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Nature of Initial Transient Period during Enantioselective Hydrogenation on Pt and Pd

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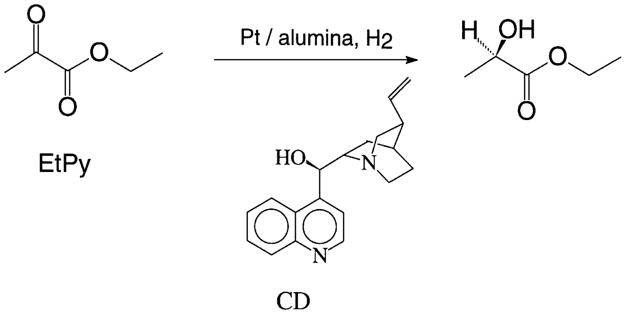
The enantioselective hydrogenation of ethyl pyruvate, trifluoroacetophenone, and tiglic acid has been studied over cinchonidine-modified Pt/alumina or Pd/alumina catalysts. *In situ* **measurement of the catalyst potential during reaction, cyclic voltammetric, and FTIR studies were used to elucidate the nature of the initial transient period. The studies demonstrate that the recently reported surprising change of enantiomeric excess (ee) with the conversion of ethyl pyruvate cannot be considered as an intrinsic feature of the catalyst system, because it is mainly caused by impurities in ethyl pyruvate (0.6–1.9% racemic ethyl lactate even after distillation) and irreversible (destructive) adsorption of ethanol or propanol used as solvents. The initial adsorption of ethyl pyruvate on Pt was also found to be irreversible, producing considerable contamination of the Pt surface by linearly bonded CO and $C_xH_yO_z$ type organic residues. Astonishingly, this side reaction suppressed the initial ee only by a few percent in the presence of hydrogen and acetic acid as solvent. These findings provide a plausible explanation for the positive influence of high surface hydrogen concentration (high pressure, efficient mixing) on the initial and final ee in ethyl pyruvate hydrogenation and for the outstanding enantioselectivity obtained in acetic acid solvent. The observed contamination renders the value of any kinetic or mechanistic analysis of enantioselective hydrogenation reactions over Pt in** *alcoholic solvents* **questionable. The hydrogenation of the carbonyl group of trifluoroacetophenone with cinchonidine-modified Pt/alumina and that of the C=C double bond of tiglic acid with cinchonidine-modified Pd/alumina provide further examples on the increase of ee during the initial transient period and on the strong influence of impurities.**

INTRODUCTION

The catalytic properties of Pt metals in redox reactions can be dramatically influenced by the addition of small amounts of foreign metal adatoms and other inorganic and organic species termed as promoters, auxiliaries, modifiers, or simply additives (for reviews see Refs. (1–4)). An excellent illustration to this possibility is the enantioselective hydrogenation of C=O, C=C and C=N bonds over chirally modified Pt metals and Ni (5–7). For example, modification of supported Pt with cinchonidine (CD) and some of its simple derivatives (8) can result in over 90% enantiomeric excess (ee) in the hydrogenation of ethyl pyruvate (EtPy) to (*R*)-ethyl lactate, as shown in Scheme 1. Moreover, only traces of chiral amine modifiers (ca. 100–300 ppm, related to the reactant) are sufficient to achieve the maximum in enantiodifferentiation (8, 9). For comparison, the commercially available EtPy contains about two orders of magnitude higher amount of foreign material (i.e., not EtPy). It is not astonishing that impurities originating from the reactant or catalyst and by-products formed during the hydrogenation reaction can affect the enantioselectivity. The influence of some unidentified impurities in EtPy and ketopantolactone on the reaction rate and ee over CD-modified Pt catalysts has been reported recently (10, 11).

It is also known from the electrocatalytic literature that the adsorption of many organic and inorganic species can be described by a bell-shaped coverage vs potential curve on Pt: the adsorption of foreign species reaches its maximum at medium potentials where the hydrogen and oxygen adsorption is negligible, as both hydrogen and oxygen can efficiently compete for the Pt^0 adsorption sites (12–15). That is, working in a batch reactor, which is the usual case in the solid-catalyzed enantioselective hydrogenation reactions, the surface coverages of Pt by the reaction components and solvent is expected to change during the initial transient period when the inert atmosphere is substituted to hydrogen.



SCHEME 1

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Interestingly, the experimental observations concerning the conversion dependence of ee during EtPy hydrogenation over CD-modified Pt catalysts are rather contradictory: there is evidence for increasing, decreasing, increasing followed by a decrease, and also to constant ee (16–22). The strikingly different correlations between ee and conversion can partly be explained by the different reaction conditions (17). Besides, some of these observations are likely distorted by catalyst deactivation, and by the partial hydrogenation of the cinchona alkaloid modifier during EtPy reduction (23). The initial period of reaction (below 10% conversion) has not been studied carefully in the papers cited above, mainly due to difficulties in sampling from the autoclave during the very fast reaction. It has been proposed recently that at the beginning of EtPy hydrogenation over CD-modified Pt the ee is very low (close to zero) and the measure of enantioselection is strongly influenced by the hydrogen transport rate (24–26). On the basis of these experimental observations, a new interpretation of rate acceleration and enantiodifferentiation has been proposed for α-ketoester hydrogenation (27).

The aim of our work was to clarify the role of impurities and side reactions during the Pt–metal-catalyzed enantioselective hydrogenation reactions, especially in the initial transient period. The emphasis will be on the hydrogenation of EtPy (Scheme 1) over CD-modified Pt, which is the most studied reaction of this category.

EXPERIMENTAL

Materials

Distilled water (after ion exchange) and purum grade reagents were used. Cinchonidine (Fluka, >98%), α,α,α-trifluoroacetophenone (Fluka, ≥98%) and tiglic acid (2-methyl-2-butenoic acid; Fluka, ≥97%; and Aldrich, 98%) were used as delivered. Ethyl pyruvate (Fluka, ≥97%; for control experiments: Aldrich, 98%) was freshly distilled in vacuum, using a Vigreux column, before each reaction. The ethyl lactate content of EtPy after distillation (0.6–1.9%, depending on the supplier and efficiency of distillation) was determined by GC-MS using two different columns (see below), NMR, and IR analysis, including checking the matrix effect.

The metal dispersion of the 5 wt% Pt/alumina catalyst (Engelhard 4759) was 0.22 as determined by transmission electron microscopy, and that of the 5 wt% Pd/alumina (Engelhard 40692) was 0.21 by transmission electron microscopy and 0.20 by CO chemisorption.

Catalytic Hydrogenation

The hydrogenation reactions were carried out at atmospheric pressure and 22°C, in a 200-ml flat-bottomed glass batch reactor, equipped with gas inlet and outlet and magnetic stirrer. In the hydrogenation of EtPy and trifluoroacetophenone the reactor operated in the transport limited regime, but during the hydrogenation of tiglic acid the conditions were chosen so as to work in the kinetic regime.

