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Asymmetric hydrogenation on platinum: nonlinear effect of coadsorbed cinchona alkaloids on enantiodifferentiation

W.-R. Huck, T. Bürgi, T. Mallat, and A. Baiker *

Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH–Hönggerberg,CH-8093 Zürich, Switzerland

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Abstract

Prominent nonlinear effects in enantioselectivity were observed with a transient technique when ethyl pyruvate was hydrogenated over Pt/Al_2O_3 in the presence of two cinchona alkaloids, which alone afford the opposite enantiomers of ethyl lactate in excess. The changes in reaction rate and ee, detected after injection of the second alkaloid, varied strongly with type and amount of the alkaloid, and with the order of their addition to the reaction mixture. For example, under ambient conditions in acetic acid cinchonidine (CD) afforded 90% ee to (*R*)-ethyl lactate and addition of equimolar amount of quinidine (QD) reduced the ee to (*R*)-ethyl lactate only to 88%, though QD alone provided 94% ee to (*S*)-lactate in a slightly faster reaction. The stronger adsorption of CD on Pt in the presence of hydrogen and acetic acid was proved by UV–vis spectroscopy. The different adsorption strengths result in an enrichment of CD on the Pt surface and also in a crucial difference in the dominant adsorption geometries. CD is assumed to adsorb preferentially via the quinoline rings laying approximately parallel to the Pt surface. In this position it can interact with ethyl pyruvate during hydrogen uptake and control the enantioselectivity. The weaker adsorbing QD adopts mainly a position with the quinoline plane being tilted relative to the Pt surface and these species are not involved in the enantioselective reaction. Competing hydrogenation of the alkaloid, and steric and electronic interactions among the adsorbed species, can also influence the alkaloid efficiency and the product distribution. Hydrogenation of the quinoline rings at low alkaloid concentration resulted in unprecedented swings in the enantiomeric excess.

Keywords: Enantioselective; Asymmetric; Hydrogenation; Cinchona alkaloids; Platinum; Ethyl pyruvate; Adsorption; Transient behavior

1. Introduction

Chirally modified metals are the most effective heterogeneous catalysts for enantioselective hydrogenation reactions (for recent reviews see [1–8]). Originally, this research field was triggered mainly by Japanese groups [9–13]. Intensively investigated catalysts are the Ni–tartaric acid [14–18], the Pt–cinchona [11], and the Pd–cinchona [19] and Pd–vinca alkaloid [7,20] systems. In these catalyst systems the source of chirality is a strongly adsorbing organic compound that creates a chiral environment on the metal surface for the hydrogenation reaction. Among these chiral modifiers, cinchona alkaloids have the broadest application range, including Pt-catalyzed hydrogenation of various activated ketones [21–28], and the Pd-catalyzed hydrogenation of α,β-unsaturated carboxylic acids [29–31], pyrone derivatives [32,33], oximes [34], and imines [35]. As a result of intensive research by various groups in the past years, 90–98% enantiomeric excess (ee) has been achieved in several reactions.

An intriguing question is the nature of enantiodifferentiation on the metal surface. Some mechanistic models have been proposed for interpretation of the metal–reactant–chiral modifier interaction for the commonly used model reaction, the hydrogenation of ethyl pyruvate to ethyl lactate (for a review see [36]). According to present knowledge, good enantioselectivity can be expected only when the adsorption mode of reactant and chiral modifier allows their appropriate interaction during hydrogen uptake in the enantiodiscriminating step. Obviously, in situ adsorption studies are indispensable for understanding the mechanism of enantioselection.

Various surface science techniques and H/D exchange have been applied to clarify the adsorption mode of cinchonidine (CD) [37–40] and its "anchoring" moiety quinoline [39,41,42] on Pt metals. The NEXAFS, STM, XPS,

* Corresponding author.
E-mail address: baiker@tech.chem.ethz.ch (A. Baiker).

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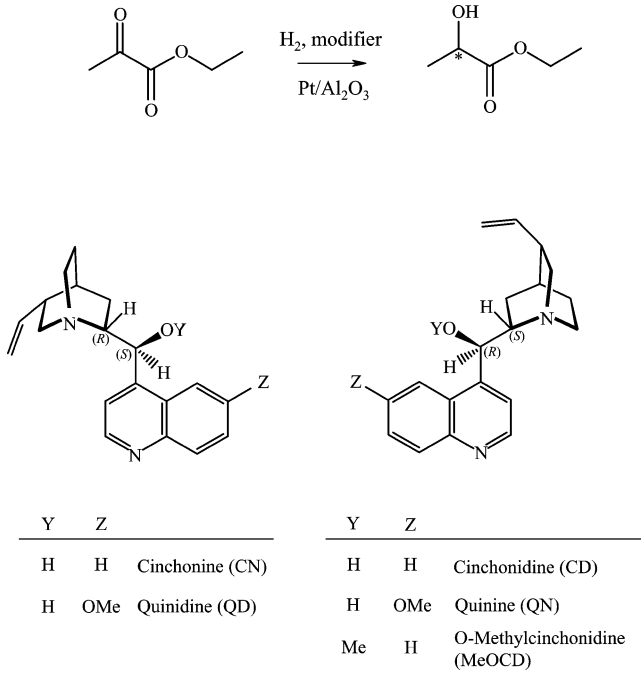
LEED, and IR studies were carried out far from the conditions of enantioselective hydrogenation; hence, the observations cannot easily be correlated with the catalytic results. In contrast, ATR-IR spectroscopy allows the choice of conditions very close to those of catalytic hydrogenation. A recent study on Pt/Al_2O_3 in the presence of solvent and hydrogen revealed three different adsorption modes of CD [43,44]. These species differ from each other not only by their adsorption strength but also by the adsorption geometries: the quinoline rings of the alkaloid may adopt a tilted or an approximately parallel orientation relative to the Pt surface. It was proposed that the latter π-bonded species is involved in enantiodifferentiation, in agreement with two mechanistic models developed for α-ketoester hydrogenation [36,45,46].

Another approach to investigating the role of modifier adsorption is to apply mixtures of modifiers [47]. When the chiral modifiers alone afford the opposite enantiomers in excess, the product distribution in the presence of both modifiers can provide useful hints concerning their adsorption on the metal surface under reaction conditions, that is, during interaction with the reactant and hydrogen. The small deviations from the expected linear correlation in the hydrogenation of ethyl pyruvate in the presence of CD–CN and QN–QD mixtures (Scheme 1) were attributed to different adsorption strength of the alkaloids [47]. The considerable nonlinearity detected when CN and NPE (1-{1-naphthyl}-2-{1-pyrrolidinyl}ethanol) were applied in equimolar amounts was explained by the low stability against saturation of the naphthyl group, the anchoring moiety of NPE [48].



Y	Z		Y	Z	
H	H	Cinchonine (CN)	H	H	Cinchonidine (CD)
H	OMe	Quinidine (QD)	H	OMe	Quinine (QN)
			Me	H	O-Methylcinchonidine (MeOCD)

Scheme 1. Hydrogenation of ethyl pyruvate over 5 wt% Pt/Al_2O_3 in the presence of cinchona alkaloids. CD, MeOCD, and QN afford (*R*)-lactate in excess, while CN and QD provide the (*S*)-enantiomer as the major product.

