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Additional data to the origin of rate enhancement in the enantioselective hydrogenation of activated ketones over cinchonidine modified platinum catalyst

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ABSTRACT

Kinetic behaviour of different substrates such as purified ethyl pyruvate, dimer containing (20%) ethyl pyruvate, methylbenzoyl formate and ketopantolactone was investigated in both racemic and enantioselective hydrogenation over Pt/Al_2O_3 catalysts. Upon introducing the chiral modifier by injection under condition of racemic hydrogenation an immediate increase in reaction rate is observed in the case of all substrates. Consequently, significant rate enhancement (RE) was obtained in the case of all substrates. The RE increased in the following order: ketopantolactone < ethyl pyruvate < methylbenzoyl formate. This order does not follow the ability of substrates to be involved in various undesired side reactions with the formation of poisonous surface residues. Accordingly, results obtained in this study confirm that the RE must be an intrinsic feature of the asymmetric hydrogenation of activated ketones in the presence of cinchona alkaloids. However, our results also indicate that the poisoning effect by organic residues originated from ethyl pyruvate cannot be neglected.

1. Introduction

Heterogeneous enantioselective hydrogenation of activated ketones over Pt-cinchona catalysts named as Orito's reaction has been widely investigated by different research groups [1–4]. The above-mentioned reaction is very unique, because in the presence of cinchonas a definite class of substrates, such as different α-keto esters, shows not only high enantioselectivities, but also strong rate enhancement (RE) [5–9]. Nowadays the origin of RE is the subject of a scientific debate. In an early work three explanations for the rate enhancement have been suggested: (i) the substrate is activated by the tertiary N of the quinuclidine part of cinchonas (the rate of racemic reaction is also increased in the presence of quinuclidine added); (ii) the H coverage is higher over the modified catalyst than over the unmodified catalyst (H_2/D_2 exchange has increased); and (iii) the quinoline part adsorbed generates an electronic interaction (the rate of racemic reaction has increased in the presence of quinoline) [10].

According to ligand-acceleration model [11] chirally modified surface sites are created by the reversible adsorption of cinchona molecules onto Pt. The number of the total surface sites is equal to the sum of modified (Pt_m) and unmodified (Pt_u) sites. "A reaction is considered ligand accelerated if there is a slower unmodified (unselective) cycle and a faster modified (selective) cycle" analogous to the phenomenon described previously for homogeneous catalysis [12]. The origin of the rate enhancement was attributed to the difference in the rate-determining step, which is the uptake of first H atom on the modified catalyst and that of the second H atom on the unmodified Pt sites [2]. Recently upon using a series of single-walled carbon nanotubes (SWNTs)-supported Pt nanoparticle as catalyst with different controlled Pt loadings it has been shown that asymmetric hydrogenation of ethyl pyruvate (EtPy) was a "ligand-accelerated" reaction [13].

Other authors have given a completely new interpretation of the RE phenomenon: "rate enhancement is now attributed to reaction occurring at a normal rate at an enhanced number of sites, not (as previously proposed) to a reaction occurring at an enhanced rate at a constant number of sites [14]. It was concluded that the "rate enhancement in the presence of an alkaloid modifier is attributed to the inhibition of the pyruvate ester polymerization at the Pt surface". These authors suggested the formation of two types of adduct: (i) a semi-ketal formed by reaction of the product and the substrate molecule, and (ii) a dimer of the substrate formed in a dimerization reaction with the involvement of the enol and the keto forms of the substrate. It has been considered that the dimer formation is an equilibrium reaction. The role of tertiary amines is to shift the equilibrium to the formation of free substrate on the

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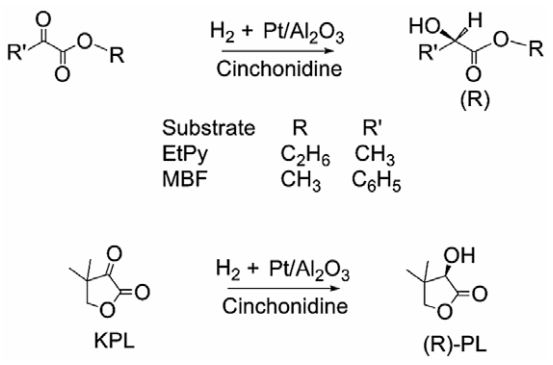
surface (see Scheme 1 in Ref. [14]). Experiments with EtPy at low concentration (10^{-2} M) have shown that the initial rate of racemic and enantioselective reaction does not differ [15]. Continuous fixed-bed reactor experiments revealed that ligand acceleration can be linked to catalyst deactivation [15], although in the recent studies [16,17] just the opposite was demonstrated. In Ref. [15] it has been concluded that cinchonidine (CD) plays a double role: (i) promoter via the inhibition of side reactions; (ii) chiral poison at high surfaces coverage. According to this idea the ligand acceleration during the hydrogenation of activated ketones over cinchona-modified platinum catalyst originates from the effect of alkaloids to prevent the deactivation of catalyst induced by EtPy [15].

The new conception discussed above is supported by several observations from different areas of the investigation of activated ketones. Formation of surface polymer under hydrogen poor circumstances was demonstrated by XPS, NEXAFS and STM [18]. The presence of adsorbed hydrogen suppressed the above-mentioned process [18]. From gas phase FTIR measurement it has became clear that EtPy decomposes at Pt surface forming CO and $C_xH_yO_z$ strongly bonded species [19]. Upon using ATR-IR method it has been proved that the decomposition of EtPy is 60-fold faster in the absence of CD than in the presence of alkaloid of 0.001 M [20]. Hydrogenation of methyl pyruvate in gas phase resulted in low optical yield values ($\leqslant$51%) without rate enhancement [21]. Furthermore, several substrates hydrogenated over CD–cinchona catalyst system give moderate RE but high ee [3].