For the hydrogenation of EtPy, the proper amounts of solvent, EtPy, and CD were put into the reactor. The system was flushed with nitrogen. The catalyst was prereduced in flowing hydrogen at 400°C for 1.5 h and transferred to the reactor under nitrogen. The reaction was started by substituting nitrogen to hydrogen and switching on mixing. These conditions were applied if not otherwise stated. Other reaction parameters are indicated in the pertinent figure legends.

Before the hydrogenation of trifluoroacetophenone, the catalyst prereduced at 400°C was added to 40 ml 1,2-dichlorobenzene and mixed ($n = 250$ min^{-1}) in air for 30 min at 22°C. After flushing the system with nitrogen, the catalyst was reduced again for 5 min in the presence of 8 mg CD or 2 ml trifluoroacetophenone. Finally, trifluoroacetophenone or CD (in 1 ml solvent), respectively, was added and the hydrogenation was continued. In the second case the amount of trifluoroacetophenone converted and that of racemic product formed during catalyst rereduction was taken into correction.

For the hydrogenation of tiglic acid, 20 mg 5 wt% Pd/alumina (without any pretreatment), 2.5 mg CD, 80 mg tiglic acid, and 17 ml *n*-hexane were used. The reaction was started by substituting nitrogen to hydrogen and switching on mixing (1200 min^{-1}).

Enantiomeric excess and conversion were determined by a HP 5890A gas chromatograph, using a chiral WCOT CP Cyclodextrin-β-2,3,6-M-19 or Chirasil DEX-CB capillary column (both from Chrompack). The enantiomeric excess is expressed as ee (%) $= |R(\%) - S(\%)|$.

Spectroscopic Analysis

The *in situ* diffuse-reflectance FTIR studies were carried out on a Perkin–Elmer (Model 2000) instrument, using a diffuse-reflection unit (Spectra-Tech, type 0030-033) (DRIFT) including a reaction chamber (Spectra-Tech, type 0030-102). The temperature of the catalyst was measured by a thermoelement (type K) with an accuracy of ±2°C and controlled by a Tecon 580. The gas flow (30 ml · min^{-1} during heat treatment, and 100 ml · min^{-1} during flushing with EtPy or ethanol) was controlled by mass flow controllers (Brooks, 5850E) and blown through the reaction chamber, in which the catalyst was filled into an Al_2O_3 sample holder. The gases (H_2, 99.999 vol%; Ar, 99.998 vol%) were used without further purification. The FTIR spectra (a–e, Fig. 1) were recorded with 10 scans and 8 cm^{-1} and presented in Kubelka–Munk function. The spectrum of dry KBr was taken for background substraction (500 scans, 8 cm^{-1}).

The general experimental procedure can be summarized as follows. The catalyst sample was heated in Ar to 400°C and kept at this temperature for 30 min before changing

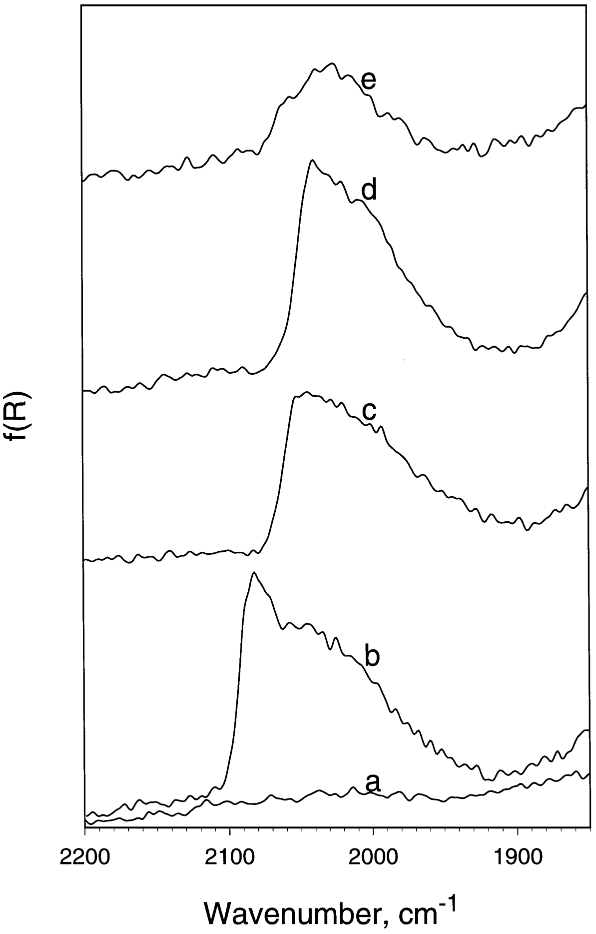


FIG. 1. FTIR spectra of the 5 wt% Pt/alumina (after *in situ* pretreatment in flowing H_2 at 400°C) in (a) Ar, (b) 0.5 vol% CO in Ar, (c) Ar saturated with ethanol, (d) Ar saturated with EtPy, and (e) H_2 saturated with EtPy. Spectra recorded at room temperature.

to hydrogen for 90 min. After 20 min flushing with Ar, the sample was cooled to room temperature in Ar. Ar was then substituted to a mixture of CO (5000 ppm) in Ar, or Ar was blown through a gas saturator filled with EtOH or EtPy (distilled). Alternatively, after treatment in hydrogen at 400°C for 110 min, the catalyst was cooled to room temperature in hydrogen and then purged with hydrogen saturated with EtPy. Several spectra were taken during flushing with the adsorbate (CO, EtPy, or EtOH) until the changes become negligible (20–45 min); these spectra are shown in Fig. 1.

Electrochemical Methods

Cyclic voltammograms were measured in 0.5 *M* H_2SO_4 at 25°C, using a conventional electrochemical cell equipped with a Pt counter electrode and a Ag/AgCl (0.1 *M* KCl) reference electrode. The latter was separated from the main compartment of the cell by two diaphragms to avoid the pollution of the electrolyte by Cl^- ions. All potentials in the text and figures are given on the RHE (reference hydrogen electrode) scale. Bubbling N_2 (99.995%) was used to deoxygenate the solution before the voltammetric runs.

For the measurement of solvent adsorption, a platinized Pt electrode (ca. 1 cm^2 geometric surface area) was immersed into 1-propanol for 1 min and then washed carefully with water. After removing the excess of organic species, the Pt electrode was polarized cathodically in the aqueous electrolyte to 50 mV, kept at this potential for 2 min, and then polarized anodically with a sweep rate of 200 mV min^{-1}. In the second cycle the potential changed continuously, without stopping at 50 mV.

The electrochemical potential of the catalyst (which can be considered as a slurry electrode) was measured with a bright Pt rod electrode during the hydrogenation of EtPy. The reaction was performed in the same 200-ml electrochemical cell which was used for cyclic voltammetry but the vessel was magnetically mixed. The reference electrode was a Ag/AgCl (0.1 *M* KCl) electrode. More details of the method, including the experimental setup, the choice of measuring electrode and the interpretation of the measured potential, can be found elsewhere (28–31).