A different strategy, based on transient experiments, is applied in the present study. Ethyl pyruvate hydrogenation was used as a test reaction. It was started in the presence of a cinchona alkaloid or its simple derivative (MeOCD), and after 30 min an equimolar amount of a second alkaloid was injected that alone affords the opposite enantiomer of ethyl lactate in excess. The transient behavior in rate and ee after the disturbance was analyzed to study the adsorption and interactions of cinchona alkaloids on Pt. The remarkable nonlinearity in enantioselectivity is traced mainly to differences in strength and geometry of adsorption of the two alkaloids.

2. Experimental

Acetic acid (AcOH, Scharlau Chemie), toluene (J.T. Baker), quinoline (Fluka), 1,2,3,4-tetrahydroquinoline (Fluka), and 5,6,7,8-tetrahydroquinoline (TCI, Japan) were used as received. Tetrahydrofurane (THF, J.T. Baker) was refluxed over $LiAlH_4$ and distilled before use. Ethyl pyruvate (Fluka) was carefully distilled in vacuum before use; the ethyl lactate content after distillation was only 0.1% by GC analysis.

The commercially available cinchona alkaloids contained a high proportion of impurities (for the abbreviations, see Scheme 1): CD (92%; impurities: 1% QN, 7% QD, determined by HPLC, Fluka), CN (85%; impurity: 15% 10,11-dihydro-CN, determined by HPLC, Fluka), QD (> 90%; impurity: < 10% 10,11-dihydro-QD, determined by HPLC, Fluka), and QN (> 95%; impurity: < 5% 10,11-dihydro-QN, determined by HPLC, Fluka). Recrystallization of CD from toluene or 2-propanol was attempted but—according to NMR analysis—no significant enrichment was achieved. MeOCD was prepared according to a known method [30]. Elementary analysis and NMR spectroscopic data were in good agreement with the structure of MeOCD. ^1H and ^{13}C NMR spectra were measured using a DPX 300 spectrometer.

The 5 wt% Pt/Al_2O_3 catalyst (Engelhardt 4759; BET surface area, 100 $m^2\,g^{-1}$; metal dispersion after reductive heat treatment, 0.27, determined by TEM) and Al_2O_3 (support of the catalyst Engelhardt 4759) were treated with flowing H_2 for 60 min at 400 °C and cooled to room temperature in hydrogen for 30 min. After flushing with Ar, the catalyst was transferred to the reactor within 10 min.

Hydrogenation of ethyl pyruvate (**1**) was carried out in a magnetically stirred (1000 min^{-1}) 100-ml glass reactor. In a *standard procedure*, 20 mg of catalyst was prereduced in 10 ml of solvent in flowing H_2 for 5 min, at 1 bar and room temperature. Then 1.7 μmol of modifier or modifier mixture was added in 0.5 ml of solvent. After a 5-min preadsorption period the reaction was started by introducing 2 ml (16.5 mmol) of ethyl pyruvate. In some experiments (see Figs. 1, 2, 8, and 9) an additional modifier (1.7 μmol in 0.5 ml of solvent) was added to the reaction mixture after 30 min of reaction time.

The conversion and enantioselectivity {ee = $|R(\%) - S(\%)|$} were determined by an HP 6890 gas chromatograph using a Chirasil-DEX CB column (Chrompack). The estimated error in the determination of the ee is less than ±0.5%. The actual or incremental ee was calculated as $\Delta ee = (ee_1 y_1 - ee_2 y_2)/(y_1 - y_2)$, where y represents the yield to ethyl lactate, and index 2 refers to a sample subsequent to sample 1.

UV–vis measurements were used to determine the amount of CD and QD remaining in solution after the preadsorption period. Measurements were performed in transmission mode on a CARY 400 spectrophotometer using a 1-cm-path-length quartz cuvette. Spectra are given in absorbance units with neat acetic acid serving as the reference. Pretreatment of the catalyst and support was performed as described for catalytic experiments (see above).

Structure optimization of the modifiers was performed at the AM1 semiempirical level using GAUSSIAN98 [49].

3. Results

3.1. Enantioselective hydrogenation of ethyl pyruvate: transient experiments with CD and QD

Under standard conditions in THF, hydrogenation of ethyl pyruvate over 5wt% Pt/Al_2O_3 modified by CD afforded 82% ee to (*R*)-ethyl lactate. When QD was applied as chiral modifier, the (*S*)-enantiomer formed in 52% excess. To study the competition between these modifiers in the enantiodifferentiation, the reaction was started with Pt/Al_2O_3 modified by CD. After a 30-min reaction time one molar equivalent QD (related to CD) was injected into the reaction mixture (Fig. 1). Clearly, the reaction rate was not affected by QD and the enantioselectivity decreased only by about 2% after addition of the second modifier. In the control experiment the hydrogenation was started with Pt/Al_2O_3 modified by QD and a solution containing one equivalent CD was injected after 30 min. Addition of CD resulted in an immediate decrease of ee and enhancement of reaction rate. The time-dependent changes of the calculated actual or incremental ee (Δee) revealed that CD controlled the enantiodiscriminating step on the Pt surface within 2–3 min after its addition. Apparently, equivalent amount of CD rapidly replaced QD on the Pt surface in the enantioselective hydrogenation reaction, indicating stronger adsorption of CD.

3.2. Influence of solvents and acids on the competition between the alkaloids

The above two experiments were repeated in toluene and acetic acid. In both solvents, addition of QD to the reaction mixture barely influenced the performance of Pt/Al_2O_3 modified by CD, similarly to the reaction carried out in THF (Fig. 1). More interesting is the reverse case, the replacement of QD by CD (Fig. 2). The time-dependent

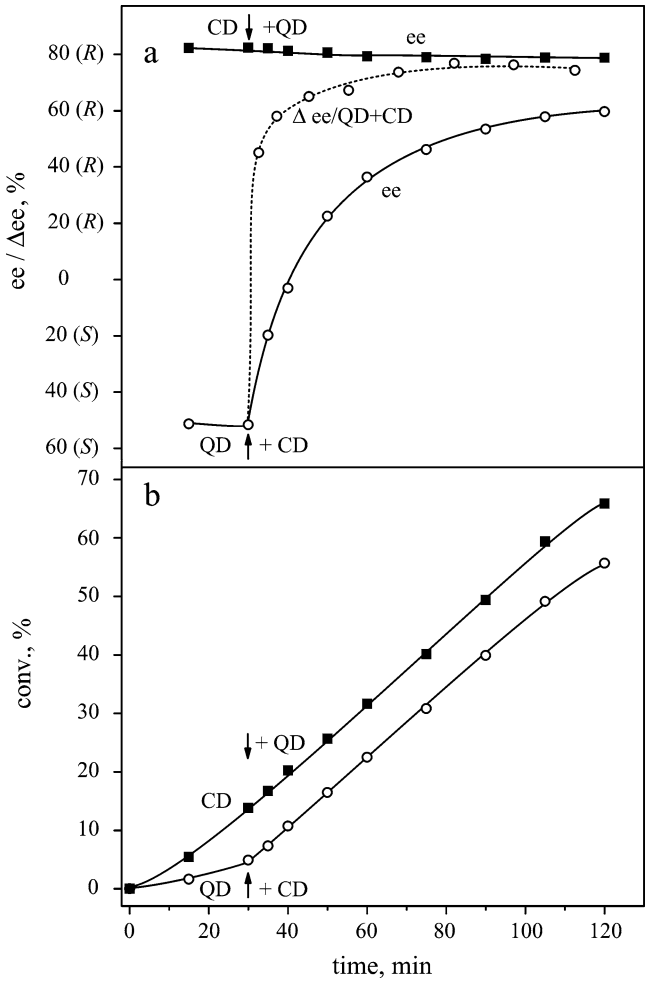


Fig. 1. Transient behavior of ethyl pyruvate hydrogenation over 5 wt% Pt/Al_2O_3 in tetrahydrofurane. Influence of the addition of one molar equivalent QD or CD after a 30-min reaction time to the reaction mixture containing CD or QD, respectively. (a) Enantiomeric excess (ee) and incremental ee (Δee) vs time; (b) conversion vs time. Standard conditions.