However, other results support the idea that the rate enhancement is the inherent feature of this catalytic reaction. Injection of CD into the racemic reaction mixture in a batch reactor has led to immediate increase in conversion [22–24]. Results obtained upon using different modes of introduction of the substrate and the modifier has indicated that the overall rate increase is a kinetic phenomenon and cannot be attributed to the suppression of the formation of oligomers [25]. In a continuous flow experiment catalyst deactivation during pyruvate hydrogenation can be avoided by proper selection of the solvent and reaction conditions, and the introduction of the chiral modifier into the reaction mixture induces considerable rate acceleration. These observations contradict again the proposal that the origin of "ligand acceleration" is the suppression of catalyst deactivation by the modifier [16]. In another view it was emphasized: "using low ethyl pyruvate concentrations (0.01 to 0.1 mol l^{-1}) in a batch reactor, two mechanistic cornerstones for Orito's reaction were no longer valid – that is, the reaction rate was not proportional to the modifier concentration, and a high ee could be obtained with no rate acceleration or even in the presence of rate deceleration" [26]. But Baiker and Mallat [27] have pointed out that even if the blocking of surface sites by byproducts and impurities is negligible, an equal or higher *overall* reaction rate on chirally modified Pt means *intrinsic* rate acceleration itself because the Pt is highly covered by CD, consequently the number of available active sites is smaller. From continuous hydrogenation experiments using methyl benzoylformate (MBF), KPL and pyruvic aldehyde dimethyl acetal as substrates and alternating CD, cinchonine, quinine and quinidine chiral modifiers in time on stream experiments it has been concluded that enantiodifferentiation and RE have the same origin, both may be traced back to the role of the intermediate complexes of the hydrogenation [17]. Recently the intrinsic kinetic acceleration (e.g. the ratio of kinetic constants for enantioselective and racemic reactions) has been formulated mathematically [28]. For the hydrogenation of 1,2-phenylpropanedione over Pt/Al_2O_3 catalyst this value has been found close to 2 [28].



Scheme 1. Hydrogenation of activated ketones (EtPy = ethyl pyruvate, MBF = methylbenzoyl formate, KPL = ketopantolactone, (R)-PL = *R*-(−)-pantolactone).

The aim of this study is to get additional experimental proof related to the intrinsic character of the rate enhancement. The use of term "intrinsic" means that we do not accept the recent views [14,15] related to the involvement of poisonous residues formed from the substrate in the increase of the reaction rate in enantioselective hydrogenation of activated ketones compared to the rate in racemic hydrogenation.

In this work we investigated the poisoning effect of the condensation byproduct formed from EtPy on the reaction rate and the optical yield in the enantioselective hydrogenation of EtPy. New kinetic treatment was applied to evaluate the effects of poisoning. In addition the behaviour of other substrates which are unable to form polymeric residues were also investigated. These studies were performed especially at low initial concentrations of these substrates. In some of these experiments transient method was applied, where the modifier was injected into the reactor under condition of racemic hydrogenation. Upon using these tools our purpose was to get further information about the character of rate enhancement in the cinchona modified catalytic hydrogenation of activated ketones. General reaction scheme of hydrogenation reactions investigated in this work is summarized in Scheme 1.

2. Experimental

2.1. Materials

MBF and KPL substrates were purchased from Fluka and Aldrich, respectively, and were used as received. EtPy was a Fluka product, and was distilled under vacuum prior to use ($(EtPy)_1$). Ethyl pyruvate contaminated with a dimer ($(EtPy)_2$, dimer content 20%) was also used as a substrate. This product was obtained from the distillation residue and was identified by ^{1}H NMR and mass spectrometry. The reactions were performed in dried toluene solvent (Reanal). CD chiral modifier was a Fluka product and was used as received. Commercial 5 wt% Pt/Al_2O_3 such as E4759 (Engelhard, H/Pt = 0.27, CO/Pt = 0.24 [29]) and CatASiumF214 (Degussa, CO chemisorption = 1.5 cm^3 CO/g catalyst, Pt dispersion: 26.3% [30]) were used as catalysts. The first one was treated in hydrogen at 400 °C for 2 h before the catalytic reaction; the second one was used as received.

2.2. Kinetic investigations

Hydrogenation of MBF, KPL and ethyl pyruvate $(EtPy)_1$ and $(EtPy)_2$ was carried out in a 300 cm^3 SS-autoclave at 20 °C. The pressure of H_2 was 50 bar in all experiments. The rate of agitation was 500 or 1000 rpm. 1.2×10^{-5} M or 1.0×10^{-4} M was chosen for the concentration of CD. The initial concentration of the substrates was in the range of 2×10^{-2} to 1.0 M. Both injection and premixing techniques were used to introduce the modifiers. In the injection