RESULTS

FTIR Study of the Adsorption of Ethyl Pyruvate and Ethanol on Pt/Alumina

The interaction of the prereduced Pt/alumina catalyst with a frequently used alcoholic solvent and the α-ketoester reactant was mimicked in an FTIR cell. The characteristic parts of the diffuse reflectance spectra are shown in Fig. 1. The spectrum taken in a 0.5 vol% CO/Ar mixture is also shown for comparison (curve b). In the latter case, the broad asymmetric peak with a maximum at 2080 cm^{-1} is similar to that reported for a 1 wt% Pt/alumina catalyst and attributed to linearly bonded CO (32). A considerable CO coverage of Pt was detected when the *in situ* prereduced catalyst was flushed with Ar saturated with ethanol or freshly distilled EtPy (curves c and d, respectively). Assuming a full CO coverage of Pt in the CO/Ar mixture, the CO coverage in the presence of EtOH and EtPy vapor in Ar is 0.74 and 0.79, respectively, based on the relative areas under the peaks. The peaks on curves c and d are slightly shifted to lower frequencies compared to that on curve b. It has been reported that the linear CO peak position is a function of the surface coverage and the crystallographic face exposed (32, 33).

When the 5 wt% Pt/alumina was contacted with EtPy vapor in hydrogen (instead of Ar), the CO peak at around 2030 cm^{-1} became considerably smaller (Fig. 1, curve e). The calculation based on the area under the curve indicated a relative CO coverage of Pt (Θ_{CO}) of only 0.33. The lower Θ_{CO} in hydrogen compared to that in Ar (0.79, curve d) is attributed to the competitive adsorption of hydrogen on Pt.

Our observations are in good agreement with numerous evidences in the literature on the destructive adsorption of compounds possessing an OH or a carbonyl group, on Pt in aqueous solutions (14, 34, 35). This irreversible "adsorption" process results in the formation of CO and $C_xH_yO_z$ type fragments. For example, the Θ_{CO} on polycrystalline Pt in aqueous $HClO_4$ under reducing conditions was 0.9, 0.5, and 0.45 in the presence of methanol, ethanol, or 1-propanol, respectively (36). A detailed FTIR study of ethanol adsorption on Pt in aqueous sulfuric acid demonstrated the presence of (Pt)–CO, (Pt)–OCH_2–CH_3, and $(Pt)_2$=COH–CH_3 adsorbed species (37). Under reducing conditions the latter is converted to ethane and an acetyl residue [(Pt)–CO–CH_3] is proposed to be the precursor of methane formation.

Ethyl Pyruvate Hydrogenation: Influence of Mass Transport

The influence of mixing efficiency on the surface state of Pt during the enantioselective hydrogenation of EtPy was investigated by *in situ* measuring the catalyst potential. Aqueous acetic acid (90 vol%) was used as a solvent and a relatively large amount of catalyst was applied due to the conductivity and charge transfer requirements of the electrochemical method. The time dependence of EtPy conversion, ee (to *R*-lactate) and catalyst potential are shown in Figs. 2a–2c. The rate of mass transport was varied by changing the mixing frequency and the size of the magnetic

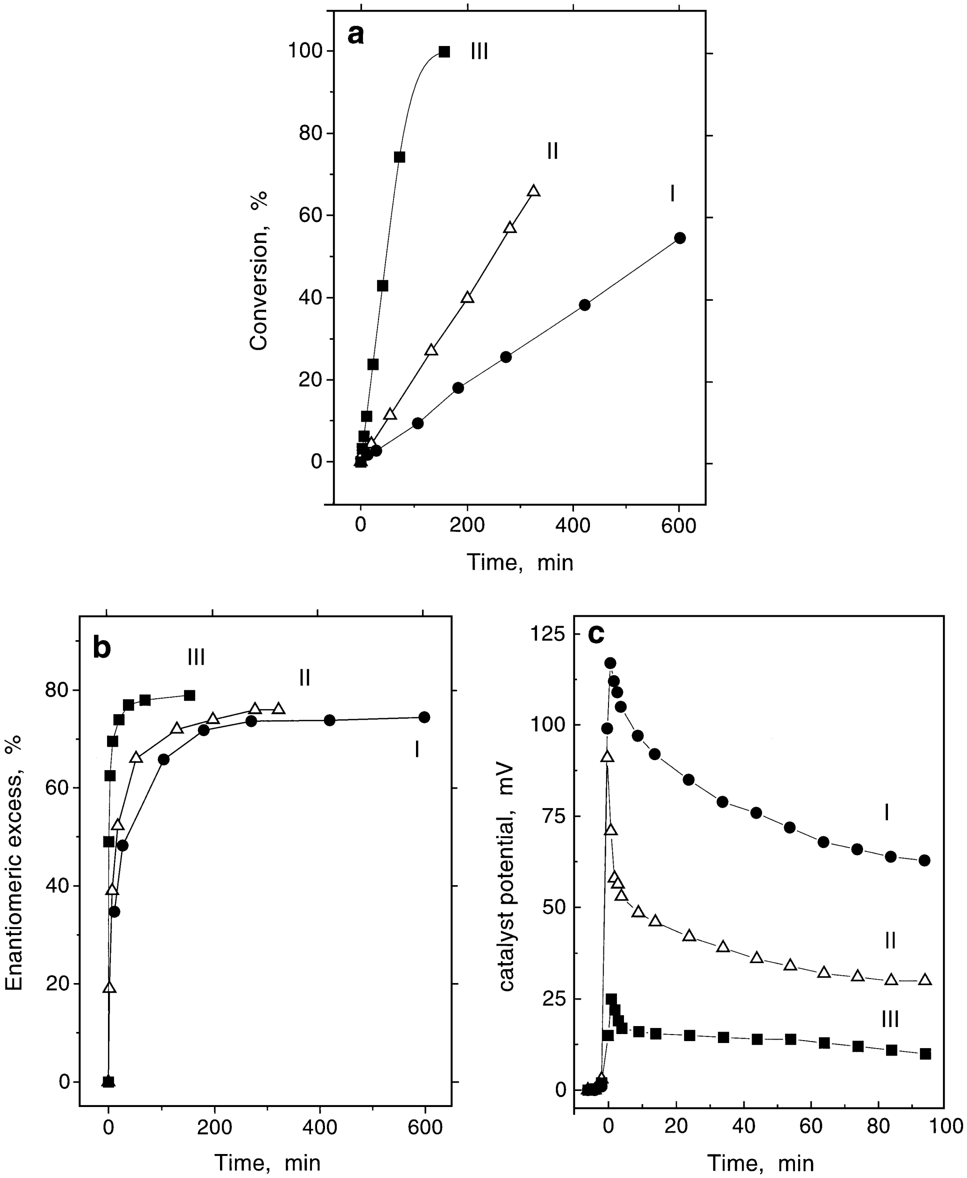


FIG. 2. Influence of mixing efficiency on the conversion (a), enantiomeric excess (b), and catalyst potential (c) during EtPy hydrogenation in aqueous acetic acid: (I) $n = 250\ min^{-1}$, mixing rod = 6 × 30 mm; (II) $n = 750\ min^{-1}$, mixing rod = 6 × 30 mm; (III) $n = 1500\ min^{-1}$, mixing rod = 7 × 40 mm; conditions, 45 ml acetic acid, 5 ml H_2O, 250 mg 5 wt% Pt/alumina, 150 mg CD; 6 ml EtPy is added after prehydrogenation of the slurry for 20 min.

rod. The reactor was operated in the mass transport limited regime, which is clearly shown by the strong influence of mixing efficiency on the reaction rate (Fig. 2a). At the beginning of the reaction the ee was very low (for the interpretation see later), but rapidly increased with time (conversion). The more efficient the mixing, the higher was the final enantioselectivity up to 80% ee at atmospheric pressure (Fig. 2b).