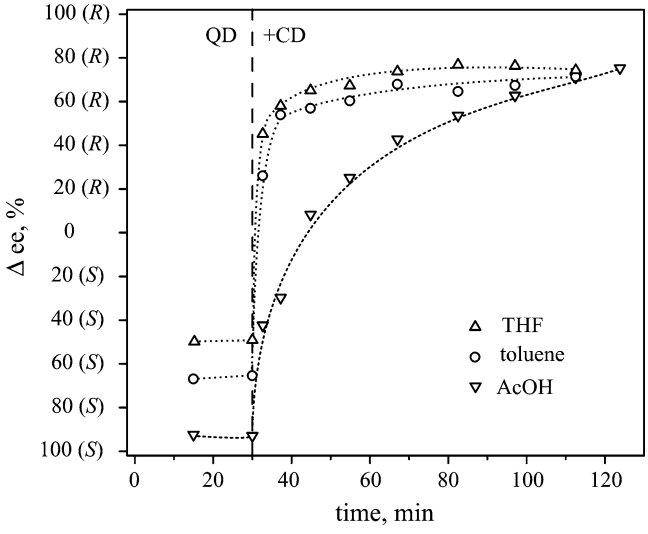


Fig. 2. Solvent effect on the exchange of QD by CD during hydrogenation of ethyl pyruvate over 5 wt% Pt/Al_2O_3. Standard conditions, addition of one equivalent CD after a 30-min reaction time.

variations in the actual or incremental ee (Δee) indicate that in toluene and THF the changes are faster than in acetic acid by a factor of about 10. In acetic acid the ethyl pyruvate were similar in the presence of QD or CD alone (0.39 and 0.36 mol h^{-1} (g cat)$^{-1}$, respectively) and no significant change in rate was observed by injection of the second modifier.

The differences in the exchange rate might be correlated with the solvent polarity. According to the mostly used empirical solvent polarity scale [50,51], toluene (E_T^N = 0.1) and THF ($E_T^N = 0.21$) are weakly polar solvents and acetic acid ($E_T^N = 0.65$) is more polar than the commonly used polar solvents dimethylformamide ($E_T^N = 0.4$) or acetonitrile ($E_T^N = 0.46$). Furthermore, polar compounds—and particularly carboxylic acids—adsorb strongly on Pt and can block the active sites from the catalytic reaction [52,53]. However, further experiments are needed to confirm these possibilities.

Another feasible explanation is that formation of an alkaloid–acid ion pair leads to slow exchange in acetic acid. We have shown recently that in the presence of a carboxylic acid solvent or additive CD forms ion pairs [54,55] and these ion pairs may be the real chiral modifiers of Pt or Pd [56,57]. The quinuclidine N and quinoline N atoms of CD are medium and weakly basic ($pK_a = 10.0$ and 5.8, respectively). Excess acetic acid ($pK_a = 4.7$) protonates the quinuclidine N while trifluoroacetic acid ($pK_a = 0.3$) protonates both N atoms [58,59].

To clarify the role of acidity, the experiment in THF (Fig. 2) was repeated and either 100 eq. AcOH or 25 eq. trifluoroacetic acid (related to both modifiers) was added to the reaction mixture. None of the acid additives induced a significant change in the exchange rate of the modifiers. Hence, protonation and building of a cyclic ion pair cannot be the reason for the slow exchange of modifiers on the Pt surface when using acetic acid as a solvent.

3.3. UV–vis study of cinchona alkaloid adsorption

A possible explanation for the striking changes in ee presented in Figs. 1 and 2 is the different adsorption strength of the alkaloid modifiers on Pt. As no data are available in the literature, the relative adsorption strength of CD and QD in the presence of hydrogen was analyzed by an indirect UV–vis spectroscopic method. The spectra of CD and QD in acetic acid are shown in Fig. 3a. The presence of the methoxy group has a strong effect on the electronic structure of the quinoline moiety, that is, the chromophore moiety of the molecule. The resulting shift in the UV spectrum allows the quantitative analysis of CD and QD mixtures. The UV spectrum of quinoline (Fig. 3b) resembles very much that of CD, confirming that the UV spectrum of CD is determined by the quinoline chromophore.

Fig. 4 illustrates determination of the individual concentration of the modifiers remaining in solution after filtering off the catalyst or support. Curve a represents the spec-

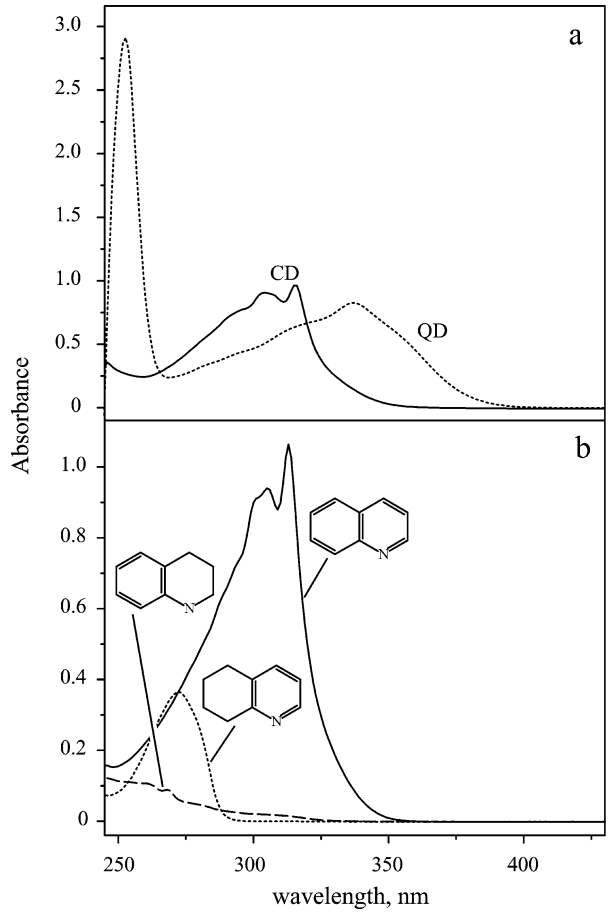


Fig. 3. UV–vis spectra of CD and QD (a), and quinoline, 1,2,3,4-tetrahydroquinoline, and 5,6,7,8-tetrahydroquinoline. (b) Concentrations: 0.17 mmol L^{-1} in acetic acid.