method the toluene solution of cinchonidine (5 vol.% of total liquid volume) was used. In all experiments dried and distilled toluene was applied and the ratio of V_{inj}/V_{total} was 1:20. Further details can be found elsewhere [7,31]. Racemic reaction was performed with premixing solvent, substrate and catalyst under inert atmosphere or with injection of substrate to the slurry of solvent and catalyst under hydrogen atmosphere. In certain experiments racemic reaction was started and the toluene solution of the chiral modifier was injected into the reactor by time delay (transient experiments). Samples were taken at different reaction times and were analyzed by a GC using a capillary column (Supelco BETA DEX 225) and flame ionization detector. The enantioselectivity is expressed as ee = [R − S]/[R + S]. The ee_{max} means the highest enantiomeric excess value measured in a given reaction. The ee_{end} values were measured at the end of reaction. Calculation of ee in the experiments of CD injection with time delay was based on the change of products concentrations during the enantioselective part. First-order rate constants k_1 were calculated from experimental points measured in the first 3 to 10 min described earlier [31,32]. Initial rate (r_0) values were calculated from d[S + R]/dt according to the method written in Ref. [25]. The comparison of catalytic activities under various experimental conditions was based on r_0 and k_1. The k_1 values were reproducible within 10% providing the use of the same batch of EtPy. The ee values in the conversion – ee dependencies had a relative error in the range of 5%, but the shapes of these dependencies were completely reproduced. The relative rate increase is expressed by k_{1e}/k_{1r} and r_{0e}/r_{0r} which is the ratio of the given parameters in enantioselective and racemic hydrogenations. The slope of dependencies in the [R − S] vs. 2[S] coordinates gives the relative RE within the enantioselective hydrogenation as the k_e/k_r ratio expresses the ratio of rate constants in enantioselective and racemic hydrogenations running parallel in the same experiment [25].

2.3. NMR measurements

All spectra were measured at 30 °C. Spectra were taken using a Varian Unity Inova 400 spectrometer. Chemical shifts (δ) are reported relative to internal TMS. 512 transients were accumulated to achieve the appropriate signal/noise ratio.

3. Results

3.1. Hydrogenation of purified ethyl pyruvate

Results obtained in two sets of experiments by using purified substrate $(EtPy)_1$ in two different initial concentrations are summarized in Figs. 1 and 2. In these experiments CD was injected into the reactor with time delay. From Fig. 1A, it can be seen that upon using substrate in the initial concentration of 1 M, the introduction of CD during racemic hydrogenation induces instantaneous rate increase and the time delay in the introduction of CD does not result in any relative rate decrease ($rr_t = r_{0,t}/r_{0,t} = 0$, where the t values corresponds to the time of injection of CD). By comparing Figs. 1A and 2A, it is obvious that upon injection of CD a definite instantaneous increase in the conversion appears at both concentrations of $(EtPy)_1$. Figs. 1B and 2B show that optical yield also increases instantaneously parallel to the immediate conversion increase, however, both the monotonic increase type behaviour and the final ee values were maintained. Figs. 1C and 2C represent the product formation in coordinates [R–S] vs. 2[S]. In our recent study [25] it was shown that the slope in these dependencies corresponds to the k_e/k_r ratio, where k_e and k_r are the first-order rate constants in enantioselective and racemic hydrogenation reactions, respectively. Fig. 1C shows that upon increasing the time between the start of the racemic hydrogenation and the introduction of CD the k_e/k_r ratios increased from 9.1 to 12.2 and 15.8, for injection time 0, 15 and 30 min, respectively. This tendency was also observed at 0.25 M of $(EtPy)_1$ (compare Figs. 1C and 2C).

3.2. Hydrogenation of dimer containing ethyl pyruvate

In the second series of experiments dimer-containing ethyl pyruvate $(EtPy)_2$, originated from the distillation residue of EtPy was used as a substrate. Based on Ref. [33] the possible structure of dimers is shown in Scheme 2. The presence of dimer was confirmed by MS and NMR measurements. Based on NMR analysis dimer **1a** content of the substrate was in the amount of 20 wt%.

Results given in Fig. 3A clearly show that upon using the $(EtPy)_2$ the reaction rates decreased significantly compared to $(EtPy)_1$ (see Fig. 1A). The decrease in the rate of racemic hydrogenation is around 11-fold (from 330 to 30 mmol × g_{cat}^{-1} h^{-1}). Consequently, there is a strong poisoning effect induced by compound **1a**. The poisoning effect can also be observed in the enantioselective hydrogenation; however, its extent is only threefold (from 2540 to 920 mmol × g_{cat}^{-1} h^{-1}). The most important observation that the introduction of CD during racemic hydrogenation of $(EtPy)_2$ also resulted in instantaneous rate acceleration in all cases (see Fig. 3A). Contrary to the results obtained in the previous series of experiments the rr_t values decreased to 0.67, 0.59 and 0.38 for experiments with delayed injection of CD in the 15th, 30th and 90th minute of racemic hydrogenation. The latter observation may indicate that the amount of organic residues formed from

