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Enantioselective hydrogenation of ethyl pyruvate. Influence of oxidative treatment of cinchonidine-modified platinum catalyst and hemiketal formation in alcoholic solvents

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The reasons for the increase in the rate and enantiomeric excess after oxidative (aerobic) treatment of Pt/alumina in ethanol have been investigated. It is demonstrated that this treatment results in the formation of acetic acid and consequently in the protonation of the quinuclidine N_1 of cinchonidine. This favours the cinchonidine–pyruvate interaction and improves enantioselectivity. In addition, the reaction rate is enhanced due to acid catalysis of the carbonyl reduction. NMR and UV measurements indicate the rapid transformation of ethyl pyruvate to the corresponding hemiketal in primary alcohols as solvents. It is shown that the possible involvement of this hemiketal (and that formed between cinchonidine and ethyl pyruvate) as an intermediate in the pyruvate hydrogenation mechanism can be excluded.

Keywords: enantioselective hydrogenation; Pt/alumina; cinchonidine; ethyl pyruvate; protonation; hemiketal formation

1. Introduction

The hydrogenation of α-ketoesters over platinum modified by cinchona alkaloids is one of the few examples, in which excellent enantiomeric excess (ee, up to 95%) can be attained with a heterogeneous catalyst [1–3]. Considerable effort has been expended in the past few years to find the mechanism of this reaction [4–6]. A feasible mechanism has to account for the rate acceleration and enantiodifferentiation observed. Although significant progress has been made towards this aim, there are still several facets which are poorly understood and need clarification. One of them is the influence of solvents. In the hydrogenation of ethyl pyruvate (ETPY) over Pt/alumina both initial rate and ee were found to decrease with increasing dielectric constant of the solvent [7]. An interesting correlation is observed, when ee is plotted as a function of the empirical solvent parameter

E_T^N [8], instead of the dielectric constant. This correlation is illustrated in fig. 1, including typical solvents. Note that there is no explanation yet for the deviations from the linear relationship measured when acetic acid or water is used as a solvent. Similarly, the hemiketal or ketal formation from ETPY in alcoholic solvents and their possible involvement in the enantio-differentiating step needs further investigation.

Another poorly understood point is the role of oxygen during the usual aerobic modification procedure between catalyst pre-hydrogenation and ETPY hydrogenation in ethanol. Mixing the prereduced catalyst in an ethanolic solution of 10,11-dihydrocinchonidine (HCD) for at least 1 h in the presence of air was reported [10] to result in an enhancement of enantioselectivity by about 20% and a rate enhancement by a factor of 16–23, compared to the reaction performed without an aerobic catalyst treatment. We believe that the explanation suggested by the authors, namely the ordered co-adsorption of alkaloid, $C_2H_5O_{ads}$ and O_{ads} on Pt, requires a revision.

In this paper we will focus on (i) the interactions between ETPY, cinchonidine (CD), platinum, oxygen, and aliphatic alcohols or acetic acid as solvents, and (ii) the possible role of these interactions in the reaction mechanism.

2. Experimental

The 5 wt% Pt/alumina (Engelhard 4759) was prereduced in flowing hydrogen at 400°C for 1.5 h. The dispersion of Pt was 0.21, as determined by CO chemisorption. ETPY (Fluka) was freshly distilled under vacuum before each reaction.

