity was measured after complete hydrogenation of the aromatic ring of **1**, whereas the addition of various amines favored the formation of isomer **3** with diastereoisomeric excess (*d.e.*) values attaining 50%.

In the present work, attention was focused on the influence of the catalyst per se on diastereoselectivity control. Thus, the effect of the rhodium particle size and of catalyst pretreatments were investigated. Ruthenium, palladium, and platinum catalysts were prepared with the same ion-exchange method on the same active carbon support to obtain similar particle sizes and particle size distributions on the support. These catalysts were then evaluated under the same reaction conditions to study the effect of the nature of the metal on the diastereoselectivity of *N*-(2-methylbenzoyl)-(*S*)-proline methyl ester hydrogenation.

EXPERIMENTAL

Synthesis of N-(2-Methylbenzoyl)-(S)-Proline Methyl Ester

The experimental procedure for the synthesis of substrate **1** was described in Ref. (14). The *N*-(2-methylbenzoyl)-(*S*)-proline methyl ester **1** was prepared as shown in Fig. 1, by coupling (*S*)-proline with *o*-toluic acid via the corresponding acyl chloride (16). A solution of *o*-toluoyl chloride (17.5 g, 110 mmol) in 4 *M* NaOH (100 ml) was rapidly added to a stirred solution of (*S*)-proline (11.5 g, 100 mmol) in 2 *M* NaOH (100 ml). Stirring of the reaction mixture was continued for 30 min, and then the solution was washed with dichloromethane. The aqueous phase was cooled in an ice bath and subsequently acidified with HCl to give a white precipitate, which was solubilized in CH_2Cl_2. After separation, the organic phase was dried over magnesium sulfate and the solvent was evaporated *in vacuo* to give the aryl amide as a white solid with a quantitative yield. The acidic function of the aryl amide was then derived to the methyl ester **1**. To a solution of the aryl amide (23.3 g, 100 mmol) in methanol (100 ml) was added dropwise thionyl chloride (37 ml, 500 mmol) at 0°C under N_2. After complete addition, the solution was boiled under reflux for 1 h. The solvent was eliminated and the resulting oil was purified by vacuum distillation (bp 159°C/3 mm Hg, yield 80%).

Catalysts

The rhodium catalyst used in most of the experiments was a commercial 5 wt% Rh/C catalyst (Aldrich 20,616-4). Other rhodium catalysts were prepared by ion-exchange with $[Rh(NH_3)_5Cl]^{2+}$ cations of a charcoal support (CECA 50S, 1400 $m^2\ g^{-1}$) previously functionalized by NaClO oxidation as described elsewhere (17). Solutions of the $[Rh(NH_3)_5Cl]^{2+}$ ions were obtained by slow addition of $RhCl_3 \cdot 3H_2O$ to a boiling ammonia solution. The catalyst precursor was filtered, washed with water, and then dried under nitrogen flow at 100°C. The sample was then reduced under flowing hydrogen (250 ml min^{-1}) by heating at 1°C min^{-1}, from 25 to 300°C, maintained for 2 h at this temperature, cooled to room temperature under hydrogen, and subsequently stored under argon. Four catalysts were prepared, containing from 3.1 to 5.9 wt% Rh. Ruthenium catalysts were prepared by ion exchange with $Ru(NH_3)_6^{3+}$ of two carbon supports previously oxidized: 4.7 wt% Ru/C_C was prepared on CECA 50S, and 1.3 wt% Ru/C_N was prepared on Norit ROX08 granules, crushed, and sieved to less than 0.5 mm. These samples were reduced under the same conditions as rhodium and then transferred under argon to the hydrogenation reactor. Pt/C (4.2 wt%) and Pd/C (3.7 wt%) catalysts were prepared similarly by ion exchange of CECA 50S with $Pt(NH_3)_4^{2+}$ and $Pd(NH_3)_4^{2+}$ ions, respectively, followed by standard hydrogen reduction.

Catalytic Hydrogenation

Hydrogenation reactions were carried out in 100- or 250-ml, magnetically stirred autoclaves (stirring speed, 1250 rpm) under 5 MPa hydrogen pressure at room temperature, unless stated otherwise. The conditions were the following: 2.5 mmol of substrate **1** were dissolved in ethanol or isopropanol (60–130 ml). The standard concentration was ca. 19 mmol $liter^{-1}$, unless given otherwise. 0.025 to 0.15 mmol of metal (carbon-supported Rh, Ru, Pt, and Pd catalysts) and, optionally, ethyldicyclohexylamine (EDCA, molar ratio EDCA/Rh ca. 3.5) were added to the solution. A rather high catalyst concentration was required to obtain a reasonable reaction time: the molar ratio substrate/Rh was approximately 17. However, under these conditions, the reactor operated in the kinetic regime (reaction rate proportional to stirring speed and mass of catalyst). The autoclave was purged with argon and filled with 5 MPa of H_2, and then stirring was started. Sampling of the mixture, to follow reaction progress, was possible by means of a special sampling valve. It was also possible to inject the substrate or the amine at any time, via a small reservoir connected to the autoclave.

Product Analysis

^1H, ^{13}C, and DEPT (distortionless enhancement by polarization transfer) NMR spectra were recorded on Bruker AM-100 or AM-200 Fourier transform spectrometers. Spectra were obtained in chloroform-*d* or methanol-*d*. Chemical shifts are reported in parts per million (ppm), using the solvent as reference ($CDCl_3$ $\delta_H = 7.24$; CD_3OD $\delta_H = 3.38$).