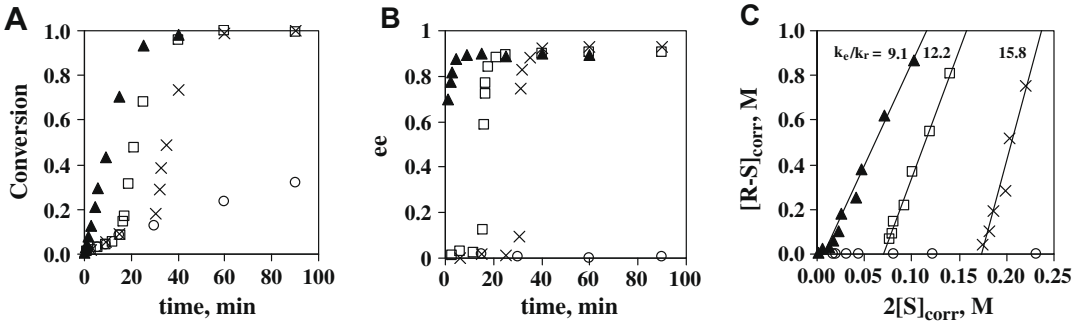


Fig. 1. A. Kinetic curves of ethyl pyruvate hydrogenation upon using purified substrate $(EtPy)_1$ at high substrate concentration. (A) Influence of the time delay in CD injection during racemic hydrogenation. (B) Enantiomeric excess – reaction time dependencies (corrected for product concentrations formed during time delay). (C) Kinetic dependencies in ([R–S]) vs. 2[S] coordinates. $[(EtPy)_1]_0$ = 1.0 M (purified by distillation prior to the use), [CD] = 5×10^{-5} M, T = 20 °C, p_{H_2} = 50 bar, stirring rate = 500 min^{-1}; total volume = 100 cm^3, catalyst = 5% Pt/Al_2O_3 (E 4759, dispersion: 0.27), m_{cat} = 0.125 g, catalyst pretreatment = 2 h in flowing H_2 at 400 °C and cooled in N_2. ▲ – CD injection at 0 min; □ – CD injection at 15 min; × – CD injection at 30 min; ○ – no CD.

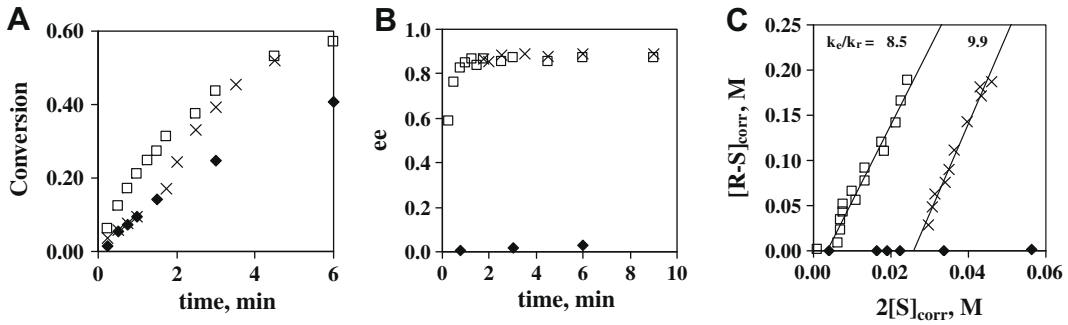
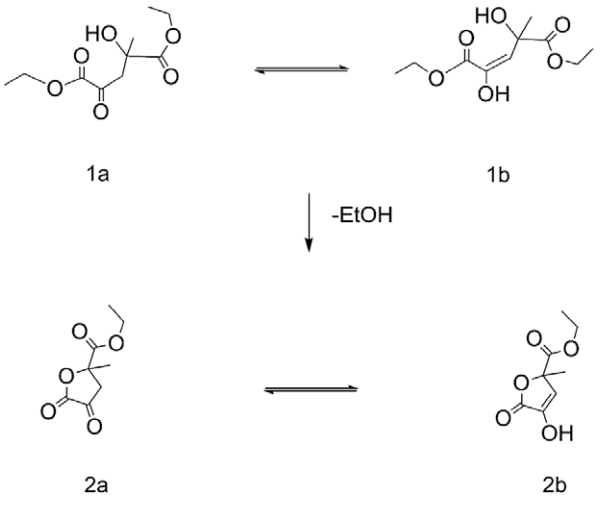


Fig. 2. Hydrogenation of purified ethyl pyruvate $(EtPy)_1$ over cinchona–Pt/Al_2O_3 catalyst at medium substrate concentration. $[(EtPy)_1]_0 = 0.25$ M; $m_{cat} = 0.063$ g, catalyst = E4759; $V_r = 50$ cm^3; $T_r = 20$ °C; $p_{H_2} = 50$ bar; speed of agitation = 1000 rpm, catalyst pretreatment see Fig. 1. ◆ – no CD; □ – 1×10^{-4} M CD injection at 0 min; × – CD injection at 1 min.

$(EtPy)_2$ increases with the time delay, i.e., the duration of racemic hydrogenation.

Fig. 3C shows that in the [R–S] vs. 2[S] dependencies upon using $(EtPy)_2$ the increase in the injection delay from 0 to 15, 30 and 90 min the k_e/k_r ratios decreased from 8.9 to 8.2, 8.0 and 7.0. It is contrary to the observation found for $(EtPy)_1$, the distilled substrate, which shows increasing tendency (compare Figs. 1C and 3C). It has to be emphasized that the direct injection of CD (delay time is zero) both purified $(EtPy)_1$ and the "distillation residue"



Scheme 2. Condensation products of ethyl pyruvate (based on Ref. [34]).

$(EtPy)_2$ have almost similar k_e/k_r ratios (9.1 and 8.9, respectively). This fact let us to conclude, that not dimer **1a** itself but poisoning products formed from it are responsible for catalyst deactivation.

The injection technique used in our previous work [25] gives a possibility to vary the order of introduction of components into the reaction mixture. Results obtained by this method on purified $(EtPy)_1$ at 1 M initial concentrations let us to suppose that rate enhancement is the intrinsic behaviour of this reaction as the rates were not really influenced by the order of introduction of interacting components [25].

Considering the observation in Ref. [15], i.e. at low substrate concentration the initial rate of racemic and chirally modified reaction does not differ, additional experiments were performed decreasing the substrate concentration by one order. Results of these measurements are summarized in Table 1. In racemic hydrogenation performed over CatASiumF214 at low $(EtPy)_1$ concentration the reaction rate (r_0 and k_1 values) was higher when the substrate was injected into the slurry of catalyst and solvent under H_2 atmosphere than that obtained at premixing the catalyst and the substrate (compare experiments. 1, 2 and 7, 8 in Table 1). This finding is in good agreement with the earlier results related to the formation of polymeric residues over Pt surface in the absence of H_2 [18] and surface poisoning by fragments of EtPy decomposition [19].