There was a rapid and immediate increase of the catalyst potential after injection of EtPy into the reaction mixture containing the prereduced catalyst and CD (Fig. 2c). After reaching a maximum the catalyst potential decreased again, at first faster than slower. The three regions of time dependence of the catalyst potential are clearly seen at high mixing frequency. The second region (fast decrease of catalyst potential) is likely connected with the transient period, and the third slow decrease is due to the conversion of EtPy.

Besides, the positive shift of the catalyst potential throughout the reaction decreased considerably with improving the mixing. In general, the more positive catalyst potential after introducing the reactant (oxidizing agent) is an indication of the decrease of surface hydrogen concentration. Unfortunately, the actual surface hydrogen concentration cannot simply be calculated, as the catalyst potential is likely influenced by both the $H \leftrightarrows H^+$ and the pyruvate $\leftrightarrows$ lactate redox processes ["mixed potential" (38, 39)]. Nevertheless, it is clear from Fig. 2c that under these conditions the rate of mass transport had a very strong influence on the surface concentrations, and the initial period of rapid changes in the surface concentrations was not longer than 3–5 min when the mixing was efficient.

A detailed study of the influence of mass transport on the rate and ee in EtPy hydrogenation has been published recently (24, 26). The authors tried to find a correlation between the catalytic performance and the amount of hydrogen dissolved in the liquid phase (gas–liquid diffusion resistance). They proposed that good mixing is necessary to increase the amount of hydrogen dissolved and the rate and ee of the reaction. However, not the "solution hydrogen concentration" (26) but the surface hydrogen concentration (or rather hydrogen activity) is the real controlling parameter of a solid-catalyzed hydrogenation reaction.

Ethyl Pyruvate Hydrogenation: Influence of Pretreatment Conditions

In the past years various pretreatment procedures have been proposed and tested in pyruvate hydrogenation, usually with the aim of improving the catalytic performance or gaining some insight into the mechanism of enantiodifferentiation (19, 21, 24, 40, 41). Hardly any attempt has been made to compare these strategies and interpret the observed differencies in reaction rate or enantioselectivity. Sutherland *et al.* (21) have addressed this question, but they carried out their studies with EtPy which was not purified and consequently these results and conclusions are not free from possible effects of contaminants.

In the following we analyze two substantially different procedures. In one case Pt/alumina prereduced in flowing hydrogen at 400°C and carefully distilled EtPy were used (Fig. 3, curves a). This is the general preconditioning procedure applied in our laboratory (9, 42), but has been first proposed by Orito *et al.* (40). For the other reaction neither the catalyst nor the reactant was pretreated and the reaction mixture was mixed in nitrogen for 2 h before introducing hydrogen (Fig. 3, curves b). The latter procedure was applied recently before a kinetic analysis of EtPy hydrogenation in a reaction calorimeter (24). The differencies are clearly demonstrated by the *in situ* measurement of catalyst potential (Fig. 3, bottom). In case a the catalyst potential dropped to 145–150 mV after introduction of hydrogen and then stabilized slowly at 220–230 mV. These values correspond to a Pt surface partially covered by hydrogen (see later in Fig. 5). Between catalyst prereduction in a tube reactor and starting the pyruvate reduction in the slurry

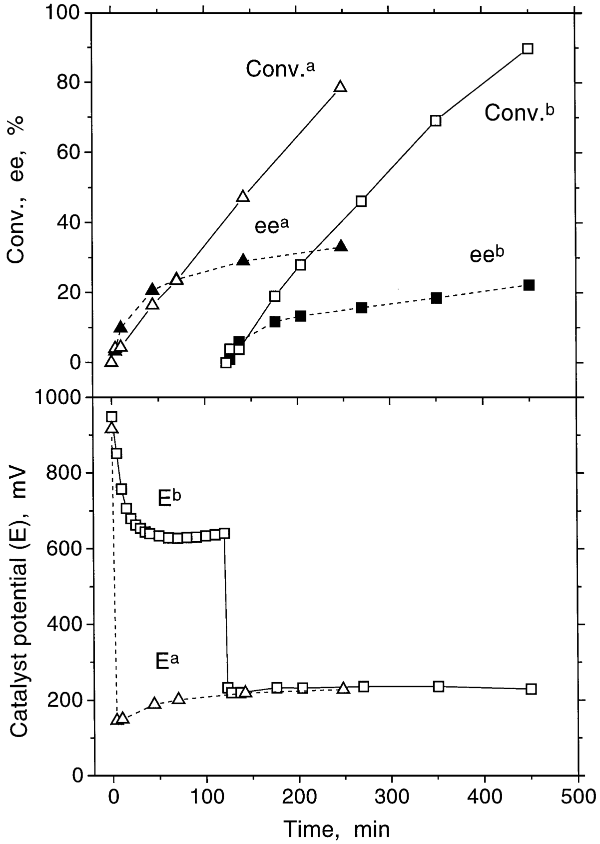


FIG. 3. Top, enantiomeric excess (ee, filled symbols) and conversion (open symbols) during EtPy hydrogenation in 1-propanol; bottom, catalyst potential (E) during reaction; (a) (▲ and △), prereduced catalyst and distilled EtPy are used; (b) (■ and □), untreated catalyst and undistilled EtPy are used, and the slurry is mixed in nitrogen for 2 h before hydrogenation; conditions, 250 mg 5 wt% Pt/alumina, 45 ml 1-propanol + 5 ml 0.1 *M* aqueous Na_2SO_4, 150 mg CD, 6 ml EtPy, $n = 1000\ \text{min}^{-1}$.