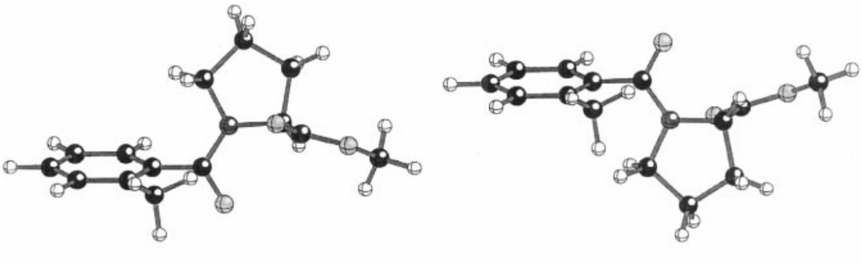
Samples of the reaction medium were analyzed by gas chromatography on a J&W DB1701 column. Figure 1 shows the products and reaction intermediates which were identified in the reaction mixtures by GC-MS and by ^1H NMR. The relative stereochemistry of the four possible diastereoisomers **2–5** was determined by comparison with the retention times of reference samples of known configuration, which were prepared separately from commercial racemic *cis*- and *trans*-2-methylcyclohexanecarboxylic acids, following the same protocol as for the synthesis of the aromatic reactant (*vide supra*). After removal of the chiral auxiliary by hydrogenolysis, the absolute configuration was determined by the rotation value of the acids ((1*S*,2*R*) 2-methylcyclohexane carboxylic acid $[\alpha]_D^{25} = -5.2$ ($c = 1$, EtOH)) (18). Gas chromatography of the corresponding methyl esters (Macherey Nagel Lipodex E column) confirmed the result. Upon reduction, the two *cis*-hydrogenated isomers **2** and **3** predominated under all conditions and the *d.e.* of *cis* isomers were defined as

$$d.e. = |[\%(1S,2R,2'S) - \%(1R,2S,2'S)]/ [\%(1R,2S,2'S) + \%(1S,2R,2'S)]| \times 100.$$

The *trans* products **4** and **5** were detected, but could not be separated by gas chromatography. It was verified that hydrogenolysis occurred without epimerization by comparing the *e.e.* of the acid with the *d.e.* of the reaction (14). An intermediate product was identified as the cyclohexenic compound **6**, with conjugated C=C and C=O bonds. Its structure was determined by GC-MS ($M^+ = 251$), ^1H NMR (there was no evidence of a cyclohexenic proton) and ^{13}C NMR (only tetrasubstituted olefin signals were obtained by DEPT).

Mechanistic Investigations

Molecular mechanics calculations have been performed using the MAD program (Molecular Advanced Design), to determine the minimum-energy conformations of the methyl ester **1**. According to these calculations and to the ^1H NMR studies of the ester, the substrate exists in the form of two epimers B and D with the same energy, with the prolinate moiety external with respect to the aromatic ring,



CONFORMER B **CONFORMER D**

FIG. 2. Ball and stick representation of energetically favored conformers of reactant **1**.

above and below the plane, respectively (14). Figure 2 shows the ball and stick representations of isomers B and D. The interconversion between B and D is not possible, because of a very high energy barrier due to steric interactions between the methyl substituent on the aromatic ring and the proline auxiliary. The ^{1}H NMR spectrum (200 MHz) of the methyl ester at 278 K is given in Fig. 3. The two doublets of doublets at 4.6 and 4.2 ppm were assigned to the proton located on the carbon adjacent to the N atom and bearing the ester group. They exist in a 80/20 ratio and were thus attributed to the two blocked geometries of **1**.

RESULTS AND DISCUSSION

1. *Characterization of the Catalysts*

For the commercial Rh/C catalyst, high-resolution electron microscopy studies on ultramicrotome sections of the grains revealed that most of the rhodium particles were

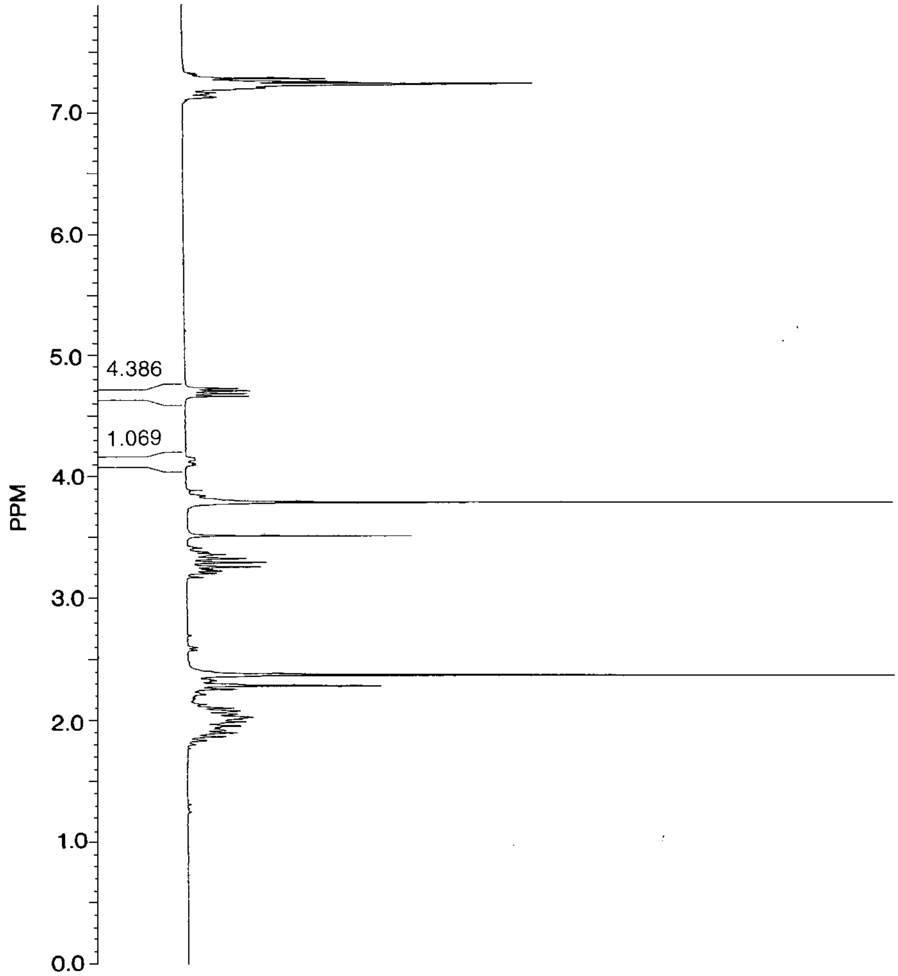


FIG. 3. ^{1}H NMR spectrum (200 MHz) of compound **1** (integrations are indicated on the spectrum).