However, in the enantioselective hydrogenation the lowest initial rates were observed when EtPy was injected. This trend was also observed when the amount of catalyst decreased. We have calculated the relative rate increase induced by CD using the r_{0e}/r_{0r} or k_{1e}/k_{1r} ratios, where r_{0e} and r_{0r} or k_{1e} and k_{1r} are initial reaction rates and first-order rate constants for enantioselective and racemic reactions. The relative rate increase was measurable in all

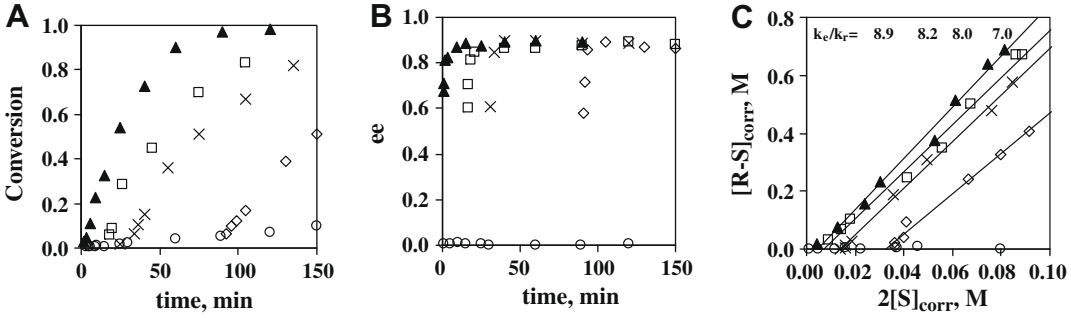


Fig. 3. Kinetic curves of ethyl pyruvate hydrogenation upon using dimmer contaminated substrate $(EtPy)_2$. (A) Influence of the time delay in CD injection during racemic hydrogenation. (B) Enantiomeric excess – reaction time dependencies (corrected for product concentrations formed during time delay). (C) Kinetic dependencies in [R–S] vs. 2[S] coordinates. $[(EtPy)_2]_0 = 1.0$ M (distillation residue containing dimer **1a** in the amount of 20%), other details of reaction conditions see in Fig. 1. ▲ – CD injection at 0 min; □ – CD injection at 15 min; × – CD injection at 30 min; ◇ – CD injection at 90 min; ○ – no CD.

Table 1
Hydrogenation of $(EtPy)_1$ over CatASiumF214 Pt/Al_2O_3 catalysts. Influence of the mode of introduction of reaction components.

No.	[CD] (10^{-5} M)	Mode of introduction	r_{0r} (M min^{-1})	r_{0e} (M min^{-1})	r_{0e}/r_{0r}	k_{1r} (min^{-1})	k_{1e} (min^{-1})	k_{1e}/k_{1r}	ee_{max}	ee_{end}	$conv_{end}$
1	–	–	0.0152	–		0.1166	–		–	–	0.988
2	–	$(EtPy)_1$inj	0.0271	–		0.2488	–		–	–	0.953
3	1.2	premix	–	0.0455	3.0	–	0.4958	4.3	0.765	0.756	0.951
4	1.2	CD inj	–	0.0580	3.8	–	0.5423	4.7	0.730	0.718	0.997
5	1.2	$(EtPy)_1$inj	–	0.0411	1.5	–	0.3880	1.6	0.702	0.679	0.965
6	1.2	CD inj at 5 min	0.0169	–		0.1488	0.3161	2.1	0.779	0.779	0.954
7[a,b]	–	–	0.0074	–		0.0567	–		–	–	0.943
8[a,b]	–	$(EtPy)_1$inj	0.0119	–		0.1127	–		–	–	0.920
9[a,c]	1.2	Premix	–	0.0262	3.5	–	0.1759	3.1	0.801	0.795	0.964
10[a,c]	1.2	CD inj	–	0.0312	4.2	–	0.1775	3.1	0.766	0.754	0.994
11[a]	1.2	$(EtPy)_1$inj	–	0.0148	1.2	–	0.1491	1.3	0.724	0.714	0.910
12[a,c]	1.2	CD inj at 5 min	0.0076	–		0.0530	0.0973	1.8	0.763	0.741	0.947

$(EtPy)_1$ = ethyl pyruvate purified, CD = cinchonidine, inj = injection $[(EtPy)_1]_0$ = 0.1 M; solvent = toluene, m_{cat} = 40 mg; catalyst = CatASiumF214 (Degussa); V_r = 40 cm^3; T_r = 20 °C; p_{H_2} = 50 bar; t_r = 30 min; stirring rate = 1000 min^{-1}; r_0 from d[S + R]/dt [25]; r-racemic; e-enantioselective.
[a] m_{cat} = 20 mg.
[b] t_r = 90 min.
[c] t_r = 60 min.

cases. Similar trends were observed at both series of experiments using different amounts of catalyst. The highest rate increase was observed when CD was injected into the reaction mixture.