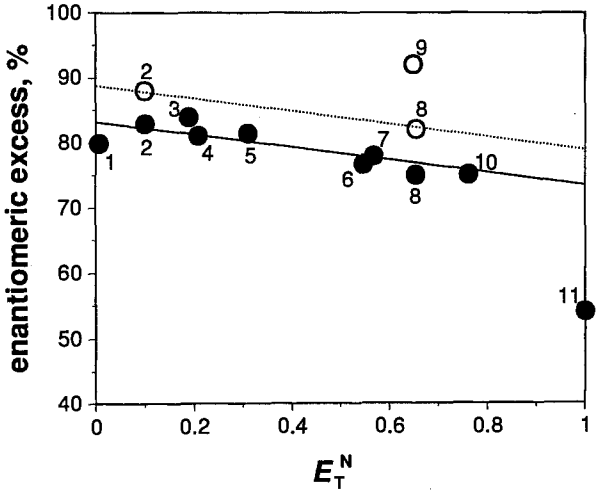


Fig. 1. Linear relationship between the empirical solvent parameter E_T^N and ee measured in our laboratory using cinchonidine (●) [7] and by Blaser et al. using 10,11-dihydrocinchonidine (○) [9] in the following solvents: cyclohexane (1), toluene (2), chlorobenzene (3), tetrahydrofuran (4), dichloromethane (5), 2-propanol (6), 1-pentanol (7), ethanol (8), acetic acid (9), methanol (10) and water (11).

Typically, the hydrogenation of ETPY was carried out at room temperature and 70 bar in a 250 ml stainless steel autoclave, with mechanical mixing at 1600 rpm. 250 mg catalyst, 50 mg CD (Fluka), 11.5 ml ETPY and 88.5 ml ethanol or acetic acid were used. For the oxidative ("aerobic") catalyst pretreatment, at room temperature, 10 ml min^{-1} oxygen was bubbled for 1 h into a mixed slurry, containing only the prereduced catalyst, CD and solvent, then ETPY was added and the hydrogenation started. GC-analysis was carried out on a Cyclodextrin-β-2,3,6-M-19 (Chrompack) capillary column. The optical yield is expressed as ee (%) = $100 \times (R - S)/(R + S)$, with a reproducibility of ±1%. Acetic acid was analysed using an FFAP (Hewlett-Packard) capillary column.

UV spectroscopic measurements were carried out with a Perkin Elmer Lambda 16 spectrometer at room temperature. The cell length was 1 cm. The concentrations of ETPY and CD were 55 mM and 85 μM, respectively. Hemiketal formation was followed by the disappearance of absorbance of the carbonyl group ($n \rightarrow \pi^*$) at around 330 nm.

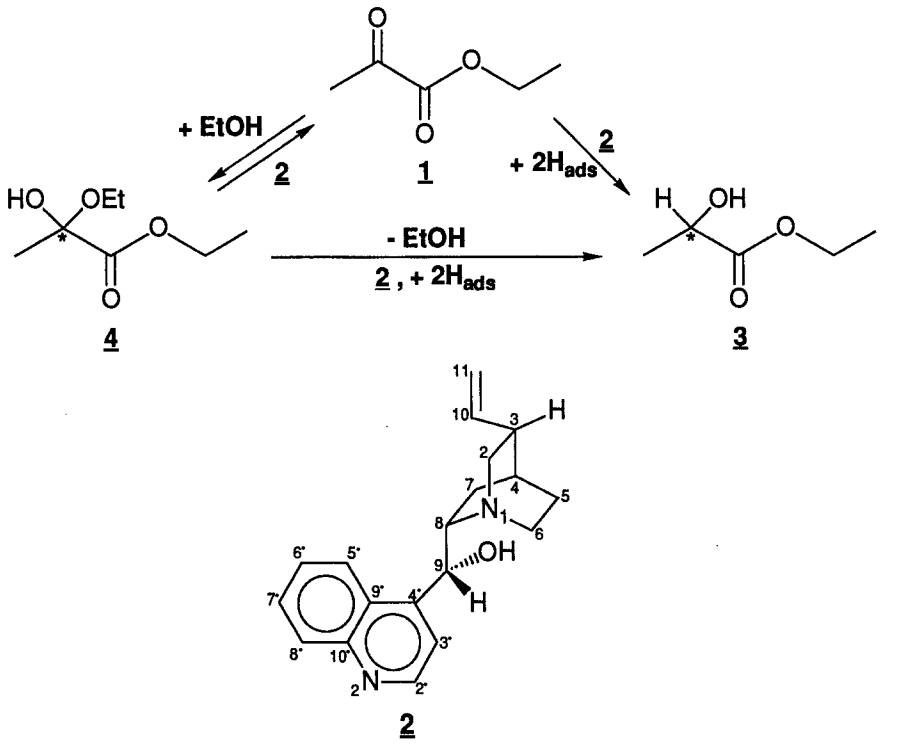
NMR studies were performed on Bruker AM 300 and AMX 500 spectrometers. The solvent was C_2D_5OD (99%) for protonation experiments of CD (68 mM) with acetic acid. Hemiketal formation has been shown in solutions with a molar ratio 9 : 1 of ethanol to ETPY, containing 10% (v/v) C_6D_{12} (99.5%) for field stabilisation. In two cases, 10 μl acetic acid or 100 mg γ-alumina (same type as used in Pt/alumina catalyst) have been added to the total volume of 7.02 ml.

