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Molecular insight into the dynamics of chiral modification of Pt/alumina

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Abstract

A simple transient method—replacement of the chiral modifier in the reactor feed with a second modifier that gives the opposite enantiomer of the product in excess—was used to investigate the competition of cinchona alkaloids on a commercial Pt/Al_2O_3 catalyst. Ethyl pyruvate was hydrogenated in a continuous-flow fixed-bed reactor with high enantiomeric excess (up to 89%) and reaction rate (TOF 12,700 h^{-1}) at a modifier/substrate molar ratio of only 307 ppm. The rate of modifier replacement indicates the following order of adsorption strength on Pt: cinchonidine > cinchonine > quinidine, which is in line with that observed with other techniques. The dynamics of the competition was investigated under different reaction conditions. The study supports the contention that the origin of "ligand acceleration" is not the suppression of catalyst deactivation by addition of the chiral modifier, because under appropriate conditions, catalyst deactivation is negligible in pyruvate hydrogenation. The catalytic experiments were completed with an ATR-IR study in a high-pressure, continuous-flow reactor cell in which the formation of (*R*)- and (*S*)-lactate, and the competition of cinchonidine and quinidine at the Pt surface, could be followed in situ.

Keywords: Enantioselective hydrogenation; Ethyl pyruvate; Continuous fixed bed reactor; Chiral switch; Inversion of sense of enantiodifferentiation; Ligand acceleration; Catalyst deactivation, Cinchona alkaloid; In situ ATR-IR spectroscopy

1. Introduction

Modification of a metal hydrogenation catalyst with a soluble chiral organic compound is a fascinating and practically useful approach in heterogeneous asymmetric catalysis [1–12]. Strong adsorption of the chiral modifier on the metal surface allows the application of low modifier/substrate (M/S) molar ratios, down to a few ppm in favorable cases [13]. It is commonly accepted that adsorption of the modifier leading to chirally modified surface sites is a key element of enantioselection. Unfortunately, our knowledge of the adsorption strength and geometry of the modifier on the metal surface is insufficient. Obtaining information on the modifier during its interaction with the substrate on the metal surface is difficult. A thoroughly investigated example is the Pt-catalyzed hydrogenation of α-ketoesters in the presence of cinchona alkaloids [14]. Surface-sensitive techniques have shown that under conditions relevant for catalysis, several species compete for the Pt surface sites and that cinchonidine (CD) adsorbs with the quinoline ring in both flat and tilted geometries [15–19]. In contrast, most mechanistic models postulate that during interaction with the pyruvate molecule, CD is adsorbed with the quinoline ring lying parallel to Pt, with, indirectly, the tilted species considered a spectator [20–24].

Because none of the known surface sensitive spectroscopic methods allows the study of the adsorption mode of the modifier during enantioselection, indirect catalytic approaches are very important. The nonlinear behavior of modifier mixtures [25–30], a phenomenon analogous to the nonlinear effect in homogeneous catalysis [31], is a simple and reliable tool for analyzing the differences in the adsorption of modifiers during enantioselection. In the original method, the hydrogenation reaction was carried out in the presence of two different modifiers that alone give the opposite enantiomers of the product in excess. The deviation from the expected linear behavior was attributed to the different adsorption strengths of the modifiers [25]. Later it was speculated that differences in the dominant adsorption modes of the modifiers also contribute to the nonlinearity [32]. The first experimental evidence in this direction was provided by our recent preliminary study in which

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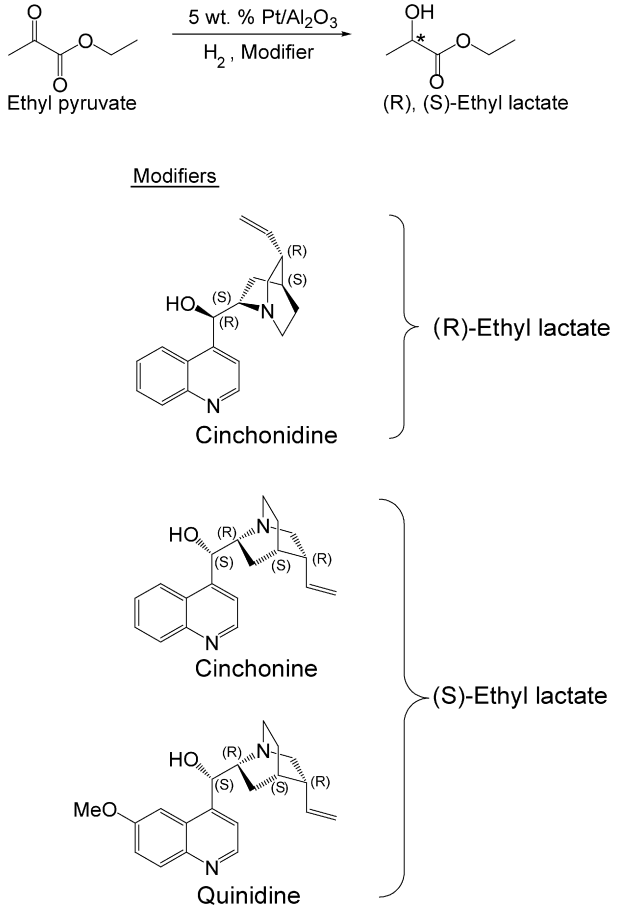
the hydrogenation of ethyl pyruvate was carried out in a high-pressure ATR-IR cell [33].

A different strategy for studying modifier competition is to start the reaction in the presence of only one modifier and after a short period add an equimolar amount of a second modifier that alone gives the opposite enantiomer in excess [32,34]. This transient method provides additional information on the kinetic aspects of competing enantioselection. A continuous reactor operation mode [13,35–37], in which the modifier is added to the feed in trace amounts, allows a third method: switching of the product from (*R*) to (*S*) and back by simply changing the modifier in the feed [33]. Applying this new technique, we have shown that CD, which adsorbs strongly and dominantly in a "flat" position, can readily replace the weakly adsorbing quinidine (QD) that is present mostly as a tilted species on the Pt surface. (Note that independent of their adsorption strength, both modifiers alone give up to 98% ee under optimized conditions [38,39].) Here we report a continuation of this work, focusing on the dynamic nature of chiral modification using a combined catalytic–ATR-IR spectroscopic approach. One of the most widely studied heterogeneous enantioselective reactions, the enantioselective hydrogenation of ethyl pyruvate on cinchona-modified Pt, has been chosen as the test reaction (Scheme 1), to facilitate the comparison to former studies of the nonlinear behavior.