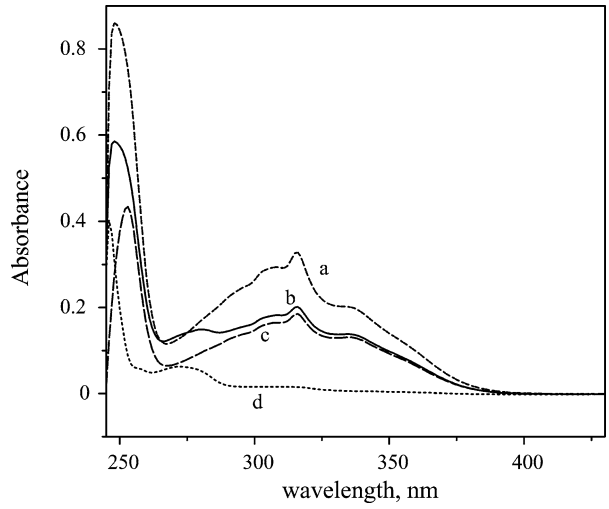
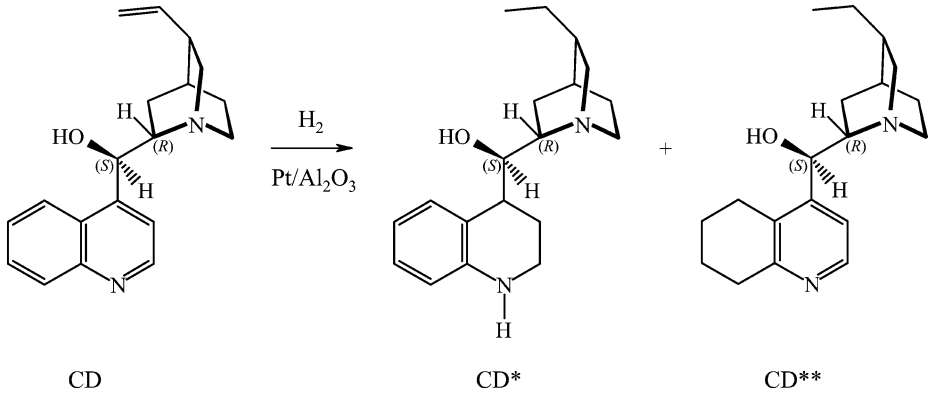


Fig. 4. Illustration to determination of the alkaloid concentration by UV–vis spectroscopy. Spectrum a represents the solution of 0.034 mmol L^{-1} CD and 0.034 mmol L^{-1} QD in acetic acid before treatment. Spectrum b was measured after a 5-min hydrogenation of the solution over Pt/Al_2O_3 (standard conditions). Spectrum c is the sum of the spectra of 0.017 mmol L^{-1} CD and 0.024 mmol L^{-1} QD. Spectrum d is the difference between the measured (b) and synthesized (c) spectra and indicates the presence of hydrogenated alkaloids.



Scheme 2. Hydrogenation of the vinyl group and the quinoline rings of cinchonidine (CD) over 5 wt% Pt/Al_2O_3 in acetic acid.

trum of an equimolar mixture of CD and QD containing 0.034 mmol L^{-1} from each alkaloid. After stirring the alkaloid solution for 5 min in hydrogen over Pt/Al_2O_3, the alkaloid concentration in solution decreased (curve b). Next, a synthetic spectrum, c, was generated by linear combination of the spectra of individual alkaloids being present in the appropriate concentration, in this case by summing up the spectra of 0.017 mmol L^{-1} CD and 0.024 mmol L^{-1} QD. This process was accepted when the difference between the measured and synthesized spectra did not exhibit the typical absorption bands of CD and QD at 315 and 338 nm, respectively. Curve d is the difference between spectra b and c, and indeed this spectrum does not show the typical features of CD and QD. The difference spectrum, however, shows a band at around 275 nm, which belongs to modifiers possessing a partially hydrogenated quinoline ring (Scheme 2). The latter band was found in all experiments where the catalyst and modifier were pretreated with hydrogen. Since this band does not overlap with the characteristic features of CD and QD at 300–350 nm, its presence does not hinder quantification of CD and QD in solution.

A test with CD–QD mixtures of known concentrations revealed that the reliability of the method is high: at a concentration of 0.034 mmol L^{-1} the relative error is estimated to be less than 2%. (A 2% change in the modifier concentration, used to synthesize the spectra, resulted in the appearance of clear features of the modifiers in the difference spectra.)

3.4. Competitive adsorption of CD and QD on Pt/Al_2O_3

Fig. 5 illustrates the competitive adsorption of CD and QD during the catalyst premodification procedure. Equal amounts of the two alkaloids were dissolved in acetic acid and the slurry containing Pt/Al_2O_3 was stirred in hydrogen for 5 min (preadsorption step in the *standard procedure*). In Fig. 5a the amount of alkaloids remaining in solution is plotted as a function of the initial total concentration of the alkaloids. The dashed line indicates the initial concentration for each modifier. Clearly, less CD than QD can be detected in solution after contact with the catalyst.

The drop in alkaloid concentration detected by UV–vis may be attributed to adsorption on the Al_2O_3 support and on Pt, and to partial or complete saturation of the quinoline rings. It is commonly assumed that saturation of the quino-

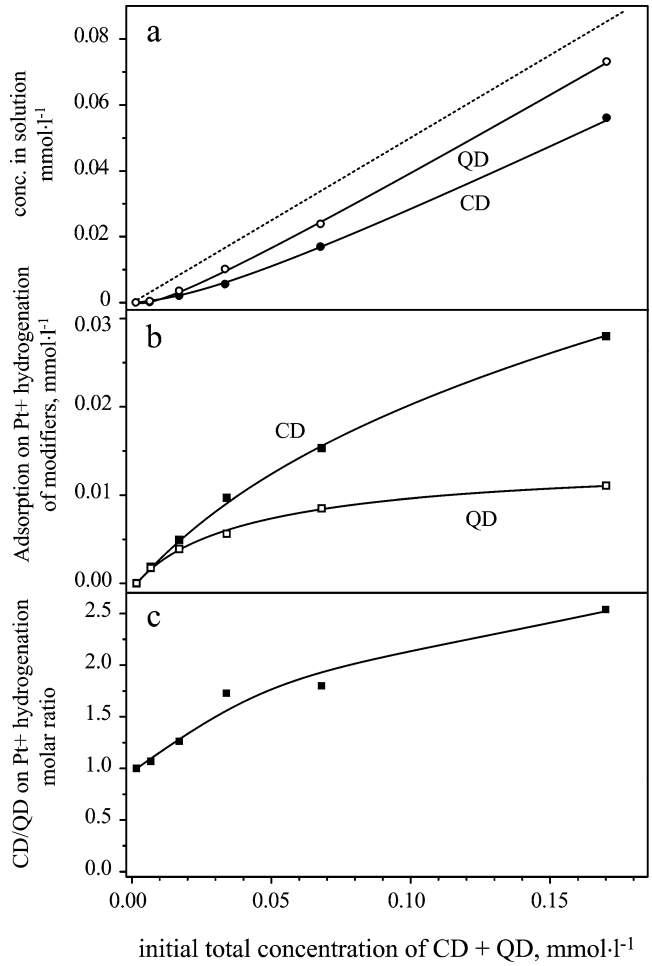


Fig. 5. Competitive adsorption of alkaloids on Pt in the presence of hydrogen. (a) Concentration of CD and QD remaining in acetic acid after preadsorption of equimolar mixtures of the alkaloids (5 min in hydrogen over Pt/Al_2O_3, standard conditions). Dashed line: initial concentration (no loss). The amount of adsorbed and/or hydrogenated alkaloids (b) and their molar ratio (c).

line rings of the alkaloid leads to weaker adsorption on Pt [8,60,61] and also on Pd [32]. Thus, the hydrogenated (destructed) alkaloid is expected to be replaced by intact molecules from solution. Adsorption on the catalyst support was investigated by repeating the experiments with the support alone (after the same pretreatment procedure as that used for the catalyst). At the highest concentration (0.17 mmol L^{-1}) the amount of alkaloid adsorbed on the support was less than 0.0017 mmol L^{-1}, corresponding to about 4% of the amount (0.041 mmol L^{-1}) removed from solution by pre-reduced Pt/Al_2O_3. At lower initial concentration the fraction adsorbed on the support increased. At a concentration of 0.0068 mmol L^{-1} the fraction adsorbed on the support was about 30% of the total amount removed from solution. It is important that no clear preference of adsorption of CD or QD on the support could be observed. A possible explanation is that on Pt, the alkaloids adsorb via the quinoline ring system, while on alumina, the basic quinuclidine N atom is assumed to be the favored "anchoring" moiety.