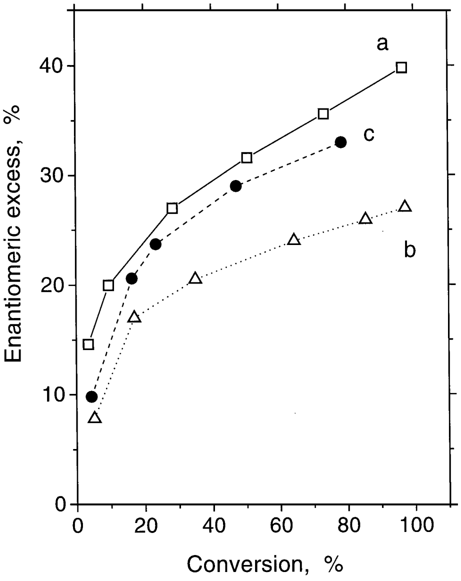


FIG. 4. Influence of catalyst pretreatment, EtPy distillation, and the presence of aqueous Na_2SO_4 in 1-propanol on the enantioselective hydrogenation of EtPy; (a) prereduced catalyst and distilled EtPy are used; (b) untreated catalyst and undistilled EtPy are used, and the slurry is mixed in nitrogen for 2 h before hydrogenation; (c) prereduced catalyst and distilled EtPy are used and 5 ml 0.1 *M* aqueous Na_2SO_4 is added to the mixture; conditions, 220 mg 5 wt% Pt/alumina, 45 ml 1-propanol, 150 mg CD, 6 ml EtPy, $n = 750$ min^{-1}.

reactor, the Pt surface was slightly oxidized which explains the positive starting potential of higher than 900 mV.

In case b in Fig. 3 the decreasing catalyst potential during mixing in nitrogen (0–60 min) indicates the reduction of Pt/alumina by the solvent 1-propanol. The reduction of surface Pt oxide (after storage in air) is slow and incomplete compared to the treatment with hydrogen, in agreement with former observations (2, 43). The minimum potential value was reached at about 60 min, and then the catalyst potential increased again due to the formation of strongly adsorbed organic species and to catalyst poisoning (see above). When hydrogen was introduced after 2 h, the catalyst potential decreased rapidly to 220 mV and remained in the potential range of 220–235 mV up to 90% conversion.

Figure 3 demonstrates that in the first part of pyruvate reduction (0–20% conversion) the catalyst potential differed by about 70 mV, depending on the pretreatment conditions. For comparison, if the organic species present on the Pt surface had no contribution to the measured catalyst potential, this potential difference would correspond to more than two orders of magnitude difference in surface hydrogen activity, due to the logarithmic correlation (Nernst equation). In fact, the difference of catalyst potential during reaction is likely due to variations in surface concentrations including hydrogen and organic species ("mixed potential").

There is a significant deviation in the ee–time curves in favor of the relatively clean system (prereduced catalyst, distilled EtPy, no mixing in nitrogen), as illustrated in the top part of Fig. 3. The conversion–time correlation is not characteristic of the rate of surface reaction as the reactor was operated in the transport limited regime. The relatively large amount of catalyst (mainly responsible for the mass transport limitation) was necessary to obtain stable and reliable catalyst potential. Similarly, the addition of aqueous Na_2SO_4 to 1-propanol solvent was inevitable for obtaining sufficient conductivity in the system.

It was proved in separate experiments that the influence of aqueous Na_2SO_4 on the enantioselectivity is minor (Fig. 4, curves a and c). Besides, Fig. 4, curves a and b, illustrate that the ee is considerably higher when working under relatively clean conditions (catalyst prereduction at high temperature, distilled EtPy, no prolonged mixing in alcohol), and in this case the reactions were performed in 1-propanol in the absence of aqueous Na_2SO_4.

As an addition to the FTIR studies previously shown, Fig. 5 demonstrates the coverage of Pt by irreversibly adsorbed species formed during the adsorption of 1-propanol. The positive sweep of the first cycle (continuous line) was measured after immersing a carefully purified platinized Pt electrode into 1-propanol for 1 min. In the hydrogen region (below 300 mV) there is only one broad maximum due to the presence of poisoning species. The big asymmetric maximum between 500 and 750 mV indicates the oxidation of these species. (CO_{ads} was likely oxidized by air during washing of the Pt electrode.) The second cyclic

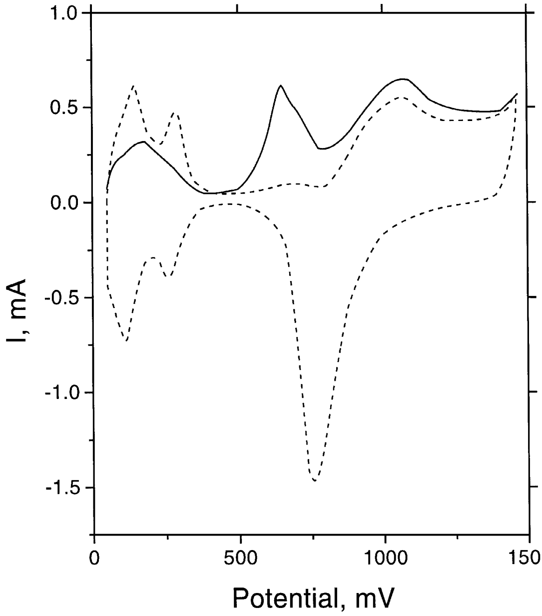


FIG. 5. Cyclic voltammograms of a platinized Pt electrode (1 cm^2 geometric surface area) after immersing it into 1-propanol for 1 min and then washing with water; continuous line, anodic branch of the first cycle; dashed line, second cycle; (0.5 *M* aqueous H_2SO_4; sweep rate, 200 mV min^{-1}).

voltammogram (dashed line) is already rather similar to that of pure Pt. Based on the area difference in the hydrogen region under the curves of poisoned and pure Pt, 45% of the hydrogen adsorption sites were covered by irreversibly adsorbed organic species after 1 min contacting of Pt and 1-propanol. Applying longer contact time, the amount of surface impurities increased slowly (not shown in Fig. 5). [Many more details of alcohol adsorption on Pt in aqueous alkaline or acidic solutions can be found in the electrocatalytic literature (34–37)].

Ethyl Pyruvate Hydrogenation: Influence of Reactant Purity

When performing the pyruvate reduction in the clean, "nonreactive" solvent acetic acid and using prereduced catalyst and distilled EtPy, the ee was still very low at low conversion and reached slowly the final value of 71% (Fig. 6). However, GC-MS, FTIR, and NMR analysis indicated that the commercial EtPy contained 0.6–1.9 wt% ethyl lactate even after a careful vacuum distillation, using a separating column. When the amount of racemic product was taken into consideration (in this example 1.8 wt%), the corrected enantiomeric excess (ee*) showed a strikingly different time dependence (Fig. 6). The standard deviation of the determination of the initial ee* values at low conversion was relatively high due to the analytical error, but even the highest difference in ee* in the whole conversion range was only 6%. The final values of ee and ee* (ca. 71 and 72%, respectively) are almost identical, as expected.

