Catalysis Letters Vol. 87, Nos. 3–4, April 2003 (© 2003)

Heterogeneous asymmetric reactions 34. New data in the enantioselective hydrogenation of ethyl pyruvate catalyzed by cinchona alkaloid-modified Pt/Al_2O_3 in toluene

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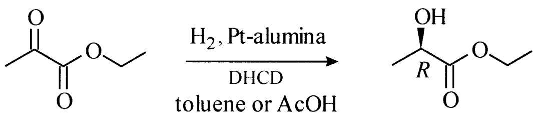
Received 9 December 2002; accepted 24 February 2003

The enantioselective hydrogenation of ethyl pyruvate (EtPy) on Pt-alumina (E 4759) catalyst modified by dihydrocinchonidine (DHCD) at a hydrogen pressure of 1 bar in toluene was studied. The effects of the modifier concentration (0.001–1 $\mathrm{mmol\,l^{-1}}$) and temperature (−10, 0, 24 °C) on the reaction rate and the enantioselectivity have been studied. Under mild experimental conditions (hydrogen pressure: 1 bar, temperature: −10 °C, DHCD concentration: 0.1 $\mathrm{mmol\,l^{-1}}$) an optical yield of 88% can be achieved. When EtPy hydrogenation was studied in AcOH under identical conditions, it was established that the DHCD/Pt_{surf} ratio necessary for achieving maximum enantioselectivity is highly solvent dependent: this ratio is 0.007 in AcOH and 0.12 in toluene. This large difference in DHCD/Pt_{surf} may be a reflection of a difference in reaction mechanism.

KEY WORDS: enantioselective; hydrogenation; Pt/Al_2O_3; cinchona alkaloids; ethyl pyruvate; solvent effect.

1. Introduction

The preparation of chiral compounds, the elucidation of the mechanisms of their synthesis and the identification of the structures of the intermediates responsible for chiral induction are important tasks of chemical research. In the field of asymmetric syntheses—for well-known reasons—special attention has been paid to heterogeneous catalytic enantioselective hydrogenations, the most widely studied of which has been the Orito reaction [1], the hydrogenation of α-ketoesters. Of these, the enantioselective hydrogenation of ethyl pyruvate (EtPy) resulting in the formation of (*R*)-ethyl lactate (EtLt) with an enantioselectivity of 97% [2,3] on alumina-supported platinum catalyst modified with dihydrocinchonidine (DHCD) has been studied in most detail.



The state of research on the enantioselective hydrogenation of α-ketoesters has been the subject of numerous reviews, some of which are quite recent [4,5]. As these are easily accessible only those results from the literature will now be discussed that are closely related to the new experimental results reported here and to their interpretation.

The major aim of this work is the presentation of our new experimental results on Pt/alumina catalyst in toluene at a hydrogen pressure of 1 bar, in the presence of DHCD. It was an open question as to whether the reaction mechanism formulated on the basis of experimental results obtained at hydrogen pressures in excess of 1 bar (see the latest reviews [4,5]) is applicable to the interpretation of enantioselectivities observed under mild experimental conditions. Another aim of this work was to study this chemistry in two solvents (toluene and AcOH) under completely identical conditions.

2. Experimental

2.1. Materials

Cinchonidine (CD), toluene, AcOH, and MeOH were purchased from Fluka. EtPy (Fluka) was distilled before use to 99.5% purity. DHCD was prepared by hydrogenation of CD (Pd/C, 1 N H_2SO_4/H_2O, 1 bar, 298 K) and used after crystallization.