Scheme 1. Asymmetric hydrogenation of ethyl pyruvate over Pt/Al_2O_3 modified by different cinchona alkaloids.

2. Experimental

2.1. Materials

Ethyl pyruvate (Acros, 98%) was carefully distilled under vacuum (applying a long Vigreux separating column and high reflux ratio) before each experiment to purify it from lactate impurity and polymers. Cinchonine (CN, Fluka, ∼99%), CD (Fluka, ⩾98%), QD (Fluka, ∼99%), acetic acid (Fluka, >99.8%), toluene (Fluka, ⩾99.7%), dichloromethane (Baker, ⩾99.5%), and (*R*)-ethyl lactate (Fluka, >99%) were used as received. Before the ATR-IR measurements, toluene was dried over activated molecular sieves. The N_2 (99.999 vol%) and H_2 (99.999 vol% for ATR-IR measurements and 99.995 vol% for catalytic experiments) were purchased from PanGas. A commercial 5 wt% Pt/Al_2O_3 powder catalyst (Engelhard 4759) was used for the hydrogenation reactions.

2.2. Catalytic experiments

The setup for the catalytic experiments shown in Fig. 1 (left panel) included three independent feed lines, one for the dissolved chiral modifier, the second for the dissolved substrate, and the third for H_2. Separate feeding of the reaction components and the appropriate order of their addition to Pt are crucial to minimize side reactions and avoid catalyst deactivation [40,41]. The different feeds were mixed directly in a mixing zone before the reactor. The rates of the two liquid flows were regulated independently by two HPLC pumps (Gilson 305 for the substrate line; Jasco PU-980 for the modifier line). Hydrogen pressure and flow rate were controlled by a two-step expansion valve (PE103, NWA) positioned at the reactor outlet. The reactor consisted of an 8-cm-long stainless steel capillary tube with an inner diameter of 1.8 mm. A sampling valve installed downstream of the reactor allowed sampling at any time desired. A quartz wool plug was used to hold the catalyst bed in place. If not otherwise specified, 75 mg of catalyst was used, resulting in a bed length of ca. 28 mm. The size distribution of the catalyst particles was 10% <46 μm, 50% <74 μm, and 90% <130 μm, as quoted by the manufacturer.

The standard reaction conditions were as follows: acetic acid solvent; ethyl pyruvate substrate (736 mM), alkaloid modifier concentration 0.225 mM (corresponding to a modifier/substrate ratio of 307 ppm), 15 bar pressure, 0.4 ml/min total liquid flow rate, and 20 °C. The hydrogen flow rate was adjusted to achieve a molar $H_2/EP > 10$. These conditions afforded maximum and reproducible enantiomeric excess (ee).

Before use, the catalyst was reduced at 400 °C in flowing H_2 for 60 min, cooled to room temperature in H_2, and finally flushed with nitrogen. The reduced catalyst was immediately transferred to the tubular reactor. TEM measurements before and after reductive heat treatment showed a decrease in metal dispersion from 0.32 to 0.20 [42]. The ee and conversion were determined with a Thermo Finnigan gas chromatograph equipped with a Chirasil-Dex CB (25 m × 0.25 mm × 0.25 μm) capillary column.

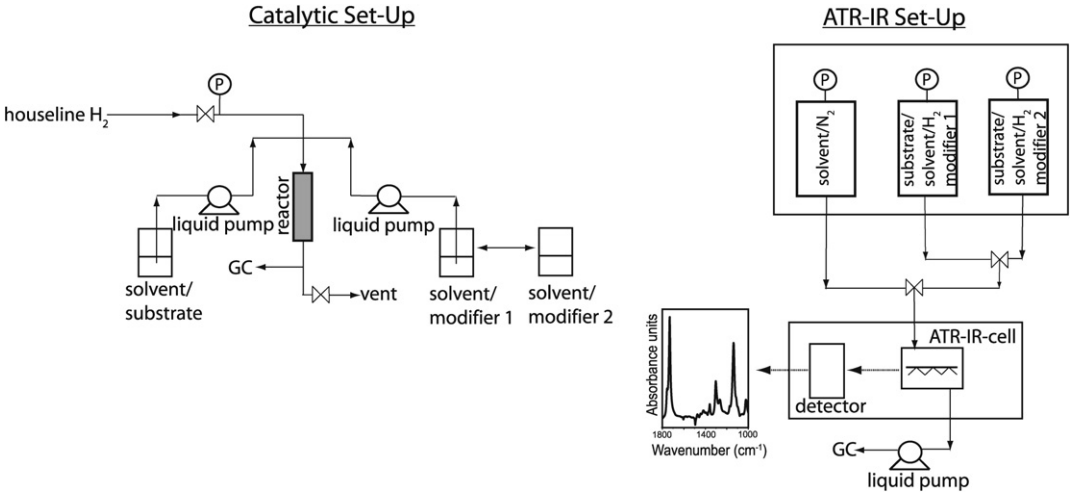


Fig. 1. Experimental setup for the catalytic studies (left) and the ATR-IR experiments (right), both in continuous flow reactors.

The turnover frequency (TOF) related to the surface Pt active sites was calculated as

$$\mathrm{TOF} = \frac{X F M_{\mathrm{Pt}}}{m_{\mathrm{cat}} \mathrm{Pt}_{\mathrm{loading}} D}\ [\mathrm{h}^{-1}], \tag{1}$$

where X is the conversion, F is the molar flow rate of ethyl pyruvate, M_{Pt} is the molar atomic mass of Pt, and m_{cat} is the catalyst amount in the reactor with the corresponding metal loading, $\mathrm{Pt}_{\mathrm{loading}}$, and dispersion, D.