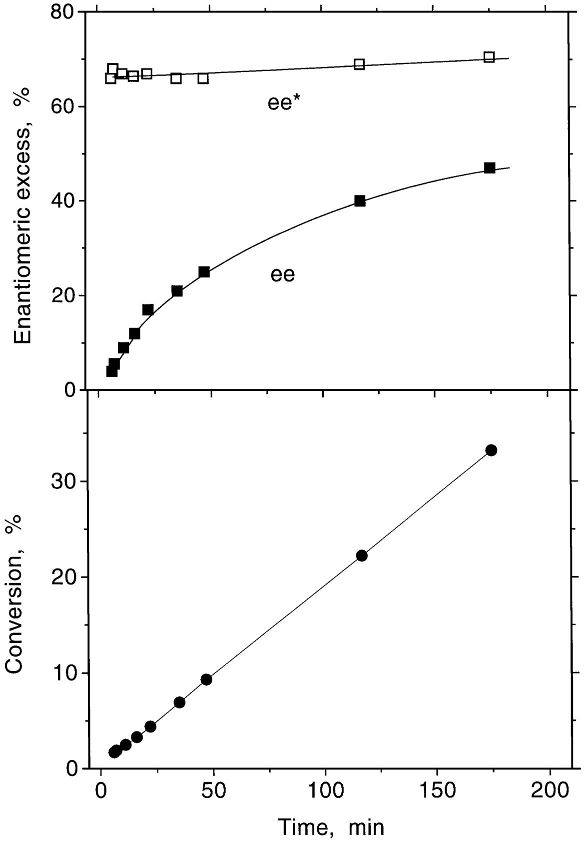


FIG. 6. Influence of ethyl lactate impurity in EtPy on the initial transient behavior in acetic acid. Top, enantiomeric excess as measured (ee, final value, 71%) and after correction with the ethyl lactate impurity (ee*, final value, 72%); bottom, conversion of EtPy. Conditions, 230 mg 5 wt% Pt/alumina, 50 ml acetic acid, 10 mg CD, 6 ml EtPy, $n = 250$ min^{-1}.

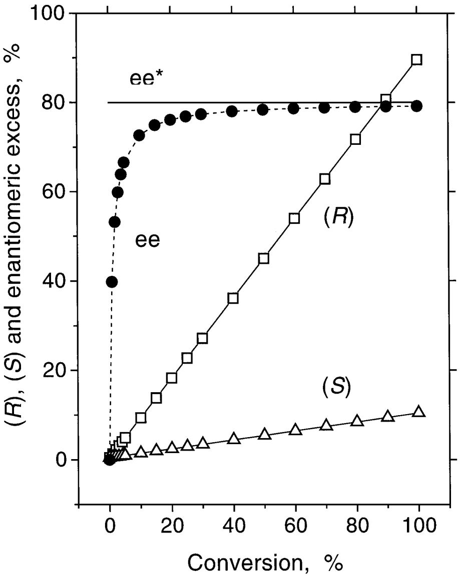


FIG. 7. Calculated formation of (*R*)- and (*S*)-lactate during EtPy hydrogenation and the development of the apparent enantiomeric excess (ee), assuming 0.5 mol% (*R*)- and 0.5 mol% (*S*)-lactate in the reactant EtPy, and a constant, 80% "real" enantiomeric excess (ee*) to (*R*)-lactate.

The following calculations were made in order to illustrate the dramatic effect of racemic ethyl lactate impurity in EtPy in the initial period of the reaction. For the sake of simplicity, it was assumed that EtPy contains 0.5% (*R*)- and 0.5% (*S*)-lactate, and the real enantiomeric excess (ee*) produced by the chirally modified Pt catalyst is 80% and independent of the conversion. The calculated amount of (*R*)- and (*S*)-lactate and the "apparent" ee (when the initial amount of ethyl lactate is not taken into consideration) are shown in Fig. 7. The conversion dependence of ee is very similar to those shown in Figs. 2–4 and 6. These calculations provide a simple explanation to the recent observation that the initial ee in EtPy hydrogenation is very low, close to zero and increases with the conversion of EtPy (24, 44, 45). Note that this peculiar behavior of the ee vs conversion curve has been used recently (44, 45) as the basis for suggesting a new mechanistic model for the enantioselective hydrogenation of α-ketoesters.

Ethyl Pyruvate Hydrogenation: Solvent Effect

The observation that the real ee is high already at the beginning of the reaction and increases only in a minor extent with the conversion of EtPy is valid only to reactions

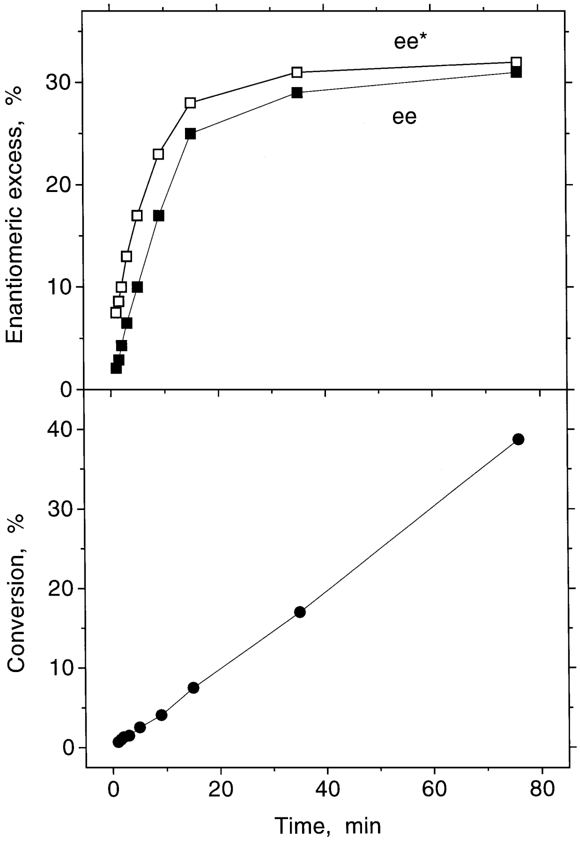
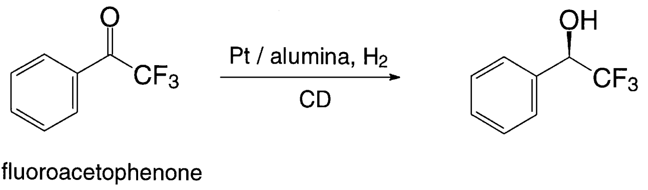


FIG. 8. Influence of ethyl lactate impurity in EtPy on the initial transient behavior in ethanol. Top, enantiomeric excess as measured (ee) and after correction with the ethyl lactate impurity (ee*); bottom, conversion of EtPy. Conditions, 230 mg 5 wt% Pt/alumina, 50 ml ethanol, 10 mg CD, 6 ml EtPy, $n = 250\ \mathrm{min}^{-1}$.

performed in clean and nonreactive solvents such as acetic acid. As was pointed out above, primary aliphatic alcohols do not belong to this class of solvents. An illustration is shown in Fig. 8. The reaction conditions are identical to those listed in Fig. 6, except that the reaction was performed in ethanol instead of acetic acid. The measured and the corrected enantiomeric excess (ee and ee*) differ only 5–7% at the beginning of the reaction, and the initial value of the real excess to (*R*)-lactate is very low, below 10%.

