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ROLE OF THE MODIFIER IN THE ENANTIOSELECTIVE HYDROGENATION OF ETHYL PYRUVATE OVER Pt/Al_2O_3 CATALYST

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The time dependence of the conversion and enantioselectivity during the hydrogenation of ethyl pyruvate has been studied over an industrial Pt/Al_2O_3 catalyst. Various cinchona alkaloids were used as modifier and two different modes were applied for their introduction into the reaction system. The dependence of the enantioselectivity on conversion is strongly influenced by the mode of introduction and the structure of the modifier used. The conversion dependence of the enantioselectivity is attributed to the chemical transformations of the parent alkaloid observed under hydrogenation conditions. Experimental evidence is shown for the dynamic nature of the interaction between the modifier and the catalyst.

1. Introduction

For heterogeneous catalytic hydrogenations of prochiral ketones two systems have been studied intensively: Raney nickel-tartrates for beta-ketoesters [1–3] and Pt-cinchona type alkaloids for alpha-ketoesters [4–9]. It has been demonstrated that for both catalytic systems above the premodification of the catalyst with an optically active compound (generally termed modifier) [1–6.] or the direct addition of the modifier to the reaction mixture [6–9], is an essential requirement for the induction of enantio differentiation. Two different modes for the introduction of cinchona type alkaloids were used in enantioselective hydrogenation of alpha-ketoesters: (i) a premodification procedure carried out prior to the hydrogenation [4,5] and (ii) direct addition of the modifier to the reaction mixture [6–9]. A characteristic feature of the latter system is the strong acceleration of the reaction rate [6,7]. Neither the interactions taking place during the premodification procedure nor the origin of the acceleration effect is well understood.

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All of the information reported so far about the enantioselective hydrogenation of alpha-ketoesters is based on the measurement of the initial rate of hydrogenation and the determination of the conversion and the enantiomeric excess (ee) at the end of hydrogenation [4–9]. The reaction was found to be zeroth order with respect to the substrate and above 50% of conversion no changes in the ee values were observed upon increasing the conversion [7,8], but no data were reported for low conversion.

The lack of information about the time and conversion dependence of the enantioselective hydrogenation of alpha ketoesters has promted us to investigate these behaviours using the hydrogenation of ethyl pyruvate in the presence of different cinchona type alkaloids as example. Efforts were also undertaken to follow the transformation of the modifier during the hydrogenation reaction.

2. Experimental

The hydrogenation reaction was carried out in a SS stirred autoclave. Reaction conditions: stirring rate, 1500 rpm; solvent: ethanol (150 ml); ethyl pyruvate (Fluka), 0.4 mol (freshly destilled); catalyst, Engelhard E4759, 0.5 g (5% Pt/Al_2O_3); reaction temperature, $23 \pm 3°C$; hydrogen partial pressure, 70 bar. Prior to its use the catalyst was pretreated in hydrogen at 400°C for 90 minutes. Special care was taken to prevent any contact of the catalyst with oxygen prior to its addition to the reaction mixture. The premodification of the catalyst (3.2 g, pretreated in H_2 at 400°C) with cinchonidine (1.9 g) was carried out at 78°C in ethanol (120 ml) under argon atmosphere for 4 hours followed by washing with ethanol.

Gas chromatographic analysis was used for product analysis and for the determination of the optical yield [7]. Thin layer chromatography (TLC) was applied to follow the transformation of the alkaloid during the hydrogenation reaction [10,11]. Cinchonidine (Cd), cinchonine (Cn) were purchased from Fluka, 11,12-dihydrocinchonidine (DhCd) and 5,6,7,8,11,12-hexahydrocinchonidine (HhCd) were kindly supplied by Ciba-Geigy.

3. Results

A. DIRECT ADDITION OF THE MODIFIERS TO THE REACTION MIXTURE

Fig. 1A shows the conversion versus time dependences for the formation of ethyl lactate in the absence and in the presence of different modifiers ((Cd), (DhCd), (HhCd)). The enantiomeric excess (ee) versus conversion dependences are shown in fig. 1B. The calculated initial or maximum rates, initial and final

