JOURNAL OF CATALYSIS **173,** 282–294 (1998)
ARTICLE NO. CA971925

Kinetic Studies of the Enantioselective Hydrogenation of Ethyl Pyruvate Catalyzed by a Cinchona Modified Pt/Al_2O_3 Catalyst

Hans-Ulrich Blaser,[1] Hans-Peter Jalett, Marc Garland,[2] Martin Studer, Hans Thies, and Amina Wirth-Tijani

Catalysis and Synthesis Services, Novartis Services AG, R-1055.6, Basel, CH-4002 Switzerland

Received January 2, 1997; revised May 16, 1997; accepted September 10, 1997

The kinetics of the hydrogenation of ethyl pyruvate to ethyl lactate on a 5% Pt/Al_2O_3 catalyst in toluene was investigated both in absence and in presence of the chiral modifier 10,11-dihydrocinchonidine. It was shown that all important prerequisites for obtaining reliable kinetic data for the reaction were fulfilled. The effects on rate and enantiomeric excess of catalyst loading, modifier and substrate concentrations, hydrogen pressure, and temperature were determined for the unmodified and the modified system. The modified reaction was approximately 20–30 times faster than the unmodified reaction. A significant increase of the enantiomeric excess from 1 to 40 bar was noticed. Apparent activation energies were estimated to be 4–6 kcal/mol. Rate equations were developed for various kinetic schemes on the basis of the Langmuir–Hinshelwood–Hougen–Watson formalism and fitted to the kinetic data. Several such schemes described the measured data reasonably well and in most cases explanations other than the one considered to be the most plausible were also in agreement with our data. For the unmodified catalyst, we propose a competitive adsorption of the α-ketoester and hydrogen and the addition of the first hydrogen atom to be rate determining. On a chiral site, the rate determining step (RDS) to the major enantiomer is proposed to be the addition of the second hydrogen, whereas the RDS for the minor enantiomer remains the first H addition. On the basis of this interpretation, different proposals advanced in the literature for the mode of action of the cinchona modified Pt catalyst were compared. © 1998 Academic Press

INTRODUCTION

Enantioselective hydrogenation is a topic of current interest not only from a synthetic but also from a mechanistic point of view (1). Until recently, most efforts concerning the elucidation of the reaction mechanism have been dedicated to homogeneous catalytic systems (2). Chiral heterogeneous catalysts have received less attention, even though they have potential technological advantages and offer some interesting conceptual opportunities (3–5). Kinetic studies for the enantioselective hydrogenation of β-ketoesters have been reported for tartrate-modified Ni catalysts both in the liquid and the gas phase (4, 6, 7). Based on these results and on other observations, several mechanistic schemes were developed for this reaction (4, 6–8). Preliminary kinetic results were also reported for Pt/Al_2O_3 and Pt/SiO_2 catalysts modified with cinchona alkaloids for the hydrogenation of α-ketoesters in the liquid phase (3, 9–15).

The Pt cinchona system was first described by Orito and co-workers in 1979 (16) (Fig. 1). The most fascinating aspect of this catalyst is the fact that the presence of the cinchona modifiers leads not only to enantioselection but also to a rate acceleration by a factor of 10–100 (12, 17). This effect was studied in more detail for the hydrogenation of ethyl pyruvate (etpy) catalyzed by Pt/Al_2O_3 modified with dihydrocinchonidine (HCd) (10). An equilibrium was proposed between unmodified, unselective Pt sites with low activity and modified, enantioselective sites with high activity. However, these studies could not answer the question about the mode of action of the chiral modifier.

We reasoned that a comparison of the kinetics of the modified and the unmodified catalyst might provide more insight into the role of the cinchona molecule during the hydrogenation. For example, a very important question is that of whether the modifier simply causes a change in the rate determining step or leads to a completely different mechanism for the hydrogenation. In this contribution, we present a kinetic study investigating the influence of hydrogen pressure, etpy concentration, modifier concentration, catalyst loading, and temperature on rate and the enantiomeric excess (e.e.). The results are interpreted in the framework of the Langmuir–Hinshelwood–Hougen–Watson (LHHW) formalism and consistent mechanistic schemes are proposed. This paper discusses in depth data that were published partly in (19) and, more importantly,

---

[1] To whom correspondence should be addressed. Fax: ++41-61-697-8453. E-mail: hans-ulrich.blaser@sn.novartis.com.

[2] Present address: Department of Chemical Engineering, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260.

0021-9517/98 $25.00
Copyright © 1998 by Academic Press
All rights of reproduction in any form reserved.

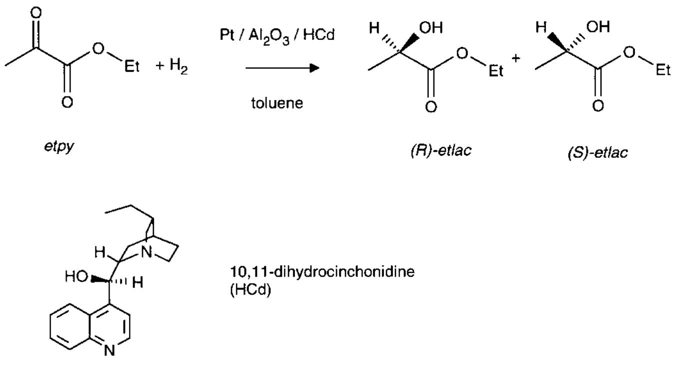

FIG. 1. Hydrogenation of etpy. Reaction scheme, catalyst, and modifier structure.

gives the derivation of all kinetic models that were considered.

METHODS

Reagents

Etpy was purchased from Fluka (purum) and Boehringer (purum). Before use, it was distilled and kept at 5°C for a maximum of 3 weeks. 10,11-Dihydrocinchonidine (HCd) was prepared from commercially available cinchonidine (100 g, Fluka, purum) by hydrogenation with 5% Pd/C (10 g, Engelhard 4522) in 600 ml 1 M aqueous HCl at room temperature and 1 bar H_2. After neutralization with 50% NaOH under stirring, the precipitated HCd was filtered off and washed with 1.5 liter deionized water until chloride-free ($AgNO_3$ test). The white solid was dried in vacuum at 100°C. Yield 87.4 g (86.8%). mp 233–235°C. Elemental analysis ($C_{19}H_{24}N_2O \cdot 0.04\ H_2O$, 297.13). Calc.: C 76.80, H 8.17, N 9.43, H_2O 0.24. Found: C 76.49, H 8.08, N 9.26, H_2O 0.24. 5% Pt/Al_2O_3 (Engelhard 4759) with a Pt dispersion of 0.24 (determined by CO adsorption (18)) was prereduced for 2 h at 400°C under flowing H_2. This catalyst could be stored for two weeks under air with no significant loss in selectivity or activity. Toluene (Fluka, puriss. p.a.) was used as received.

Kinetic Measurements

All reactions were carried out in a thermostated 50 ml autoclave equipped with baffles, two thermocouples, and a magnetic stirrer ($\varnothing = 5$ mm, $l = 20$ mm). A reservoir and a pressure regulator allowed experiments to be carried out under isobaric conditions. Pressure and temperature were measured in the autoclave and in the reservoir every 10 s and recorded with a Micromec data recorder (Suprag AG, Zürich, Switzerland).

For a description of the measured datasets see Table 1. In the unmodified system (Series U1–U9) 5–450 mg prereduced 5% Pt/Al_2O_3, 1–30 ml etpy, and 0–29 ml toluene were introduced into the autoclave in this sequence. The

TABLE 1

Datasets U1–U9 and M1–M10

Series	Supplier	Activity coefficient	pH_2 (bar)	[Mod] (mM)	[E] (M)	Cat (mg)	T (°C)	Number of datapoints
U1	Boeringer	1.00	21	0	3.0	50–350	20	4
U2	Fluka	1.00	101	0	3.6	50–450	22	9
U3	Fluka	1.00	0–34	0	1.4	100	20	20
U4	Fluka	1.00	0–161	0	1.4	400	22	11
U5	Boeringer	1.00	0–101	0	3.0	250	20	6
U6	Fluka	1.00	21	0	0–9.0	250	20	13
U7	Fluka	1.00	101	0	0–9.0	400	22	11
U8	Boeringer	1.00	21	0	3.0	250	0–70	8
U9	Fluka	1.00	101	0	1.4	400	0–70	8
M1	Boeringer	1.00	21	1.1E-03	3.0	5–150	20	7
M2	Boeringer	1.00	0–101	1.1E-03	3.0	50	20	6
M3	Boeringer	1.00	0–101	1.1E-03	3.0	50	20	7
M3a	Fluka I	0.86	1–101	1.1E-03	3.0	50	20	8
M4	Fluka II	2.21	0–141	6.7E-04	5.0	25	20	13
M4a	Fluka I	0.86	0–41	6.7E-04	1.8	25	20	6
M4b	Fluka I	0.86	0–101	6.7E-04	5.0	50	20	11
M5	Boeringer	1.00	21	1.1E-03	0–3.9	50	20	12
M6	Boeringer	1.00	21	1.1E-03	0–9.0	50	20	15
M7	Fluka II	2.21	101	6.7E-04	0–9.0	25	22	15
M8	Boeringer	—	21	1.1E-03	3.0	50	0–70	8
M9	Fluka I	—	101	6.7E-04	1.8	25	0–70	8
M10	Fluka I	0.86	101	0-1.1E.3	3.0	50	22	22

autoclave was purged five times with argon (21 bar) while stirring and three times with hydrogen (21 bar) without stirring. Then both the reservoir and the autoclave were pressurized with hydrogen. Negligible hydrogen absorption occurred prior to stirring, and the experiments were started by turning the magnetic stirrer on (900–1300 rpm). Under the reaction conditions, the liquid phase became saturated with hydrogen within 1–3 min. After 10–60 min, the autoclave was purged with argon, and the solution was filtered. After evaporating the toluene, the products were analyzed. In all experiments, the conversion was higher than 15%.