in the size range 1–3 nm and distributed inside the grains. Larger particles of up to 8 nm were observed close to the external surface of the grains, but a closer examination indicated that they were actually constituted of agglomerated small particles forming a sponge-like texture. Catalysts 5.9 wt% Rh/C and 3.9 wt% Rh/C contained particles smaller than 2 nm, homogeneously distributed throughout the active charcoal grains. While these two rhodium catalysts exhibited high metal dispersions typical of those usually obtained by ion exchange (17), the two other catalysts, 3.6 wt% Rh/C and 3.1 wt% Rh/C, exhibited more heterogeneous dispersion. In 3.6 wt% Rh/C, the particles were in the size range 3–4 nm with a uniform distribution in the active charcoal grains, and the particles were still larger ($\geq$5 nm) in 3.1 wt% Rh/C. This was attributed to an incomplete dissolution of $RhCl_3$ in boiling ammonia, which may lead to inhomogeneous metal loading processes. TEM study of catalyst 4.7 wt% Ru/$\mathrm{C_C}$ showed particles smaller than 2 nm homogeneously distributed in the support, whereas in 1.3 wt% Ru/$\mathrm{C_N}$ the ruthenium particles were at the limit of detection by TEM, i.e., $\leq$1 nm. Platinum and palladium particles in 4.2 wt% Pt/C and 3.7 wt% Pd/C, were in the size range 1–2.5 nm and homogeneously distributed in the charcoal grains. Table 1 gives the particle sizes measured by TEM in the different catalysts.

2. *Hydrogenation on Rhodium Catalysts*

In the previous work (14), it was observed that the hydrogenation carried out over the commercial rhodium catalyst was nonselective up to nearly complete conversion of **1**, as the two *cis* diastereoisomers **2** and **3** were produced in nearly the same amounts. The diastereoselectivity observed at the end of the reaction (17% in favor of the (1*R*,2*S*,2′*S*) isomer) was actually due to the subsequent hydrogenation of the cyclohexenic compound **6** formed (25% of the analyzed products at 100% conversion of **1**). In the presence of EDCA, the most remarkable fact was that the major hydrogenation product was found to have the (1*S*,2*R*,2′*S*) configuration with a *d.e.* of 43% at 100% conversion.

Influence of substrate concentration. The effect of the substrate concentration on the activity and selectivity for the hydrogenation of **1** in ethanol in the presence of EDCA, as a function of either the volume of solvent or the amount of substrate, was further examined. The rate was independent of the substrate concentration above 15 mmol liter^{-1}, suggesting that the reaction is zero order with respect to the substrate **1**. This is commonly encountered in the hydrogenation of unsaturated organic compounds and is indicative of a strong adsorption of the aromatic compound on rhodium. The selectivity at 100% conversion decreased

TABLE 1

Characterization and Reaction Data

Catalyst	Particle size[a] (nm)	Reaction conditions	Initial rate (mol h^{-1} mol$_{\mathrm{met}}^{-1}$)		*d.e.* (%)[b]		Configuration of major product
			EtOH	iPrOH	EtOH	iPrOH	
5% Rh/C Aldrich	1–3	[c]	15	15.5	0 (17)	0 (18)	(1*R*,2*S*,2′*S*)
5% Rh/C Aldrich	1–3	[d]	1.6	8	43 (42)	26 (15)	(1*S*,2*R*,2′*S*)
5.9% Rh/C	<2	[d]	1.3		42 (40)		(1*S*,2*R*,2′*S*)
3.9% Rh/C	<2	[d]	1.2	4.1	48 (46)	25 (15)	(1*S*,2*R*,2′*S*)
3.6% Rh/C	3–4	[d]	0.3	2	44	28	(1*S*,2*R*,2′*S*)
3.1% Rh/C	>5	[d]	0.05	1	[e]	25	(1*S*,2*R*,2′*S*)
4.7% Ru/$\mathrm{C_C}$	<2	[c]	0.75		14 (21)[f]		(1*R*,2*S*,2′*S*)
1.3% Ru/$\mathrm{C_N}$	<1	[c]	3.4		19 (32)		(1*R*,2*S*,2′*S*)
1.3% Ru/$\mathrm{C_N}$	<1	[d]	3.4		8 (11)[g]		(1*R*,2*S*,2′*S*)
4.2% Pt/C	1–2.5	[h]	3.5[h]		12		(1*S*,2*R*,2′*S*)
3.7% Pd/C	1–2.5	[h]	2.3[h]		6		(1*S*,2*R*,2′*S*)

[a] Measured by TEM.

[b] Diastereoisomeric excess at 100% conversion of **1**. Values in parentheses given at 100% conversion of **6**, unless otherwise specified.

[c] Reaction conditions: room temperature, 2.5 mmol **1**, 0.12 mmol metal, 60 ml solvent.

[d] Same as *c*, with 0.42 mmol EDCA.

[e] Not measurable at 5% conversion of **1**.

[f] At 38% conversion of **6**.

[g] At 8% conversion of **6**.

[h] Same as *c*, reaction temperature 60°C.

very slightly from 46 to 40% upon increasing the substrate concentration.

Influence of the hydrogen pressure. The dependence of the initial reaction rate (r_0) and diastereoselective excess on the hydrogen pressure was studied in the range 1 to 5 MPa. The initial reaction rate showed a linear increase with the hydrogen pressure indicating a positive reaction order close to one, but diastereoselectivity was not modified. The standard pressure was 5 MPa.

