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Enantioselective hydrogenation of α-keto esters over cinchona–Pt/Al_2O_3 catalysts
New interpretation of the rate acceleration and the induction of enantio-differentiation

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Abstract

The hydrogenation of ethyl pyruvate over the cinchonidine–Pt/Al_2O_3 catalyst system has been investigated in different solvents. Experimental variables used were as follows: (i) substrate and modifier concentration, (ii) presence of acetic acid, (iii) presence of (*R*)-ethyl lactate, (iv) mode of introduction of the interacting components. A completely different kinetic pattern was observed in ethanol and toluene. This difference is attributed to the lack of half-ketal formation in toluene. The optical yield vs. conversion dependencies show a monotone increase at low conversion, i.e. the optical yield extrapolated to zero conversion is close to zero. It is suggested that the rate acceleration is due to the enhanced reactivity of the substrate induced by substrate–modifier interaction. It is proposed that the induction of enantio-differentiation is attributed to the following interactions: (i) conformational changes of the modifier induced by substrate or acetic acid, (ii) formation of a substrate–modifier complex, (iii) shielding effect induced by the quinoline ring of the modifier.

Keywords: Platinum; Alumina; α-Keto esters; Cinchonidine; Enantio-differentiation; Hydrogenation; Ethyl pyruvate; Shielding effect

1. Introduction

The enantioselective hydrogenation of α-keto esters over a cinchona–Pt/Al_2O_3 catalyst (see Scheme 1) is one of the most selective heterogeneous catalytic systems. In the presence of cinchonidine (CD) preferential formation of (*R*)-lactate has been reported with optical yield up to 95% [1–4].

With respect to the mechanism of the above reaction the most disputed issue is related to the nature of interactions responsible for the rate acceleration (r.a.) and enantio-differentiation (e.d.) steps. In this respect there are two possibilities: the r.a and e.d. steps are controlled by (i) the modifier-active phase (Pt) interaction or (ii) modifier–substrate interactions taking place in the liquid phase.

Both in the template [1,2] and the ligand acceleration models [3,4] proposed earlier the modifier–metal interaction was favored. In contrast we suggested that both in the r.a. and the induction of e.d. modifier–substrate interactions taking place in the liquid phase are involved [5,6]. In the above two models [1–4] the exact chemical nature of interactions was not discussed. Recently new ideas were proposed with respect to the nature of

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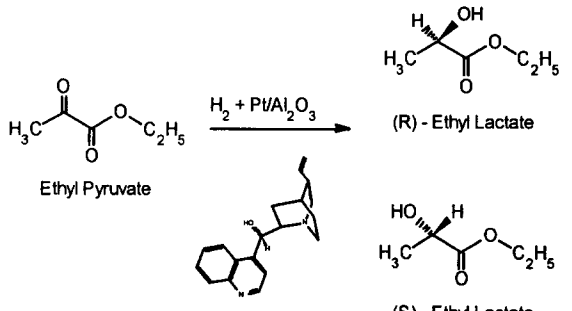

Scheme 1.

both r.a and e.d. steps. Based on computer modeling and quantum chemical calculations Pt-modifier–substrate interaction was suggested [7,8].

There is one serious contradiction in earlier studies: initial reaction rates, but with optical yields obtained at relatively high conversion, were used for kinetic analysis [1–4]. In the present work further investigation of both racemic and enantioselective hydrogenation of ethyl pyruvate (EtPy) is carried out and the focus is laid on the kinetic behaviour observed in the whole range of conversion.