The reactions shown in Figs. 6 and 8 were performed in the transport-limited region in order to emphasize the detrimental effect of ethanol. The comparison of the two figures demonstrates that in acetic acid the hydrogen "starvation" conditions had only moderate negative influence on the initial and final enantioselectivities. However, in ethanol or propanol good ee can be achieved only with high surface hydrogen concentration. For example, when working in the kinetic regime and at high hydrogen pressure (70 bar), 82 and 92% ee was obtained in ethanol and acetic acid, respectively, under otherwise identical conditions (8). Under the conditions of Figs. 6 and 8, the difference in the final ee obtained in these two solvents was much higher, 36%. It seems that the sufficiently high surface hydrogen concentration "cleans" the Pt surface and reduces the duration of the initial transient period which is necessary for obtaining good final (integral) ee.



SCHEME 2

Enantioselective Hydrogenation of Trifluoroacetophenone over Pt/Alumina

The influence of the order of addition of reactant and modifier was studied in the hydrogenation of 2,2,2-trifluoroacetophenone to (*R*)-1-phenyl-2,2,2-trifluoroethanol (Scheme 2). In this case the reactant was free from product. It has been shown previously (46) that in this reaction the measure of enantiodifferentiation is inversely proportional to the hydrogen pressure and good ee (50–60%) can be achieved only at low surface hydrogen concentration. Accordingly, atmospheric pressure and low mixing efficiency were applied.

The conversion dependence of enantioselectivity is plotted in Fig. 9. There was a moderate initial increase of ee,

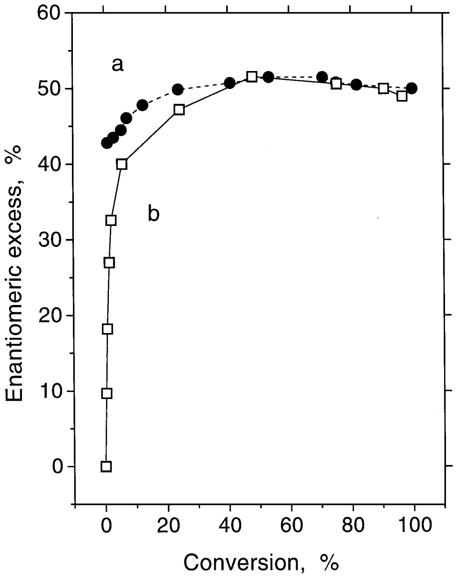
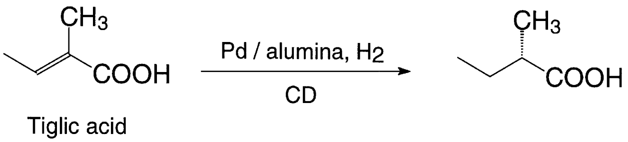


FIG. 9. Influence of the order of addition of reactant and modifier; (a) trifluoroacetophenone was added to the mixture of prereduced catalyst, modifier, and solvent; (b) CD was added to the mixture of prereduced catalyst, reactant, and solvent (racemic product formed during prereduction was taken into correction); conditions, 230 mg 5 wt% Pt/alumina, 40 ml 1,2-dichlorobenzene, 8 mg CD, 2 ml trifluoroacetophenone, $n = 250\ \mathrm{min}^{-1}$.



SCHEME 3

when the reactant was injected into the reaction mixture in a hydrogen atmosphere. When the reaction was started as a racemic hydrogenation and the cinchona alkaloid was added afterward, the ee increased rapidly and after a few minutes (5–6% conversion) the difference between the two curves was less than 5%.

When the order of addition to the reactor of Pt/alumina, reactant, solvent, and CD was varied and the reaction was started by introducing hydrogen, the change in the conversion dependence of ee was even smaller, barely exceeding the analytical error. A similar behavior was observed in the enantioselective hydrogenation of EtPy, at least in acetic acid solvent.

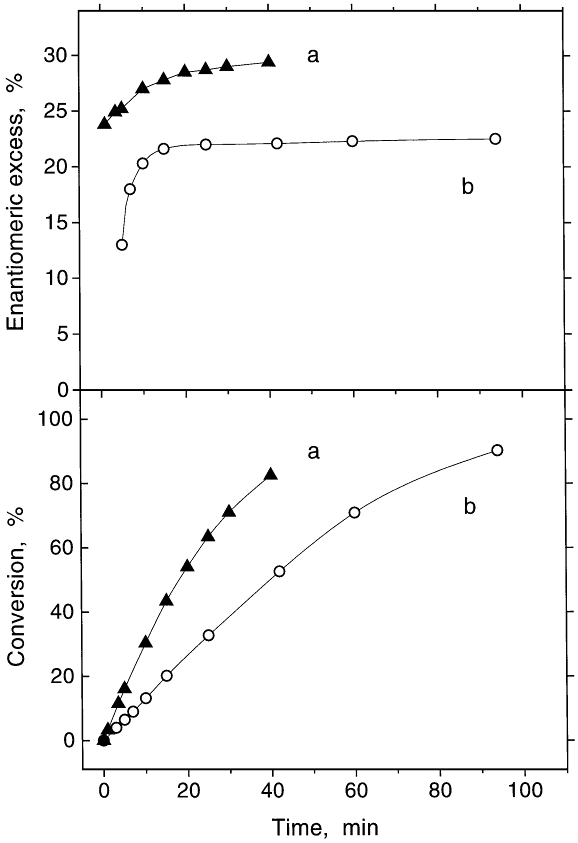


FIG. 10. Enantioselective hydrogenation of tiglic acid over a 5 wt% Pd/alumina using reactants from different suppliers; (a) Fluka; (b) Aldrich. For conditions, see Experimental.

Enantioselective Hydrogenation of Tiglic Acid over Pd/Alumina

The saturation of the C=C double bond of 2-methyl-2-butenoic acid (tiglic acid) to form (*S*)-2-methyl-butanoic acid over a 5 wt% Pd/alumina catalyst (Scheme 3) provides a further example on the dramatic influence of impurities. The reactant was purchased from two different suppliers and no significant alteration in their composition could be detected by GC analysis. Nevertheless, the rate of tiglic acid conversion differed by a factor of 2.2, as illustrated in Fig. 10. The final (integral) values of enantiomeric excess and the time dependence were also strikingly different. Similarly strong influence of reactant purity on the initial rate and final ee has been reported very recently for EtPy hydrogenation under high pressure (10).

DISCUSSION

The observation of an initial transient period in a catalytic hydrogenation reaction is not new, neither is the influence of impurities and side reactions on the transient period and on the final, "steady-state" performance of the catalyst. But there are only very few studies aiming at revealing the real nature of the transient period in such a complex and demanding reaction as asymmetric hydrogenation over chirally modified Pt metals. It has been proposed recently (24–26) that the striking effects observed during the enantioselective hydrogenation of EtPy on CD-modified Pt are free from any influence of impurities and side reactions, and the astonishing coupling of ee with conversion is an intrinsic feature of the catalyst system.