Effect of the addition of ethyldicyclohexylamine. It was shown that the presence of various amines in the reaction medium produced a change of configuration (14). In order to exemplify further the inversion of configuration occurring in the presence of EDCA, the amine concentration was deliberately changed during reaction. Figure 4 gives the conversion of the methylester **1**, as a function of time, when the hydrogenation was carried out without amine (curve a), and when EDCA was injected after 30 min (curve b) or 100 min (curve c) of reaction, i.e., at 25 and 65% conversion, respectively. Upon introducing the amine into the reaction medium, a strong decrease in the reaction rate was observed, which clearly indicated that adsorption of EDCA on the rhodium surface occurred rapidly. This confirmed the partial poisoning of the catalyst by the adsorbed amine, which was responsible for the difference in conversion rates observed without and with amine (initial reaction rates 15 and 1.6 mol h^{-1} mol_{Rh}^{-1}, respectively). The rate of formation of the cyclohexenic compound **6** was also greatly slowed down (maximum yield ca. 25 and 2%, respectively). Figure 5 shows that upon EDCA addition, the diastereoselectivity shifted from almost zero (characteristic of a reaction performed without amine) to a selectivity in favor of the (1*S*,2*R*,2′*S*) isomer (characteristic of the presence of the amine); the absolute value of the *d.e.* at complete conversion depended on the proportion of the substrate remaining before amine addition.

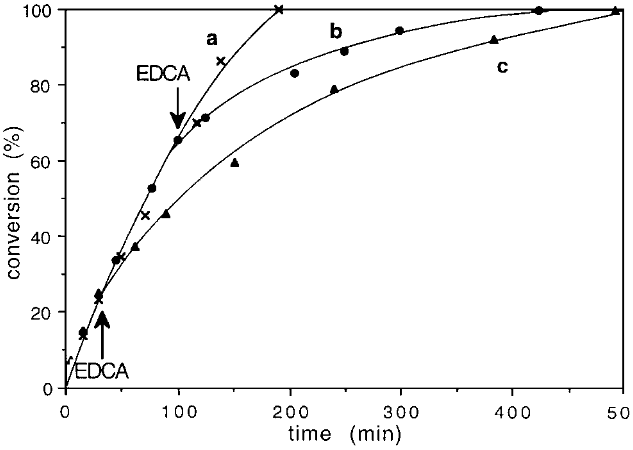


FIG. 4. Influence of amine injection on the conversion of **1** in isopropanol as a function of time. Reaction conditions: 2.5 mmol **1**, 0.073 mmol Rh, 130 ml isopropanol, (a) no amine added, (b) and (c) addition of 0.25 mmol EDCA at 30 and 100 min, respectively.

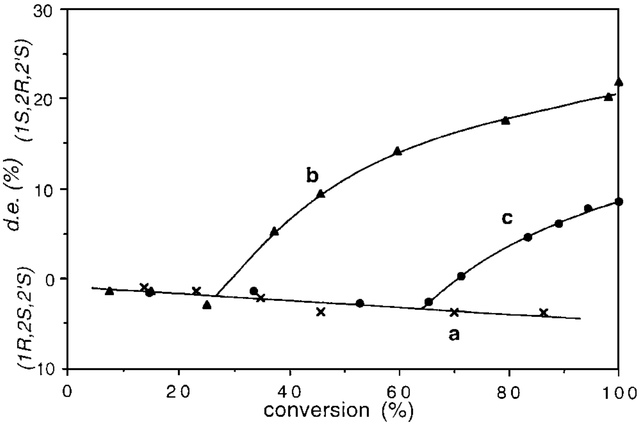


FIG. 5. Change in diastereoselectivity upon introduction of EDCA during hydrogenation of **1**. (a–c) See Fig. 4.

These reaction data confirm the remarkable effect of EDCA on the final diastereoselectivity, even though it has no asymmetric center. The following interpretation for the role of amines in the mechanism of diastereoselection was proposed on the basis of molecular modeling and NMR studies (14). We considered the adsoption of the substrate in the form of the two most probable conformations existing in a nonequal ratio. This adsorption should occur with the plane of the aromatic ring parallel to the rhodium surface and the hydrogenation should then proceed by the addition of hydrogen atoms from below the plane of the adsorbed aromatic ring. Figure 6 shows a schematic representation of molecule **1** (conformer D), adsorbed (a) on a particle of rhodium of 2 nm and (b) on the same particle modified with amine ligands. Without amine (Fig. 6a), the hydrogenation was unselective, because the adsorption and subsequent hydrogenation could take place via both faces of the conformers B and D without significant hindrance, because of the external position of the prolinate group with respect to the aromatic ring. On the other hand, the presence of EDCA molecules adsorbed on the rhodium surface exerts steric constraints (Fig. 6b). Conformers B and D should now be adsorbed via the aromatic ring from their less bulky face and hydrogenated into corresponding (1*S*,2*R*,2′*S*) and (1*R*,2*S*,2′*S*) configurations, respectively. Because the conformers are in a nonequal ratio and assuming that this ratio is retained in the adsorbed state, the final diastereoselectivity is enhanced in favor of the (1*S*,2*R*,2′*S*) configuration.

Effect of particle size on catalyst activity and diastereoselectivity. Table 1 gives the activities and selectivities of the commercial catalyst and of the rhodium catalysts prepared by ion exchange as the hydrogenation of **1** was conducted in ethanol or isopropanol in the presence of ethyldicyclohexylamine (EDCA/rhodium = 3.5). In both solvents, the