2. Experimental

The hydrogenation of EtPy was carried out in a 300-cm^3 SS autoclave equipped with an injection chamber for separate introduction of either the cinchonidine (CD) or the substrate. In certain experiments CD was introduced by mixing all of the interacting components in the reactor. This mode of introduction of CD is called premixing; this technique was applied in earlier studies exclusively [1–4]. Different batches of substrate (Fluka) and Pt/Al_2O_3 catalysts (Engelhard E 4759, 5% w Pt, $D_{Pt} = 25\%$) were used. Both reaction kinetic data and optical yields showed a definite variation depending on the batches of substrate and catalyst used. Prior to the reaction the catalyst was rereduced in a hydrogen atmosphere at 400°C and after cooling in a nitrogen atmosphere it was slurred into the solvent without any contact with air. Prior to use EtPy was distilled under vacuum. Before the reaction the solvents used were carefully dried and purged with an inert gas. Due to the limited solubility of CD in hydrocarbons EtPy or ethyl acetate (AcOEt) (1.5 cm^3) was added into the injection chamber to ensure the entire dissolution of the modifier. GC analysis was carried out on a modified cyclodextrine coated capillary column resulting in complete separation of (*R*)- and (*S*)-ethyl lactate and EtPy. The optical yield was calculated as e.e. $= ([R] - [S])/([R] + [S])$ or e.e., % = e.e. × 100.

3. Results

3.1. General observations

The substrate and the modifier can in several ways be introduced into the reactor. In earlier works [1–4] all of the interacting components were introduced into the reactor prior to its purging with an inert gas, i.e. the modifier was premixed with the substrate and catalysts. In our experiments the substrate was introduced into the reactor first and the modifier was injected by high pressure hydrogen. In this way undesired chemical reactions (e.g. oligomerization, half-ketal formation, etc.) induced by the modifier prior to the hydrogenation reaction could partly be eliminated [5,6]. In some experiments either the substrate was injected into the reactor containing Pt/Al_2O_3 and CD or all of the interacting components were premixed in the reactor. In transient experiments the reaction started as a racemic hydrogenation and the modifier was introduced at a given moment.

Typical kinetic curves of the hydrogenation of EtPy are shown in Fig. 1a and 1b. The kinetic curves were analyzed as described elsewhere [5]. The calculated first-order rate constants obtained in ethanol and toluene under different experimental conditions are given in Table 1. In ethanol the racemic hydrogenation can be described by a first-order rate equation with rate constant k_0, while two first-order rate equations with rate constants k_1 and k_2 ($k_1 \gg k_0$, $k_2 < k_1$) are needed to describe

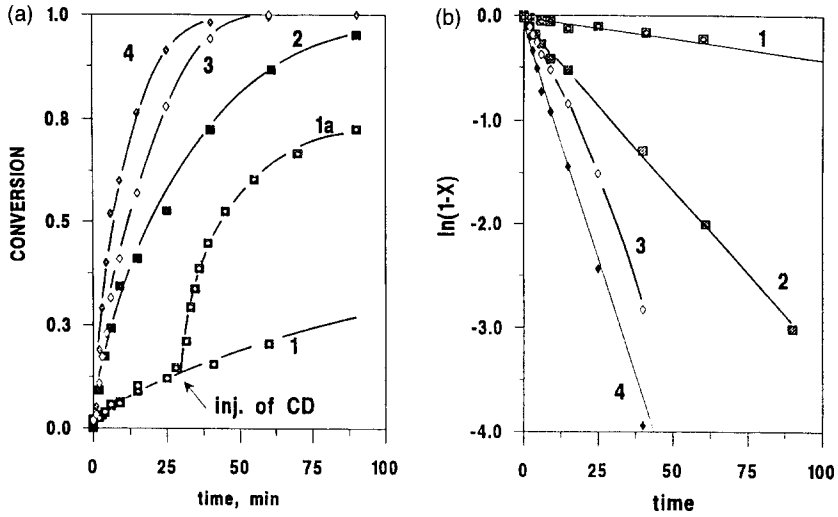

Fig. 1. Kinetic curves obtained under different experimental condition in the hydrogenation of ethyl pyruvate. (1) Racemic hydrogenation in ethanol. (1a) Injection of cinchonidine during racemic hydrogenation in ethanol. (2) Enantioselective in ethanol ($CD_{inj.}$). (3) Enantioselective hydrogenation in toluene ($CD_{inj.}$). (4) Enantioselective hydrogenation in toluene ($CD_{inj.}$), 5.0 M AcOH, $[Etpy]_0 = 1.0$ M, reaction conditions: see Table 1.