The nonlinear behavior of CD-QD mixtures was studied in a stainless steel autoclave (Baskerville) equipped with a 50-ml glass liner and a PTFE cover. Magnetic stirring was at 1000 rpm. A Büchi BPC 6002 constant volume–constant pressure setup was used to control the total pressure.

2.3. ATR-IR spectroscopy

Spectra were acquired by co-adding 300 scans at 4 cm^{-1} resolution with an IFS66/S spectrometer (Bruker Optics) equipped with a liquid nitrogen-cooled MCT detector and a commercial ATR accessory (Optispec). When required, water vapor and CO_2 signals were subtracted.

A dilute suspension of grinded Pt/Al_2O_3 in water was placed onto the ZnSe internal reflection element (IRE, $52 \times 20 \times 2$ mm, Crystran Ltd.) and dried overnight. The dry catalyst film was then reduced at 350 °C [33]. After reduction, the coated IRE was fixed in a homemade stainless steel flow-through high pressure ATR-IR cell.

The cell was purged with nitrogen for 3–4 h, after which pure solvent saturated with N_2 was circulated over the coated IRE for 1 h. H_2-saturated solvent was fed for the next 10 min to clean the surface. Finally, the dissolved modifier was fed in H_2-saturated solvent for 30 min before being replaced by the second modifier. Between the modifier replacement H_2-saturated toluene was flown over the catalyst for 10 min. The temperature in the cell was held at 20 °C throughout the experiments, and the liquids were fed to the cell from independently pressurized vessels via an HPLC pump (Jasco PU-980) (Fig. 1, right panel). Solutions were provided from stainless steel vessels fitted with glass inserts. All ATR-IR experiments were carried out at 10 bar and a total liquid flow rate of 0.4 ml/min. The substrate and modifier concentrations were identical to those used in the experiments in the catalytic reactor.

3. Results and discussion

3.1. Chiral switching induced by changing the modifiers

The enantioselective hydrogenation of ethyl pyruvate was performed mostly in acetic acid solvent to minimize the side reactions and avoid catalyst deactivation [40,43]. (*S*)-Ethyl lactate was obtained in the presence of CN and QD as modifiers, and the (*R*)-enantiomer was formed in excess with CD.

Fig. 2 shows that replacing CN by CD in the feed switched the major product from (*S*)-lactate to (*R*)-lactate (82% ee after 45 min). The amount of catalyst was increased until nearly full conversion was achieved (75 mg) to avoid possible complications at low conversion (initial transient period [21,44–46]).

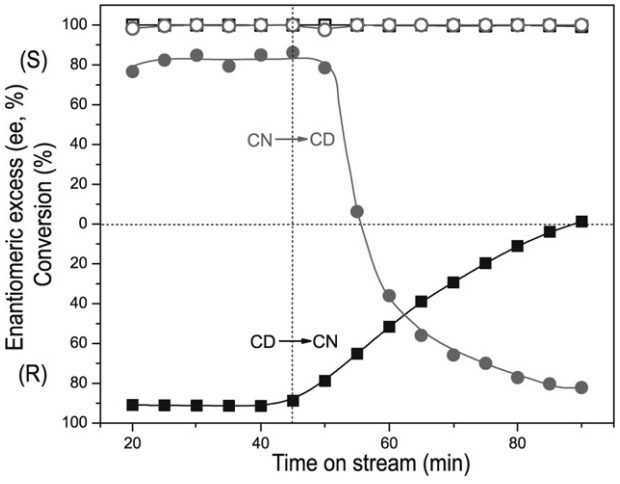


Fig. 2. Chiral switch induced by replacing CN with CD (filled circles) and vice versa (filled squares). The conversion is shown with open symbols (the open squares are barely seen due to overlapping). The second modifier reached the catalyst after about 45 min (vertical dashed line); standard conditions.

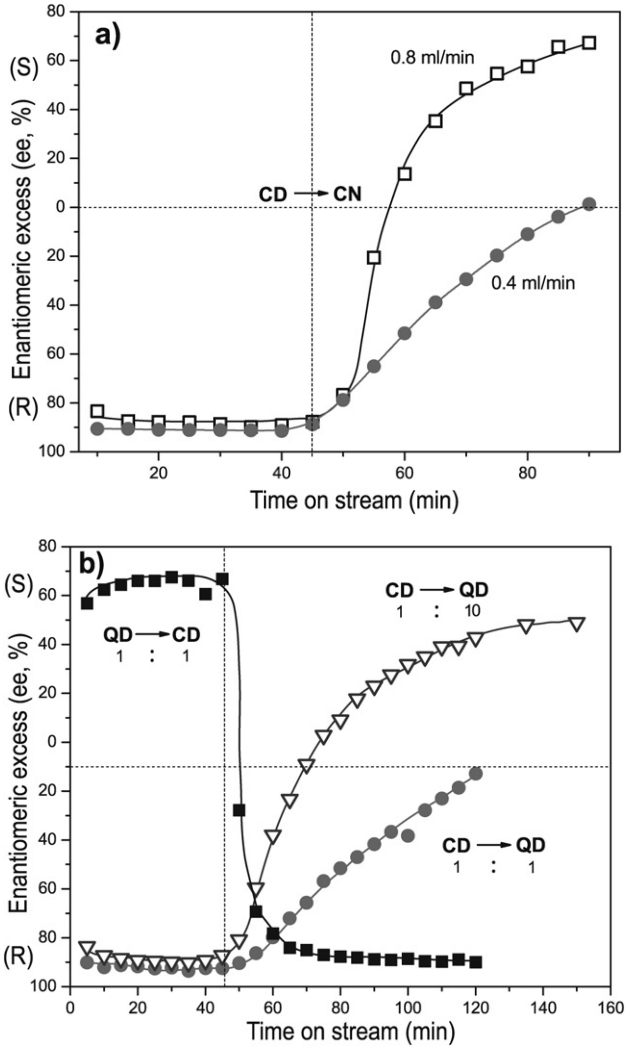


Fig. 3. (a) Influence of the total flow rate on the chiral switch from (*R*)- to (*S*)-ethyl lactate by changing the chiral modifier form CD to CN is shown. Filled circles: 0.4 ml/min total flow; open squares: 0.8 ml/min total flow rate (standard conditions, full conversion). (b) Influence of the modifier concentration on the dynamics of the chiral switch. Conditions: 0.226 mM CD, 0.226 mM QD concentration for 1:1 ratio of CD and QD (filled circles and squares) and 2.26 mM for the 10 fold amount of QD relative to CD (open triangles); standard conditions, 100% conversion.