If we accept that the simple addition of traces of chiral modifiers to the reaction mixture (a few 100 ppm related to the reactant) before the hydrogenation of EtPy can change the product distribution from (*R*)-lactate: (*S*)-lactate = 50 : 50 (racemic reaction) to 97 : 3 (8), we cannot neglect the presence and possible influence of other foreign materials. (The term foreign material means here any inorganic or organic species except the reactant, product, solvent, and modifier.) On the basis of the results presented in this work, we attempt to interpret some interesting phenomena observed during enantioselective hydrogenation reactions. The common feature of these reactions is that CD was applied as the source of chiral information, together with the active metal Pt or Pd. We propose that the variations in enantioselectivity and reaction rate during the initial period of the reactions, and in a certain extent also in the final integral values, can be attributed to the following two main reasons.

(i) Impurities in the reactant. It has been shown for EtPy (10) and demonstrated now for tiglic acid in Fig. 10 that impurities present in the reactant can have a dramatic influence on the rate and enantioselectivity of the reaction, and not only in the initial transient period. Accordingly,

the results of some kinetic analysis of enantio-selective hydrogenation reactions obtained without any purification of the reactant should be considered with due care.

The considerable amount of ethyl lactate impurity in commercial EtPy cannot be completely removed by distillation due to the rather similar boiling points. The presence of the racemic product in the reactant provides at least in part the explanation to the conversion dependent change of ee at the beginning of the reaction, up to 10–20% conversion (24, 44, 45). (The other reason is the use of alcoholic solvent, as will be discussed below.) The unexpectedly large effect of about 1 wt% racemic ethyl lactate on the initial ee has been illustrated by a simple calculation in Fig. 7. But this effect is minor at full conversion (does not surpass the usual standard deviation of determining ee by GC analysis). Consequently, the formerly reported enantiomeric excesses measured at the end of the reaction (usual procedure) are barely distorted by this impurity.

(ii) Destructive adsorption of EtPy and alcoholic solvents on Pt. The *in situ* FTIR analysis of the interaction of Pt/alumina with EtPy or ethanol vapor in inert atmosphere (Fig. 1) proved that the destructive adsorption of the reactant and the commonly applied primary alcohol solvent result in a considerable coverage of Pt by CO. Necessarily from the stoichiometry of the decomposition reaction, some organic residues are also formed, as illustrated by the simple cyclic voltammetric model experiment of the 1-propanol–Pt interaction (Fig. 5). On the basis of former studies on polycrystalline Pt in aqueous acidic medium (34–37) we can expect a similar destructive adsorption of many aliphatic and aromatic alcohols and carbonyl compounds on Pt, but the behavior of Pd is yet unclear.

It is reasonable to assume that the destructive adsorption of the carbonyl compound type reactant may be influenced by the presence of the strongly adsorbing CD. But this assumption could not be proved yet: a change in the order of addition of reactant and modifier did not result in significant deviation in the reaction rate or enantioselectivity, at least not under the conditions applied.

The combined electrocatalytic and catalytic experiments (Figs. 3–5 and 7) explain why the use of primary alcohol solvents (e.g., ethanol, propanol) results in relatively poor ee in the enantioselective hydrogenation over Pt catalysts. It must be emphasized that any kinetic analysis performed in alcohols provides questionable results due to the rapid decomposition of the solvent on the active sites. A further uncertainty in using short-chain primary alcohols as solvents is the formation of hemiketal from the activated carbonyl compound reactant (47). In the presence of a base catalyst (e.g., CD) the hemiketal formation is rapid (48) and precedes the main reaction. Accordingly, it is not even clear what is the reaction studied: the hydrogenation of the hemiketal (which is already a chiral compound) or that of the free carbonyl compound.

Interestingly, when working in acetic acid there is only a small change in the ee with conversion (Fig. 6). Seemingly, the development of the chirally modified surface (steady-state conditions) in this solvent is barely disturbed by the destructive adsorption of EtPy on Pt. It is understandable now why acetic acid is the best solvent for the enantioselective hydrogenation of EtPy and the use of protonated CD (e.g., cinchonidine hydrochloride) in another solvent is less efficient.

The FTIR studies (Fig. 1) also indicated that the presence of hydrogen diminished the impurity level on Pt. It is known (6, 7) that high hydrogen pressure has a positive effect on the ee in the hydrogenation of α-ketoesters. On the basis of our catalytic, electrocatalytic and FTIR results we propose that the initial increase of ee with conversion and the positive effect of high hydrogen concentration are mainly due to the rapid and efficient removal of impurities from the Pt surface. The term impurity is used in a rather broad sense, including all foreign materials which can disturb the proper adsorption of reactant and chiral modifier and their interaction on the Pt surface. A strongly adsorbing foreign material can hinder the proper adsorption and/or interaction of reactant and modifier and diminish the ee. On the other hand, it is also possible that under certain conditions the foreign material hinders the racemic (unmodified) reaction to a higher extent than the enantioselective (modified) reaction. An example is the increase of the final ee by 10% in the presence of 0.4 $\mathrm{g \cdot liter^{-1}}$ quinoline in EtPy hydrogenation over a CD–Pt/alumina catalyst system (8).

The hydrogenation of trifluoroacetophenone on the CD–Pt/alumina and tiglic acid on the CD–Pd/alumina catalyst systems indicate that the increasing ee with reaction time in the initial transient period is a phenomenon which is not restricted to the enantioselective hydrogenation of α-ketoesters. Besides, the "cleaning" effect of hydrogen in the initial transient period and the positive effect of high hydrogen concentration on the final, integral ee are not necessarily coupled. In case of trifluoroacetophenone high surface hydrogen concentration decreases the ee (46). Nevertheless, after starting the reaction by introducing hydrogen the ee increased by 5–20%, depending on the conditions.

CONCLUSIONS

The intriguing transient behavior at the beginning of the enantioselective hydrogenation of ethyl pyruvate over cinchonidine-modified Pt, reported recently (24, 25), has been studied by means of *in situ* measurements of catalyst potential, cyclic voltammetry, and FTIR. The studies indicate that the observed phenomenon of a rising rate and increasing enantioselectivity in the initial period can be traced back to impurities in the reactant ethyl pyruvate and to contamination of the Pt surface caused by adsorbed CO and $C_xH_yO_z$ type organic residues, originating from destructive adsorption of ethyl pyruvate and alcoholic solvents. In light of these findings the proposed explanation for the transient behavior observed, a "reaction-driven equilibration" of the chiral surface environment needs to be reexamined.

Studies of other enantioselective hydrogenation reactions catalyzed by cinchonidine-modified Pt or Pd revealed that the effect of surface contamination by uncontrolled side reactions or impurities is much more prominent than that of surface equilibration after perturbation of the system at start up.

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