Based on the data in the literature, from several catalysts the one most often used is Engelhard 4759 (E 4759). E 4759 was pretreated before use in a fixed-bed reactor by flushing with 30 $\mathrm{ml\,min^{-1}}$ helium at 27–400 °C for 30 min and 30 $\mathrm{ml\,min^{-1}}$ hydrogen at 400 °C for 100 min. After cooling to room temperature in

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hydrogen, the catalyst was flushed with helium for 30 min and was stored under air before use.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric batch glass reactor with volume of 10 ml [6]. The agitator speed was 1200 rpm to avoid the diffusion range. The catalytic system including catalyst and 2 ml of solvent was purged three times with hydrogen and, after prehydrogenation (30 min), the calculated amount of modifier and 0.1–0.5 ml of EtPy were introduced and stirred in the presence of hydrogen for the required reaction time. Standard conditions were: 25 mg E 4759, 2 ml solvent, 1 bar H_2, 24 °C, 1200 rpm, 0.1 ml EtPy. The quantification of conversion and ee are based on GC data [6].

2.3. ESI-MS and ESI-MS/MS measurements

These have been described in an earlier publication [6].

3. Results and discussion

Our new results obtained with AcOH as solvent have been described in detail in a recent publication [6]. Of these, attention should be called to the identification of a new type of compound ($^{+}O(Al(OAc)_2)_3$) by ESI-MS and the proposition that it may play a role in the hydrogenation reaction. Since ESI-MS gave valuable results, it was also applied to chiral hydrogenation in toluene. It was already recognized by Orito [1] that toluene is a suitable solvent for the chiral hydrogenation of α-ketoesters. Toluene later turned out to be the most often used solvent in studies on the details and the mechanism of the reaction [3,7,8]. In these studies hydrogenation was usually carried out in the pressure range 20–140 bar. We chose mild experimental conditions (H_2 pressure 1 bar, low temperature) to achieve as high an ee as was achieved in AcOH.

Table 1
Adducts detected by positive ESI-MS and ESI-MS/MS ($m = 23$ (Na), 39 (K), 32 (MeOH), 116 (EtPy), 118 (EtLt), 296 (DHCD))

m/z	Adducts
173	$[EtLt + MeOH + Na]^+$
203	$[EtPy + 2MeOH + Na]^+$
289	$[EtPy + EtLt + MeOH + Na]^+$
297	$[DHCD + H]^+$
299	$[THCD + H]^+$
301	$[HHCD + H]^+$
307	$[DDHCD + H]^+$
329	$[DHCD + MeOH + H]^+$ or/and $[DDHCD + Na]^+$
339	$[DDHCD + MeOH + H]^+$
349	$[3EtPy + H]^+$
393	$[3EtLt + K]^+$
605	$[4EtPy + EtLt + Na]^+$
635	$[5EtPy + MeOH + Na]^+$
721	$[5EtPy + EtLt + Na]^+$

Note: EtPy = ethyl pyruvate, EtLt = ethyl lactate, DHCD = dihydrocinchoniinchonidine, THCD = tetrahydrocinchonidine, DDHCD = dodecahydrocahydrocinchonidine.

3.1. Unknown adducts in the reaction mixture

ESI-MS data indicating the formation of adducts of various types in the solvents $CHCl_3$/MeOH and AcOH have been reported earlier [6,9]. In toluene, in addition to the already reported adducts ($m/z = 141$, 171, 255, 257, 299, 307, 371, 373, 387, 403, 491, 521, 551, 719, 751), previously unknown compounds appeared in the spectra. These are listed in table 1. A considerable number of the adducts are products of the base-catalyzed aldol condensation of EtPy. The presence of MeOH in some adducts is due to its use as solvent in MS. Na^+ and K^+ ions are contaminants present in all components of the system: catalyst, solvents, glass reactor, etc. Studies on the effects of the various adducts on enantioselectivity may constitute the subject of further experiments.

Hydrogenation products of DHCD [10,11] with hydrogenated quinoline skeleton (table 1) were also observed in toluene (table 2). The formation of hydrogenated

Table 2
Relative abundances of $[M + H]^+$ ions in the ESI mass spectra of cinchonas formed from DHCD in the enantioselective hydrogenation of EtPy (standard conditions)[a]

DHCD (mmol l^{-1})	Solvent	Time (min)	Conversion (%)	m/z values (relative peak intensity %)				
				297	299	301[b]	307	ee (%)
0.1	T	9	77	47	100	18	–	79
0.1	T	15	99	8	100	35	28	79
1	T	10	65	100	24	34	–	79
1	T	25	100	100	40	70	–	69
0.1	AcOH	10	49	100	47	45	23	91
1	AcOH	15	80	100	20	15	5	92

[a] For abbreviations, see table 1; T = toluene.