As soon as CD reached the catalyst bed, the ee decreased; after about 12 min, an excess of (*R*)-lactate was formed. In the complementary experiment, replacement of CD by CN was significantly slower and incomplete, and around 40 min were necessary to produce the opposite enantiomer of lactate in excess. For comparison, applying mixtures of CD and CN in pyruvate hydrogenation in a batch reactor revealed only a minor deviation from the calculated linear behavior [25].

The mutual replacement of the modifiers is influenced by the flow rate in the reactor, which in turn affects the external mass transfer. The chiral switch induced by replacing CD with CN was accelerated significantly by doubling the overall flow rate (Fig. 3a).

Increasing the concentration of the modifier is another way to speed up the chiral switch. This effect is shown in Fig. 3b, where the slow replacement of CD by QD can be accelerated

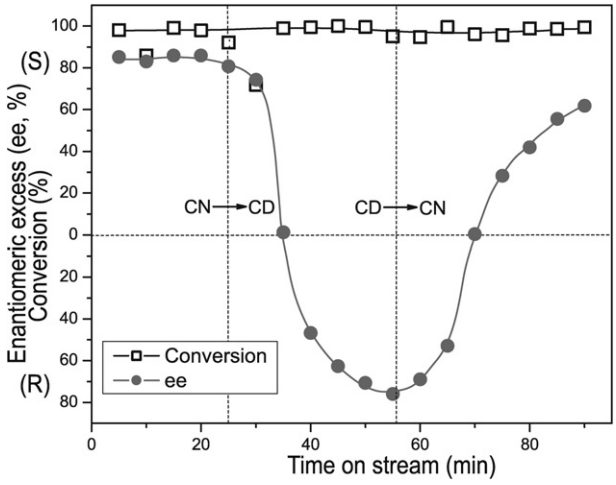


Fig. 4. Chiral switch from (*S*) to (*R*) to (*S*) by replacing CN with CD and then feeding CN again. Conversion was around 96%; fluctuations in conversion are due to instabilities of the flow rate of 0.8 ml/min. Otherwise standard conditions were employed.

by using a tenfold amount of QD relative to CD. Interestingly, even at this higher modifier concentration, replacement of CD by QD was slower than the reverse process—replacement of QD with an equal concentration of CD (curve imported from Ref. [33], Fig. 1). The bigger difference between CD and QD and the quasi-enantiomers CD and CN is due to the differences in the anchoring moieties of the alkaloids (quinoline and 6′-methoxy-quinoline rings for CD and QD, respectively), which moiety of the modifiers has the greatest influence on adsorption on the metal surface [28].

A full cycle of chiral switch from CN to CD to CN is shown in Fig. 4. Here a total flow rate of 0.8 ml/min was used to speed up the process. The fluctuation in conversion at around 96% was due to instability of the increased flow rate. Also in this experiment, the switch from CN to CD was faster than in the opposite direction. The vertical dashed lines in Fig. 4 indicate the calculated approximate time when the next modifier reached the catalytic bed.

Reducing the amount of catalyst from 75 to 25 mg allowed us to obtain differences in the reaction rates while still working at high conversion (Fig. 5). In this case, replacement of QD by CD is indicated by the enhanced conversion as well as the inversion of the ee from 58% (*S*) to 89% (*R*). The TOF increased after feeding of CD by >10% to 12,700 h^{-1} at almost full conversion.

Note that the enantioselectivity in pyruvate hydrogenation increases with increasing pressure [11,47,48] corresponding to higher surface hydrogen concentration. Hydrogen transport limitation in the system leads to lower surface hydrogen concentration and thus to lower enantioselectivity. The high enantioselectivities and reaction rates (TOF) achieved in our reactor are the second best values reported yet [49] and they confirm indirectly the good mass transport in the system.

A comparison of the results in Figs. 2 and 3 suggests the following "superiority" order of the alkaloids: CD > CN > QD. The same order was found by studying the nonlinear behavior of cinchona alkaloids in pyruvate hydrogenation in

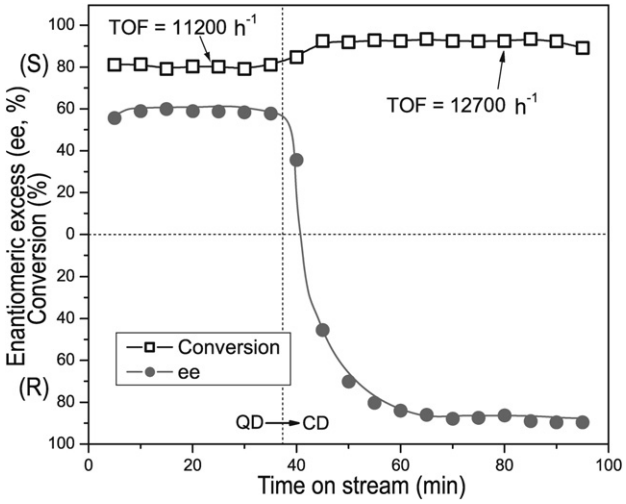


Fig. 5. Rate acceleration by changing the modifier on stream from QD to CD; standard conditions but 25 mg (instead of 75 mg) catalyst.

batch reactors on Pt/Al_2O_3 [25,29,34]. We have proved that the inferior behavior of QD as chiral modifier of Pt is due to its weaker adsorption ([34], including the dominantly tilted adsorption geometry, in contrast to adsorption of the quinoline ring of CD parallel to the Pt surface [33]). Interestingly, Ma and Zaera [50] found the opposite order of adsorption strength based on RAIRS measurements in CCl_4, but at unusually high alkaloid concentrations. Because CCl_4 is not stable on Pt in the presence of hydrogen, we tried to clarify the effect of alkaloid concentration in toluene in an autoclave using equimolar mixtures of CD and QD. At full conversion of ethyl pyruvate (after 2 h at 15 bar and room temperature with 50 mg catalyst), the ee to (*R*)-lactate was 84.2% at 0.22 mmol/L concentrations of CD and QD, which correspond to our standard conditions. When the alkaloid concentration was increased to 1.0 mmol/L, the ee to (*R*)-lactate decreased to 80.8%. These values confirm that CD is far more effective than QD and that the influence of alkaloid concentration is minor.