3. Results

3.1. HEMIKETAL FORMATION IN ALCOHOLIC SOLVENTS

When choosing an alcohol as a solvent for the enantioselective hydrogenation of α-ketoesters, the equilibrium transformation of the carbonyl compound to hemiketal (scheme 1) and ketal has also to be taken into consideration. In general, the hemiketal formation is catalyzed by N-bases, such as CD (2), while ketal formation needs acid catalysis [11].

For ethanol as solvent we have found by ^{1}H-NMR spectroscopy that with a molar ratio of 9 : 1 of ethanol to ETPY the ketal is not formed in detectable amounts. Irrespective of the presence or absence of acetic acid or alumina (acidic catalyst support), the equilibrium between ETPY and its hemiketal was established within 1 h, the carbonyl : hemiketal ratio being 1 : 1.62 (ethanol), 1 : 1.45 (acetic acid in ethanol) and 1 : 1.60 (alumina in ethanol). In contrast to the C_2H_5– part of the ^{1}H-spectrum of ETPY, which is an A_2X_3 spin system, in the hemiketal both C_2H_5– groups were identified as ABX_3 spin systems. The negligible ketal formation is likely due to the presence of the strong electron-attracting group in the α-position, which rather favours the hemiketal formation than that of the ketal [11].



Scheme 1. Formation of hemiketal (**4**) as a possible intermediate during the hydrogenation of ETPY (**1**) to ethyl lactate (**3**) in the presence of CD (**2**).

Fig. 2 depicts the rate of hemiketal formation as determined by UV spectroscopy. In a neutral ethanolic solution the equilibrium has been reached in 30 min. After addition of traces of CD (in a concentration of 85 μM), the equilibrium was established in 10 min, showing the catalytic effect of the N-base modifier. Note that during ETPY hydrogenation the CD concentration was 20 times higher, than in the UV measurements. This indicates that by the time the hydrogenation starts in the autoclave, more than 60% of ETPY is present as the corresponding hemiketal.

The influence of the structure of various aliphatic alcohols as solvents on the extent of hemiketal formation is illustrated in table 1. As expected [11], the hemiketal formation is suppressed in secondary and especially in tertiary alcohols, compared to the equilibrium observed in ethanol or methanol.

The influence of the chemical structure of alcoholic solvents on the enantiomeric excess in the hydrogenation of methyl pyruvate (MEPY) of ETPY is shown in table 2. Our present work and some data from the literature [1,7] indicate that there is no correlation between ee and the extent of hemiketal formation (table 1) in the hydrogenation of pyruvic acid esters over pre-modified Pt. However, ee seems to be lowered by the preceding formation of hemiketal in the hydrogenation of methyl benzoylformate [2] and MEPY in the presence of excess CD [1]. These data demon-

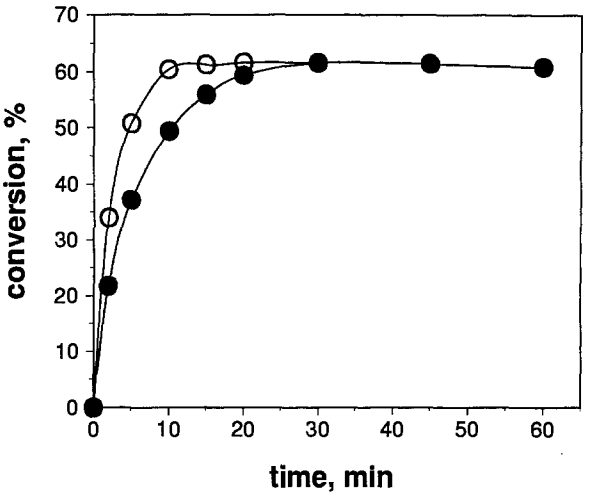


Fig. 2. Hemiketal formation between ETPY and ethanol in the presence (○) or absence (●) of CD.

strate that hemiketal formation and its diastereoselective hydrogenation to α-hydroxyacid cannot be crucial for the mechanism of α-ketoester hydrogenation.