3.3. Hydrogenation of methylbenzoyl formate

Results obtained in the hydrogenation of MBF are summarized in Fig. 4 and Table 2. Introduction of CD into the racemic reaction led to immediate increase both in the conversion (Fig. 4A) and the enantioselectivity (Fig. 4B) similarly to $(EtPy)_1$ although this increase is smaller. Note the different characters of substrates, i.e., MBF is not able to form condensation products. In spite of this fact the rate enhancement appeared instantaneously. These results show again that the rate enhancement must be considered as an inherent property of Orito's reaction. Tendencies of [R–S] vs. 2[S] dependencies obtained upon using MBF substrate (Fig. 4C) are very similar to those of $(EtPy)_1$ (Fig. 1C and 2C. Table 2 shows the kinetic results of MBF hydrogenation upon the variation of initial concentration of the substrate in the range of 0.02 to 0.5 M. It is noteworthy that the ee values slightly increase with increasing the concentration of substrate till 0.25 M. A similar tendency has been observed for EtPy [34]. Data in Table 2 show that the initial rate of

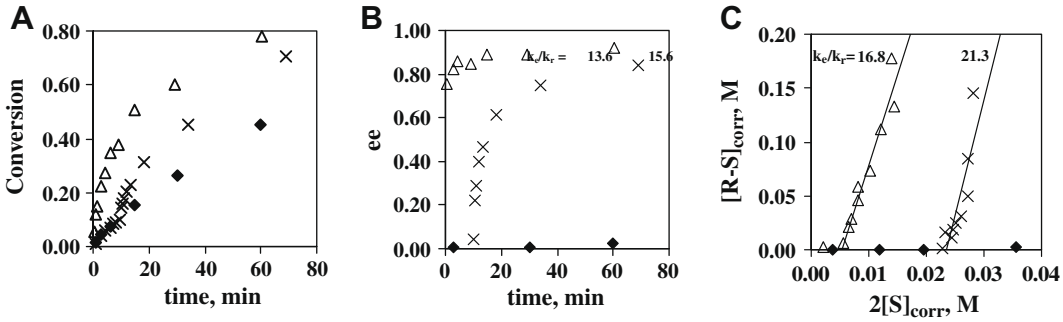


Fig. 4. Hydrogenation of methylbenzoyl formate (MBF) over cinchona–Pt/Al_2O_3 catalyst. (A) Influence of the time delay in CD injection during racemic hydrogenation. (B) Enantiomeric excess – reaction time dependencies (corrected for product concentrations formed during time delay). (C) Kinetic dependencies in [R–S] vs. 2[S] coordinates. $[MBF]_0$ = 0.25 M; m_{cat} = 0.063 g, catalyst = E4759; V_r = 50 cm^3; T_r = 20 °C; p_{H2} = 50 bar; speed of agitation = 1000 rpm, catalyst pretreatment see Fig. 1, ◆ – no CD; △ – 1×10^{-4} M CD injection at 0 min; × – CD injection at 9 min.

Table 2
Hydrogenation of methylbenzoyl formate over cinchona-Pt/Al_2O_3 catalyst system. Influence of substrate concentration.

No.	$[MBF]_0$ (M)	$[CD]_0$ (10^{-4} M)	r_0[a] (M min^{-1})	r_{0e}/r_{0r}	k_1 (min^{-1})	k_{1e}/k_{1r}	ee_{max}	ee_{end}	t_r (min)	$conv_{end}$
1	0.02	–	0.0021		0.1347		–	–	180	0.990
2	0.05	–	0.0033		0.0770		–	–	180	0.986
3	0.10	–	0.0040		0.0508		–	–	180	0.906
4	0.25	–	0.0042		0.0122		–	–	240	0.961
5	0.50	–	0.0046		0.0073		–	–	240	0.716
6	0.02	1	0.0040	1.9	0.2547	1.9	0.768	0.768	120	0.990
7	0.05	1	0.0078	2.4	0.1642	2.1	0.838	0.838	90	0.990
8	0.10	1	0.0161	4.0	0.1405	2.8	0.888	0.875	120	0.978
9	0.25	1	0.0211	5.0	0.0624	5.1	0.919	0.904	120	0.918
10	0.50	1	0.0255	5.5	0.0542	7.4	0.898	0.895	240	0.989

MBF = methylbenzoyl formate; m_{cat} = 0.063 g, catalyst = E4759; V_r = 50 cm^3; T_r = 20 °C; p_{H_2} = 50 bar; stirring rate = 1000 min^{-1}; r – racemic; e – enantioselective.
[a] r_0 from d[S + R]/dt [25].

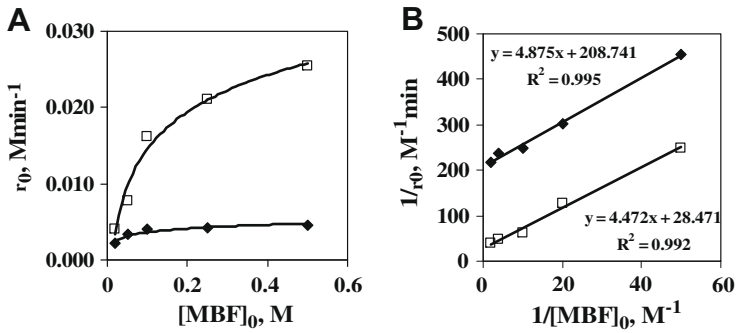


Fig. 5. Initial rate-substrate concentration dependences (r_0 from d[S + R]/dt [27]) MBF = methylbenzoyl formate, m_{cat} = 0.063 g, catalyst = E4759; V_r = 50 cm^3; T_r = 20 °C; p_{H_2} = 50 bar; speed of agitation = 1000 rpm, catalyst pretreatment see Fig. 1 ◆ – no CD; □ – 1 × 10^{-4} M CD.

racemic and enantioselective reaction at very low initial concentration of the substrate is different. This observation is in contrast to the results obtained in EtPy in Ref. [15], whereas r_0 of racemic and enantioselective hydrogenation was equal in the concentration range of 0.01 to 0.1 M.