the kinetics of enantioselective hydrogenation. Rate constant k_1 describes the conversion of EtPy in the first 7–12 min, which roughly corresponds to the increasing part in the optical yield vs. conversion dependence (see Fig. 2). The rate constant k_2 is valid for the conversion range, where the optical yield is near constant (see Fig. 2). The r.a. induced by CD (or any tertiary amine) is instantaneous (see Fig. 1a, exp. 1a). In ethanol the rate constant k_1 was independent of the concentration of EtPy (in the concentration range of 0.1–1.0 M), however, the optical yield measured

Table 1
Hydrogenation of ethyl pyruvate. Summary of experimental data

No.	Experimental conditions	[Ethyl pyruvate], M	Rate constant k_0, min^{-1}	Rate constant k_1, min^{-1}	Rate constant k_2, min^{-1}	Optical yield[a], e.e, %
1	Racemic, EtOH	1.00	0.006	–	–	–
2	Enantiosel., EtOH, $CD_{inj.}$	1.00	–	0.046	0.035	68.2
3	Enantiosel., EtOH, $(CD + Etpy)_{inj.}$	1.00	–	0.044	0.033	69.0
4	Enantiosel., EtOH, premixing 15 min	1.00	–	0.030	0.029	66.0
5	Enantiosel., EtOH, premixing 30 min	1.00		0.026	0.023	67.2
6	Racemic, EtOH, $CD_{inj.}$ after 15 min	1.00	0.007	0.053	0.040	69.1
7	Racemic, EtOH, $CD_{inj.}$ after 30 min	1.00	0.005	0.055	n.a. $k_2 < k_1$	69.5
8	Enantiosel., toluene, $CD_{inj.}$	1.00	–	0.066	n.a. $k_2 > k_1$	84.7
9	Enantiosel., toluene, premixing 15 min	1.00	–	0.052	n.a. $k_2 > k_1$	84.1
10	Enantiosel., EtOH, $CD_{inj.}$	0.50	–	0.044	0.027	62.4
11	Enantiosel., EtOH, $CD_{inj.}$	0.27	–	0.043	0.023	59.2
12	Enantiosel., EtOH, $CD_{inj.}$	0.10	–	0.044	0.022	54.7

[a] Optical yields measured at 90–100% of conversion, catalyst = batch1, EtPy = batch1. Reaction conditions: total liquid volume = 100 cm^3, $T = 23°C$, $P = 50$ bar, $[CD] = 8.4 \times 10^{-4}$ M, catalyst = 0.125 g.

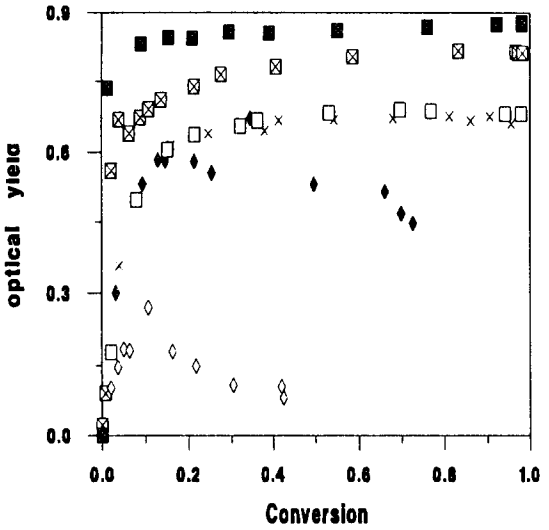

Fig. 2. Optical yields vs. conversion dependencies. (■, ⊠) in toluene, $CD_{inj.}$, $[Etpy]_0 = 1.0$ M, $[CD]_0 = 8.4 \times 10^{-4}$ M, 3.4×10^{-5} M, respectively; all other experiments in ethanol, $[Etpy]_0 = 1.0$ M, (◇) $[CD]_{0\ inj.} = 6.8 \times 10^{-6}$ M, (◆) $[CD]_{0\ inj.} = 3.4 \times 10^{-5}$ M, (×) $[CD]_0 = 0.4 \times 10^{-4}$ M, $(CD + EtPy)_{inj.}$, (□) $[CD]_0 = 8.4 \times 10^{-4}$ M, $(EtPy)_{inj.}$, $(CD)_{premixed}$. Reaction conditions: see Tables 1 and 3.

at 95–100% conversion showed a strong concentration dependence (see Table 1, exps. 2, 10, 11, 12).