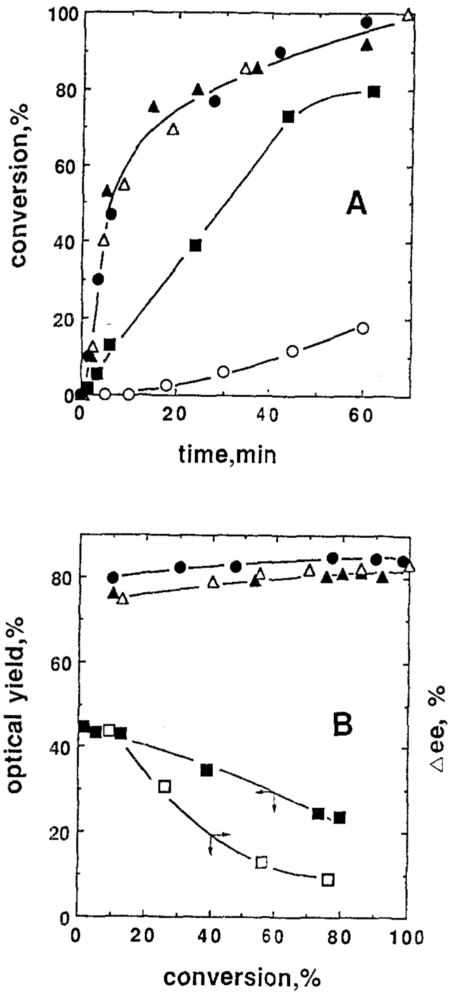

Fig. 1. Hydrogenation of ethyl pyruvate over Pt/Al_2O_3 catalyst used without premodification; A: Conversion versus time measured in the presence and absence of modifier; ▲, △ – Cd (two independent runs), ● – DhCd, □ – HhCd, ○ – absence of modifier. B: Optical yield version conversion for Cd, DhCd and HhCd; □ represents Δee versus conversion for HhCd.

optical yields and conversion values are listed in table 1. These data are in good agreement with literature data [6–9].

The initial rate of hydrogenation of ethyl pyruvate in the absence of alkaloid is very slow. The reaction shows a relatively long "induction period". In the presence of Cd or DhCd the "induction period" is almost entirely suppressed and the rate of hydrogenation is high. As shown in fig. 1A, there is no measurable difference in the conversion versus time behaviour between Cd and DhCd. In the presence of DhCd the optical yield is slightly higher than for Cd. For both modifiers above 50% of conversion the optical yield appears to be almost

Table 1
Hydrogenation of ethyl pyruvate in the presence of Pt/Al_2O_3 catalyst used with and without premodification

Exp. N°	Premodification	Modifier added	Initial rate conversion[a] (mol/kg sec)	(%)	ee (%) initial	final[a]
1	–	–	0.08[b]	17.0	–	1.6
2	–	Cd[c]	1.89	92.0	76.0	80.0
3	–	Cd[c]	1.75	99.0	75.0	83.5
4	–	DhCd[c]	1.44	98.0	80.0	84.0
5	–	HhCd[c]	0.34	80.0	45.0	23.4
6	+	–	0.14[b]	35.0	68.5	45.0
7	+	Cd[d]	0.93	88.0	74.5	76.8
8	+	Cd[c]	1.85	96.5	77.1	76.1
9	+	Cn[d]	1.07	93.5	22.5	−39.9

Amount of catalyst: 0.5 g,
[a] determined after 1 hour of reaction;
[b] maximum rate measured after induction period;
[c] in amount of 0.1 g;
[d] in amount of 0.025 g.

independent of conversion. However, between 10 and 50% of conversion a slight but reproducible increase of the optical yield is observed.

In the presence of HhCd the initial rate of hydrogenation is lower than in the presence of Cd or DhCd. Furthermore a continuous decrease of the enantioselectivity with conversion is observed. The initial ee value is only 45%, i.e. much lower than in the case of Cd or DhCd. Further information is obtained from differential values of the optical yields ($\Delta ee = \Delta Y_R - \Delta Y_S)/(\Delta Y_R + \Delta Y_S)$, where ΔY_R and ΔY_S are differential yields of the two enantiomers calculated as $\Delta Y = Y_{(t+1)} - Y_t$). In the conversion range between 73 and 80% the Δee value is only 10%. Thus in the presence of HhCd the catalytic system almost entirely losses its ability for enantio-differentiation during the progress of the reaction.

B. HYDROGENATION USING PREMODIFIED CATALYST

Results obtained on premodified catalysts are shown in fig. 2 and table 1. The premodification resulted in a catalytic system with low activity and modest initial optical yield. After 15 minutes of reaction a strong decrease both in the activity and enantioselectivity was observed. The complete loss of enantiodifferentiation in this system is illustrated by the Δee versus conversion plot shown in fig. 2B.