3.2. PROTONATION OF CINCHONIDINE IN ETHANOL AND ACETIC ACID

Protonation of CD, particularly at N_1, is expected to lead to conformational changes around its chiral center [12,13]. Therefore, the observed ^{13}C-titration shifts are not as straightforward as for simple aliphatic amines. However, the extent of chemical shift changes for α, β and γ carbons next to N_1 (+0.88 to −3.98 ppm) compared to +0.63 to −0.68 for carbon atoms next to N_2, clearly demonstrate the preferential protonation at N_1, which is to be expected judged from the different basicities of N_1 and N_2 (pK_a = 10.03 and 5.83, respectively [14]). In addition, fig. 3 demonstrates for the α carbons 2 and 2′ that with two equivalents of acetic acid in ethanol, N_1 is protonated to the extent of ca. 95%, whereas N_2 would need more than 10 equivalents (or rather a stronger acid) for the same extent of protonation.

Table 1
Extent of hemiketal formation from ETPY in various alcohols after 1 h, in the absence of catalyst

Solvent (ROH)	ETPY/ROH (10^{-3} mol mol^{-1})	Conversion[a] (%)	Method
MeOH	8.92	75	NMR
EtOH	3.33	63	UV
i-PrOH	4.24	10	UV
t-BuOH	5.16	<1	UV

[a] Measured by integral ratios (NMR) or by the disappearance of the absorbance of the carbonyl group (n→π*) at 330 nm (UV).

Table 2
Enatiomeric excess (ee) obtained in the hydrogenation of methyl or ethyl pyruvate and methyl benzoylformate (MEBF) in various alcoholic solvents on CD-modified Pt, at 25°C and 70 bar

Reactant	Catalyst[a]	ee (%)				Ref.
		MeOH	EtOH	*i*-PrOH	*t*-BuOH	
ETPY	Pt/alumina	–	62	64	61	this work
MEPY	Pt/C	65	70	73	73	[1]
MEPY	Pt/C[b]	71	77	72	–	[1]
ETPY	Pt/alumina	75	75	77	–	[7]
MEBF	Pt/C	–	62	69	76	[2]

[a] 5 wt% Pt on support.
[b] 0.1 g CD also added to the reaction mixture.

It is evident from these results that not only in acetic acid, but also in ethanol in the presence of 1–2 molar equivalent of acetic acid, the protonated CD (at N_1) has to be taken into consideration when discussing the nature of enantio-differentiation [6]. The importance of this observation will be shown below.

3.3. CHEMICAL PROCESSES OCCURRING DURING AEROBIC (OXIDATIVE) CATALYST TREATMENT IN ETHANOL AND ACETIC ACID

Fig. 4 demonstrates that during the oxidative treatment of the prereduced Pt/alumina in ethanol, in the presence of CD, some acetic acid is formed from ethanol. Note that Pt is a good catalyst for the oxidation of alcohols to carbonyl compounds and carboxylic acids with molecular oxygen [15]. The amount of free acid,