In toluene both in racemic and enantioselective hydrogenation after a short period characterized by first-order rate constant k_0 (racemic) and k_1 (enantioselective) monotonous increase of k_0 and k_1 in time is always observed without the formation of a definite second part with rate constant k_2.

The premixing of interacting components in both ethanol and toluene always resulted in significant decrease of the reaction rate (see Table 1, exps. 4, 5, 9), without noticeable change in the optical yield. Similar results have been observed in earlier studies [9–11]. In these experiments the k_1/k_2 ratio is close to one.

3.2. *Analysis of the optical yield-conversion dependencies*

Fig. 2 shows the optical yield vs. conversion dependencies obtained under various experimental conditions, while Fig. 3 illustrates the variation of the optical yield as a function of the actual concentration of ethyl lactate (EtLa) formed. The latter results were obtained in a series of experiments with various initial concentrations of EtPy. The optical yield-conversion dependencies always show a monotone increasing character [12]. Both the increasing part and the maximum value strongly depended on the experimental conditions. In toluene at high CD concentration (8.4×10^{-4} M) the increasing part hardly can be seen, however, the pronounced slope on the increasing part was observed at low concentration of the modifier. Contrary to that in ethanol the increasing part is very pronounced in all experiments. The initial slope strongly depended on both the initial modifier and substrate concentration. At low concentration of modifier not only the initial slope is small, but the e.e.-conversion dependence shows a definite maximum. The decreasing part is attributed to the loss of modifier during the hydrogenation reaction. As emerges from Fig. 3 the optical yield strongly correlates with the amount of ethyl lactate formed. It should be emphasized that in earlier studies the optical yield extrapolated to zero conversion was equal to the optical yield measured at high conversion and no attempt was done to investigate these dependencies [1–4].

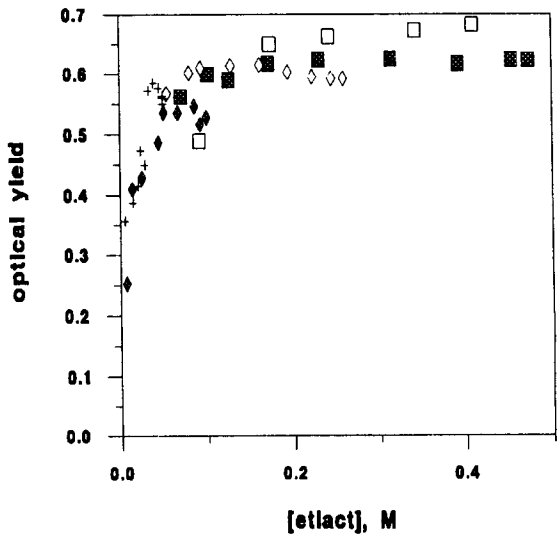

Fig. 3. Optical yield vs. ethyl lactate concentration dependencies obtained at different ethyl pyruvate concentration. $[EtPy]_0$, M: (+) 0.05, (◆) 0.10, (◇) 0.27, (■) 0.52, (□) 1.0. Reaction conditions: see Table 1. CD was injected in all experiments.