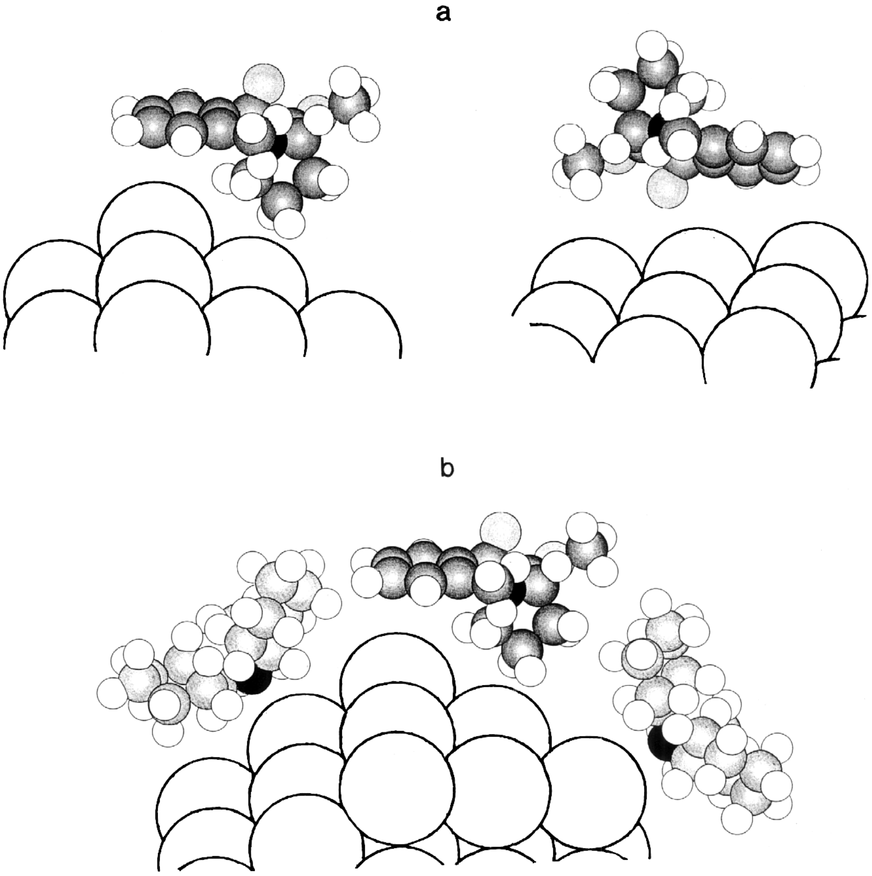


FIG. 6. Schematic representation of the proposed mode of **1** adsorption onto (a) a rhodium particle in the absence of an amine and (b) a rhodium particle partially covered with EDCA ligands (example conformer D).

specific activities decreased as the mean particle size increased but the decreases were much larger than that of metal active area. This could be due to a particle-size-dependent steric hindrance of the rhodium surface by the adsorbed amine. Either the amine coverage could be higher on the large particles or, for a similar surface coverage, the steric hindrance exerted by the adsorbed amine could be higher on a flat surface than on the corner and edge atoms of small particles.

In contrast, the diastereoselectivity was not particle size dependent since the *d.e.* values at 100% conversion of **1** measured on the different catalysts were in the range 42–48% in ethanol and 25–28% in isopropanol (Table 1). This means that in the presence of adsorbed amines, the aromatic ring of substrate **1** was always preferentially adsorbed via its less bulky face, which, as discussed previously (14), accounts for the preferential formation of the (1*S*,2*R*,2′*S*) configuration. However, further studies conducted with and without adsorbed amines on catalysts of more different morphology (e.g., particles smaller than 1 nm compared to large facetted particles) would be needed to detect any possible effect of the rhodium surface morphology on diastereoselectivity.

Effect of catalyst pretreatment. In a first series of experiments, the commercial rhodium catalyst was retreated at 100, 200, and 300°C for 2 h, under flowing hydrogen or argon. The samples were then cooled to room temperature and special care was taken to avoid exposure to air before the hydrogenation reaction was carried out in ethanol in the presence of EDCA. In another set of experiments the catalyst was treated *in situ* in the autoclave under 3 MPa of hydrogen pressure before the introduction of the substrate. The initial rates and diastereoselectivities as a function of pretreatment temperatures are shown in Fig. 7. These data show that the treatments under flowing hydrogen above 100°C resulted in much lower activities; diastereoselectivities were also decreased from 42% (without pretreatment) to 12% (after treatment) at 300°C. Following the addition of 1 ml of water to the catalyst treated at 300°C under H_2, the selectivity was partially recovered (12 to 37%), but the activity was still very low. Heating treatments under flowing argon produced the same effect as under hydrogen, albeit at higher temperatures. *In situ* treatment in the autoclave of the catalyst up to 100°C and under H_2 pressure resulted in a 30% decrease in the rate at 50°C and the activity was 10 times smaller after the 100°C pretreatment. The

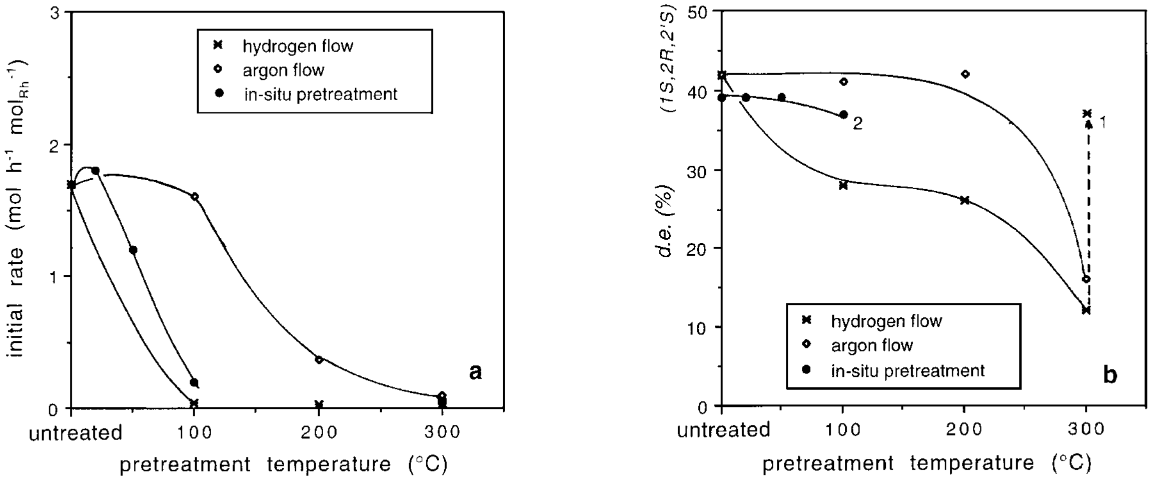


FIG. 7. Influence of pretreatment temperature on (a) initial reaction rates and (b) *d.e.* on commercial 5% Rh/C catalyst. Reaction conditions: 25°C, 2.5 mmol **1**, 0.15 mmol Rh, 0.53 mmol EDCA, 65 ml ethanol (130 ml for *in situ* pretreatments). 1, impregnation of the catalyst with 1 ml water after 300°C H_2 treatment; 2, at 13% conversion of 1.

selectivity (ca. 39% *d.e.*) was not affected by the *in situ* pretreatment.