[b] The m/z value is not characteristic, because this is not purely hydrogenated DHCD but also contains EtPy adduct.

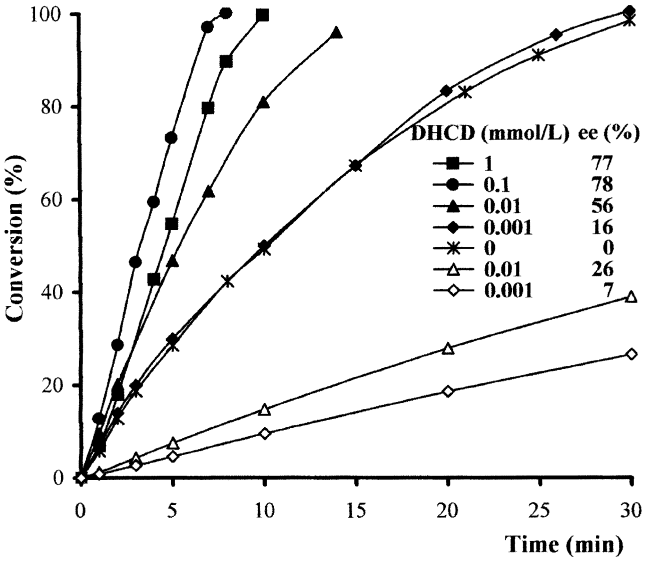

Figure 1. Effect of DHCD concentration in enantioselective hydrogenation of EtPy (standard conditions: 25 mg E 4759, 1 bar H_2, 24 °C, 2 ml toluene, 0.1 ml EtPy; 0.5 ml EtPy: ee at 80% conversion).

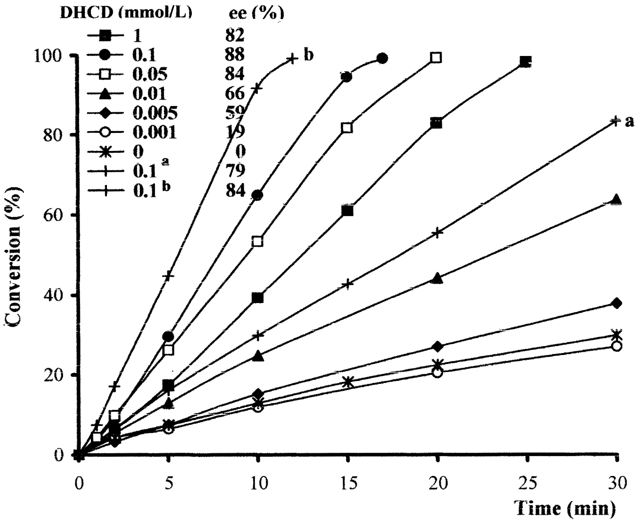

Figure 2. Effect of DHCD concentration in enantioselective hydrogenation of EtPy (conditions: 25 mg E 4759, 1 bar H_2, −10 °C, 2 ml toluene, 0.1 ml EtPy; ^{a} −20 °C, ^{b} 0 °C).

cinchonas is also indicated by the gradual decrease in the initial reaction rate at 0.001 mmol l^{-1} DHCD concentration. The concentration of hydrogenated cinchonas increases with increasing conversion of EtPy. Since the adsorption strength of hydrogenated cinchonas is considerably lower than that of DHCD, they are easily desorbed at high DHCD concentrations, whereas at low DHCD concentrations (below 0.1 mmol l^{-1}) enantioselectivity will decrease because there is insufficient DHCD present to produce optimal surface coverage. The same is confirmed by the results obtained when the concentration of EtPy was increased under identical experimental conditions, as shown in figure 1.