3.2. Ligand acceleration

The rate acceleration induced by the modifier was studied by starting the hydrogenation of ethyl pyruvate without feeding any modifier (Fig. 6a). Formation of the racemic mixture was slow at ca. 16% conversion, corresponding to a TOF of 760 h^{-1}. On admission of CN after 1.5 h, the conversion increased to 100%. Although the exact value of "ligand acceleration" cannot be determined due to complete conversion of ethyl pyruvate on chirally modified Pt, the phenomenon is clearly shown. It is also important that no catalyst deactivation was observed during the experiment over 3 h. In another experiment, the reaction was started on CN-modified catalyst, and feeding of the alkaloid was stopped for 30 min (Fig. 6b). As a result, the ee dropped rapidly, but the original ee of 87% was regained after the modifier was refed. The conversion also dropped, as expected, and the initial value (99%) could be well reproduced (97%) after returning to the standard conditions.

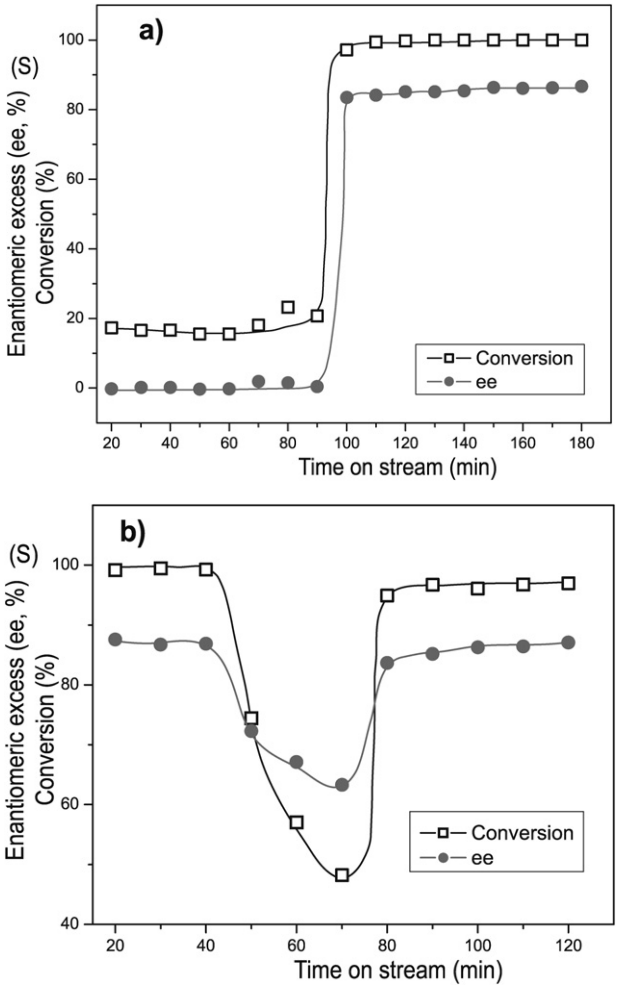


Fig. 6. (a) Changes in conversion and enantioselectivity in pyruvate hydrogenation by addition of CN to the unmodified catalyst bed after about 90 min. (b) Variation in reaction rate and enantioselectivity induced by stopping feeding of CN after 40 min and restarting its feed after 70 min. Standard conditions except the pressure in (b) (10 bar instead of 15 bar).

Because acetic acid is not suitable for the IR study, we extended the catalytic studies using toluene and dichloromethane as solvents. Rapid inversion of the major enantiomer by changing the feed from QD to CD was observed in a bridging experiment using toluene, as expected, but the enantioselectivity was poor with QD [only 13% ee to (*S*)-lactate, using 25 mg of catalyst and the standard conditions]. Nevertheless, the catalyst performance was stable, and only minor deactivation was detected. In contrast, application of dichloromethane, which would be an ideal solvent for the IR measurements, was unsuccessful; the conversion of ethyl pyruvate decreased rapidly with time (Fig. 7), and the enantioselectivity varied in an irreproducible manner. Although Pt is not a good hydrodehalogenation catalyst, we assume that at 15 bar pressure, Pt/Al_2O_3 dehalogenated the solvent and the resulting hydrochloric acid catalyzed extensive side reactions (hydrolysis, dimerization, and oligomerization of pyruvate) at the catalyst surface, leading to catalyst deactivation. It is known that even the cinchona modifier restructures in the presence of a strong acid [51,52]. For comparison, pyruvate and CD are stable in acetic acid, which

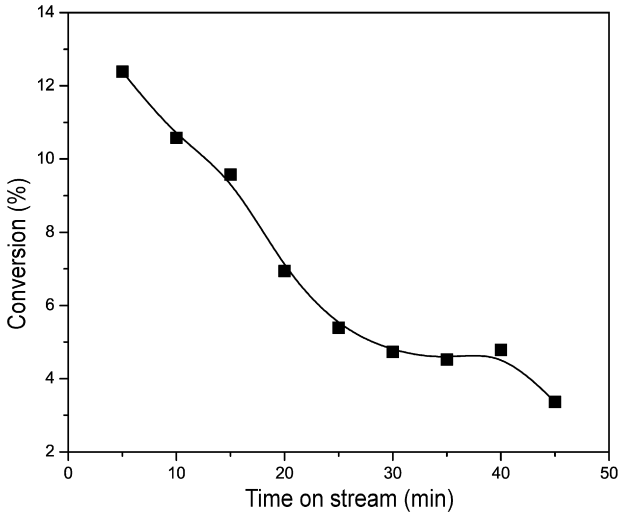


Fig. 7. Change of conversion with time on stream in ethyl pyruvate hydrogenation using dichloromethane as solvent, QD as modifier and 25 mg catalyst. Otherwise standard conditions.

is a weaker acid by several orders of magnitude. Catalyst deactivation (probably due to formation of oligomers or polymers) during hydrogenation of ethyl pyruvate was already observed in dichloromethane even at low pressure (1.25 bar), and the contribution of impurities in the substrate could be excluded due to its careful purification before use [53]. Based on these experiments, toluene was chosen as a compromise for the subsequent ATR-IR measurements.