The decrease in activity occurring after *ex situ* or *in situ* treatments under H_2 or argon could be due to an increase in particle size in agreement with the preceding discussion on particle size dependence (*vide supra*). Although it was not possible to detect any significant particle growth after these treatments, they may affect the smallest particles or produce a rearrangement of the metal surface, but these transformations would be hardly detectable given the small size of particles.

At any rate, particle size growth cannot account for the decrease in selectivity (*vide supra*) nor for the effect of water addition restoring partially the selectivity. This raises the question of the possible role of traces of water on the catalyst which would be eliminated by the *ex situ* thermal treatments in H_2 or argon, thus modifying activity and selectivity. Indeed, the commercial catalyst used without pretreatment contained water and, since the reactions were performed at room temperature, the presence of a stable layer of water on the surface of the catalyst could indeed produce a modification of the adsorption of reactants. The water coverage, the oxidation state of rhodium surface in the moment of contacting the surface with the substrate, and the amine are crucial. The importance of this point is further illustrated by studies performed on different samples of the same commercial catalyst which did not have the same humidity content and displayed differences in activity and selectivity. Systematic studies on the influence of water would be required to determine the influence of the amount of water present on the catalyst and of the hydrophilicity of the support. Indeed, carbon supports, even those which are partially oxidized, are far less hydrophilic than oxide supports such as alumina or silica where an even more pronounced effect of water content might be expected.

Alternatively, the *in situ* or *ex situ* hydrogen pretreatments of the catalysts may affect the state of reduction and the hydrogen coverage of the surface (19) and thus the activity and selectivity pattern. Some dependence on the reduction state of catalysts was reported for the hydrogenation of optically active Schiff bases (20); presaturation of a palladium catalyst with hydrogen led to lower *d.e.* than simultaneous contact of the reactant and hydrogen with the catalyst. The reduction and thermal treatment procedure used for different alumina-supported platinum catalysts modified with cinchonidine was also found to be a critical parameter for the enantioselective hydrogenation of α-ketoesters (21). Catalysts obtained by reduction with hydrogen exhibited lower enantioselectivities than by reduction in aqueous solution with organic agents. Moreover, increasing the hydrogen treatment temperature from 115 to 300°C decreased the optical yield from 65 to 36%. Similarly, pretreatment with hydrogen at 80°C of a carbon-supported palladium (prepared in the presence of tetraalkylammonium compounds) increased the activity and decreased the menthol selectivity during hydrogenation of thymol (22).

For an attempt to clarify the respective role of the three parameters discussed above (particle size, water content, and hydrogen coverage), systematic studies would be required where only one of the parameters would be allowed to vary (e.g., the hydrogen coverage of the surface), while keeping constant other parameters (e.g., particle size and amount of water).

3. Hydrogenation on Ruthenium Catalysts

Figure 8 gives the product distribution obtained on 1.3% Ru/C_N catalyst as a function of time during hydrogenation of **1** in ethanol without amine. The hydrogenation of **1** occurred with an initial reaction rate of 3.4 mol h^{-1} mol_{Ru}^{-1}

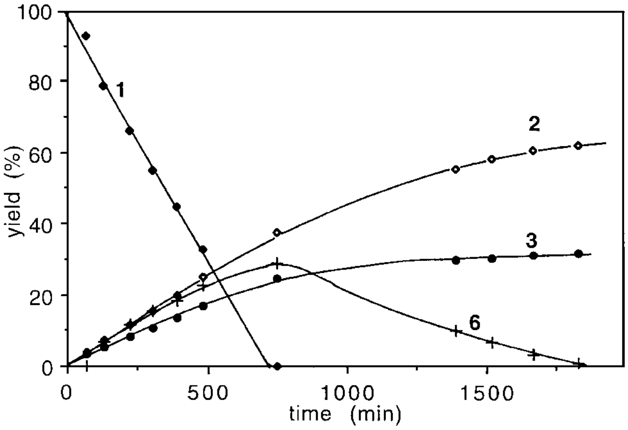


FIG. 8. Product distribution vs time for the hydrogenation of **1** in ethanol without amine on 1.3% Ru/C_N. Reaction conditions: 25°C, 2.5 mmol of substrate **1**, 0.057 mmol ruthenium, 130 ml ethanol.

(Table 1) and the reaction order with respect to substrate concentration was zero; the rate remained constant until complete conversion was achieved (Fig. 8), which is indicative of a strong adsorption of the substrate on the metal. The two diastereoisomers **2** and **3** were produced with a *d.e.* of 19% in favor of **2**. After complete conversion of **1**, the cyclohexenic compound **6**, formed with a 29% yield, was hydrogenated preferentially to **2**, so that at the end of the reaction the *d.e.* was 32% in favor of the (1*R*,2*S*,2′*S*) configuration. On 4.7% Ru/C_C, the reaction proceeded similarly but at a lower rate (0.75 mol h^{-1} mol_{Ru}^{-1}, Table 1) with a *d.e.* of ca. 14% in favor of **2** up to complete conversion of **1**; then, **6** was hydrogenated selectively to **2**.

Figure 9 gives the product distribution obtained as the hydrogenation was carried out in the presence of the same 1.3% Ru/C_N catalyst but in the presence of EDCA with an EDCA/ruthenium ratio of 3.5. The initial reaction rate (3.4 mol h^{-1} mol_{Ru}^{-1}) was the same as that observed in the absence of EDCA but it decreased with time, which is indicative of a positive reaction order and of a weaker adsorption of the substrate in the presence of amine. This is probably due to the effect of EDCA acting as an electron-donating ligand to the metal which produces a decrease in the adsorption coefficient of the aromatic substrate. At complete conversion of **1**, the diastereoisomers **2** and **3** were formed with a selectivity of 8% in favor of **2**. The cyclohexenic compound **6** formed with a 31% yield was then hydrogenated very slowly toward the (1*R*,2*S*,2′*S*) configuration, thus increasing the *d.e.* in favor of **2**.