For the modified system (Series M1–M10) experiments were similar to those described above. However, only 3–75 mg prereduced 5% Pt/Al_2O_3 was used and 5–20 mg HCd was added after loading the catalyst.

Conversion to ethyl lactate (etlac) was calculated by the pressure drop in the reservoir and confirmed by glc (2 m OV 101; 45°C). The e.e.'s were determined by glc after derivatization of etlac with isopropyl isocyanate (25 m capillary Chirasil-L-Val; 140°C); in some instances both conversion and e.e. were determined by analyzing the crude reaction mixture (30 m capillary β-Dex 100; 75°C). The R-enantiomer of etlac was the major enantiomer in all experiments with HCd modifier.

The initial rates of hydrogenation were calculated from the pressure drop in the reservoir ($r_1 = dH_2/dt$ in mmol H_2/min, taking the compressibility of hydrogen into account (20)). Usually, the rate of hydrogenation was evaluated at reaction times of 3–8 min. Both a graphical and a linear least square method were used for determination of the initial rates. The results were similar for both methods with a reproducibility of ±10%.

For all calculations below, the actual hydrogen concentration in the reaction mixture was used. The solubility of hydrogen in toluene and mixtures of toluene and etpy was determined by measuring the amount of gas dissolved at 20 and 100 bar and at five different etpy concentrations. A simple linear approach with two adjustable parameters a and b described the concentration dependence of hydrogen on pressure and varying etpy/toluene ratios well. For the temperature dependence, the approach of (21) was used (exponential part of the equation). The constant c was determined from a third data set with varying temperatures ((22), data not shown). The following expression allows one to calculate the hydrogen concentration:

$$[\mathrm{H_2}] = \mathrm{pH_2}(a + b[\mathrm{etpy}])e^{c\left(\frac{1}{293} - \frac{1}{273+T}\right)}$$

$$a = 2.633 \times 10^{-3}\ \frac{\mathrm{mol}}{\mathrm{liter} \cdot \mathrm{bar}}$$

$$b = -7.5 \times 10^{-5}\ \frac{1}{\mathrm{bar}} \quad c = 764\ \mathrm{K}.$$

All curve fitting was done using the Excel-Solver subroutine (MS Excel 7.0) with the settings "Newton," "Forward," and "linear." In some cases, e.g., model MV2 and MV6 for the unmodified system (see below), local minima were observed. To circumvent this problem, different sets of initial estimates were tested. With our data, however, only models with a maximum of three (unmodified system) or five parameters (modified system) *always* gave unambiguous results.

RESULTS

In this section, two issues are addressed. First, the prerequisites for obtaining reliable kinetic data are discussed. Next, the dependencies of the observed rates and enantioselectivities on catalyst loading, etpy concentration, hydrogen pressure, and temperature will be described and discussed. A preliminary description of selected results has appeared (19).

Prerequisites for Obtaining Reliable Kinetic Data

Stoichiometry and Stability of the System Components

Under the conditions used in this experimental study, the selectivity to etlac was >99% as determined by glc, and the amount of hydrogen consumed was equal to the amount of etlac formed. Problems due to deterioration of both etpy and cinchona alkaloids are known to occur. However, such difficulties usually occur under reaction conditions considerably different from those in this study and at longer reactions times (23–25). To minimize these problems, only initial rate data were used in this study.

Reproducibility of Rate and e.e. Measurement

The evaluation of the measured rates by the graphical or the least square procedure allowed a reproducibility of approximately ±10%. However, in the course of this investigation, which lasted several years, a number of different batches of etpy, catalyst, and solvents were used. In addition, different autoclaves were used and different investigators carried out experiments. Not surprisingly, variations of the optical yields and especially of the rates were observed for series having the same initial conditions but performed at different dates during the investigation. The etpy quality was the major factor affecting the observed rates (26, 27). In order to be able to fit the kinetic models to the data points of all series, it was necessary to introduce an "activity factor" for the modified system. For relative rates see Table 1. At the moment we have no reasonable explanation for this phenomenon. For the unmodified system, the differences were much smaller and no correction was made.

Induction Periods

An increase in e.e. with conversion was described for the hydrogenation of β-keto esters using tartrate-modified Ni catalysts in the liquid (7) and the gas phase (28). Careful analysis of our reaction mixtures has confirmed the findings recently published by the group of Blackmond (29, 30) that the initial e.e.'s determined at very low conversions are consistently lower than subsequent e.e.'s. This can lead to a significant difference of 3–30% between measured e.e. at a specific reaction time and the actual incremental e.e. being produced (19). Indeed, it is important to recognize that measured e.e.'s are the average value obtained over the preceding reaction period. In the present investigation, the e.e. was consistently measured at conversions greater than 15%. Consequently, calculations indicated that the difference between the measured and the incremental e.e.'s is smaller than 5%. As reported by other investigators (13, 17, 31), S-shaped curves can arise in plots of pressure versus time and similar behavior was occasionally obtained in this study. In these cases, the initial rates were lower than the maximum rates but the difference was less than 10–20%. Such induction phenomena indicate that these modified heterogeneous catalysts can require appreciable time before they reach maximal activity. However, the exact reason for this behavior is still unknown.

Mass Transfer

In a previous study, mass transfer effects on the rate and e.e. during the hydrogenation of etpy with cinchona modified Pt/Al_2O_3 was studied in detail (11). It was shown that the overall mass transfer rate for hydrogen into the liquid phase significantly affected both rate and e.e. (10, 11). Upper limits for catalyst loading and minimum stirring speeds were identified for the autoclaves used in this study, and consequently, it was possible to avoid regions of hydrogen transfer limitation. Except for reactions with very high catalyst loading, we can exclude that hydrogen diffusion was rate limiting. One to three minutes was required to saturate the liquid phase with hydrogen for the experiments presented here. These initial mass transfer difficulties are one factor that can contribute to the observed induction period and the lower initial e.e.'s.

Effects of Changing Polarity of the Reaction Mixture

Changes in the dielectric constant of the reaction mixture might also affect the e.e. and rate. Two effects have to be considered: the conversion of etpy to etlac during the reaction and the changing of the etpy/toluene ratio. The dielectric constant (d.e.) of etlac is 15.4 at 30°C (32), while that of etpy is not known. Since molecular modeling gives very similar dipole moments for both etpy and etlac (33), we estimate a d.e. for etlac of approximately 15. This means that conversion of etpy to etlac does not affect the polarity of the reaction mixture very much. This is different for changing etpy concentrations in toluene, where the d.e. changes from approximately 3 at very low etpy concentration to 15 when the reaction is run in neat etpy. Figure 2 illustrates the apparent dependence of e.e. on the dielectric constant of the reaction mixture. The d.e. dependence found here is very similar to the one observed with different solvents (34). From this we conclude that the observed e.e. changes are due mainly to changes in polarity. On the other hand, the effect of etpy concentration on the rate is due to the changing substrate concentration (see below).

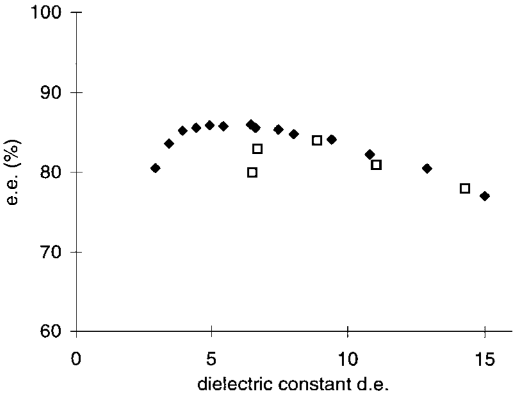

FIG. 2. Dependence of e.e. on the polarity of the reaction mixture. (◆) [etpy] = 0.4–9.0 M in toluene, 22°C, data from M7; (□) [etpy] = 3.4 M in solvents of various d.e., 20°C, 100 mg 5% Pt/Al_2O_3 (Engelhard 4759), (33). d.e. for reaction mixtures from a linear interpolation between the values of the solvent and etpy.

Conclusions with Respect to the Present Investigation

We must admit that some of the above prerequisites are not met as well as we thought at the beginning of our investigation. In some respects, the hydrogenation of α-ketoesters on Pt catalysts modified with cinchona alkaloids is more complex than we (and others as well) expected. Nevertheless, we are convinced that the data we have gathered allow not only a qualitative but also a quantitative interpretation. On the other hand, it is also clear that the quality of our results does not allow the discrimination of closely related kinetic models.