3.2. The effect of DHCD concentration

DHCD concentration has a significant influence on the rate and selectivity of the enantioselective hydrogenation of EtPy in toluene at hydrogen pressures of 20–100 bar [7,8]. However, there are no data published for the effect of the DHCD concentration on the reaction rate and enantioselectivity in toluene at 1 bar hydrogen pressure. This study had to be carried out, as such experimental data may be essential in studying the reaction mechanism. Our pertinent experimental results are summarized in figures 1 and 2. Similarly to hydrogen pressures in excess of 1 bar, the function describing the dependence of the reaction rate on DHCD concentration has a maximum. For the interpretation of this maximum there are two explanations in the literature [7,12]. Blaser *et al.* explained this phenomenon by the so-called "three site model" on the basis of their kinetic study [7], while LeBlond *et al.* [12] interpreted it by the change of the optimal adsorption geometry of DHCD at higher concentrations of the modifier in AcOH. The latter was verified by attenuated total infrared spectroscopy [13].

The experimental data indicate that, under the standard conditions described in section 2, the minimum amount of DHCD necessary for attaining maximum enantioselectivity (78%) is in the range 0.01–0.1 mmol l^{-1}. This range is one order of magnitude larger than in AcOH under similar conditions [6], while in the latter ee reaches 90%.

3.3. The effect of temperature

The role of temperature was first studied under relatively severe experimental conditions (high hydrogen pressure and DHCD concentration). As far as we know, results obtained under the mild experimental conditions applied by us (hydrogen pressure 1 bar, DHCD concentration 0.001–1 mmol l^{-1}, temperature −20, −10, 0 °C) in toluene have not been published before. Our experimental results are summarized in figure 2.

Naturally, it was to be expected that the hydrogenation rate of EtPy would decrease as a consequence of reducing temperature. The time *versus* conversion curves resemble those in figure 1. As temperature is decreased to −10 °C, ee increases and reaches 88%. It seems that the increase in hydrogen concentration due to temperature reduction enhances chiral hydrogenation more than it does racemic hydrogenation. At −20 °C ee decreased to 79%. This decrease may be attributed to several reasons.

3.4. Comparison of toluene and AcOH as solvents

Experimental results compared include data published by Blaser *et al.* obtained at a hydrogen pressure of 100 bar [8] and our earlier results obtained at a hydrogen pressure of 1 bar in AcOH [6], as well as the data reported here. The

Table 3
Solvent effect on the rate and ee in the enantioselective hydrogenation of EtPy

Solvent	DHCD ($\mathrm{mmol\,l^{-1}}$)	Rate [8] ($\mu\mathrm{mol\,s^{-1}}$)	ee [8] (%)	Rate[a] ($\mu\mathrm{mol\,s^{-1}\,g^{-1}}$)	ee[a] (%)
T	0.001	8	35	35	16
T	0.01	20	75	57	64
T	0.1	48	82	96	78
T	1	25	83	71	77
AcOH	0.001	35	83	16	69
AcOH	0.01	80	92	55	91
AcOH	0.1	105	94	85	92
AcOH	1	135	94	63	92

[a] This work, standard conditions; ref. [8], hydrogen pressure 100 bar.

experimental results allowing the following important conclusions to be drawn are summarized in table 3:

(i) In AcOH, at a hydrogen pressure of 100 bar, both ee values and rates are higher than in toluene;
(ii) maximum ee in toluene can be attained at a DHCD concentration (0.1 $\mathrm{mmol\,l^{-1}}$) one order of magnitude higher than in AcOH;
(iii) at a hydrogen pressure of 1 bar ee values are also higher in AcOH, but under identical conditions hydrogenation proceeds at approximately identical rates in the two solvents (except for one case);
(iv) the exception is the reaction at a DHCD concentration of 0.001 $\mathrm{mmol\,l^{-1}}$ which is faster in toluene than in AcOH.