3.3. Influence of the added reaction product

We observed a pronounced increase in the rate of hydrogenation if a small amount of (*R*)-(EtLa) was added to the reaction mixture prior to the hydrogenation. In these experiments EtLa was either injected into the reactor (together with CD) or premixed with the substrate and catalyst. The rate increase strongly depended on the mode of introduction of ethyl lactate into the reactor. The addition of (*S*)-lactate resulted also in a slight increase in the rate of hydrogenation. The rate increase is substantial both in the first and second parts of the kinetic curves. The calculated first-order rate constants obtained in this series of experiments are given in Table 2. In the light of these results the slight increase of k_1 observed when CD was injected during racemic hydrogenation (see Table 1, exps. 5, 6) can also be attributed to the presence of EtLa. The corresponding optical yield vs. conversion dependencies obtained in these experiments show that the form of the optical yield vs. conversion dependencies was not altered by addition of (*R*)-EtLa. This observation strongly indicates that the monotone increasing character of the optical yield observed at low conversion is a common feature of this enantioselective hydrogenation reaction.

3.4. Effect of solvents and acetic acid

Results obtained in different solvents and in the presence of acetic acid are given in Table 3. The rate of hydrogenation and the optical yields were strongly influenced by the nature of alcohol used. In methanol about 5% of EtPy and ethyl lactate was transesterificated. Significant increase of both the rate of hydrogenation and optical yields was observed if acetic acid was added either to ethanol or toluene. Analogous high rates and high optical yields were obtained in pure acetic acid [4]. It is noteworthy that the nature of solvent used to dissolve cinchonidine in hydrocarbons had a slight influence on the rate of hydrogenation and the optical yield (see Table 3, exps. 4, 5 vs. 6, 7).

Table 3
Solvent effects and influence of acetic acid

No.	Solvent	k_1, min^{-1}	k_2, min^{-1}	Optical yield [c], e.e., %
1	methanol	0.022	0.019	62.2
2	ethanol	0.057	0.034	72.0
3	n-butanol	0.099	$k_2 > k_1$	75.0
4	toluene (EtPy) [a]	0.057	$k_2 > k_1$	86.3
5	MCH (EtPy) [a]	0.106	0.106	78.1
6	toluene (AcOEt) [a]	0.063	$k_2 > k_1$	84.0
7	MCH (AcOEt) [a]	0.069	0.060	75.3
8	ethanol + AcOH [b]	0.074	0.048	91.4
9	toluene + AcOH [b]	0.120	0.120	93.1

Reaction conditions: $T = 23$°C, $P = 50$ bar, $[EtPy]_0 = 1.0$ M, $[CD] = 8.4 \times 10^{-4}$ M, CD injection. Catalyst = batch2, EtPy = batch3.
[a] Ethyl pyruvate or ethyl acetate (1.5 cm^3) is added to dissolve cinchonidine in these solvents (8.5 cm^3).
[b] The solvent is mixed with acetic acid; $[AcOH]_0 = 5.0$ M.
[c] Measured at 90–100% conversion.

4. Discussion

Our key issues for the discussion are as follows: (i) the instantaneous character of the rate accel-

Table 2
Influence of added ethyl lactate

No.	Experimental conditions	Rate constant k_1, min^{-1}	Rate constant k_2, min^{-1}	Optical yield[a], e.e., %
1	EtOH, without (*R*)-lactate, $CD_{inj.}$	0.057	0.034	72.0
2	EtOH, ((*R*)-lactate + CD)$_{inj.}$	0.082	0.039	72.4
3	EtOH, ((*R*)-lactate + CD)$_{premixed}$	0.058	0.045	72.4
4	EtOH, (*R*)-lactate$_{premixed}$, $CD_{inj.}$	0.085	0.041	73.1
5	EtOH, (*S*)-lactate$_{premixed}$, $CD_{inj.}$	0.068	0.043	70.0

Reaction conditions: $T = 23$°C, $P = 50$ bar, $[EtPy]_0 = 1.0$ M, $[Ethyl\ lactate]_0 = 0.1$ M, $[CD] = 8.4 \times 10^{-4}$ M, catalyst = 0.125 g. Catalyst = batch2, EtPy = batch2.
[a] Optical yields measured at 90–100% conversion and corrected for the added EtLa.

eration induced by the alkaloid or other tertiary amines, (ii) alteration of the reaction kinetics by experimental conditions and by the nature of solvents used, (iii) the initial optical yield extrapolated to zero conversion is close to zero [12], (iv) strong dependence of the optical yield of substrate concentration, and (v) formation of different by-products in reactions catalyzed by cinchona alkaloids. None of these experimental results can be rationalized by existing models [1–4].