Kinetic Measurements

Table 1 describes the datasets used for this investigation (series U1–U9 for the unmodified system, series M1–M10 for the modified system; tables with the detailed results are available from the authors). Calculated curves in Figs. 3–7 represent the best fits obtained with the kinetic model variants MV1 (unmodified) and MV8 (modified, see below). In the preliminary publication (19), the fitting was carried out with slightly different assumptions and kinetic models.

The effect of *catalyst concentration* for the unmodified system was investigated for the interval of 50–350 mg catalyst at 21 bar and for the interval 50–450 mg catalyst at 101 bar (U1 and U2). The effect of catalyst loading for the modified system was examined with 3 M etpy and 1.1 mM HCd in the reaction mixture at 21 bar (M1) for the interval 5–150 mg catalyst. In both cases, the initial rates showed a

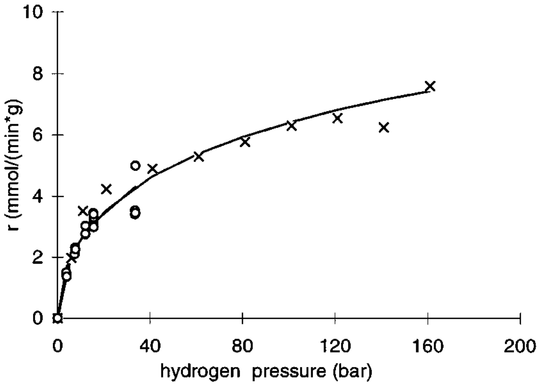

FIG. 3. Effect of hydrogen pressure on rate for the unmodified system. (×) Measured rate for series U3; (○) measured rate for series U4; (—) calculated rate.

first-order dependence on the catalyst concentration except for the modified catalyst above 50 mg catalyst, when the reaction order in hydrogen began to decrease due to non-negligible mass transport resistance for hydrogen. The optical yields obtained were constant (e.e. = 76 ± 1%) for the interval 5–75 mg catalyst, but began to decrease at higher catalyst loading, i.e., when the system got hydrogen starved. These results are in agreement with those in several studies for the hydrogenation of etpy with modified Pt catalysts (11, 35–37).

The effect of the *hydrogen concentration* for the unmodified system in the liquid phase was studied for hydrogen pressures of 3–160 bar at etpy concentrations of 1.4 and 3.0 M (see Fig. 3). The specific measured rates (rate per gram catalyst) were similar for 1.4 and 3 M etpy concentration. The rates increased with increasing hydrogen partial pressure, but there is a clear trend to lower reaction order above 60 bar. This type of saturation curve for hydrogen is rather uncommon, and we are unaware of similar results for ketone hydrogenations in the literature.

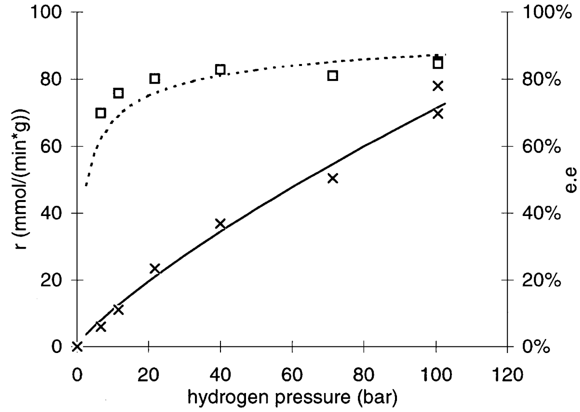

FIG. 4. Effect of hydrogen pressure on rate and e.e. of the modified system: Series M3a (1.8 M etpy). (×) Measured rate; (—) calculated rate; (□) measured e.e.; (· · ·) calculated e.e.

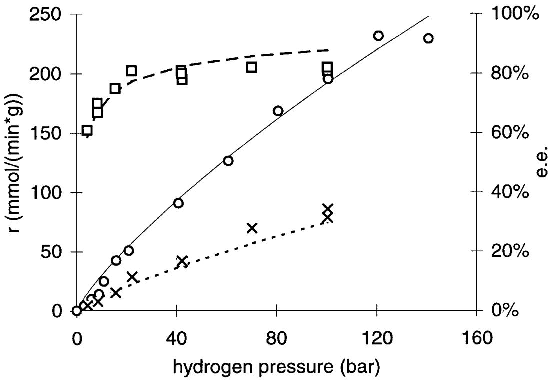

FIG. 5. Effect of hydrogen pressure on rate and e.e. of the modified system: Series M4a and M4b (3.0 M etpy). (○) Measured rate for series M4a; (×) measured rate for series M4b, (· · ·) and (—) calculated rates; (□) measured e.e. for series M4b; (- - -) calculated e.e.

For the modified system, the effect of the hydrogen concentration was studied at hydrogen pressures of 2–140 bar at etpy concentrations of 1.8 and 3.0 M (see Figs. 4 and 5). The rate of hydrogenation was essentially proportional to the hydrogen partial pressure over the entire interval. The observed e.e.'s increased noticeably in the interval of 0–40 bar, and then remained constant.

The effect of hydrogen pressure has been investigated by several groups and most reported a first-order rate dependence. Increases in enantioselectivity were reported by Augustine *et al.* (35), the group of Blackmond (29, 38), and by Böhmer *et al.* (39). Unsystematic variations (9, 13) and a drop (36) in e.e. with increasing pressure were described as well, plausibly explained for the latter case by a fast hydrogenation of the modifier at higher pressures.

The effect of the *ethyl pyruvate concentration* in absence of HCd was studied in a concentration range of 0.2–9 M (pure etpy), at both 21 and 101 bar hydrogen pressure (see Fig. 6). In both cases, maxima are observed. They occur at 0.6 M etpy for the 21 bar experiments and at 2.0 M for the

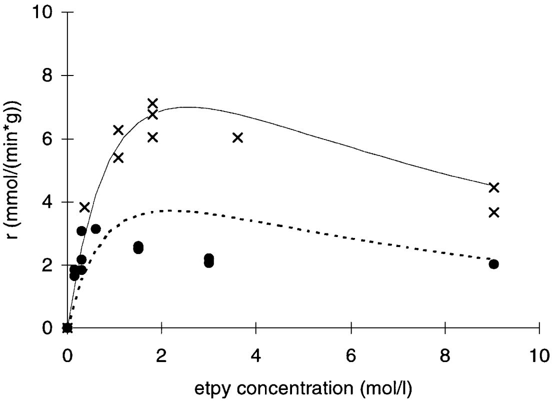

FIG. 6. Effect of etpy concentration for the unmodified system. (●) Measured rate for series U6; (×) measured rate for series U7; (· · ·) and (—) calculated rates.

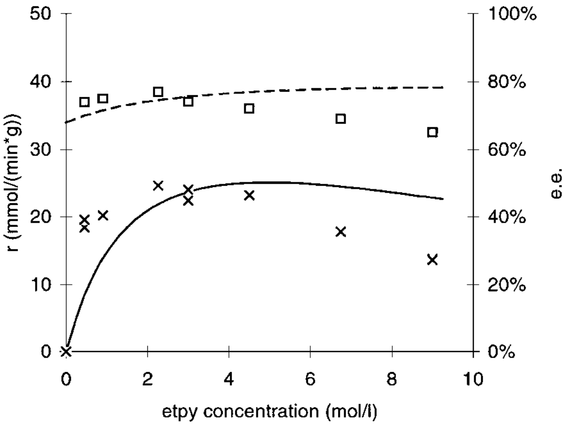

FIG. 7. Effect of etpy concentration for the modified system, series M6 (21 bar). (×) Measured rate; (—) calculated rate; (☐) measured e.e.; (- - -) calculated e.e.

101 bar experiments. At higher concentrations of etpy the rates decrease. In neat etpy (9 M) the rates are approximately 60% of their maximal value.

In the modified system, the effect of the etpy concentration was studied in the range of 0.4 to 9 M etpy at both 21 and 101 bar hydrogen pressure (M6, M7; Fig. 7 and (19)). As for the unmodified system, the rates showed a maximum but this was less pronounced. For the reaction at 21 bar there was some problem with the reproducibility but a maximum was observed between 1 and 3 M etpy. At 101 bar, the maximum rate was obtained at approximately 5 M etpy and it was 32 times higher than in the unmodified system. At both low and high pressure, a weak e.e. maximum was observed at approximately 2 M etpy. As discussed above, this effect is reproducible and is attributed to changes in the polarity of the reaction solution. In comparison, literature reports described dependencies similar to those described above (36, 39), almost constant rates (23, 29) but an increase of e.e. from 20–30% to >60% (23) as well as strong substrate inhibition (35).

The effect of the modifier concentration for a fully modified catalyst was studied, and a HCd concentration between 0.03 and 0.6 mM is necessary in the enantioselective hydrogenation of etpy in toluene (10, 40). This condition was fulfilled for all modified data sets except for M10, where the modifier concentration was varied between 0 and 1.1 mM. M10 shows the typical saturation curve with maximum e.e. and rate already at very low modified concentration as described by Garland *et al.* (10). M10 was incorporated in our kinetic analysis and it was shown that these data can be fitted well even with a simplified model (adsorption of only one HCd) with only small deviation at higher HCd concentrations.