The addition of the modifier to the reaction mixture containing premodified catalyst leads to a strong increase both in the initial rate of hydrogenation and the optical yield. Thus the addition of Cd to the solution resulted in an active

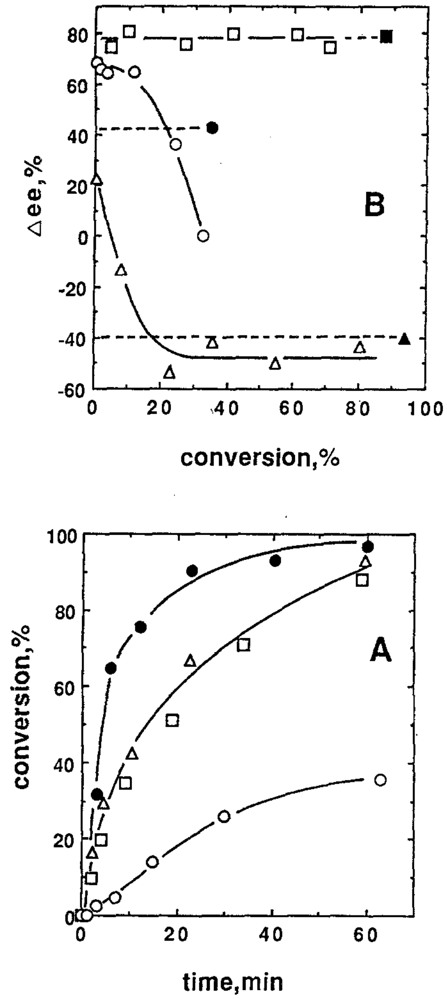

Fig. 2. Hydrogenation of ethyl lactate over Pt/Al_2O_3 catalyst premodified with cinchonidine; A: conversion versus time measured in the absence and presence of added modifier; (□ – Cd:0.025 g, ● – Cd:0.10 g, △ – Cn:0.025 g; ○ – absence of added modifier). B: Δee versus conversion; ○ – no modifier added; □ – Cd:0.025 g; △ – Cn:0.025 g. ------ yields measured after one hour of reaction (integral ee values).

catalytic system with high ee values and no decrease in the ee values with time was observed.

C. CHANGING THE CHIRALITY OF THE MODIFIER ADDED

It was shown earlier that when using cinchonine (Cn), the diastereoisomer of cinchonidine, S-lactate was the main reaction product [6]. In the present work cinchonine was added to the reaction mixture containing catalyst premodified with cinchonidine. This experiment should allow to differentiate roughly between the catalytic behaviour of the two forms of the modifier, i.e form M_R introduced by premodification and form M_S added directly to the reaction mixture.

Upon introducing Cn into the reaction mixture containing catalyst premodified with Cd a strong increase in the initial rate was observed. The extent of the rate increase was the same as observed in the case of added Cd. However, as emerges from fig. 2B the dependence of Δee versus conversion shows an unusual behaviour. This characteristic is attributed to different contributions of the forms M_R and M_S of the modifier to the overall enantioselectivity.

D. EXPERIMENTAL EVIDENCES FOR THE TRANSFORMATION OF THE ALKALOID

Preliminary TLC analysis shows that during the hydrogenation reaction the parent alkaloids (Cd or DhCd) were transformed into different derivatives. When Cd or Dh was added to ethyl pyruvate, even in the absence of hydrogen, the formation of an unknown alkaloid derivative (X) was observed.

When Cd was directly added as a modifier it transformed rapidly (within 10–15 min) under the hydrogenation conditions used. In this case not only the formation but also the consumption of DhCd was observed. After 15–20 minutes of hydrogenation the reaction mixture contained besides two major compounds (the unknown derivative (X) and DhCd) ten minor unidentified components.

DhCd and other unidentified derivatives were also observed in the solution obtained after premodification of the catalyst with Cd. However, no alkaloids were detected in the reaction mixture when the premodified catalyst was used in the hydrogenation reaction.

4. Discussion

As emerges from our results the rate of hydrogenation of ethyl pyruvate strongly increases upon introduction of the modifier (fig. 1A). The modifier in its adsorbed form, as obtained by premodification of the Pt/Al_2O_3 catalyst, contributes less to the overall control of both the reaction rate and the enantioselectivity than the modifier introduced directly to the solution.

