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Enhanced Enantioselectivity in Ethyl Pyruvate Hydrogenation Due to Competing Enantioselective Aldol Reaction Catalyzed by Cinchonidine

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IR and NMR experiments revealed that the enantioselective hydrogenation of ethyl pyruvate in nonacidic solvents is complicated by the simultaneously occurring self-condensation (aldol reaction) of the reactant. Both enantioselective reactions are catalyzed by the chiral base cinchona alkaloid, but the hydrogenation is faster by several orders of magnitude than the aldol reaction. Catalytic experiments proved that the aldol products are not spectator species. The enol form of the major aldol product protonates the quinuclidine N of cinchonidine and enhances the enantiomeric excess of the hydrogenation reaction. The significance of this observation with respect to kinetic and mechanistic studies is discussed.

Key Words: **enantioselective hydrogenation; Pt/alumina; cinchonidine; ethyl pyruvate; enantioselective aldol reaction.**

INTRODUCTION

Enantioselective hydrogenation of activated ketones has received great attention in the past years. Important information has been collected since the first report by Orito *et al.* on the hydrogenation of pyruvic acid esters over Pt modified by cinchonidine (CD) or other cinchona alkaloids (Scheme 1) (1–4). One reason for the undamped enthusiasm is the complexity of the reaction, due to the bi- and multifunctional character of reactant and modifier, respectively. Understanding of the crucial enantio-differentiating interaction between the α-ketoester and CD on the Pt surface is complicated by the occurrence of several other interactions and the formation of spectator species. Competing hydrogenation of the C=C double bond of CD is an irrelevant side reaction but saturation of the quinoline moiety is detrimental to the adsorption and hence the efficiency of the modifier (5, 6).

It has been shown that protonation of the quinuclidine N of CD has a significant positive influence on the enantioselectivity (2, 7). O- and N-acylation of CD, parallel to ethyl pyruvate (EP) hydrogenation in acetic acid, has been proposed recently (8). However, the formation of these doubly or triply acylated compounds at room temperature and the importance of these species in the enantio-differentiating process are doubtful.

The basic quinuclidine N atom ($pK_a = 8.4$ (9)) can catalyze several reactions of EP. Equilibrium formation of hemiketals in primary alcoholic solvents complicates kinetic analysis (10) but has no significant influence on the enantioselectivity of the hydrogenation reaction (7). Apparently, the free carbonyl compound is reduced on the Pt surface and the chiral hemiketal is only a spectator species.

Another possible base-catalyzed reaction of activated ketones is aldol condensation (11). Tertiary amines are poor aldol catalysts except when general base catalysis exists and the proton removal is slower than the subsequent condensation step (12, 13). Aldol dimerization of EP and its derivatives is well demonstrated in the literature (14–19). We observed this reaction when investigating the CD–EP interactions in aprotic solvents. This prompted us to explore the double role of CD and the influence of chiral aldol products on the enantio-differentiation during pyruvate hydrogenation.

EXPERIMENTAL

*Preparation of 2-Methyl-4,5-dioxo-tetrahydro-furan-2-carboxylic Acid Ethyl Ester (**1**)*

The cyclic aldol dimer **1** was prepared according to Gault (14), starting from EP and CD (Scheme 2). CD (12.2 g, 43 mmol; Fluka, 98%) was added in small portions at room temperature to a stirred solution of EP (10 g, 86 mmol, Aldrich, 98%) in toluene (60 ml). The mixture was stirred for 24 h in a dark flask. The resulting light yellow mixture was acidified with aqueous HCl (pH of approximately 2). The organic layer, which contained no CD (TLC), was treated with aqueous K_2CO_3 (pH of approximately 13). The aqueous phase was acidified with HCl (pH of approximately 1) and extracted with diethyl ether. Drying over

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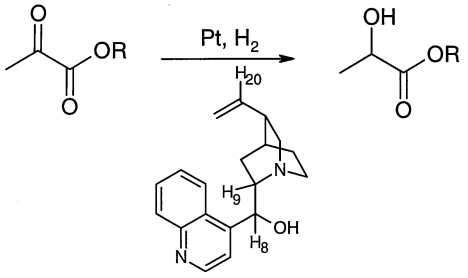


SCHEME 1

$MgSO_4$, followed by flash chromatography over silica gel (MTBE : hexane = 5 : 2) yielded a colorless oily product, which was stored under nitrogen in diethyl ether at −20°C. TLC indicated the presence of two compounds which were stable at −20°C but considerable restructuring was observed within a few hours at room temperature. Optical rotation was measured in EtOH ($[\alpha] = -7.6°$). The synthesis was repeated using Et_3N as the base catalyst, providing racemic aldol products.