The adsorption on the support was taken into account, and Fig. 5b shows the amount of each modifier that either adsorbed on Pt or had its quinoline rings saturated. In Fig. 5c the same amount of alkaloids are presented as the molar ratio of CD to QD. At low concentrations this ratio is close to one and increases with the initial concentration up to 2.5. Hence, the preferential disappearance of CD (by stronger adsorption and/or faster hydrogenation) on Pt is important only at sufficiently high concentrations.

3.5. Hydrogenation of the alkaloids

Hydrogenation of the aromatic rings of CD (Scheme 2) and QD disturbs the quantitative determination of alkaloid adsorption by UV–vis spectroscopy. The importance of hydrogenation of the aromatic rings of modifiers during the adsorption study is addressed next. It is known that hydrogenation of the vinyl group is much faster than that of the aromatic rings, but this transformation barely influences the enantioselectivity [61–63]. Hydrogenation of the aromatic and heteroaromatic rings of the quinoline moiety of CD and QD has been followed by UV–vis spectroscopy (Fig. 6). After 45 min no intact alkaloid molecule could be detected in acetic acid. In both cases a band at around 275 nm appeared, which is assigned to species with the quinoline moiety partially hydrogenated (compare to the spectra of the reference compounds in Fig. 3b). The intensity of this peak is higher for QD than for CD.

An important observation is that the rates of disappearance (partial hydrogenation) of the original alkaloid molecules are about the same, independent of the presence (QD) or absence (CD) of the methoxy group on the quinoline ring. This is illustrated in Fig. 7, where the absorbance at 315 nm for CD and at 338 nm for QD, as well as the absorbance of the signals at 275 nm, are plotted as a function of reaction time. The markers at zero time refer to the reference solu-

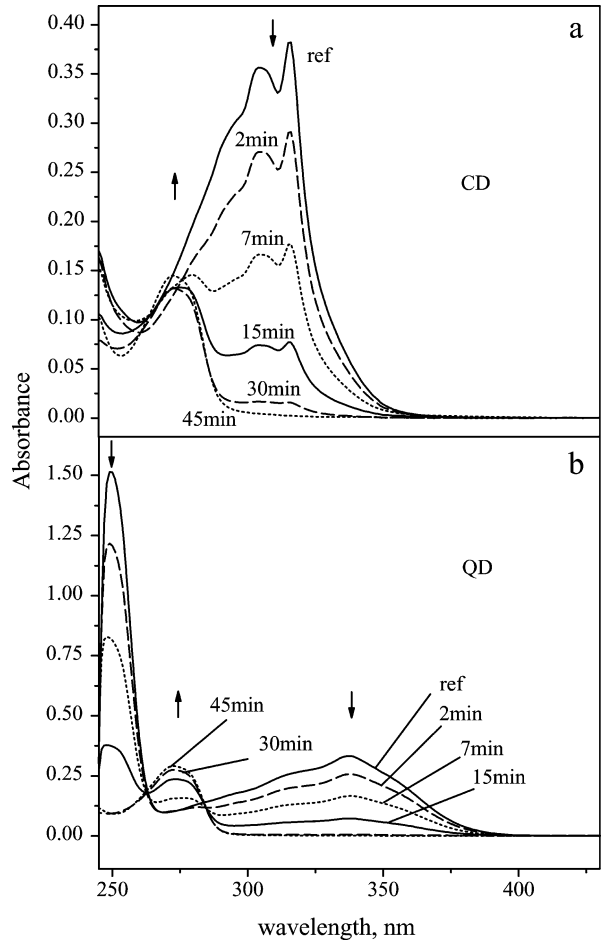


Fig. 6. Hydrogenation of CD (a) and QD (b) over Pt/Al_2O_3 in acetic acid, followed by UV–vis spectroscopy. Spectra of the initial solutions (0.068 mmol L^{-1}) are shown as reference.

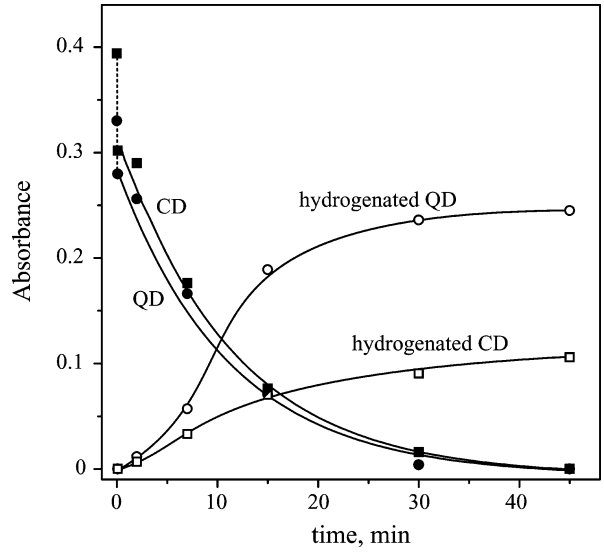


Fig. 7. Kinetic analysis of the hydrogenation of CD and QD in acetic acid, derived from the data in Fig. 6. The actual concentrations are determined from the absorbances at 315 nm (CD), 338 nm (QD), and 275 nm (partial hydrogenation products). The two values at $t = 0$ refer to the reference solution and the sample, which was only manually shaken for a few seconds.

Table 1
Influence of prehydrogenation of CD (in the absence of reactant) on the rate and enantioselectivity of ethyl pyruvate hydrogenation[a]

Prehydrogenation period (min)	Rate ($mol\,h^{-1}\,g^{-1}$)	ee[b] (%)
0	0.32	88 (*R*)
30	0.30	87 (*R*)
60	0.27	79 (*R*)

[a] Standard conditions, 0.068 $mmol\,L^{-1}$ CD in acetic acid.
[b] Determined after a 60-min reaction (at ca. 30–35% conversion).

tions (no treatment), and to samples that were not stirred but only shaken manually for a few seconds. Curve fitting and extrapolation to zero time indicated practically the same initial rates (3.6 and 3.7 $\mu mol\,h^{-1}$ for CD and QD, respectively, under standard conditions, at 0.068 $mmol\,L^{-1}$ initial modifier concentration). In contrast, Fig. 5 shows that from equimolar mixtures of the two modifiers CD disappears preferentially.