The kinetic analysis shows (see Fig. 1b and Table 1) that not only the initial reaction rates, but the overall kinetic behaviour is altered by the solvents used. In earlier studies using ethanol, toluene and acetic acid the solvent induced differences in reaction rates and optical yields were not discussed at all [4]. Our results indicate [5,6] that solvents such as alcohols have a unique behaviour, they react with substrate resulting in the formation of a half-ketal. The formation of half-ketal from methyl pyruvate (MePy) and CD_3OD as well as deuterium exchange and transesterification of MePy with CD_3OD has been shown in earlier works [5,6]. The half-ketal formation takes place in an equilibrium reaction. CD appeared to be an effective catalyst both for half-ketal formation and transesterification. The strong decrease of the reaction rate after 8–10 min of enantioselective hydrogenation, at least partly, can be attributed to the formation of a half-ketal and oligomers with a half-ketal structure. With respect to the results obtained in alcohols the observed trend in rate constants k_1 and k_2 (see Table 3) is in a good agreement with the ability of alcohols to form half-ketals. As far as CH_3O^- is the strongest nucleophile among the alcohols used, its poisoning effect, via half-ketal formation, should be the highest.

The dependence of both k_1 and k_2 on the mode of introduction of the modifier (see Table 1) shows that other unknown chemical interactions can take place upon mixing EtPy, cinchonidine and ethanol. The effect of the solvation media (see Table 3, exps. 4–7) also indicates that the character of interactions involved in this reaction is very complex. The detection of transesterification products formed from EtPy in methanol gives further evidence for the complexity of interactions involved in the enantioselective hydrogenation reaction.

We have recently proposed that in the enantioselective hydrogenation of EtPy interactions taking place in the liquid phase can be involved both in the r.a. and e.d. steps [5,6]. The formation of different by-products (half-ketals and transesterification products) strongly indicates that in the presence of cinchona alkaloid the reactivity of both carbonyl groups of the substrate is strongly increased. The increased reactivity of the substrate in the presence of cinchona alkaloids or tertiary amines is the basis for our new model.

The marked difference in the kinetics observed in alcohols and hydrocarbons can also be attributed to the by-product formation. In toluene or methylcyclohexane the number of interacting components is much less than in alcohols, consequently no decrease of the rate of hydrogenation is observed in the enantioselective hydrogenation after 10–15 min. However, the elucidation of the rate increase observed in toluene after 10–20% of conversion requires further investigations.

We consider that the instantaneous rate acceleration induced by the alkaloid (see Fig. 1a, exp. 1a) is due to the enhanced overall reactivity of the substrate caused by substrate–modifier interaction. We suggest the formation of a week complex between substrate and modifier in an equilibrium. According to computer modeling and quantum chemical calculations [7,13] the modifier in this complex can act either as a nucleophile or an electrophile. Due to the presence of a conjugated double bond in the substrate the calculated reaction pocket for a nucleophilic attack is between the two carbonyl groups [13], consequently after a nucleophilic attack on the substrate, both of its carbonyl groups are activated. The perturbation of the ester carbonyl group results in the transesterification products, while the perturbation of the keto group leads to the formation of half-ketals and oligomers.