The literature contains contradictory data concerning the origin of catalyst deactivation and "ligand acceleration" during pyruvate hydrogenation. Garland and Blaser [54] suggested at first, that hydrogenation of α-ketoesters is faster on chirally modified Pt due to involvement of the chiral modifier in the reaction mechanism, analogous to the phenomenon described previously for homogeneous catalysis. Most investigators, including ourselves, assume that under appropriate conditions, catalyst deactivation is negligible, and the rate acceleration induced by addition of the modifier is an intrinsic part of the reaction mechanism and due to the substrate–modifier interaction [11,20,47,48,55]. Catalyst deactivation is commonly attributed to site blocking by high-molecular-weight byproducts, probably oligomers formed from the reactive α-ketoester. Important side reactions leading to the formation of high-molecular-weight byproducts and extensive catalyst deactivation are the aldol condensation of ethyl pyruvate catalyzed by the basic amine-type modifier [56] and the basic sites on the catalyst support (alumina) [57], and the dimerization–oligomerization induced by the surface Pt atoms at low surface hydrogen concentrations, in the absence of modifier [41]. Knowing the characteristics of these reactions, we can minimize catalyst deactivation by (i) applying acetic acid as solvent, which deactivates the amine modifier and the alumina support for aldol reaction; (ii) decreasing the modifier/substrate ratio to reduce the rate of side reactions in solution; (iii) working at high surface hydrogen concentrations, that is, at high hydrogen pressure and in the absence of mass transport limitation; and (iv) carefully avoiding the contact of Pt with pyruvate in the absence of modifier at low surface hydrogen concentrations, and minimizing the contact of pyruvate and the modifier before entering into the reactor.

The literature data on pyruvate hydrogenation strongly support these considerations. The highest enantioselectivities and reaction rates were achieved in acetic acid under high hydrogen pressure; the ee decreased in other solvents and in cases of mass transport limitations, resulting in lower surface hydrogen concentrations [11,47,48]. Böhmer et al. reported significant catalyst deactivation in cyclohexane, but the activity did not decrease in acetic acid, and the deactivation in cyclohexane could be reduced by applying more acidic zeolites as catalyst supports [58]. Recently, Kraynov and Richards [59] also found no deactivation during pyruvate hydrogenation in acetic acid.

Astonishingly, Jenkins et al. [60] proposed that the origin of rate enhancement may be inhibition of pyruvate dimerization/polymerization by the strongly basic cinchona alkaloid. They carried out experiments in CH_2Cl_2 at 30 bar; under these conditions, rapid hydrodehalogenation of the solvent is expected. The strong acid can catalyze numerous side reactions, as mentioned previously, and the observed positive effect of alkaloid addition may be linked to partial neutralization of the acid adsorbed on the Pt surface. Clearly, these observations made under very specific conditions cannot be generalized, and it cannot be concluded that the rate acceleration with the addition of the amine-type modifier is due to suppression of side reactions.

Recently, Toukonitty and Murzin [61] lent support to Jenkins' proposal on the inverted effect of the alkaloid modifier. They carried out experiments in toluene in a continuous-flow reactor and concluded that the rate enhancement achieved by addition of CD would be due to suppression of catalyst deactivation. Interestingly, they did not acknowledge that 2 years earlier, they had arrived at the opposite conclusion—that CD would always lead to rate deceleration [62]. We speculate that the probable reason for this discrepancy is the difficult control of side reactions in the nonacidic solvent. This assumption is supported by other work from the same group involving the hydrogenation of another α-ketoester substrate, ethyl benzoylformate, that found no deactivation in acetic acid in a continuous-flow reactor but a rapid loss of activity in toluene [36], exactly in line with our proposal concerning the solvent effect on catalyst deactivation. For the same reaction, Bartók et al. [63] reported excellent ee's up to 98% and a significant rate acceleration by addition of a cinchona alkaloid to the Pt-catalyzed reaction in acetic acid. It is highly probable that the mechanisms of the hydrogenation of pyruvates and benzoylformates are the same, including the substrate–modifier interaction and the resulting rate acceleration.

Finally, a frequently neglected point is the purification of pyruvate. It has been shown that a simple distillation was not sufficient to remove the impurities from the highly reactive substrate; the impurities remaining in the distillate caused an up to sixfold variation in the hydrogenation rate, depending on the source of pyruvate [64]. Nevertheless, only a few studies addressing catalyst deactivation in pyruvate hydrogenation have reported careful purification of the substrate before use.