A characteristic feature of the conversion versus time dependences observed is the decrease of the rate of hydrogenation at certain conversion (figs. 1A and 2A). This behaviour is not expected for a zeroth order reaction and is attributed to the transformation of the modifier during the hydrogenation reaction. The product (ethyl lactate) was found to have no significant effect on the reaction rate.

The observed strong rate acceleration induced by direct addition of the modifier can be attributed to the modifier-substrate interaction in the solution, i.e. to a pre-equilibrium between the alkaloid and ethyl pyruvate. In the above pre-equilibrium different nitrogen bases can also be involved. It was evidenced earlier that the addition of bases such as triethylamine, quinuclidine, etc. resulted also in an increase in the rate of hydrogenation [6]. It seems likely that due to the nucleophilic attack of the nitrogen base to the carbon atom of the carbonyl group the reactivity of the keto group towards hydrogen increases.

The low initial rate of hydrogenation in the premodified catalytic system is attributed to the absence of the modifier in solution. When using premodified catalyst the addition of the modifier to the solution resulted in a very significant increase in the inital rate. This rate increase is proportional to the amount of modifier used, but independent of the configuration at the C(8) and C(9) atoms of the alkaloid. These observations support the crucial role of the interaction between the substrate and the modifier in the solution.

The observed differences in the behaviour between Cd or DhCd and HhCd (see fig. 1A and 1B) are attributed to the structural differences of these modifiers. With HhCd due to the presence of a half hydrogenated quinoline ring the formation of an adsorption complex on the Pt sites is sterically hindered. Any change in the structure of the modifier can also influence the modifier-subtrate interaction in the solution.

The preliminary results obtained by TLC indicate that the alkaloids used as modifier undergo chemical changes during the hydrogenation reaction. These changes are much more complex than the simple hydrogenation of Cd to DhCd observed earlier [7]. These primary results suggest that different active and inactive forms of the modifier may be formed during hydrogenation. The ee versus conversion dependences (fig. 1B) indicate that for Cd and DhCd the overall enantio-differentiating ability of the derivatives of the modifier is higher than that of the modifier itself, while for HhCd it is lower.

With the premodified catalyst both the activity decrease and the complete loss of ee with time (figs. 2A and 2B) strongly indicates that during the hydrogenation reaction after some turnovers, the modifier is transformed into a less active form without enantio-differentiation ability. A decrease of the enantioselectivity with time was also observed by Garland et al. [12] with the same catalyst when direct addition of DhCd in low concentration was used.

We note that the transformation of the modifier under hydrogenation condition is particularly critical for maintaining the activity and enantioselectivity of this catalytic system when the modifier is present in low concentration as with the premodified catalyst or when only a small amount of the modifier is added to the solution.

High enantioselectivity can be obtained if under hydrogenation conditions the required surface concentration of the active form of the modifier can be maintained by suppressing undesired structural changes of the modifier.

The experiment, where the chirality of the modifier was changed (exp. N° 9, table 1) reveals a dynamic equilibrium between the two forms of the modifier, M_R introduced by premodification and M_S added directly to the solution. At the very beginning of the reaction, i.e. when $ee > 0$, the contribution of form M_R originating from Cd prevails, however, the contribution of form M_S cannot be neglected since in this experiment the initial ee is much lower than in the absence of added cinchonine. As the reaction proceeds (S)-lactate becomes the dominant product (ee < 0), i.e. form M_S controls the optical yield. The Δee versus conversion plot (see fig. 2B) strongly indicates that in the whole conversion range both cinchonidine (Cd), i.e. modifier in form M_S, and cinchonine (Cn), i.e. modifier M_R, contribute to the apparent overall enantioselectivity. The net optical yield is determined by the ratio of the two existing active surface species originated either from M_S or M_R.

The present results also indicate that in the hydrogenation of ethyl pyruvate the enantioselectivity at the end of the reaction cannot be considered as an intrinsic value of the given catalytic system as it was used earlier [4–9]. Depending on the experimental conditions and the chemical nature of the cinchona alkaloid used the enantioselectivity may be stable or either increase or decrease during the hydrogenation reaction. Detailed knowledge of the chemical changes and interactions of the chiral modifier occuring during hydrogenation is crucial for a better understanding of this catalytic system. Research towards this aim is presently under way in our laboratories.

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