To clarify the impact of saturation of the quinoline rings of the alkaloids, we carried out the hydrogenation of ethyl pyruvate after different preadsorption (prehydrogenation) periods (Table 1). In the *standard procedure* the preadsorption step, in which the reduced catalyst is stirred with the alkaloid modifier in hydrogen before addition of ethyl pyruvate, is 5 min. Here this period was varied between 0 and 60 min. The initial concentration of CD was the same as that used in the UV–vis study (Figs. 6 and 7). After a 30-min prehydrogenation of CD in the absence of ethyl pyruvate, the ee was 87%, barely smaller than without any prehydrogenation (Table 1). According to the UV–vis study in Fig. 6a, after a 30-min prehydrogenation only 4% of initial amount of CD was present in solution. Prehydrogenation for 60 min resulted in complete conversion of the quinoline rings of CD (Fig. 6a) but in the subsequent reaction the ee to (*R*)-lactate dropped only by 9%. Similarly, the changes in initial rate of pyruvate hydrogenation were also small. Note that the partial loss of ee due to competitive hydrogenation of CD during enantioselective hydrogenations over Pt [8,60,61,64] and Pd [32,65] is a well-known phenomenon.

According to NMR analysis, at 36% saturation of the quinoline rings of CD in acetic acid the ratio of homoaromatic and heteroaromatic hydrogenation products (CD* to CD** in Scheme 2) was 2.5 to 1. (Note that in nonacidic solvents only CD* formed.) The presence of heteroaromatic hydrogenation products of CD and QD was confirmed by UV–vis spectroscopy in Fig. 6 but the method is not sensitive to the homoaromatic hydrogenation products (Fig. 3b). It is known [66] that hydrogenation of the heteroaromatic ring of quinoline and its derivatives is remarkably faster on most catalysts and in most solvents, but in strongly acidic medium on Pt the homoaromatic ring is reduced almost exclusively [67,68].

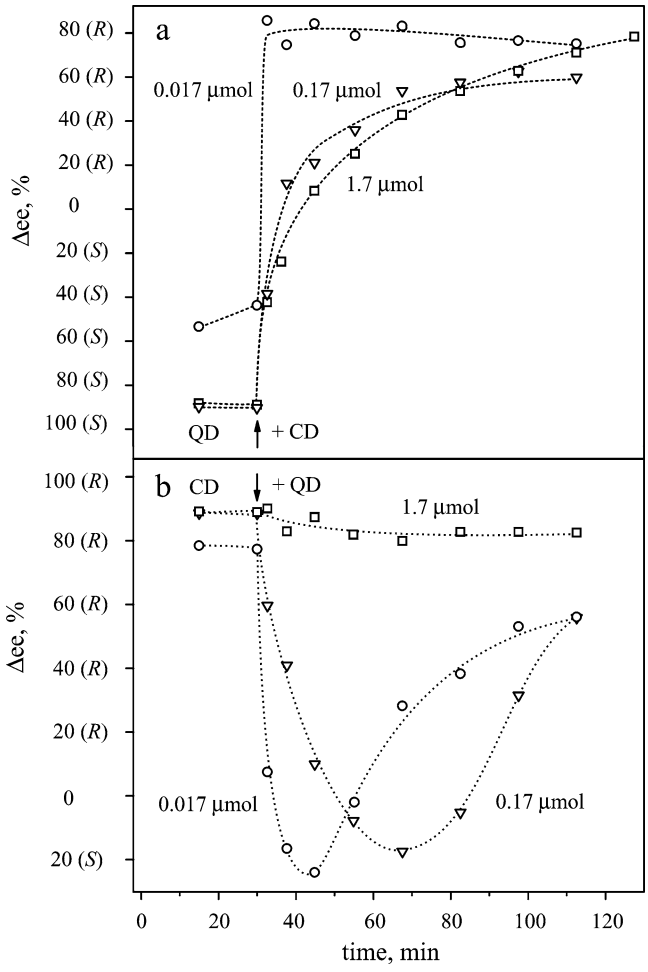


Fig. 8. Influence of modifier concentration on the transient behavior of ethyl pyruvate hydrogenation over Pt/Al_2O_3. (a) Addition of one molar equivalent CD after a 30-min reaction carried out in the presence of QD; (b) addition of one molar equivalent QD after a 30-min reaction carried out in the presence of CD. Standard conditions; acetic acid; amounts of the modifiers: 1.7, 0.17, and 0.017 µmol.

3.6. Effect of modifier hydrogenation on the transient behavior of pyruvate hydrogenation

Saturation of the quinoline rings of the modifiers has a strong influence on the transient behavior of ethyl pyruvate hydrogenation. This effect is best illustrated by repeating the transient experiment shown in Fig. 2 with different amounts of modifiers in acetic acid. Considering at first the highest amount of modifier (1.7 µmol; Fig. 8b), the initial incremental ee of 90% to (*R*)-lactate in the CD-modified reaction decreased by only 2% after addition of equivalent amount of QD. On the other hand QD, which provided 94% ee to (*S*)-lactate before addition of CD, was replaced by CD very slowly (Fig. 8a). According to UV–vis analysis, 76% of the modifier was intact after the 5-min preadsorption time and we assume that further hydrogenation of the quinoline rings is considerably slower after addition of large excess of ethyl pyruvate.

Starting the experiment with 10-fold lower modifier concentration (0.17 µmol CD or QD), only about 33% of the modifiers were still intact after a 5-min preadsorption, as indicated by the UV–vis analysis. This amount was enough to maintain the same initial ee (90% with CD and 95% with QD). However, the exchange of QD by CD was faster and the final ee was lower (Fig. 8a). A more interesting behavior was observed when the reaction was started with 0.17 µmol CD, and after 30 min 0.17 µmol QD was added (Fig. 8b). The incremental ee dropped rapidly and in the extreme point 18% actual ee to the (*S*)-enantiomer was produced, and then it changed back to the (*R*)-enantiomer in excess (58%). A possible (simplified) explanation for this unusual transient behavior is that the quinoline rings, the "anchoring" part of CD, were mostly converted to partially hydrogenated rings (Scheme 2) by the time QD was added to the reaction mixture. CD* and CD** are assumed to adsorb much more weakly than the original alkaloid and, apparently, more weakly than QD. Hence, the added QD rapidly replaced the hydrogenation products of CD on the Pt surface. Explanation for the next part, the shift back to (*R*)-lactate as the main enantiomer, might be that QD was slowly hydrogenated and the partially saturated products were replaced by CD* and CD**. It is also possible that intact CD, adsorbed on the alumina support, migrated to the Pt particles and replaced QD and its partially hydrogenated derivatives.

A further 10-fold decrease in the initial amount of modifier (0.017 µmol) led to significant changes in the initial ee. UV–vis measurements revealed that at this concentration no original (intact) modifier was present in solution after the 5-min preadsorption period. The exchange of this small amount of hydrogenated QD by CD (Fig. 8a) was very fast and around 80% ee to (*R*)-lactate was obtained after 2–3 min. The subsequent slow decrease in incremental ee by about 3–4% is attributed to the slow hydrogenation of CD. The reverse case, addition of 0.017 µmol QD to a hydrogenation reaction started with 0.017 µmol CD (Fig. 8b), showed a behavior similar to that described above for 0.17-µmol modifier. Here, due to the lower modifier concentrations, the changes in incremental ee were faster and an extreme value of 23% ee to (*S*)-lactate was reached 15 min after addition of QD.

3.7. Comparison of different cinchona alkaloids

The transient experiments in Fig. 1 were repeated with different cinchona alkaloids in acetic acid using high modifier concentration (0.17 mmol L^{-1}) in order to minimize the effect of modifier hydrogenation. In Fig. 9a the hydrogenation of ethyl pyruvate was started with Pt/Al_2O_3 modified by CD, MeOCD, or QN. MeOCD and QN provided 95% initial ee to (*R*)-lactate, higher than that achieved with CD (90% ee). After a 30-min reaction time one equivalent QD was added to the reaction mixture. The incremental ee to (*R*)-lactate in the reactions modified by CD, MeOCD, or QN decreased by 2, 27, and 40%, respectively, but in all cases the initially used modifier was dominant in controlling the enantioselection and (*R*)-lactate formed in excess.