The influence of initial concentration on the r_0 values of MBF hydrogenation is depicted in Fig. 5. Initial rates vs. initial concentration of MBF (Fig. 5A) resulted in the same saturation type of dependencies for both racemic and enantioselective reactions. The dependencies in co-ordinates reciprocal rates ($1/r_0$) vs. reciprocal concentration ($1/M_0$) are demonstrated in Fig. 5B. This type of linear dependencies is characteristic for substrates having reaction orders between one and zero.

Similarly to MBF substrate KPL is not capable to form condensation product. For this reason it seemed to be worthwhile to compare the behaviour of all three substrates $(EtPy)_1$, MBF and KPL under identical reaction conditions. Results of this series of experiments are collected in Table 3. All three substrates showed a significant rate enhancement. The analysis of r_{0e}/r_{0a} and k_{1e}/k_{1r} ratios shows the following trend in the rate enhancement MBF > $(EtPy)_1$ > KPL, however, the above-mentioned order does not correlate with the ability of these compounds for the decomposition at the catalyst surface.

4. Discussion

In this study four different substrates $(EtPy)_1$, $(EtPy)_2$, MBF and KPL were hydrogenated under condition of racemic and enantioselective hydrogenation. In all enantioselective hydrogenations CD was used as a modifier. The aim of this study was to collect new data supporting the view that RE is the intrinsic feature of Orito's reaction.

Both static and transient kinetic experiments were performed to find comprehensive evidences for the validity the rate enhancement phenomena. Upon using distilled substrate $(EtPy)_1$ the injection of CD during racemic hydrogenation resulted in instantaneous rate acceleration in the whole concentration range of the substrate. As emerges from Figs. 1A and 2A at $[(EtPy)_1]_0$ = 1.0 and 0.25 M the calculated initial rates at the moment of injection, within the experimental error, were not altered. The relative rate increases (k_{1e}/k_{1r}) are 12 and 3 at $[(EtPy)_1]_0$ = 1.0 and 0.25, respectively.

Figs. 1C and 2C show that upon increasing the time between the start of the racemic hydrogenation and the introduction of CD the k_e/k_r ratios increased slightly. Based on this observation it is assumed that organic residues formed during racemic hydrogenation have a positive effect on the enantioselectivity; they suppress the rate of racemic hydrogenation without substantial influence on the overall rate.

In these experiments the delay in the injection of CD had no influence on either the final ee values or the form of ee-conversion dependencies. All these findings indicate that racemic products formed up to 10% conversion have no measurable influence on the enantioselective hydrogenation of EtPy; consequently the size of free Pt surface available for enantioselective hydrogenation is not altered during racemic hydrogenation. When similar series of experiments were performed in ethanol at $[(EtPy)_1]_0$ = 1 M in the above conversion range, a slight decrease in the initial rates was observed [22]. The relative rate decrease, rr_{22} ($rr_t = r_{0,t}/r_{0,t} = 0$, where the t values correspond to the time of injection of CD), was in the range of 0.88. Further increase in the time of injection resulted in more pronounced rate decrease ((rr_{80} = 0.35) see data given in Table 1 in Ref. [22]). In ethanol it is assumed that the poisoning effect is induced by the semi-ketal formed during racemic hydrogenation. The semi-ketal formation in alcoholic solvents and possible negative effect has been evidenced and discussed in different studies [35–37].

Upon using $(EtPy)_2$ contrary to results obtained for $(EtPy)_1$ the rr_t values decreased to 0.67, 0.59 and 0.38 for experiments with delayed injection of CD during racemic hydrogenation (15th, 30th and 90th min) (see Fig. 3A). Parallel to that the slopes in the [R–S] vs. 2S coordinates decreased also with the time delay. This decrease is quite substantial (from 8.9 to 7.0). These data may indicate that in the racemic hydrogenation the amount of poisonous organic residues formed from $(EtPy)_2$ increases with the time

Table 3
Hydrogenation of different substrates over cinchona-Pt/Al_2O_3 catalyst system.

No.	Substrate	[CD] (10^{-4} M)	r_{0r} (M min^{-1})	r_{0e} (M min^{-1})	r_{0e}/r_{0r}	k_{1r} (min^{-1})	k_{1e} (min^{-1})	k_{1e}/k_{1r}	ee_{max}	ee_{end}	t_r (min)	$conv_{end}$
1	$(EtPy)_1$	–	0.0225	–		0.0869	–		–	–	60	0.976
2	$(EtPy)_1$	1	–	0.0585	2.6	–	0.1803	2.1	0.878	0.860	60	0.978
4	MBF	–	0.0042	–		0.0122	–		–	–	240	0.961
5	MBF	1	–	0.0211	5.0	–	0.0624	5.1	0.919	0.904	120	0.918
7	KPL	–	0.0155	–		0.0528	–		–	–	180	0.938
8	KPL	1	–	0.0283	1.8	–	0.0966	1.8	0.674	0.630	180	0.879

$(EtPy)_1$ = ethyl pyruvate purified, MBF = methylbenzoyl formate, KPL = ketopantolactone, $[Substrate]_0$ = 0.25 M; reaction time = 120 min; m_{cat} = 0.063 g, catalyst = E4759; V_r = 50 cm^3; T_r = 20 °C; p_{H_2} = 50 bar; stirring rate = 1000 min^{-1}; r_0 from d[S + R]/dt [25]; r-racemic; e-enantioselective.

delay. This finding is an indication that in the enantioselective hydrogenation of $(EtPy)_2$ the component **1a** can be considered as a definite source of poison. The longer the reaction time in racemic hydrogenation the higher the extents of rate decrease. This observation strongly resembles our earlier results obtained in ethanol solvent upon using freshly distilled substrate [22].