The effect of the *temperature* on the initial rate was studied between 0 and 70°C at both 21 bar (3 M etpy, U8) and 101 bar (1.4 M etpy, U9). The plot of ln r_{obs} versus $1/T$ showed in both cases a linear behavior over the whole temperature range. The resulting values for the apparent activation energy were low, namely $E_a = 6.1 \pm 0.4$ kcal/mol (26 ± 1.6 kJ/mol, 21 bar) and 4.5 ± 0.3 kcal/mol ($19 + 1.4$ kJ/mol, 101 bar). In presence of modifier, the reaction was studied between 0 and 70°C at both 21 bar (3 M etpy, M8) and 101 bar (1.8 M etpy, M9). The plot of ln r_{obs} versus $1/T$ showed in both cases a linear behavior between 0 and 50°C and a slight deviation for 70°C. The resulting values for the apparent activation energy between 0 and 50°C were also low, namely $E_a = 4.1 \pm 0.3$ kcal/mol (17.3 ± 1.3 kJ/mol, 21 bar) and 5.06 ± 0.21 kcal/mol (21.2 ± 0.9 kJ/mol, 101 bar). The e.e. was in both cases constant from 0 to 50°C, but decreased noticeably from 50 to 70°C, especially at 101 bar. An activation energy of 38 kJ/mol was reported by Sutherland *et al.* (12) but both rate and e.e. strongly decreased above 50°C. These deviations are probably due to desorption of the modifier from the Pt surface at higher temperatures.

DISCUSSION

Any adequate mechanistic model must be able to account for the following significant kinetic effects:

- the first-order dependence of the observed rate on the catalyst loading for both the unmodified and the unmodified system;
- the local rate maximum as a function of the etpy concentration in both the unmodified and the unmodified system;
- the different dependencies of rate on hydrogen partial pressure observed with the unmodified and the unmodified system;
- the hydrogen pressure dependence of the e.e.;
- the dependence of the rate on modifier concentration ("first order" with saturation).

Development of Kinetic Models and of Rate and e.e. Equations

Several descriptions and discussions of the kinetics of the hydrogenation of ketones have appeared (41, 42). Usually, the kinetic results are discussed in the framework of the Langmuir–Hinshelwood (LH) formalism; i.e., it is assumed that the reaction occur in the adsorbed state. For the practical application of this formalism, two approaches have been used. In most cases the LHHW approximation (43) is applied, assuming that adsorbed species are in fast equilibrium before the rate limiting step, characterized by adsorption constants K_i and reacting with rate constants k_i. The observed rate is then proportional to the surface coverage of species that react in the rate determining step and the rate constant k, leading to the typical LHHW rate equations (kinetic terms in the numerator and the adsorption term in the denominator). The second approach takes the forward and back reaction of every elementary step before the RDS into account and applies a steady state assumption, i.e., assumes that the concentration of these intermediates are constant. This approach was for example used by Halpern for the Rh-catalyzed homogeneous hydrogenation of enamides (44) and recently also for the hydrogenation of etpy with the Pt cinchona system (15).

Even though we fully realize that the LHHW formalism is an oversimplification, we use it here exclusively for the analysis of both the modified and the unmodified system. The main reason for this choice is that the steady-state approach (15) would involve more adjustable constants than we can handle with our experimental basis. As a further simplification, we assume only one kind of active center that can competitively adsorb hydrogen, etpy, or HCd and we neglect the adsorption of etlac (because of low conversion) as well as of the solvent. Generally, different combinations of elementary steps can give similar or equal sets of rate expressions in the LHHW formalism (43). It should be noted that the number of parameters increases rapidly with the complexity of a kinetic model often affording a fit as good as or better than a simpler expression, due only to the increase in the number of parameters and not necessarily because of an intrinsically better model. Our goal was to find the simplest plausible model with the lowest number of adjustable parameters that can explain all significant effects and that gives a reasonable fit to our measured data.

Discussion of the Unmodified Catalyst

Kinetic Models

For the hydrogenation of etpy, the following equilibria and elementary steps are considered: adsorption of hydrogen and etpy (Eqs. [1] and [2]) on the active sites, fast surface diffusion, stepwise addition of the dissociated H_2 to the C=O bond (Eqs. [3] and [4]), and desorption of the product alcohol (Eq. [5]). Based on our previous calculations and experimental studies, significant bulk diffusion resistance is neglected (11). Since all rates obtained are initial rates, the back reaction was not considered. Depending on which step in this sequence is assumed to be rate determining, different rate expressions are finally obtained.

Reaction step	Adsorption and rate constants	
$H_2 + 2{*} \rightleftarrows 2{*}\text{-H}$	K_{H}, (k_{H} and $k_{-\mathrm{H}}$)	[1]
$\mathrm{E} + {*} \rightleftarrows {*}\text{-E}$	K_{E}, (k_{E} and $k_{-\mathrm{E}}$)	[2]
${*}\text{-H} + {*}\text{-E} \rightleftarrows {*}\text{-EH} + {*}$	K_{EH}, (k_{EH} and $k_{-\mathrm{EH}}$)	[3]
${*}\text{-H} + {*}\text{-EH} \rightleftarrows {*}\text{-EH}_2 + {*}$	$K_{\mathrm{EH_2}}$, ($k_{\mathrm{EH_2}}$ and $k_{-\mathrm{EH_2}}$)	[4]
${*}\text{-EH}_2 \rightarrow {*} + \mathrm{EH}_2$	k_{D}, fast	[5]

Using classical LHHW calculations, the following rate equations were determined:

Model variant MV1: RDS first H-addition
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{EH}} K_{\mathrm{E}}[\mathrm{E}]\sqrt{K_{\mathrm{H}}[\mathrm{H_2}]}}{(1 + K_{\mathrm{E}}[\mathrm{E}] + \sqrt{K_{\mathrm{H}}[\mathrm{H_2}]})^2} \qquad [6]$$

Model variant MV2: RDS second H-addition
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{EH_2}} K_{\mathrm{E}} K_{\mathrm{H}} K_{\mathrm{EH}}[\mathrm{E}][\mathrm{H_2}]}{(1 + K_{\mathrm{E}}[\mathrm{E}] + \sqrt{K_{\mathrm{H}}[\mathrm{H_2}]} + K_{\mathrm{E}} K_{\mathrm{EH}}[\mathrm{E}]\sqrt{K_{\mathrm{H}}[\mathrm{H_2}]})^2} \qquad [7]$$

Model variant MV3: RDS reaction of etpy from solution with ∗-H (Eley-Rideal)
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{EH'}}[\mathrm{E}]\sqrt{K_{\mathrm{H}}[\mathrm{H_2}]}}{1 + \sqrt{K_{\mathrm{H}}[\mathrm{H_2}]}} \qquad [8]$$

Model variant MV4: RDS dissociative adsorption of hydrogen (etpy adsorbed reversibly)
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{H}}[\mathrm{H_2}]}{(1 + K_{\mathrm{E}}[\mathrm{E}])^2} \qquad [9]$$

Model variant MV5: RDS ketone adsorption (hydrogen adsorbed reversibly)
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{E}}[\mathrm{E}]}{1 + \sqrt{K_{\mathrm{H}}[\mathrm{H_2}]}} \qquad [10]$$

Model variant MV6: RDS desorption of etlac
$$r_{\mathrm{calc}} = \frac{k_{\mathrm{D}} K_{\mathrm{E}} K_{\mathrm{EH}} K_{\mathrm{EH_2}} K_{\mathrm{H}}[\mathrm{E}][\mathrm{H_2}]}{1 + K_{\mathrm{E}}[\mathrm{E}] + \sqrt{K_{\mathrm{H}}[\mathrm{H_2}]} + K_{\mathrm{E}} K_{\mathrm{EH}}[\mathrm{E}]\sqrt{K_{\mathrm{H}}[\mathrm{H_2}]} + K_{\mathrm{E}} K_{\mathrm{EH}} K_{\mathrm{EH_2}}[\mathrm{E}] K_{\mathrm{H}}[\mathrm{H_2}]} \qquad [11]$$

Many other schemes could be considered, e.g., adsorption of the α-ketoester on two sites as proposed by Simons *et al.* (45), or on a dual site, the simultaneous addition of two hydrogen atoms in one step, etc., as discussed in great detail for the acetone hydrogenation by Simonikova *et al.* (42). Several of their more complex model variants were indeed fitted with about the same results as MV1 and MV2. Because these models have more adjustable variables but do not give more insight into the reaction mechanism, only the most simple ones were further pursued.