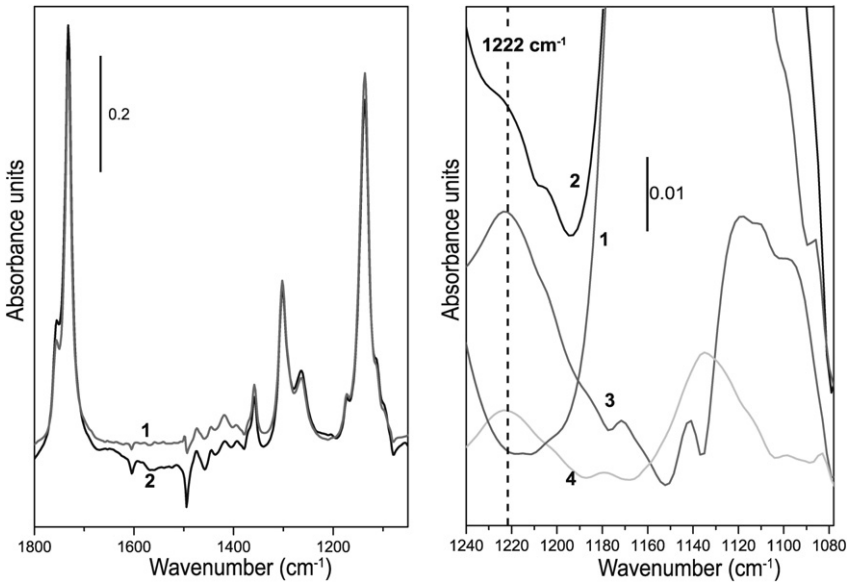


Fig. 8. Left panel: ATR-IR spectrum of ethyl pyruvate (735 mM) on the neat ZnSe crystal (1) and a spectrum of ethyl pyruvate (735 mM), ethyl lactate, and CD (0.226 mM) after 26 min on stream over 15 mg 5 wt% Pt/Al_2O_3 (deposited onto ZnSe) (2). Spectra are offset for clarity. Right panel: ATR-IR spectra of ethyl pyruvate (735 mM) on ZnSe (1); (2) ethyl pyruvate, ethyl lactate and CD (0.226 mM) after 26 min on stream over 15 mg 5 wt% Pt/Al_2O_3 (deposited onto ZnSe). Spectrum (3) was obtained by subtraction of spectrum (1) from spectrum (2). (4) Ethyl lactate (26.8 mM) on the neat ZnSe crystal. Conditions: H_2-saturated toluene; 0.4 ml/min total flow rate, 20 °C, 10 bar.

3.3. Spectroscopic study of the solid–fluid interface

Some fundamental aspects of the competition of cinchona alkaloids on Pt, including their different adsorption strengths and geometries, have been analyzed by ATR-IR spectroscopy in our preliminary report [33]. The present study focused on spectroscopic evidence for the formation of ethyl lactate in a high-pressure IR cell and on the complications arising from the presence of the large surface area support in the catalyst.

The experimental setup for the ATR-IR study (Fig. 1, right panel) was designed to probe the catalyst–liquid interface under conditions close to those applied in the catalytic experiments. A ZnSe internal reflection element was coated with the same Pt/Al_2O_3 catalyst used for pyruvate hydrogenation. The most important difference in the design of the catalytic reactor and spectroscopic cell is related to the mass transport. Admission of the H_2-saturated toluenic ethyl pyruvate–CD solution to the ATR-IR cell containing 15 mg Pt/Al_2O_3 afforded 4% conversion and 44% ee to (*R*)-ethyl lactate, as determined by gas chromatographic analysis. Changing the cinchona alkaloid from QD to CD in the flow inverted the ee from 21% (*S*) to 22% (*R*) at a maximum conversion of 4% [33]. The inversion from (*S*)- to (*R*)-lactate occurred in less than 15 min after introduction of CD, with a value comparable to that measured in the catalytic reactor. The inferior conversion and enantioselectivity with respect to the catalytic studies are attributed mainly to the cell design; due to the spectroscopic requirements, the solution does not pass through the catalyst bed, but rather flows over the bed, rendering the external mass transport of ethyl pyruvate and hydrogen to the Pt surface less efficient. Nonetheless, these experiments demonstrate that the high-pressure ATR-IR cell actually functions as a tiny catalytic reactor.

The left panel in Fig. 8 shows the IR spectra of the reaction mixture and the evolving ethyl lactate, as well as neat ethyl pyruvate on the bare ZnSe crystal as a reference. The large excess of substrate covers the IR signals of the evolving ethyl lactate and of the chiral modifier. The spectra of overlapping and covered signals require careful analysis; they are shown enlarged in the 1240–1080 cm^{-1} region in the right panel of Fig. 8. Spectrum (3) of the hydrogenation product is obtained by subtraction of the spectrum of ethyl pyruvate from that of the reaction mixture. Comparison of the reference spectrum (4) of (*R*)-ethyl lactate with spectrum (3) demonstrates the formation of ethyl lactate on the catalyst particles. The only signal of ethyl lactate not covered by ethyl pyruvate and the solvent is seen at 1222 cm^{-1} [65].

Next, we analyzed the mutual replacement of CD and QD on Pt/Al_2O_3 in the ATR-IR cell. The basis for discriminating between the two alkaloids is presented in Fig. 9. Addition of the $–OCH_3$ group to the quinoline generates important spectral changes. The methoxy-quinoline ring of QD is characterized by the signal at 1622 cm^{-1} (ring stretch), which is very weak in case of CD. The presence of this signal allows us to distinguish between QD and CD and thus facilitates a molecular-level investigation of the modifier replacement on the Pt/Al_2O_3 catalyst.

Fig. 10a shows the ATR-IR spectra during the replacement of QD by CD on the Pt/Al_2O_3 catalyst in the spectral region of interest. First, a toluenic solution of QD was fed to the catalyst to equilibrate the surface. The intensity of the signal at 1622 cm^{-1} is projected on the xz-plane. As QD reached the catalyst surface, the signal intensity increased quickly. In this region (up to 20 min), all major signals belonging to the quinoline modes (1510, 1570, 1590, and 1622 cm^{-1}) and to bending modes of the methylene groups of the quinuclidine moiety (ca.

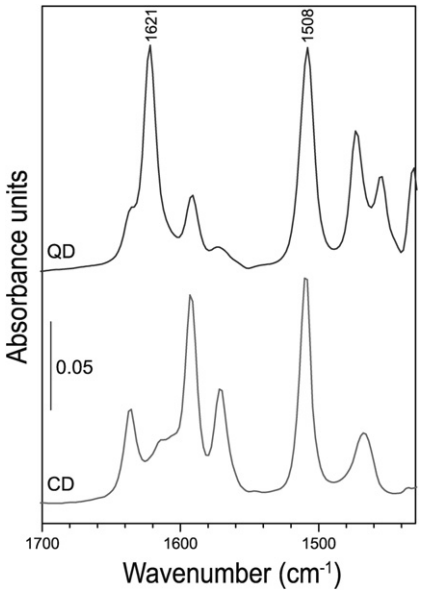


Fig. 9. Transmission FT-IR spectra of CD and QD (10 mM in CH_2Cl_2) in the spectral region of interest. Spectra are offset for clarity.