The solvent alters the conformation of cinchona alkaloids [14] and, consequently, affects enantioselectivity. It has been verified by earlier studies that DHCD present in the intermediate responsible for enantioselectivity is in the so-called open-3 (according to another nomenclature, anti-open) conformation [4,5] (see figure 3). From NMR measurements, in toluene *ca.* 70% of DHCD (for AcOH no data) is in the open-3 conformation. The relative stability of open-3 is increased upon protonation [14]. The complex formed on the protonation of quinuclidine N of the DHCD (**A** and **B**) is more stable on the molecular mechanics calculation [3] than the complex formed in toluene by the half-hydrogenated state of EtPy (**C**). In addition, oxonium cations forming on platinum–alumina catalyst in AcOH also enhance enantioselectivity [6].

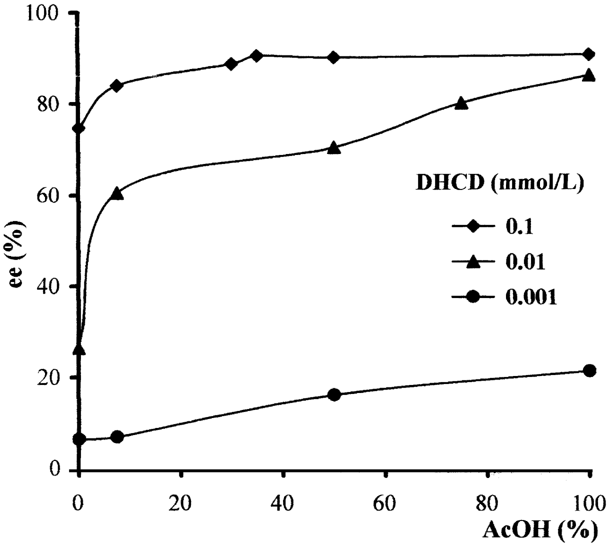

Figure 4. Effect of AcOH on ee in the enantioselective hydrogenation of EtPy in toluene (for conditions, see figure 1; 2 ml solvent, 0.5 ml EtPy).

But why is the ratio of reaction rates different in the two solvents under the effect of hydrogen pressure? The solubility of hydrogen is an important factor [15]. Hydrogen is a non-polar molecule and more readily dissolves in apolar solvents such as toluene. At 10 bar partial hydrogen pressure in toluene the solubility is 3×10^{-3} mol fraction and 2×10^{-3} mol fraction in AcOH [16]. For this reason the hydrogenation at a DHCD concentration of 0.001 $\mathrm{mmol\,l^{-1}}$ may be faster in toluene than in AcOH. At higher DHCD concentrations the effect of DHCD to increase reaction rate in AcOH exceeds the effect of higher hydrogen concentrations to increase reaction rate, observed in toluene. According to another suggestion [17] it may be true that the solubility of hydrogen in AcOH increases faster with pressure than the solubility in toluene.

The advantageous features described above of both solvents (higher ee in AcOH, higher hydrogen solubility and lower hydrogen pressure in toluene) may be exploited simultaneously to optimize the enantioselective hydrogenation of EtPy by using a mixture of the two solvents. Experimental data to this effect are shown in figure 4.

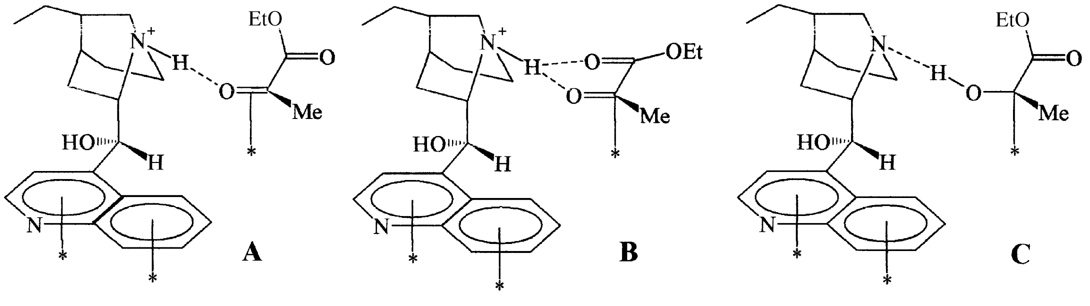

Figure 3. Proposed adsorbed adduct complexes between DHCD in open-3 conformation and EtPy.