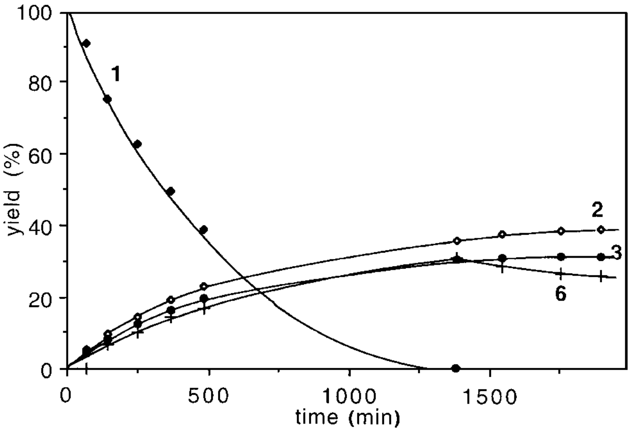


FIG. 9. Product distribution vs time during hydrogenation of **1** on 1.3% Ru/C_N in the presence of EDCA. Reaction conditions: 25°C, 2.5 mmol of substrate **1**, 0.061 mmol Ru, 0.21 mmol EDCA, 130 ml ethanol.

Comparison of rhodium and ruthenium catalysts. The *d.e.* and the yield of cyclohexenic compound **6**, obtained from the hydrogenation of **1** conducted on 5% Rh/C and 1.3% Ru/C in the absence of amine, are given in Fig. 10. The diastereoselectivity obtained on rhodium was nearly zero up to 100% conversion, whereas it was constant at 19% in favor of (1*R*,2*S*,2′*S*) on ruthenium (Fig. 10a). On both metals compound **6**, which was formed in equal amounts (Fig. 10b), was hydrogenated with a high selectivity to **2**; consequently, the diastereoselectivity improved to attain finally 17 and 32% on rhodium and ruthenium catalysts, respectively (Fig. 10c). The different behavior of the two metals in the absence of EDCA can be interpreted by the following mechanism. In the absence of steric constraints, substrate **1** should adsorb on the metal via any of the two faces of the aromatic ring with equal probability, thus resulting in *d.e.* = 0, as observed and discussed previously for rhodium (14). However, ruthenium is a more electropositive metal than rhodium and the particles size is also much smaller (<1 nm in 1.3% Ru/C_N compared to 1–3 nm in Rh/C), which further enhances its affinity for oxygen atoms. Therefore, one can expect that an interaction may occur between ruthenium surface atoms and the oxygenated functional groups of substrate **1**. This anchoring (or haptophilic) effect involving the carbonyl and carboxylic groups should orient the substrate relative to the surface, thus promoting the adsorption of the molecule on the side which holds the oxygen moieties. Figure 11 suggests a possible scheme for the molecular orientation of conformer B with respect to the ruthenium surface. While B would be adsorbed via the “down-side” of the molecule, conformer D would be adsorbed by the “top-side” of the molecule. These conformers, which exist in a 80/20 ratio (as determined by NMR (Fig. 3)), should be hydrogenated into **2** and **3**, respectively, which accounts for the observed diastereoselectivity in favor of **2**. Accordingly, the larger *d.e.* observed on the 1.3% Ru/C_N catalyst (19%) compared to that of the 4.7% Ru/C_N catalyst (14%) would be due to the higher affinity of the smaller Ru particles for the oxygen atoms of the functional groups, resulting in a larger haptophilic effect.

The *d.e.* and the yield of cyclohexenic compound **6**, obtained for the reactions on ruthenium and rhodium catalyst conducted in the presence of EDCA, are compared.

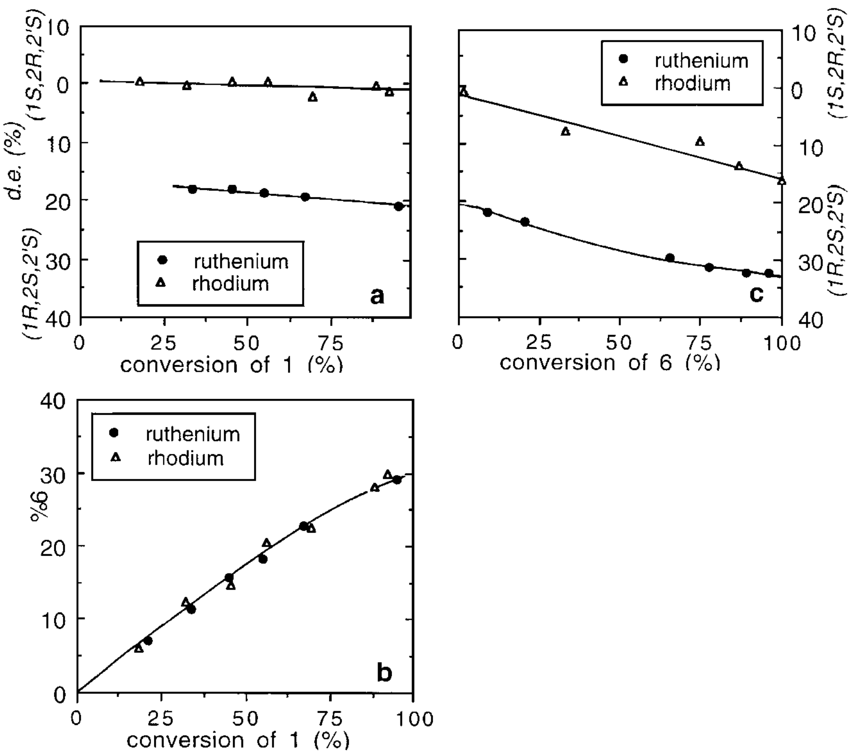


FIG. 10. Comparison of 5% Rh/C and 1.3% Ru/C_N catalysts in the hydrogenation of **1** in the absence of EDCA: (a) diastereoisomeric excess vs conversion of **1**; (b) yield of compound **6** vs conversion of **1**; (c) diastereoisomeric excess vs conversion of **6**.