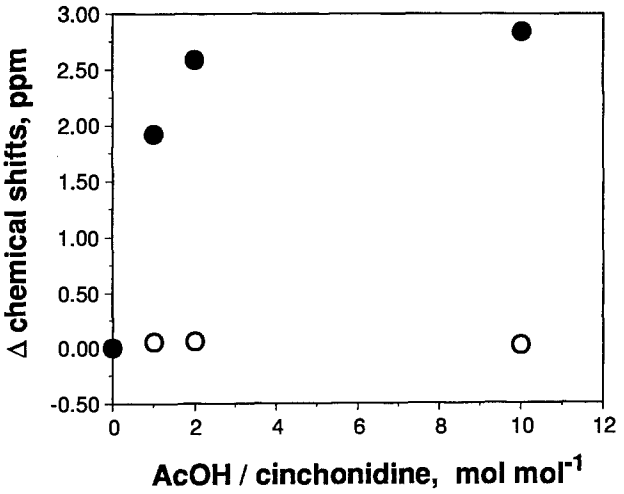


Fig. 3. Titration shifts of C_2 (α to N_1 (●)) and $C_{2'}$ (α to N_2 (○)) of CD as a function of molar equivalents of acetic acid in ethanol (C_2D_5OD; 68 mM CD).

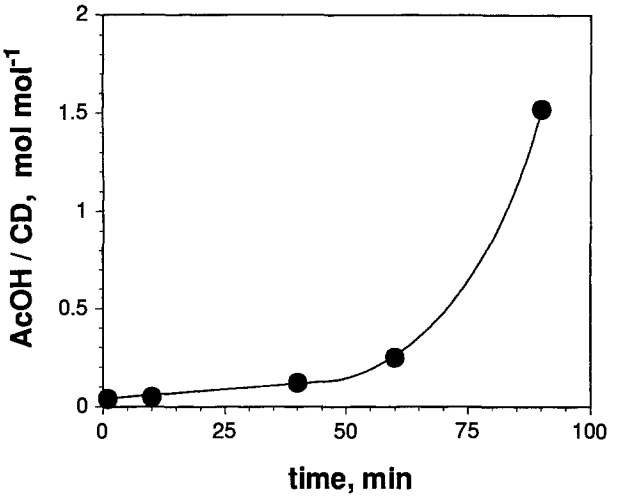


Fig. 4. Formation of free acetic acid during oxidative modification of the catalyst slurry in ethanol, in the presence of CD.

detectable by GC analysis of the solution, increases abruptly after about 1 h, indicating the saturation of the catalyst surface and presumably the protonation of CD adsorbed on the catalyst surface. These results suggest that the higher optical yield obtained after oxidative catalyst treatment is – at least partly – due to acetic acid formation and protonation of CD.

The oxidative treatment influenced also the rate of the hydrogenation reaction. Some characteristic results are shown in table 3. In order to separate the rate acceleration effect of CD from that of the oxidative treatment, no modifier was used in the first pair of reactions (racemic hydrogenation). The observed rate enhancement is clearly connected to the catalysis of carbonyl reduction by acetic acid formed during oxidative catalyst modification. Surprisingly, the enantioselective hydrogenation of ETPY in acetic acid showed some rate acceleration after oxidative catalyst treatment, which, however, had no influence on ee. This indicates that the influence of oxidative catalyst treatment cannot be explained solely by the oxidation of ethanol to acetic acid on Pt and by the protonation of CD.

Table 3
Influence of oxidative catalyst treatment on the initial rate and ee of ETPY hydrogenation at 25°C

Oxidative treatment	Solvent	Modifier	P (bar)	r_0 (mol g^{-1} h^{-1})	ee (%)
+	EtOH	–	70	0.23	–
–	EtOH	–	70	0.10	–
+	AcOH	HCD	10	3.17	87
–	AcOH	HCD	10	1.00	86

4. Discussion

4.1. HEMIKETAL FORMATION

The hemiketal (**4**, scheme 1) of ETPY is a chiral compound. Consequently, if the hemiketal is involved in the α-ketoester → α-hydroxyester transformation, the hydrogenation of ETPY should be considered as a diastereoselective reaction. According to the UV and NMR analysis, alkyl substituents at the α-C atom of the alcohol solvent suppress the hemiketal formation, as could be expected. If the good ee values, characteristic to the hydrogenation of α-ketoesters in alcoholic solvents, were due to the enantioselective hemiketal formation (in the presence of CD), then the highest ee should be observed in methanol or ethanol and the lowest in *t*-butanol. However, the results presented in table 3 show no positive correlation between hemiketal formation and ee. In some cases ee is even lower in primary alcohols than in secondary or tertiary alcohols.