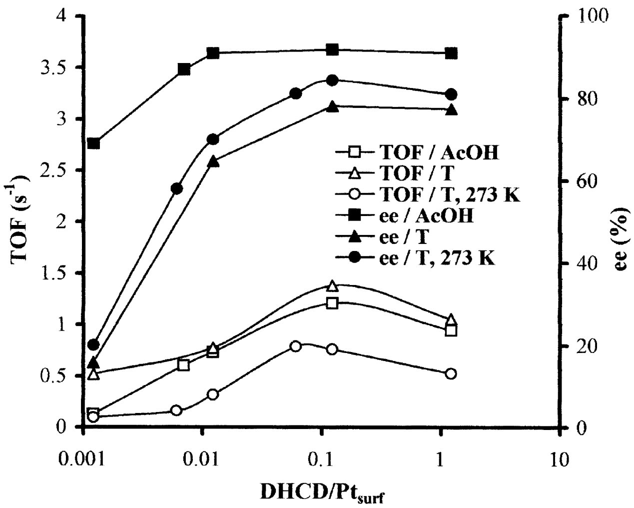

Figure 5. Initial rate and enantioselectivity as function of DHCD/$Pt_{surface}$ for hydrogenation of EtPy (for conditions, see figure 1; T = toluene).

3.5. *Interpretation of the enantioselective hydrogenation of α-ketoesters*

Suggestions, propositions and interpretations presented in recent reviews [4,5] basically fall into one of two categories: chiral induction is supposed to take place either on the catalyst or in the liquid phase. Experimental data published to date [4,5] and calculations [3,18] as well as our own observations [6,19,20] seem to support the so-called adsorption model, proposing that chiral induction takes place on the catalyst (figure 3). The essential point of the adsorption model is that not only DHCD but also metal atoms of the surface participate in enantiodifferentiation.

Reaction rates and enantioselectivities measured in AcOH and toluene at a hydrogen pressure of 1 bar are summarized in figure 5. According to figure 5 the minimum DHCD/Pt_{surf} value required for the maximum ee in the case of AcOH is 0.007 [6] (conditions: 25 mg E 4759, $Pt_{surf} = 0.00173$ mmol, 0.006 mmol l^{-1} DHCD = 0.0000125 mmol, 0.1 ml EtPy, 2 ml AcOH, 23–25 °C); in the case of toluene this value is 0.12 (0.1 mmol l^{-1} DHCD = 0.00021 mmol, the other conditions are the same as for AcOH). On the basis of these data, in toluene about one order of magnitude more DHCD is necessary for maximal ee than in AcOH.

This phenomenon could be interpreted in several ways; lacking experimental evidence, however, meaningful evaluation is impossible. Blaser *et al.* applied the assumption of double modification to the experiments on the DHCD–E 4759 system in toluene [7]. The higher modifier loading needed may be a result of competition between the components of the system (EtPy, modifier, toluene, hydrogen) for adsorption on Pt, because in toluene DHCD is also adsorbed on the support (in AcOH the adsorption of protonated DHCD on the support is inhibited). Finally, it cannot be excluded that the reaction mechanism in toluene is entirely different from that operating in AcOH.

In our opinion, hydrogenation in AcOH may be interpreted by the formation of intermediate (**A**) [4,5] shown in figure 3, because in mildly acidic media DHCD protonated on the quinuclidine skeleton is present not only in the solution but also on the surface of the catalyst (in highly acidic media the less basic N of quinoline is also protonated). We assume that the stabilization of the intermediate is also promoted by the oxonium cations and their dendrimers generated