We suggest that the modifier–substrate complex should be in equilibrium between the liquid

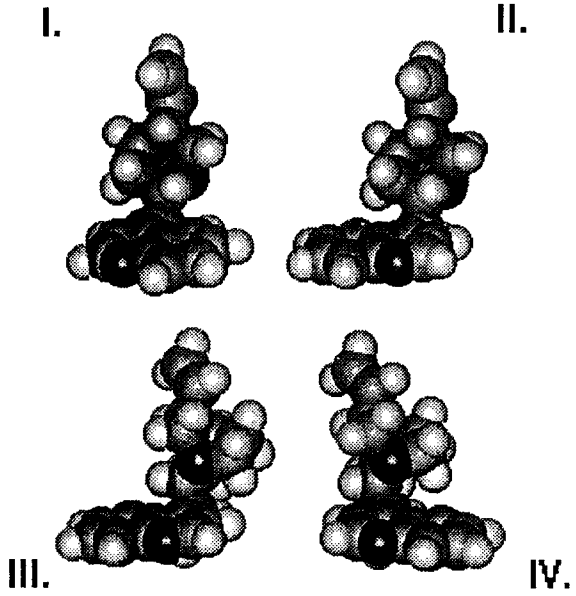

Fig. 4. The possible four conformations of cinchonidine.

phase and the Pt sites, too. In this complex the keto carbonyl group has a strongly enhanced reactivity towards adsorbed hydrogen formed on Pt sites, due to the overall perturbation of the molecule mentioned above, although the formation of ethyl lactate from corresponding half ketals cannot be excluded. The hydrogenation of free substrate gives the racemic product, while the hydrogenation of the substrate–modifier complex leads to the preferential formation of (*R*)-ethyl lactate.

The optical yield vs. conversion and optical yield vs. [ethyl lactate] dependencies show that the initial optical yield is close to zero (see Figs. 2-4). It should be emphasized the lower the initial concentration of the substrate the lower the final optical yield. There are at least two explanations for the monotone increasing type dependencies shown in Figs. 2-4. It can be suggested that species responsible for the induction of enantio-differentiation should be formed in the first 10 min of the enantioselective hydrogenation reaction, however, it is not excluded either that this behavior is common if either the substrate–modifier or the substrate–modifier–product complex is involved in the hydrogenation step over Pt leading to the preferential formation of (*R*)-lactate. The key issue is that interactions responsible for the formation of the above complexes take place in the liquid phase. Detailed kinetic analysis of the possible reaction mechanism will be needed to elucidate this issue.

The strong dependence the optical yield of the initial concentration of substrate indicates that either the substrate–modifier or the substrate–modifier–product interaction might be involved in the e.d. step. The fact that both in toluene and in the presence of acetic acid the optical yields were much higher than in pure ethanol indicates that the suppression of the formation of half-ketal from ethanol and EtPy is favourable for the high optical selectivity. In this respect the study of the half-ketal formation between EtPy and ethyl lactate has a major importance [14].

We also suggest that the substrate–modifier complex can exist in various forms and the intrinsic enantio-differentiation ability of the above forms can be different. The form of the substrate–modifier complex strongly depends on the conformation of the modifier in the liquid phase.

Both NMR measurements and quantum chemical calculations show that cinchona alkaloids can exist in different conformations [8,15–17]. We suggest that both the substrate and the solvent can change the conformation of the alkaloid. However, in the models proposed recently only the most stable conformer of cinchonidine was used to simulate interactions taking place over Pt sites [7,8].

Our NMR experiments in CD_3OD showed that the C(9) proton of CD has a well pronounced doublet at 5.65 ppm. In the presence of 0.15 M methyl pyruvate (MePy) the doublet was slightly shifted to 5.85 ppm and a small singlet appeared at 6.0 ppm. However, upon increasing the concentration of MePy to 0.6 M the doublet disappeared and only the new singlet at 6.0 ppm was found. The proton signal at 6.0 ppm is attributed to the new conformer of CD. More pronounced shift of the C(9) proton (up to 6.3–6.4 ppm) and formation of a singlet was observed in pure CD_3COOD or if small amount of CD_3COOD was added into the solution of cinchonidine in CCl_3D

or C_6D_6. These data indicate that due to the presence of methyl pyruvate or acetic acid the torsion angle between the hydrogen atoms at C(8) and C(9) carbon atoms is changed resulting in a new conformer of CD. The formation of a new conformer requires the rotation of the quinuclidine and/or the quinoline ring around the C(8)–C(9) or C(9)–C(4′) axis. The energy required for such transformation is in the range of 3–5 kcal/mole [17,18]. The most stable conformers of cinchonidine are shown in Fig. 4 [17]. In conformers (III) and (IV) (closed forms of CD) the lone electron pair of the quinuclidine nitrogen is directed towards the quinoline ring.