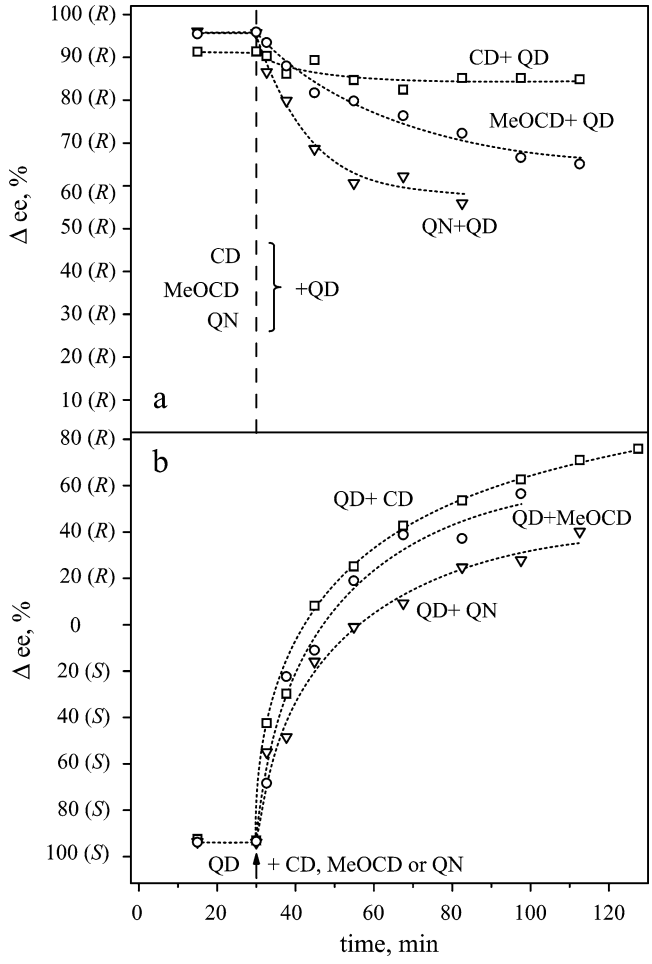


Fig. 9. Transient behavior of ethyl pyruvate hydrogenation over Pt/Al_2O_3 after addition of a second modifier, which provides the opposite enantiomer in excess. (a) Addition of one molar equivalent QD to reactions that were started with CD, MeOCD, or QN; (b) addition of one molar equivalent CD, MeOCD, or QN to reactions that were started with QD. Standard conditions; acetic acid; 1.7 µmol from each modifier.

Fig. 9b presents the reverse case, the transient behavior of those reactions, which were started with QD as modifier, and after 30 min one equivalent of CD, MeOCD, or QN was added. The initial ee was 94% to (*S*)-lactate and after addition of the second modifier, which alone provides the opposite enantiomer, the incremental ee successively shifted to (*R*)-lactate as the major product. Another interesting point is the outcome of the reaction in the presence of equimolar amounts of QD and QN. Independent of the order of addition, i.e., whether the reaction was started with QD or QN, the final ee approaches around 50% ee to (*R*)-lactate. These two alkaloids possess identical "anchoring" moieties (6-methoxy-quinoline fragment, Scheme 1); thus the difference in their efficiency as chiral modifiers of Pt should be attributed to their different configuration.

A small deviation from linearity has already been found for the QD–QN and CD–CN couples when using mixtures

of these modifiers [47]. The small shift in ee related to the calculated value was attributed to stronger adsorption of the alkaloid affording (*R*)-lactate in excess. The present transient experiments confirmed this behavior also for the CD–CN couple: the incremental ee approached very slowly about 20% to (*R*)-lactate, independent of the modifier which was added to the slurry after 30 min (not shown). It is interesting that the CN–MeOCD combination was the only example in this study where equimolar mixtures of modifiers afforded racemic ethyl lactate (about 90 min after injection), though the modifiers alone provide the opposite enantiomers in excess.

4. Discussion

Hydrogenation of ethyl pyruvate over Pt/Al_2O_3 has been studied in the presence of two cinchona alkaloids, which alone provide the opposite enantiomers of ethyl lactate in excess (Scheme 1). A transient method has been applied: the reaction was started with one alkaloid and after establishment of the rate and enantioselectivity a second alkaloid in an equimolar amount was injected. The changes in rate, ee, and incremental ee, observed after addition of the second modifier, depended dominantly on the alkaloid pair and the order of their addition but the alkaloid concentration and the solvent also played some role (Figs. 1, 2, 8, and 9).

4.1. The role of strength and geometry of alkaloid adsorption

For the interpretation of the results we can start from the remarkable nonlinearity uncovered in the case of the CD–QD alkaloid pair. In acetic acid QD is slightly more effective than CD: both the reaction rate (0.39 vs 0.36 $\mathrm{mol\,h^{-1}\,(g\,cat)^{-1}}$) and the enantioselectivity (94% to (*S*)-lactate vs 90% to (*R*)-lactate) were higher with QD when using the modifiers alone. Still, after addition of QD to the reaction mixture already containing CD, the ee to (*R*)-lactate dropped only by 2% and the effect on the reaction rate was negligible (Fig. 1). Apparently, QD has barely any influence on the enantiodifferentiating step in the presence of equimolar amounts of CD. This conclusion has been confirmed by repeating the experiment with the reverse order of alkaloid addition.

A feasible explanation for this nonlinearity is the different adsorption strength of the alkaloids on Pt. The adsorption of CD–QD mixtures on alumina-supported Pt from acetic acid solutions in the presence of hydrogen was measured by UV–vis spectroscopy. The values were corrected with the amounts adsorbed on the support but partial hydrogenation of the aromatic rings disturbed the analysis. At the highest total modifier concentration ($0.17\ \mathrm{mmol\,L^{-1}}$) the contribution of modifier hydrogenation was the smallest and the molar ratio of CD to QD on the Pt surface was about 2.5. This result supports the preferential adsorption of CD on Pt, though it cannot fully account for the observed large nonlinearity in enantioselectivity.

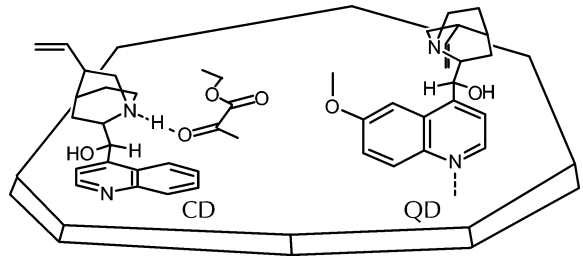


Fig. 10. Simplified illustration of the enantioselective hydrogenation of ethyl pyruvate over a hypothetical flat Pt surface modified by an equimolar mixture of CD and QD. Ethyl pyruvate interacts with the strongly adsorbed CD; the carbonyl groups of the reactant and the quinoline rings of the alkaloid lay almost parallel to the surface. Hydrogen uptake in this position leads to the formation of (*R*)-lactate. QD is adsorbed more weakly via its quinoline N-atom, adopting a tilted position of the aromatic rings relative to the surface ("spectator" species for enantioselective hydrogenation).