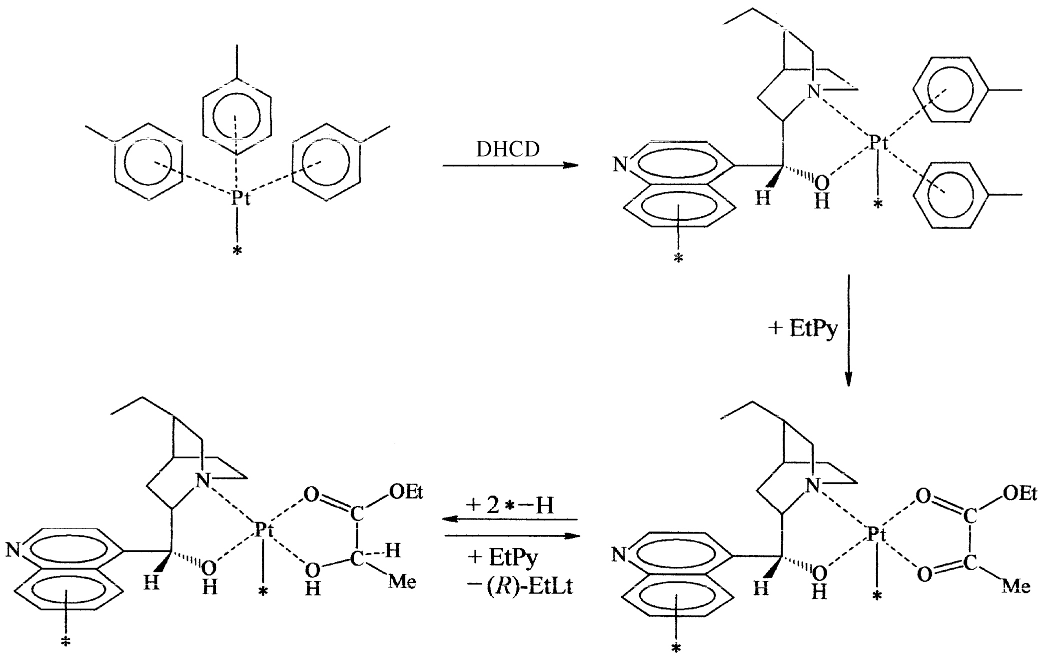

Figure 6. Assumed reaction path of the enantioselective hydrogenation of EtPy in toluene.

on the surface under these conditions ($Pt/Al_2O_3 + AcOH \rightarrow {}^{+}O(Al(OAc)_2)_3$) [6,21].

The mechanism of the hydrogenation of EtPy on Pt–alumina catalyst in toluene, under extremely mild experimental conditions (hydrogen pressure 1 bar, room temperature and below), may be identical to that formulated for higher pressures (10–120 bar), postulating that the intermediate responsible for enantiodiscrimination is the 1 : 1 adduct of DHCD adsorbed on platinum and half-hydrogenated EtPy (figure 3 (**C**)) [22]. We call attention to the proposal of Augustine *et al.* [23] that more coordinatively unsaturated active sites (corners, adatoms) participate in enantioselective hydrogenation. We proposed [20] that the modifier and the hydrogenation substrate (in the present case, EtPy) participate in the formation of the surface complex as ligands of the surface Pt atoms (figure 6). These "ligands" bind to Pt *via* their non-bonded electron pairs.

4. Conclusion

This study presents our new experimental results obtained in the course of studies on the enantioselective hydrogenation of EtPy under a novel set of conditions (hydrogen pressure of 1 bar, temperature below 0 °C, toluene solvent). It has become possible to compare the effects of the two most suitable solvents (AcOH, toluene) under identical experimental conditions. A significant difference was observed in values of $DHCD/Pt_{surf}$ required for maximum enantioselectivity. The new results prompted us to express our opinion on some debated issues of the reaction mechanism. It appears that the difference between the mechanisms of the enantioselective hydrogenation of α-ketoesters in toluene and in AcOH is larger than previously assumed.

In toluene the hydrogenation of α-ketoesters a hydrogen pressure of 1 bar may be explained by the so-called adsorption model formulated at hydrogen pressures of 5–120 bar. Another possibility has also emerged for the interpretation of the reaction in which the critical step of the process is the reaction of DHCD with platinum atoms. A further task awaiting resolution is to find experimental proof for this model and to study its role in enantioselection.

Acknowledgment

Financial support by the Hungarian National Science Foundation (OTKA Grant T031707) is highly appreciated.

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