Discrimination of Kinetic Models

The data sets U1–U9 were used to test and discriminate the kinetic models MV1–MV6. The quality of fit was judged by the unweighted least square method as well as by visual inspection. A simple visual inspection of the observed rate data rules out the models MV3–MV5. The model MV6 gives a reasonable fit. However, five variables are required to fit the data, and there are no indications that the desorption of etlac is the slow step. Therefore, MV6 was also excluded from further consideration. The principal difference between the rate equations of models MV1 and MV2 is a half-order dependence of the rate on $[\mathrm{H_2}]$ in MV1 and

TABLE 2

Kinetic Constants and Least Square Sums for Models MV1, MV2, and MV6

	MV1	MV2	MV6
Least square:	42.2	40.92	56.77
$k\ (\frac{l^2}{1000\cdot\mathrm{min}\cdot\mathrm{g}\cdot\mathrm{mol}})$:	110	133	23.0
K_{H} (M^{-1}):	0.475	16,500	0.00162
K_{E} (M^{-1}):	0.497	17.4	66700
K_{EH}:	—	0.0044	2820
$K_{\mathrm{EH_2}}$:	—	—	0.00330

a first-order dependence in MV2. In spite of this significant difference, it was possible to fit the data U1–U9 equally well with both MV1 and MV2 (Table 2) because of the saturation behavior. This means that we cannot distinguish between the two alternatives. However, since the adsorption constants for MV1 are more reasonable than those for MV2, and MV2 needs one variable more to obtain a similar fit, MV1 is slightly favored. Accordingly, the calculated curves in Figs. 5a, 6, and 8 were obtained using this model variant. Both models are in agreement with the reaction intermediates most often depicted for the hydrogenation of ketones on noble metal surfaces (see Fig. 8).

Discussion of the Modified Catalyst

The Modified Site (✪)

As discussed by Blaser *et al.* (10, 40), the modification of the Pt catalyst can be described quite well by assuming a reversible adsorption of the cinchona molecules on active sites of the Pt surface; the symbol ✪ is used to describe a modified site. It is plausible that not all racemic active sites can be modified. A similar approach was used by Tai and Harada for the surface of Raney nickel (7). However, kinetic models cannot discriminate between a fully or only partially modifiable surface and indeed both scenarios can describe existing kinetic results (10, 40). The kinetic treatment can formally be carried out as for the unmodified site, except for an important difference: Since ✪ is chiral, the interactions with the prochiral etpy lead to intermediates that are diastereomeric, i.e., they are different in geometry as well as in energy and reactivity. This gives more complicated kinetic schemes because the catalytic cycles leading to (R)-etlac and to (S)-etlac have to be considered separately. The same approach indeed was used by Landis and Halpern (44) as well as by Tai and Harada (7). For the sake of simplicity we assumed that the activation of H_2 occurs only on unmodified sites $*$ and that adsorbed hydrogen and etpy undergo fast surface migration to other active sites. It must be stressed that these assumptions are not necessary requirements to arrive at the results and conclusions described below. For several kinetic models we have obtained the same quality of fit to our data assuming partially modifiable surfaces, or by H_2 activation on ✪.

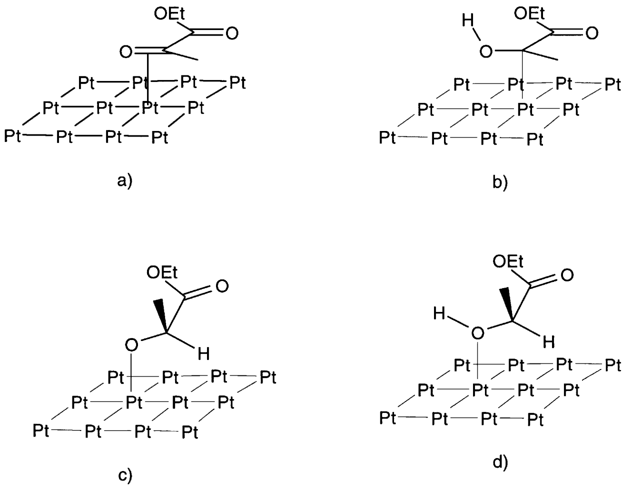

FIG. 8. Artist's view of the structure of adsorbed reaction intermediates on the unmodified Pt surface. (a) Adsorbed etpy, si-face; (b) half-hydrogenated ketone (first H addition to carbonyl oxygen, si-face); (c) half hydrogenated ketone (first addition to C, R-form); (d) weakly adsorbed (R)-lactate.

The Kinetic Models

For the modified system the following additional assumptions compared to the unmodified case were made:

- The unmodified sites react as described by the model MV1 or MV2 (same adsorption and rate constants).
- A modified site, ✪ consists of one cinchona molecule adsorbed reversibly on a platinum site, $*$:

$$* + \mathrm{HCd} \rightleftarrows ✪ \quad K_{\mathrm{m}}^{0}. \qquad [12]$$

- The addition of the H-atoms to the adsorbed etpy occurs from the side of the metal. Therefore, etpy adsorbed via the re-face of the keto group leads to (S)-etlac whereas that adsorbed via the si-face leads to (R)-etlac.

Detailed derivation of MV7. In this variant it is assumed that all active sites are modifiable and that etpy is reversibly adsorbed on a modified site and reacts with hydrogen that is activated at an unmodified site ($*$-H). In order to have as few adjustable parameters as possible, K_{siE}^{A} and K_{reE}^{A} are taken as equal even though the two species are known to be diastereomeric. As a consequence, the fitting will lead to apparent kinetic constants K_{reEH}^{A}, K_{siEH}^{A}, and $K_{\mathrm{siEH_2}}^{A}$:

$$\mathrm{E} + ✪ \rightleftarrows ✪\text{-si/re-E} \quad K_{\mathrm{E}}^{A}. \qquad [13]$$

For the formation of (S)-etlac it is assumed that the first addition of H to the adsorbed etpy is rate determining (analogous to MV1):

$$\text{✪-re-E} + \text{H-}{*} \rightarrow \text{✪-re-EH} + {*} \quad k^{A}_{\text{reEH}} \text{ (RDS to (S)-etlac)} \qquad [14]$$

$$\text{✪-re-EH} + \text{H-}{*} \rightarrow \text{✪-(S)-EH}_2 + {*} \quad \text{fast} \qquad [15]$$

$$\text{✪-(S)-EH}_2 \rightarrow \text{✪} + \text{(S)-etlac} \quad \text{fast.} \qquad [16]$$

For (R)-etlac the second addition of H is assumed to be rate determining (as for MV2):

$$\text{✪-si-E} + \text{H-}{*} \rightleftarrows \text{✪-si-EH} + {*} \quad K^{A}_{\text{siEH}} \qquad [17]$$

$$\text{✪-si-EH} + \text{H-}{*} \rightarrow \text{✪-(R)-EH}_2 + {*} \quad k^{A}_{\text{siEH}_2} \text{ (RDS to (R)-etlac)} \qquad [18]$$

$$\text{✪-(R)-EH}_2 \rightarrow \text{✪} + \text{(R)-etlac} \quad \text{fast.} \qquad [19]$$

The mass balance for the active sites is

$$[{*}] + [{*}\text{-H}] + [{*}\text{-E}] + [\text{✪}] + [\text{✪-si-E}] + [\text{✪-re-E}] + [\text{✪-si-EH}] = 1. \qquad [20]$$

Using the equilibria defined above, the following adsorption term A is obtained:

$$A = [{*}] = \frac{1}{1 + \sqrt{K_{\text{H}}[\text{H}_2]} + K_{\text{E}}[\text{E}] + K^{0}_{\text{m}}[\text{HCd}]\{1 + 2K^{A}_{\text{E}}[\text{E}](1 + K^{A}_{\text{siEH}}\sqrt{K_{\text{H}}[\text{H}_2]})\}}. \qquad [21]$$

The individual rates for formation of the (S)- and the (R)-enantiomers of etlac on the modified (r_{mod}) and unmodified (r_{rac}) sites can then be calculated as

$$\begin{aligned} r_{\text{modS}} &= k^{A}_{\text{reEH}}[\text{✪-E}][{*}\text{-H}] \\ &= k^{A}_{\text{reEH}} K^{A}_{\text{E}}[\text{E}]\sqrt{K_{\text{H}}[\text{H}_2]} K^{0}_{\text{m}}[\text{HCd}]A^2 \qquad [22] \end{aligned}$$

$$\begin{aligned} r_{\text{modR}} &= k^{A}_{\text{siEH}_2}[\text{✪-si-EH}][{*}\text{-H}] \\ &= k^{A}_{\text{siEH}_2} K^{A}_{\text{siEH}} K^{A}_{\text{E}}[\text{E}] K_{\text{H}}[\text{H}_2] K^{0}_{\text{m}}[\text{HCd}]A^2 \qquad [23] \end{aligned}$$

$$r_{\text{rac}} = k_{\text{EH}} K_{\text{E}}[E]\sqrt{K_{\text{H}}[\text{H}_2]}A^2 \quad \text{(see MV1).} \qquad [24]$$

The observed rates and e.e.'s can be calculated as

$$r_{\text{calc}} = r_{\text{modR}} + r_{\text{modS}} + r_{\text{rac}} \qquad [25]$$

$$r_{\text{R}} = r_{\text{modR}} + 0.5 r_{\text{rac}} \qquad [26]$$

$$r_{\text{S}} = r_{\text{modS}} + 0.5 r_{\text{rac}} \qquad [27]$$

$$\text{e.e.}_{\text{calc}} = 100(r_{\text{R}} - r_{\text{S}})/(r_{\text{R}} + r_{\text{S}}). \qquad [28]$$