Modification of the rhodium surface induced a drastic decrease in the reaction rate, which suggested a large coverage of the rhodium surface by the amine ligands. Moreover, there was an inversion of diastereoselectivity, and the (1*S*,2*R*,2′*S*) isomer was the major product with a *d.e.* of 42–48%. However, the rate of hydrogenation on ruthenium catalysts was only a little affected (Table 1) upon addition of the amine, showing that the amine coverage of the ruthenium surface is lower than in the case of rhodium, or that the amine is more easily displaced by the adsorption of the aromatic substrate on ruthenium. No inversion of the diastereoselectivity occurred, which is coherent with the assumption that the amine is little adsorbed or is easily displaced on ruthenium. Whereas a decrease in the yield of **6** occurred with modified rhodium compared to unmodified rhodium (ca. 3% instead of 30%), approximately the same yield of **6** (ca. 30%) was obtained on ruthenium with or without EDCA. The selective hydrogenation of **6** to **2** occurred at a low rate on both metals: due to the low yield of **6** on rhodium, the *d.e.* in favor of **3** was hardly modified, whereas on ruthenium the hydrogenation of comparatively high amounts of **6** (30%) increased the *d.e.* in favor of **2**.

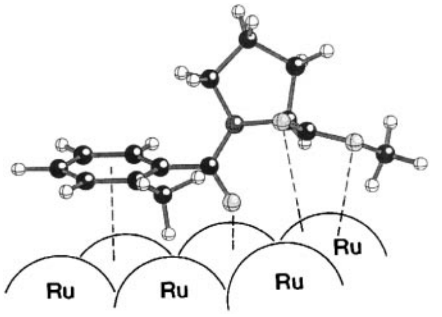


FIG. 11. Scheme of adsorption of substrate **1** on the ruthenium surface.

4. *Hydrogenation on Platinum and Palladium Catalysts*

The hydrogenation of **1** was performed on 4.2% Pt/C and 3.7% Pd/C catalysts in the absence of EDCA. The activities of the catalysts were very low at room temperature so that the hydrogenation reactions were carried out at 60°C. The initial reaction rates were 3.5 and 2.3 mol h^{-1} $mol^{-1}_{(Pt\ or\ Pd)}$, respectively (Table 1). The lower activity of platinum and palladium is not surprising as these metals are known to be less active in the hydrogenation of aromatics than rhodium and ruthenium (23).

Although the reaction temperature was higher, some comparisons with Rh and Ru catalysts may be made. The cyclohexenic compound **6**, once formed, was hydrogenated at the same time as the aromatic substrate **1**, in contrast with the rhodium and ruthenium catalysts where **6** was hydrogenated only after the aromatic substrate was completely converted. The maximum yields of **6** were 25 and 8.6% on platinum and palladium, respectively. A diastereoselectivity of 12% in favor of **3** (1*S*,2*R*,2′*S*) was observed on platinum up to the maximum yield of **6**; it then decreased as **6** was hydrogenated into **2** (1*R*,2*S*,2′*S*). On palladium, the *d.e.* was almost constant at 5–6%. The other remarkable result was the comparatively high amounts of *trans* products **4** and **5** which attained a maximum of 10 and 17% on platinum and palladium, respectively, at complete conversion of **1**, whereas these products were produced with a maximum yield of 3% over rhodium and ruthenium. This might be due to the weaker adsorption of the aromatic substrate on platinum and palladium which favors desorption of intermediate cyclohexenic compounds and their isomerization to *trans* products.

The addition of EDCA (EDCA/metal = 3.5) completely inhibited the activity of the platinum and palladium catalysts. Even at low amine loading (EDCA/metal < 1), the activities of the catalysts were very low. This indicates that, compared to the aromatic substrate, EDCA molecules were much more strongly adsorbed on these metals than on rhodium and especially on ruthenium.

CONCLUSION

To complement the preceding investigations (13, 14), the effects of the morphology and nature of metal catalysts on the activity and diastereoselectivity in *N*-(2-methylbenzoyl)-(*S*)-proline methyl ester hydrogenation were studied. It was shown that for rhodium catalysts an increase in particle size and thermal pretreatments in hydrogen or argon resulted in a loss of activity, but diastereoselectivity was only a little affected. Unexpectedly, the presence of water in the reaction medium, most probably on the catalyst, was shown to modify both the activity and the diastereoselectivity. However, further studies will be needed to evaluate the respective importance of the hydrogen coverage of the surface, the amount of water present in relation with support hydrophilicity, and the particle size, especially by comparing clusters smaller than 1 nm with faceted particles.

More interestingly, it was shown that the nature of the metal is a crucial parameter in diastereoselectivity control. Whereas in the absence of amine the rhodium catalyst was nonselective for the hydrogenation of the aromatic compound, the ruthenium catalyst led to a moderate selectivity of ca. 19% toward the **2** configuration; this selectivity increased to 32% because of the subsequent hydrogenation of **6** into **2**. It was suggested that the carbonyl and carboxylic groups of substrate **1** were involved in the adsorption of this molecule on the ruthenium surface which favored a preferential approach of the aromatic ring via a specific face and the formation of the (1*R*,2*S*,2′*S*) configuration. Another clear experimental result was that the inversion of configuration observed in the presence of EDCA on rhodium catalyst was not observed with ruthenium. This is probably due to the weaker bonding of the amine on ruthenium, or rather to the higher adsorption strength of the aromatic substrate with the ruthenium surface which may displace the amine. However, the adsorption of the aromatic substrate was much weaker on platinum and palladium which accounts for the formation of *trans* products in the absence of amine and the very low activity of these metals in the presence of adsorbed EDCA molecules blocking the surface. Therefore, the different behavior of the different metals could be rationalized by their respective bonding strength with the aromatic substrate which decreases in the series Pd < Pt < Rh < Ru, as previously shown in a study of the competitive hydrogenation of aromatics (24).

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