The analysis of results shown in Figs. 1–3 indicates that the intrinsic RE cannot be questioned in the enantioselective hydrogenation of $(EtPy)_1$. Results obtained in the hydrogenation of $(EtPy)_2$ are even more convincing as in the presence of around 20 wt% high molecular weight organic compound the rate enhancement was instantaneous, although the initial rates both in racemic and enantioselective hydrogenation decreased substantially (see Fig. 3). This rate decrease is attributed to the presence of compound **1a**.

Please note that in all experiments in Figs. 1–3 the conversion in the moment of CD injection was not higher than 10%. It can be concluded that the instantaneous rate increase observed in all experiments is in a strong contradiction to the statement given in Ref. [14], namely "rate enhancement is now attributed to reaction occurring at a normal rate at an enhanced number of sites, not (as previously proposed) to a reaction occurring at an enhanced rate at a constant number of sites". It is hardly to suggest that the addition of 5×10^{-5} M modifier will compete with 0.2 M high molecular weigh product and can remove their adsorbed forms instantaneously from the Pt surface.

On the other hand our results indicate also that the poisoning effect by organic residues originated form EtPy cannot be neglected. In the experiments at $[(EtPy)_1]_0 = 0.1$ M presented in Table 1 the variation of the mode of introduction of reaction components was investigated. In racemic hydrogenation higher reaction rates were obtained upon injection than upon premixing of the substrate in both sets of experiments (compare exps. 1 vs. 2 and 7 vs. 8.). This behaviour can be attributed to the decomposition of EtPy in the period of premixing. Data given in Table 1 show that in enantioselective hydrogenation the relative rate increase expressed by ratios r_{0e}/r_{0r} and k_{1e}/k_{1r} is quite substantial even at $[(EtPy)_1]_0 = 0.1$ M. Even at this low concentration of substrate the conversion increased instantaneously after the introduction of CD during racemic reaction (see experiments 6 and 12). This fact provided further proof related to the origin of RE phenomena.

It is interesting to mention that in enantioselective hydrogenation in both sets of experiments the rate order was as follows: CD_{inj} > premix > $(EtPy)_{1inj}$. This is an opposite trend compared to results obtained in racemic hydrogenation. This observation might have two possible explanations: (i) the lowest rate at $(EtPy)_{1inj}$ can be attributed to the loss of CD over hydrogen covered pure Pt sites. This side reaction has great importance only at low concentration of CD [38]; the fact that the lowest ee values are obtained when EtPy is injected (see experiments 5 and 11) strongly supports this view; (ii) in addition, these results might also indicate that the CD injected into the reaction mixture counterbalance the poisonous effect induced by the decomposition of EtPy on the Pt surface.

Experiments with MBF substrate provided further evidence for the intrinsic character of the RE phenomena. The extent of RE increases upon increasing the concentration of MBF (compare r_{0e}/r_{0r} and k_{1e}/k_{1r} ratios in Table 2). Results shown in Fig. 5B unambiguously demonstrate that upon using MBF enantioselective and racemic hydrogenations must have different r_0 even at extremely low initial concentration of this substrate. These results can be considered as an additional proof that the RE is the intrinsic property of Orito's reaction and the attribution of the observed rate increase to surface cleaning as the only reason for RE may not be valid.

Results given in Table 2 also show a slight dependence of ee_{max} and ee_{end} values of the initial concentration of the substrate. Similar dependence was found for EtPy [34]. This finding and the same trend in the extent of RE might indicate that the formation of [substrate–modifier] complex and its concentration either at the Pt surface or in the liquid phase controls all the key events, i.e., both the enantio-differentiation and the RE.

Finally let us discuss the behaviour of three substrates under identical condition (Table 3). The results show that all these substrates have RE. The extent of RE increases in the following order KPL < EtPy < MBF. This order does not follow the ability of substrates to be involved in various undesired side reactions with the formation of poisonous surface residues. Consequently, the RE cannot be attributed to the poisoning effect.

5. Conclusions

In this study it has been shown that the introduction of cinchonidine during racemic hydrogenation of different activated ketones induces instantaneous rate increase. The extent of rate enhancement depends on the type of substrate and experimental condition. Pronounced rate enhancement was observed upon using both purified $(EtPy)_1$ and $(EtPy)_2$ containing 20 wt% high molecular weight condensation product. Higher substrate concentration favours pronounced rate acceleration, however, in the case of methylbenzoyl formate higher reactions rates were observed in enantioselective hydrogenation in the whole concentration range. The increase in the extent of RE does not follow the ability of substrates to form poisonous byproducts. The observed RE in Orito's reaction may be related to the formation of [substrate–modifier] complex involved both in the rate acceleration and the enantiodifferentiation. All results obtained in this study unambiguously demonstrated that the RE is an intrinsic feature of Orito's reaction and cannot be attributed to poisoning effects. However, our results also show that poisoning of the Pt is unavoidable during the hydrogenation of activated ketones especially EtPy, which can decompose at the Pt surface and form various condensation products in the liquid phase. The ability of cinchona alkaloids or other tertiary amines to clean the catalyst surface has only inferior contribution to the rate enhancement.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcat.2009.06.009.

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