Derivation of MV8. Hydrogen is activated on $*$ (Eq. [1]) and is transferred to ✪ giving a protonated adsorbed cinchona modifier. Etpy is also adsorbed on a nonmodified site (Eq. [2]) and can migrate to the protonated modified site. In addition, it is arbitrarily assumed that only 10% of the active sites are modifiable:

$${*}\text{-H} + \text{✪} \rightleftarrows \text{✪-H} + {*} \quad K^{B}_{\text{m}}. \qquad [29]$$

For the formation of (S)-etlac it is again assumed that the *first* addition of ✪-H to $*$-etpy give ✪-re-EH (Eq. [30]) is rate determining, followed by a fast addition of the second H and desorption of the product (Eqs. [15] and [16]).

$$\text{✪-H} + {*}\text{-E} \rightarrow \text{✪-re-EH} + {*} \quad k^{B}_{\text{reEH}} \text{ (RDS to (S)-etlac)} \qquad [30]$$

For (R)-etlac it is also assumed that the *second* addition of H is assumed to be rate determining, followed by fast desorption (Eqs. [31], [18], and [19]):

$$\text{✪-H} + {*}\text{-E} \rightleftarrows \text{✪-si-EH} + {*} \quad K^{B}_{\text{siEH}}. \qquad [31]$$

The balance for the modified active sites (10% of the total Pt atoms) is

$$[{*}] + [{*}\text{-H}] + [{*}\text{-E}] + [\text{✪}] + [\text{✪-H}] + [\text{✪-si-EH}] = 0.1. \qquad [32]$$

Solving for $*$ gives the adsorption term

$$B_1 = [{*}] = \frac{0.1}{1 + \sqrt{K_{\text{H}}[\text{H}_2]} + K_{\text{E}}[\text{E}] + K^{0}_{\text{m}}[\text{HCd}]\{1 + K^{B}_{\text{M}}\sqrt{K_{\text{H}}[\text{H}_2]}(1 + K_{\text{E}}[\text{E}])\}}. \qquad [33]$$

The balance for the unmodified site (90% of the total) is

$$[{*}] + [{*}\text{-H}] + [{*}\text{-E}] = 0.9. \qquad [34]$$

Solving for $*$ gives the adsorption term

$$B_2 = \frac{0.9}{1 + \sqrt{K_{\text{H}}[\text{H}_2]} + K_{\text{E}}[\text{E}]} \qquad [35]$$

leading to the rate equations for (S)- and (R)-etlac, produced on the modified sites

$$\begin{aligned} r_{\text{modS}} &= k^{B}_{\text{reEH}}[{*}\text{-E}][\text{✪-H}] \\ &= k^{B}_{\text{reEH}} K_{\text{E}}[\text{E}] K^{0}_{\text{m}}[\text{HCd}] K^{B}_{\text{M}}\sqrt{K_{\text{H}}[\text{H}_2]} B_1 B_2 \qquad [36] \end{aligned}$$

$$\begin{aligned} r_{\text{modR}} &= k^{B}_{\text{siEH}_2}[\text{✪-si-EH}][{*}\text{-H}] \\ &= k^{B}_{\text{siEH}_2} K_{\text{E}} K^{B}_{\text{siEH}} K^{0}_{\text{m}}[\text{HCd}] K^{B}_{\text{M}} K_{\text{H}}[\text{H}_2] B_1 B_2 \qquad [37] \end{aligned}$$

$$r_{\text{rac}} = k_{\text{EH}}\sqrt{K_{\text{H}}[\text{H}_2]} K_{\text{E}}[\text{E}](B_1 + B_2)^2 \quad \text{(see MV1).} \qquad [38]$$

The observed rates and e.e.'s can be calculated as shown above (Eqs. [25]–[27]).

Other model variants. The same procedure can be carried out assuming different RDS for both the two model variants described above. Several such model variants were actually derived and tested. Table 3 lists the rate determining steps for the most plausible models MV7–MV12.

Discrimination of Kinetic Models

Data sets M1–M10 were used to test the models for the modified system. The quality of fit to both the rate and

TABLE 3

Characterization of Different Model Variants for the Modified System

Model variant	Unmodified sites	Formation of (R)-etlac: RDS addn of	Formation of (S)-etlac: RDS addn of	Percentage of modifiable sites
MV7	MV1	Second H	First H	100
MV8	MV1	Second H	First H	10
MV9	MV1	First H	First H	100
MV10	MV1	Second H	Second H	100
MV11	MV1	First H	Second H	100
MV12	MV2	Second H	First H	100

e.e. data was again judged by the unweighted least square method as well as by visual inspection. For the unmodified sites the above-determined parameters for MV1 and MV2 were used. Simple visual inspection of the measured data leaves MV7, MV8, and MV12 as the only valid candidates. MV9 and MV11 (first H-addition is rate determining for the formation of the R-enantiomer) are not consistent with the observed first-order dependence of rate on hydrogen pressure. MV10 (second H addition is rate determining for the formation of both R- and S-etlac) gives a good fit to the rate of reaction for the data sets M1–M10 but because the formation of the R- and the S-enantiomer have the same order in hydrogen, the e.e. dependence on hydrogen concentration is not adequately modeled (the same holds for MV9).

The relatively simple models MV7, MV8, and MV12 describe with only five adjustable parameters the rate and e.e. dependence on hydrogen, etpy and modifier concentration for a wide range of pressure and substrate concentration. Table 4 presents the best constants obtained for MV7, MV8, and MV12. Not unexpectedly, all three models give a similar fit and it is not possible to discriminate between them. The adsorption constant K_{E}^{A} is in the same order of magnitude as K_{E}, and K_{siEH}^{A} has a value similar to K_{EH} in MV2. The adsorption of the modifier is much stronger than for both etpy and hydrogen. when comparing the rate constants for the modified and the unmodified system, the formation of the half-hydrogenated intermediate is accelerated much more for the (R)-enantiomer than for the (S)-enantiomer, leading to both enantiodiscrimination and ligand acceleration. For the calculated curves of rate and e.e. as depicted in Figs. 4 and 7 we used model variant MV8. Indeed with the exception of the rates in Fig. 7, the fit is satisfactory.

TABLE 4

Kinetic Constants and Least Square Sums for Models MV7, MV8, and MV12

	MV7	MV12		MV8
Least square:	16,900	15,500	Least square:	13,400
$k_{\mathrm{siEH_2}}^{A}$ $\left(\frac{I^2}{1000 \cdot \mathrm{min} \cdot \mathrm{g} \cdot \mathrm{mol}}\right)$:	441,000	345,700	$k_{\mathrm{siEH_2}}^{B}$ $\left(\frac{I^2}{1000 \cdot \mathrm{min} \cdot \mathrm{g} \cdot \mathrm{mol}}\right)$:	4,200
k_{reEH}^{A} (min^{-1}):	751	130	k_{reEH}^{B} (min^{-1}):	70
K_{E}^{A} (M^{-1}):	0.098	0.134	K_{M}^{B} (M^{-1}):	0.282
K_{m}^{0} (M^{-1}):	5,280	200,700	K_{m}^{0} (M^{-1}):	122,000
K_{siEH}^{A}:	0.0832	0.0000981	K_{siEH}^{B}:	1.51

We also tried to fit our data to the steady-state model discussed by Wang *et al.* (15). Their treatment is based on the assumption that the reaction occurs through irreversible addition of adsorbed hydrogen to adsorbed etpy as depicted in Eqs. [14] and [17], contributions from unmodified sites are neglected. Steady-state treatment leads to rate equations for r_{R} and r_{S} with seven adjustable parameters that are able to model the dependence of e.e. on pressure very well. However, the hydrogen dependence of the rate is calculated to be $\sqrt{[\mathrm{H_2}]}$ or lower. This means that the data of our modified system, which shows first-order rate dependence on the hydrogen pressure over a wide range, cannot be explained by the approach. For this reason, the steady-state approach was no longer pursued.

Proposed Mechanistic Schemes

The detailed reaction mechanism of the heterogeneous hydrogenation of ketones is much less understood than the analogous hydrogenation of C=C bonds (46). Nevertheless, there is general agreement that the addition of hydrogen to the C=O group occurs in the adsorbed state in a stepwise manner. Accordingly, the rate determining step is assumed to be either the first or the second hydrogen addition. There is less agreement as to whether the first addition occurs at the oxygen (probably as a proton) or at the carbon atom of the carbonyl group (probably as a hydride). Both reaction pathways have been proposed to explain results observed for different catalysts and different ketones (47). Our interpretation of the kinetic results obtained for the unmodified system fits quite well into this framework. But kinetic data provide of course no information on the structure of the decisive species, e.g., whether the addition occurs at the carbon or oxygen end of the carbonyl group or how these intermediates are bound to the Pt surface.