To explain this nonlinearity we have to take into account also the adsorption mode of alkaloid on the Pt surface. In situ ATR-IR spectroscopy in the presence of solvent and hydrogen revealed three different adsorption modes [43,44]. A strongly adsorbed π-bonded species that adsorbed via its quinoline rings approximately parallel to the Pt surface was assumed to interact with ethyl pyruvate in the enantiodiscriminating step. This position of the reactant is necessary for the uptake of two hydrogen atoms from the Pt surface. The other two alkaloid species adsorbed weaker and adopted a position in which the quinoline rings of the alkaloid were tilted relative to the Pt surface. In this adsorption mode the alkaloid may be considered a spectator species, which serves as a reservoir but is not involved in the crucial reactant–modifier interaction.

We propose that when CD–QD modifier mixtures are applied in the hydrogenation of ethyl pyruvate, most of the alkaloid that adsorbs stronger (CD) will occupy a position in which the quinoline rings are bound via π-bonding to the Pt surface (Fig. 10). The weaker adsorbing component (QD) will mainly adopt a "tilted" position. By this, the overall adsorption free energy is minimized.

4.2. Steric and electronic interactions

A refined consideration has to take into account also the various steric effects and electronic interactions among the surface species present on Pt. During reaction the surface is covered by the reactant, modifier(s), hydrogen, and solvent, but also by degradation products originated from solvent [43] and reactant [69,70]. Interaction of the modifier or a mixture of two modifiers with the other adsorbed species may increase or decrease the nonlinearity, but this effect cannot be reliably estimated yet. Let us consider only one point, the possible modifier–modifier interactions on the Pt surface. The importance of these interactions ("dimer formation" [71]) has been proposed and it can be expected also from the well-known nonlinear effects in homogeneous

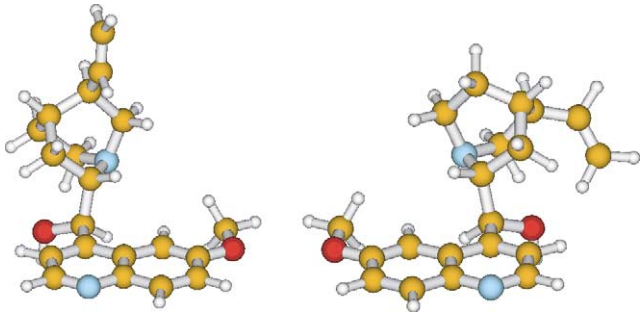


Fig. 11. Energetically optimized structures of QN and QD.

asymmetric catalysis (see Kagan's pioneer work in this field [72,73]). Figure 11 illustrates the energetically optimized structure of the diastereomeric pair QN and QD located over a hypothetical flat metal surface. In this case the so-called anchoring moieties of the alkaloids are the same; thus, their different adsorption strength on Pt cannot simply be attributed to the methoxy functional group on the quinoline rings, as was the case for the CD–QD pair. Still, it is easily understandable that the different structure of the alkaloids may have a strong influence on their mutual interaction, on the interactions with other surface species, and thus also on the adsorption strength. This is the explanation for the ca. 50% ee to (*R*)-lactate obtained with equimolar mixtures of these modifiers (Fig. 9). Note that the smaller nonlinearity reported earlier by Wells' group [47] is presumably due to the different reaction conditions applied (high pressure, other solvent).

4.3. Influence of hydrogenation of cinchona alkaloids

We have to consider also the influence of competing hydrogenation of the modifier (Scheme 2) on the adsorption strength. This phenomenon and its unfavorable consequences on enantioselectivity when using either cinchona-modified Pt [8,60,61] or Pd [32,65] have been thoroughly discussed in the recent literature. It is commonly assumed (though not yet proved) that partial hydrogenation of the aromatic ring system of the modifier leads to weaker adsorption on Pt and Pd, and to a successive loss of ee. Here we proved (Figs. 6 and 7) that the rate of saturation of one of the quinoline rings is the same for CD and QD, at least under the conditions applied. That is, partial hydrogenation of the alkaloid as an explanation can be excluded for the strong nonlinear effect depicted in Fig. 1. Still, partial transformation of the alkaloids can have a dramatic effect on the transient behavior of ethyl pyruvate hydrogenation when the modifiers are applied in low concentration. The unusual shift of ee from (*R*)- to (*S*)-lactate and than back to (*R*)-lactate (Fig. 8) is attributed to the combined effects of different adsorption strengths of the modifiers and their hydrogenated products.

A distinctly different case applies when the two modifiers possess anchoring moieties with substantially different resistance against hydrogenation. This is the explanation for a former observation: the high-pressure hydrogenation of ethyl pyruvate on Pt/Al_2O_3 modified by mixtures of CN and NPE [48]. Rapid hydrogenation of the naphthyl rings of NPE resulted in a remarkable nonlinearity, as the hydrogenated modifier could not compete with CN for the active sites on Pt.

4.4. Comparison to nonlinear effects in homogeneous asymmetric catalysis

Finally, it should be stressed that the observed nonlinear behavior cannot be related to the classical nonlinear effect (NLE), as originally defined by Kagan in his pioneer work in asymmetric homogeneous catalysis (see [72,73] and references therein). Their basic observation is that in many enantioselective reactions the ee in the product is not proportional to the ee in the chiral auxiliary or ligand. This asymmetric amplification or depletion is attributed to molecular interactions (associations) involving two enantiomers of the (impure) auxiliary.

In contrast, our observations are related to hydrogenation reactions in which diastereomer pairs (e.g., QD and QN) or even chemically different chiral modifiers (e.g., CD and QD) are applied. Besides, the nonlinear behavior is mainly traced to differences in the strength and geometries of modifier adsorption on Pt and only partly to modifier–modifier interactions. It remains a challenge for future research to investigate the importance of NLE in heterogeneous catalysis, that is, carrying out a reaction in the presence of two enantiomers of a chiral modifier.

5. Conclusions and outlook

Pairs of cinchona alkaloids, which afford opposite enantiomeric products when used in the asymmetric hydrogenation of ethyl pyruvate, have been applied in transient experiments. Hydrogenation in the presence of equimolar amounts of cinchonidine (CD) and quinidine (QD) provided 88% ee to (*R*)-lactate, as compared to 90% ee to (*R*)-lactate with CD alone. The strong nonlinear effect is traced to differences in the adsorption strength, and partly to steric and electronic effects.

The observed nonlinearity is of great practical importance in heterogeneous asymmetric synthesis, as cheap but low purity chiral compounds can be used as effective chiral modifiers. In the present study, the commercial CD contained a considerable amount of QD (in our sample, 7%) and smaller amount of quinine (QN) (1%). CD and QN afford the opposite enantiomer in excess compared to that induced by QD in all known hydrogenation reactions catalyzed by Pt or Pd. Our observations can rationalize how the commercial CD–QD–QN mixture can afford 94–98% ee in the hydrogenation of 2-pyrones [33], α-ketoacetals [26,27], α,α,α-trifluoromethyl ketones [74], and α-ketoesters [75]. Still, in the design of chirally modified metal catalysts for new reactions special care has to be given to the application of pure

modifiers, because other catalyst systems may be more sensitive to the optical purity of the modifier.

Albeit a single chiral modifier is generally used to transfer the chiral information, it could be challenging to explore whether a mixture of two different modifiers can afford better enantioselectivities in some reactions. This possibility remains the target of future studies.

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