1450 cm^{-1}) [15] grow in simultaneously. Next, QD was replaced by CD in the feed solution. During the short period without dissolved modifier (before admission of CD), the signal intensity decreased slightly due to the removal of QD by the flowing H_2-saturated solvent. This region is indicated by the shaded spectra. After CD reached the catalyst, the signal at 1622 cm^{-1} characteristic of QD dropped quickly, whereas that at 1570 cm^{-1} grew in, signaling the replacement of QD by CD on the catalyst surface.

In the reverse experiment shown in Fig. 10b, the catalyst was first pre-equilibrated with CD. In this region, the signal at 1622 cm^{-1} barely increased, because this signal was very weak for CD (Fig. 9). After replacement of CD by QD in the feed solution, the signal at 1622 cm^{-1} increased, confirming the replacement of CD by QD. In both experiments, the intensities of the bands at 1590 and 1571 cm^{-1} reached the maximum after 20–25 min. In contrast to the signal at 1622 cm^{-1}, these signals remained rather unperturbed when QD was admitted to the cell, indicating constant modifier coverage on the catalyst. A comparison of the final part of the switching experiments in Figs. 10a and 10b reveals a considerably smaller difference than that observed in the catalytic reactor by following the stereochemical outcome of the reaction (Fig. 2).

The strong resemblance of the spectra of QD and CD on the catalyst with those in solution (Fig. 9) indicates that adsorption does not perturb the molecular structures of the modifiers. The spectra are dominated by adsorption of the alkaloids on the alumina surface. The only chemical difference between CD and QD is the 6′-methoxy group in the latter, which is not expected to contribute to adsorption on alumina. Thus, adsorption on alumina is likely to be similar for the two modifiers and probably involves interaction of the quinuclidine N atom with surface OH groups and that of the OH function of the alkaloids with basic O-atoms of the alumina. Indeed, a negative signal at ca. 3615 cm^{-1} indicates perturbation of the OH groups of the support on contact of the two modifiers. The large excess of Al_2O_3 in the catalyst relative to Pt limits the analysis of the process occurring on the metal surface. In other words, the ATR-IR spectra are related to the total amount of alkaloids present on the metal and the support together, whereas the enantioselectivity of the hydrogenation reaction followed by gas chromatographic analysis is characteristic of the fraction of alkaloids that interact with ethyl pyruvate on the metal surface. Note that it is still possible to follow the adsorption of the modifiers on the surface of Pt particles based on the competition of the alkaloids with CO, as described previously [33].

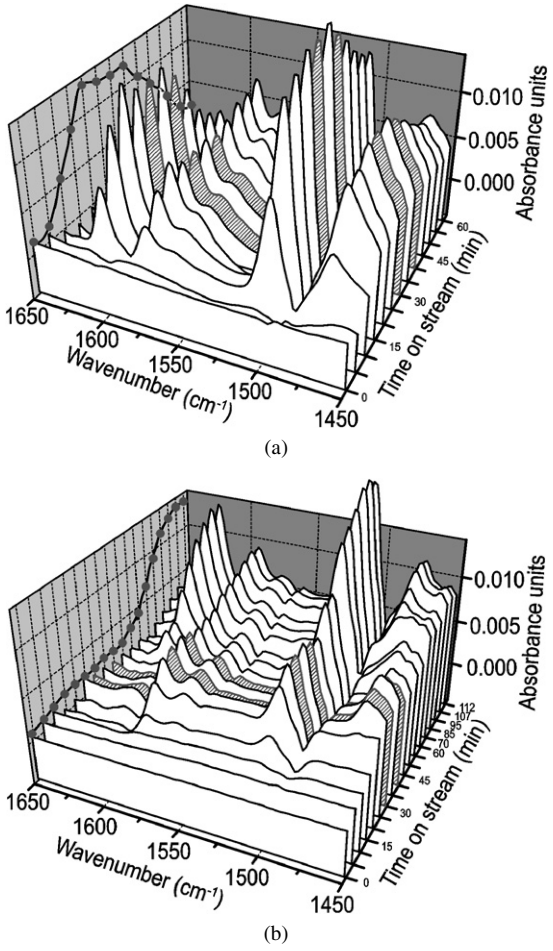


Fig. 10. Time-dependent ATR-IR spectra of the switch (a) from QD to CD and (b) from CD to QD on the 5 wt% Pt/Al_2O_3 catalyst in H_2-saturated toluene. The intensity of the signal at 1622 cm^{-1} is projected on the xz-plane. Shaded spectra indicate the 10 min period before the solution of the second modifier reached the cell. Conditions: 0.225 mM alkaloid concentration, 5 mg catalyst coating on ZnSe, 0.4 ml/min total liquid flow rate, 20 °C, 10 bar.

4. Conclusion

As discussed in Section 1, the mechanistic models developed for α-ketoester hydrogenation rely on assumptions rather than on experimental evidence concerning the adsorption geometry of the modifier during interaction with the substrate, because obtaining in situ information on the adsorption of the chiral modifier on the metal surface is very difficult. A new method [33] that involves switching the major enantiomer of the

product in a continuous-flow reactor by changing the modifier fed in trace amounts offers useful information on the adsorption strength and geometry of the modifier. The present study focuses on the dynamics of the competition of cinchona alkaloids used as chiral modifiers of Pt/Al_2O_3 in the hydrogenation of ethyl pyruvate. The results of the combined catalytic–ATR-IR study can be summarized as follows:

(i) The rate of replacement of one modifier by another is influenced by the reaction conditions and the rate of mass transfer in the reactor. The relative adsorption strength deduced from these experiments (CD > CN > QD) is in agreement with that obtained by the study of the nonlinear behavior of modifier mixtures in batch reactors.
(ii) It is possible to follow the transformation of ethyl pyruvate to (*R*)- and (*S*)-lactate and the competition of CD and QD, in the continuous-flow ATR-IR reactor cell on Pt/Al_2O_3.
(iii) Catalyst deactivation during pyruvate hydrogenation can be avoided by proper selection of the solvent and reaction conditions, and introduction of the chiral modifier into the reaction mixture induces considerable rate acceleration. These observations contradict the recent proposal that the origin of "ligand acceleration" is the suppression of catalyst deactivation by the modifier.

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