For the modified catalyst, a review of the different reaction mechanisms proposed up to now was presented in (5). Most proposals address only the mode of enantiodiscrimination, i.e., the structure of the product-controlling reaction intermediate, even though most investigators probably agree that rate enhancement and enantiocontrol are closely connected effects and should be discussed together. There is general agreement that very specific interactions between the modifier and the substrate are necessary in order to give the observed rate enhancement and such high enantioselectivities. However, there is less agreement concerning the structure of the reaction intermediates and about the role of the platinum surface in these transformations. Two distinct types of mechanisms have been proposed thus far and will be discussed below. The first type of mechanism assumes the adsorption of the modifier on platinum to give modified Pt sites, product formation being due to the reaction between adsorbed species (5, 10, 35, 45). The second type of mechanism proposed by Margitfalvi *et al.* (23, 26) assumes the existence of a substrate-modifier complex in the liquid phase as the controlling species for the modified hydrogenation.

Proposals Involving a "Modified Catalyst"

From kinetic evidence, Blaser *et al.* (10) suggested that a stereoselective site consists of one cinchona molecule adsorbed on an ensemble of approximately 15 platinum surface atoms. From the effect of catalyst dispersion it was speculated that a flat arrangement of the Pt atoms should be favorable. Adsorption of the modifier was thought to be with the quinoline part, probably parallel to the surface (via the π system). The question of the structure of the reaction intermediates was left open.

Sutherland *et al.* (12) considered at first that an array of adsorbed cinchona molecules might be responsible for enantiocontrol. They explained the observed rate enhancement by three effects: (1) the activation of the substrate by the quinuclidine nitrogen (higher rate when quinuclidine is added); (2) a higher hydrogen coverage of the modified catalyst (enhanced H_2/D_2 exchange on the modified catalyst); and (3) the electronic effect of the adsorbed quinoline part (higher rate when quinoline is added). This interesting idea of an ordered adsorption had to be abandoned for several reasons. The most important one was that the observed dependence of e.e. and rate on the modifier concentration was not in agreement with the formation of an array of modifier molecules (45). Instead, the one-to-one model described above was used with the suggestion that the adsorbed cinchonidine would stabilize the half-hydrogenated etpy via the quinuclidine nitrogen, thereby leading to the observed rate enhancement.

From molecular modeling studies, Baiker *et al.* and Schwalm *et al.* (5, 48, 49) deduced that it is the protonated cinchona modifier that interacts with the oxygen of the carbonyl bond, thereby activating etpy for hydrogenation and at the same time also exerting the enantioface discrimination of the ketone adsorption. This proposal is very similar to the mode of action proposed for the hydrogenation of methyl ketones catalyzed by tartrate modified nickel catalysts. There, a hydrogen bond between one OH group of the adsorbed tartaric acid and the oxygen of the carbonyl group is proposed to control the adsorption mode of the ketone (7).

In contrast, Augustine *et al.* (34, 50) postulated that the cinchona molecule is adsorbed either via the π-system or via the N of the quinoline close to a Pt ad-atom on which both hydrogen atoms and etpy are adsorbed. In this proposal the nitrogen atom of the quinuclidine interacts with the keto group whereas the ester carbonyl of etpy interacts with the lone pair of the hydroxy group, giving a six-membered arrangement that is thought to be important for controlling the stereochemistry. After the addition of the first hydrogen atom, the intermediate c in Fig. 9 is assumed.

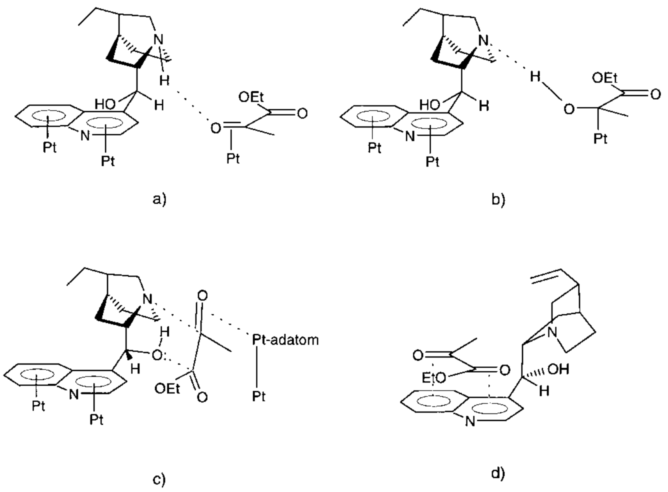

FIG. 9. Artist's view of the structure of adsorbed reaction intermediates: (a) Interaction of protonated HCd with si-form; (b) interaction of HCd with half-hydrogenated ketone (si-form); (c) interaction of HCd with etpy adsorbed at Pt adatom (Augustine *et al.* (51)); (d) solution complex between Cd and etpy (Margitfalvi *et al.* (20)).

All these proposals are basically in agreement with the kinetic results discussed above except for the array model. The two suggestions by Wells and by Baiker concerning the hydrogen-bridged species are almost identical. As the source of the proton, Baiker has proposed acetic acid or a protic solvent. In our model we propose that the proton comes from dissociatively adsorbed hydrogen (it is not excluded that the transfer can occur via the solvent, especially in presence of acetic acid). In this scenario, the second H-atom would be added as hydride and the Pt bulk would serve as a reservoir for the electrons involved. At the moment this reaction sequence seems the most plausible to us. It should be noted that we get about the same fit in kinetic modeling assuming a reaction between H-$*$ and an adsorbed etpy on a modified site to give the stabilized half-hydrogenated ketone as proposed by Augustine *et al.* (50) except that in our model hydrogen and etpy are adsorbed on different Pt atoms (MV7). Augustine's proposal of an adsorption on the same Pt adatom is not in agreement with the rate decrease observed at high etpy which is interpreted as competition between the adsorption of etpy and H_2.

Proposals Involving a "Modified Substrate" (Shielding Effect)

Margitfalvi *et al.* (23, 26) have proposed that in solution etpy forms a complex with the aromatic part of the effective modifiers (d in Fig. 9) and that this activated complex is hydrogenated. The authors have described two different scenarios of how this might happen. In the first (26), the role of the metal is described as being "to provide adsorbed hydrogen for the hydrogenation," implying some sort of Eley–Rideal mechanism. In the second (23), the substrate-modifier complex was proposed to adsorb on the metal surface where it is then hydrogenated.

The first proposal concerning an Eley–Rideal mechanism can be excluded with considerable certainty due to the saturation effects observed at extremely low HCd concentration as well as at increasing etpy concentration. Adsorption of a preformed modifier-substrate complex, however, leads to the same rate and e.e. dependencies if the RDS for the formation of both the (R)- and the (S)-enantiomer is a reaction between adsorbed species. Indeed, fitting our results to the corresponding kinetic model gave a fit similar to that of MV8. On the other hand, these assumptions reduce the importance of the modifier-substrate complex in solution to a mere pre-equilibrium because all important reactions again would take place between adsorbed species.

Mechanism: Conclusions

With the information summarized above, and at this stage of understanding, the most convincing explanation for both the enantiodiscrimination and the rate acceleration is the preferential stabilization of one of the two possible diastereomeric intermediates (or transition states) toward the half-hydrogenated etpy. As to the precise structure of these intermediates, no direct information is currently available. At this time, we favor the following reaction sequence for the major pathway to (R)-etlac: Adsorption of etpy on a non-modified site; migration to a modified site due to the attractive interactions between the ketone oxygen and the protonated cinchona modifier (Baiker's complex, a in Fig. 9); fast transfer of the proton to the oxygen (Well's complex, b in Fig. 9) followed by the slow addition of the second hydrogen and desorption. For the unmodified catalyst as well as for the formation of (S)-etlac we propose that the addition of the first hydrogen is rate limiting. The difference in RDS between the two enantiomeric pathways would be due to a more effective stabilization of the si-complex. Compared to the reaction without modifier or the reaction with the re-complex, the first addition would be accelerated, thereby leading to the second addition being rate limiting. We realize of course that this picture is probably too simplistic. With differences of 2–3 kcal/mol for the activation energies of the rate determining steps we are on the limits of the LHHW formalism which does not consider gradual changes in the RDS. A second concern is that such a good enantioselectivity should have it's cause in a rather loose modifier–catalyst–substrate complex and, further, that this particular hydrogen bridge should have such an extraordinary character.

CONCLUSIONS

It was shown that all important prerequisites can be met for obtaining reliable data for the kinetics of the hydrogenation of etpy to etlac on a 5% Pt/Al_2O_3 catalyst in toluene both in absence and in presence of the chiral modifier, 10,11-dihydrocinchonidine (HCd). The kinetic investigation of the hydrogenation of etpy on Pt catalysts is complicated by several problems that demand a careful evaluation of the experimental conditions. Nevertheless, the experimental data presented here allowed the identification of a few possible schemes as well as the exclusion of many other reaction schemes.