The above NMR results and the strong increase of the optical yield upon increasing the concentration of EtPy form 0.1 M to 1.0 M (see Fig. 3 and Table 1) indicate that the substrate itself should be involved in the control of the e.d. by changing the conformation of the modifier. Our NMR measurements and quantum chemical calculations support this conclusion [17].

With respect to the role of acetic acid the protonation of quinuclidine nitrogen was suggested [4,7,8]. We cannot exclude the protonation of the quinoline nitrogen either. The protonation of the quinuclidine nitrogen can be responsible for the increase of the initial reaction rate, but it cannot explain the pronounced increase of the optical yield, that was very substantial both in ethanol and toluene (see Fig. 2). Our alternative explanation is that, similarly to the substrate, acetic acid might be involved in the change of the conformation of the modifier. In the new conformation the alkaloid has more a favourable geometry for the formation of the desired modifier–substrate complex.

The role of ethyl lactate in the rate acceleration can be rationalized by suggesting the following interactions: (i) formation of an alkaloid–lactate complex, (ii) formation of unknown derivatives of the alkaloid in the presence of (*R*)-ethyl lactate and EtPy, (iii) formation of half-ketal from (*R*)-ethyl lactate and EtPy and involvement of the optically active half-ketal in the product formation via diastereoselective hydrogenolysis of the C–O bond in the half-ketal. Further experiments will be needed to elucidate this issue.

The role of metal in this reaction should also be discussed. The adsorption of free modifier onto the platinum leads to the hydrogenation of the vinyl group [1–6]. This reaction is relatively fast. More strong adsorption of the modifier results in the hydrogenation of the quinoline ring too [18]. The hydrogenation of the vinyl group has almost no influence on the overall behavior, however, the hydrogenation of the quinoline ring leads to the complete loss of e.d. [18]. We suggest that in this catalytic system the key role of the metal is (i) to provide adsorbed hydrogen for the hydrogenation and (ii) to be relatively inactive in the hydrogenation of the quinoline ring of the alkaloid.

With respect to the nature of the modifier–substrate interaction we suppose that the interaction between the modifier and substrate via the quinuclidine nitrogen is not sufficient for the induction of e.d. We consider that the 'shielding effect' of the quinoline ring is also very important. Similar 'shielding effect' induced by the conjugated aromatic ring was found recently in asymmetric Diels–Alder and hydrogenation reactions of acrylates and pyruvates, respectively [19,20]. The similarity between these two substrates is that both have a conjugated π-bond system.

It has been shown if the quinoline ring of the alkaloid is hydrogenated the optical yield can be completely lost [18]. Based on the above loss of e.d. we suggest that the π-orbitals of the quinoline ring might be involved in the stabilization of the substrate via π–π overlapping with its conjugated double bond. On the other hand the modifier should interact with the substrate via the quinuclidine nitrogen. The simultaneous π–π overlapping between the quinoline ring and the conjugated double bound in the α-keto esters and the donor–acceptor interaction between the quinuclidine nitrogen and the keto group can take place if CD changes its conformation from (I) to (III) [17].

It is worth mentioning that the ability of cinchona alkaloids to induce enantio-differentiation strongly increases if the substrate has a conjugated

double bond system [21], similar to that in α-keto esters. It is not excluded that the presence of the above conjugation is the key structural factor responsible for the induction of e.d. by cinchona alkaloids even in the presence of supported metals. However, further studies are needed to elucidate the exact nature of the enantio-differentiation step in the hydrogenation of α-keto esters in the presence of cinchona-supported platinum catalysts system.

Acknowledgements

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