Further evidence against the involvement of chiral hemiketals in the enantio-differentiating step of α-ketoester hydrogenation is provided by our former series of experiments, in which CD was added during the hydrogenation of ETPY in ethanol [16]. Without CD the product was racemic, but high ee was measured immediately after alkaloid addition, though the hemiketal was formed previously, in the absence of chiral modifier ("racemic" ketalization).

A further possibility for the involvement of chiral hemiketals in the reaction mechanism is the formation of a hemiketal from ETPY and CD (with the OH group at C_9). The existence of this adduct has been proposed earlier, based on thin layer chromatographic analysis [17]. An involvement of this species in the enantio-differentiating step can also be excluded, as the use of CD methylated at C_9-O position yields the same or even higher ee than CD (or HCD) itself [9].

4.2. OXIDATIVE ("AEROBIC") CATALYST TREATMENT

Wells and coworkers [10] explained the significant enhancement of rate and enantioselectivity observed after an oxidative catalyst treatment by a specific co-adsorption of CD, "C_2H_5O" and "O" species on Pt. However, O_{ads} is reduced to water during the following hydrogenation reaction and $C_2H_5O_{ads}$ is only one possible intermediate of the destructive chemisorption and oxidation of ethanol on Pt [18]. Combined electrocatalytic and spectroscopic studies revealed the existence of several other intermediates (e.g. CO_{ads}, CH_3CHOH_{ads}, CH_3CO_{ads}) and products (acetaldehyde, acetic acid, CO_2, CH_4, C_2H_6) of ethanol adsorption and oxidation [19]. Our results presented in fig. 4 demonstrate the formation of acetic acid in amounts sufficient for the protonation of N_1 in the quinuclidine part of CD.

We propose that the higher ee observed after an oxidative catalyst treatment in ethanol is mainly due to acetic acid formation from ethanol and to the protonation of CD. Our recent theoretical calculations show [6] that the interaction of proto-

nated CD with the α-ketoester via hydrogen bonding of the N_1 atom of CD and the carbonyl O atom of α-ketoester is energetically favoured, compared to the interaction with unprotonated CD. Addition of acetic acid before reaction, carried out in toluene or ethanol, increases both initial rate and enantioselectivity, as reported in a previous investigation [9].

The comparative experiments shown in table 3 indicate that the rate acceleration after an oxidative catalyst treatment in ethanol is, at least partly, due to acetic acid formation and to acid catalysis of the carbonyl reduction. Interestingly, a considerable rate enhancement has been observed also in acetic acid. We propose that in this case the explanation is the oxidative removal of CO, chemisorbed on Pt. During the first, reductive catalyst pretreatment, most of the impurities are removed by hydrogen at 400°C, which results in higher ee in the following enantioselective reaction. However, under these conditions some CO_2 or carbonates, trapped on Pt/alumina during storage, can be reduced to CO on Pt surface. CO_{ads} cannot be removed completely by hydrogen, but can easily be oxidized to CO_2 in the liquid phase on Pt (partially) covered by oxygen [20]. The oxidative removal of CO from Pt should increase the rate of the subsequent α-ketoester reduction. The influence of oxygen on CO poisoning in carbonyl reduction on Pt is well documented in the literature [21]. CO chemisorption on Pt during ETPY hydrogenation is currently being investigated in our laboratory.

Summarizing the results we can conclude that it is not advantageous to use alcohols as solvents for the enantioselective hydrogenation reactions. The reactivity of alcohols on Pt creates considerable difficulties in the interpretation of the results and neither the ee nor the reaction rate achieved in these solvents are outstanding [7]. The excellent enantioselectivity obtained in acetic acid [9] is likely due to the favourable interaction between the protonated N-base alkaloid modifier and the activated carbonyl compound reactant [6]. As a consequence of the oxidative catalyst treatment, acetic acid is formed from ethanol which protonates CD indicating that the reaction mechanism is the same in ethanol and acetic acid.

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