From the observed dependencies of the reaction rates on the catalyst, etpy, hydrogen, and HCd concentrations and from the effect of these parameters on the optical yield in presence of HCd, it was possible to propose coherent reaction schemes both for the reaction with and without modifier. The data allowed the exclusion of the following steps as rate determining: dissociative adsorption of hydrogen, adsorption of etpy, and desorption of etlac. Also excluded were all forms of Eley–Rideal mechanisms where adsorbed hydrogen reacts with etpy directly from solution. The adsorption of hydrogen and etpy on the catalyst was shown to be competitive. However, it was not possible to ascertain that all Pt surface atoms can adsorb a modifier molecule. In absence of the modifier, it was difficult to distinguish between the first and the second H-addition being rate limiting. Mainly on the basis of the adsorption constant for hydrogen, the addition of the first hydrogen was considered as the more likely RDS. The results in presence of HCd were more complex to interpret. The rate for major enantiomer is clearly controlled by the second H-addition, as indicated by a first order dependence on H_2 concentration. It was possible to fit the data, assuming that the RDS of the minor etlac enantiomer remains the first hydrogen addition. A proposal was made concerning the origin of the rate acceleration as well as the enantiodiscrimination on the basis of the models proposed by Baiker and Wells.

ACKNOWLEDGMENTS

We thank J. Mastio, D. Imhof, and J. Salathin for carrying out some of the experimental work; D. G. Blackmond for helpful discussion; and R. Bader for the continuous support of this work.

REFERENCES

1. (a) Koenig, E. K., *in* "Asymmetric Synthesis" (J. D. Morrison, Ed.), Vol. 5, Chapter 3. Academic Press, New York, 1985; (b) Takaya, H., Ohta, T., and Noyori, R., *in* "Catalytic Asymmetric Synthesis" (I. Ojima, Ed.), p. 1. VCH, Weinheim, 1993.
2. See for example Halpern, J., *in* "Asymmetric Synthesis" (J. D. Morrison, Ed.), Vol. 5, Chapter 2. Academic Press, New York, 1985.
3. Blaser, H. U., and Müller, M., *Stud. Surf. Sci. Catal.* **59**, 73 (1991).
4. Izumi, Y., *Adv. Catal.* **32**, 215 (1983).

5. Baiker, A., Mallat, T., Minder, B., Schwalm, O., Simons, K. E., and Weber, J., *in* “Chiral Reactions in Heterogeneous Catalysis” (G. Jannes and V. Dubois, Eds.), p. 95. Plenum Press, New York, 1995.
6. Sachtler, W. M. H., *Chem. Ind.* **189**, 22 (1985).
7. Tai, A., and Harada, T., *in* “Tailored Metal Catalysts” (Y. Iwasawa, Ed.), p. 265. Reidel, Dordrecht, 1986.
8. Klabunovskii, E. I., *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 505 (1984).
9. Webb, G., and Wells, P. B., *Catal. Today* **12**, 319 (1992).
10. Blaser, H. U., Garland, M., and Jalett, H. P., *J. Catal.* **144**, 569 (1993).
11. Garland, M., Jalett, H. P., and Blaser, H. U., *Stud. Surf. Sci. Catal.* **59**, 177 (1991).
12. Sutherland, I. M., Ibbotson, A., Moyes, R. B., and Wells, P. B., *J. Catal.* **125**, 77 (1990).
13. Meheux, P. A., Ibbotson, A., and Wells, P. B., *J. Catal.* **128**, 387 (1991).
14. Bond, G., Meheux, P. A., Ibbotson, A., and Wells, P. B., *Catal. Today* **10**, 371 (1991).
15. Wang, J., LeBlond, C., Orella, C. J., Sun, Y., Blackmond, D. G., and Bradley, J. S., *Stud. Surf. Sci. Catal.* **108**, 183 (1997).
16. Orito, Y., Imai, S., Niwa, S., and Nguyen, G. H., *J. Synth. Org. Chem. Jpn.* **37**, 173 (1979); Orito, Y., Imai, S., and Niwa, S., *J. Chem. Soc. Jpn.*, 1118 (1979), 670 (1980), and 137 (1982).
17. Blaser, H. U., Jalett, H. P., Monti, D. M., Reber, J. F., and Wehrli, J. T., *Stud. Surf. Sci. Catal.* **41**, 153 (1988).
18. Blaser, H. U., Jalett, H. P., Monti, D. M., Baiker, A., and Wehrli, J. T., *Stud. Surf. Sci. Catal.* **67**, 147 (1991).
19. Blaser, H. U., Jalett, H. P. Müller, M., and Studer, M., *Catal. Today* **37**, 441 (1997).
20. Redlich, O., and Kwong, J. N. S., *Chem. Rev.* **44**, 233 (1949); Soave, G., *Chem. Eng. Sci.* **27**, 1197 (1972); Peng, D. Y., and Robinson, D. B., *Ind. Eng. Chem. Fundm.* **15**, 59 (1976).
21. Koelliker, R., and Thies, H., *J. Chem. Eng. Data* **38**, 437 (1993).
22. Mastio, G., and Thies, H., Novartis Services AG, unpublished results.
23. Margitfalvi, J. L., Hegedüs, M., and Tfirst, E., *Tetrahedron: Asymmetry* **7**, 571 (1996).
24. Margitfalvi, J. L., *in* “Catalysis of Organic Reactions” (M. G. Scaros and M. L. Prunier, Eds.), Chem. Ind. 62, p. 189. Dekker, New York, 1995.
25. Margitfalvi, J. L., and Hegedüs, M., *J. Mol. Catal.* **107**, 281 (1996).
26. Margitfalvi, J. L., *J. Catal.* **156**, 175 (1995).
27. Blaser, H. U., Jalett, H. P., and Spindler, F., *J. Mol. Catal. A: Chemical* **107**, 85 (1996).
28. Yasumori, I., Yokozeki, M., and Inoue, Y., *Faraday Discuss.* **72**, 385 (1981).
29. Wang, J., Sun, Y., LeBlond, C., Landau, R. N., and Blackmond, D. G., *J. Catal.* **161**, 752 (1996).
30. Singh, U. K., Landau, R. N., Sun, Y., LeBlond, C., Blackmond, D. G., Tanielyan, S. K., and Augustine, R. L., *J. Catal.* **154**, 91 (1995).
31. Margitfalvi, J. L., Minder, B., Talas, E., Botz, L., and Baiker, A., *in* “Proceedings, 10th International Congress on Catalysis, Budapest, 1992” (L. Guczi, F. Solymosi, and P. Tetenyl, Eds.), p. 2471. Akadémiai Kiadó, Budapest, 1993.
32. “Landolt-Börnstein, Numerical Data and Functional Relationships in Science and Technology,” New Series, Group 4, Vol. 6, p. 80, #517. Springer-Verlag, Berlin/New York.
33. Wolf, R., Ciba-Geigy AG, personal communication.
34. Wehrli, J. T., Baiker, A., Monti, D. M., Blaser, H. U., and Jalett, H. P., *J. Mol. Catal.* **57**, 245 (1989).
35. Augustine, R. L., Tanielyan, S. K., and Doyle, L. K., *Tetrahedron: Asymmetry* **4**, 1803 (1993).
36. Minder, B., Mallat, T., Baiker, A., Wang, G., Heinz, T., and Pfaltz, A., *J. Catal.* **154**, 371 (1995).
37. Reschetilowski, W., Böhmer, U., and Wiehl, J., *Stud. Surf. Sci. Catal.* **84C**, 2021 (1994).
38. Sun, Y., Landau, R. N., Wang, J., LeBlond, C., and Blackmond, D. G., *J. Amer. Chem. Soc.* **118**, 1348 (1996).
39. Böhmer, U., Morgenschweis, K., and Reschetilowski, W., *Catal. Today* **24**, 195 (1995).
40. Blaser, H. U., Imhof, D., and Studer, M., *Stud. Surf. Sci. Catal.* **108**, 175 (1997).
41. see for example Geneste, P., Bonnet, M., and Rodriguez, M., *J. Catal.* **57**, 147 (1979); Godolets, G. I., *Kinetika i Kataliz* **28**, 35 (1987).
42. Simonikova, J., Hillaire, L., Panek, J., and Kochloefl, K., *Z. Phys. Chem.* **83**, 287 (1973).
43. Hougen, O. A., and Watson, K. M., *in* “Chemical Process Principles,” Kinetics and Catalysis, Vol. 3. Wiley, New York, 1947.
44. Landis, C. R., and Halpern, J., *J. Amer. Chem. Soc.* **109**, 1746 (1987).
45. Simons, K. E., Meheux, P. A., Griffiths, S. P., Sutherland, I. M., Johnston, P., Wells, P. B., Carley, A. F., Rajumon, M. K., Roberts, M. W., and Ibbotson, A., *Recl. Trav. Chim. Pays-Bas* **113**, 465 (1994).
46. Cremer, P. S., and Somorjai, G. A., *J. Chem. Soc. Faraday Trans.* **91**, 3671 (1995).
47. Tanaka, K., *in* “Catalytic Hydrogenation” (L. Cerveny, Ed.), Chapter 3. Elsevier, Amsterdam, 1986.
48. Schwalm, O., Minder, B., Weber, J., and Baiker, A., *Catal. Lett.* **23**, 271 (1994).
49. Schwalm, O., Weber, J., Minder, B., and Baiker, A., *J. Mol. Struct. (Theochem)* **330**, 353 (1995).
50. Augustine, R. L., and Tanielyan, S. K., *J. Mol. Catal. A: Chemical* **112**, 93 (1996).