IR (CH_2Cl_2): 3228 (νO–H), 1781 (s, νC=O), 1749 (s, νC=O), 1672 (νC=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.3 (m, CH_3), 1.7 and 1.8 (d, CH_2), 4.3 (m, CH_2 and OH), 6.2 (s, CH).

IR Spectroscopy

Infrared spectra were recorded on a Bruker IFS-66 spectrometer equipped with a 1-mm CaF_2 cell. Experiments were carried out at room temperature (200 scans at 4-cm^{-1} resolution). Curve fitting was performed by the Bruker OPUS/IR 2.0 program applying the Levenberg–Marquardt algorithm. CD, EP, quinuclidine (Fluka, >97%), and 2-propanol (Baker, >99.5%) were used as received. CH_2Cl_2 solvent was stored over molecular sieve 4A.

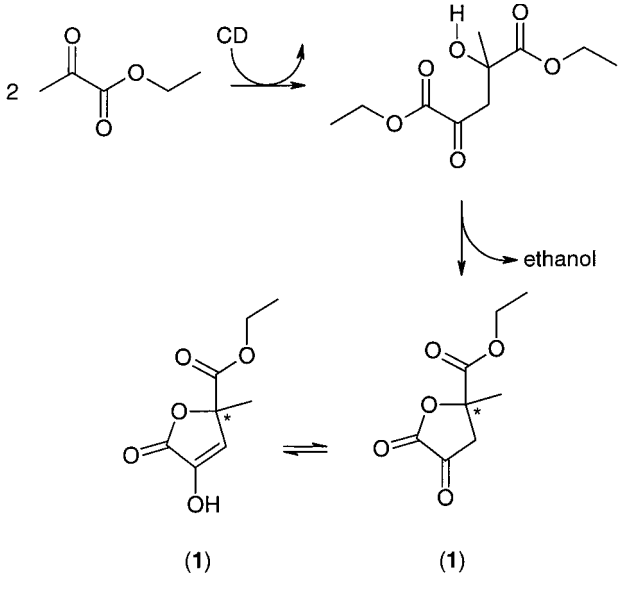
NMR Spectroscopy

NMR experiments were performed on Bruker DPX 300 and AMX 500 spectrometers at room temperature. $CDCl_3$ and d_6-benzene were used as solvents. Signal assignment was assisted through correlation spectroscopy (COSY).

Catalytic Hydrogenation

A 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was pretreated in a fixed bed reactor in flowing hydrogen for 2 h at 400°C. After being cooled to room temperature, the catalyst was transferred to the autoclave. The catalytic tests were carried out in a magnetically stirred (1000 rpm) stainless steel 100-ml autoclave. A 50-ml glass liner with Teflon cover was used to keep the system inert. H_2 uptake was monitored by a Büchi Pressflow gas controller. Standard reaction conditions were as follows: 0.66 ml (6 mmol) of ethyl pyruvate, 14.3 ml of toluene, 50 mg of catalyst, 50 bar, room temperature, and 1 h of reaction time. The modifiers used were CD, *O*-methyl cinchonidine (MeOCD, synthesized according to a former recipe (20)) and/or **1** (15–18 mg, prepared by CD as a catalyst).

Conversion and enantiomeric excess were determined by gas chromatographic analysis using an enantioselective column (Chirasil-DEX CB, Chrompack). Enantiomeric excess is defined as $ee = |R(\%) - S(\%)|$.



SCHEME 2

RESULTS

IR Spectroscopy

Figure 1 shows the time-resolved IR spectra in the ν(O–H) region of a mixture of CD and EP in CH_2Cl_2. Difference spectra, obtained by subtracting the EP signals, are displayed as a function of time after the solution was prepared. The region around 3450 cm^{-1} is slightly affected by the overtone $2 \cdot \nu$(C=O) of EP (dotted vertical line). The spectra change considerably with time, indicating chemical reaction(s) in the CD–EP solution. The fitting curves, displayed also in Fig. 1, are helpful to follow the spectral changes. The ν(O–H) of the free OH of CD at 3598 cm^{-1} (Fig. 1, bottom) seems to split into two peaks at higher and lower frequencies. A broad signal centered at 3542 cm^{-1} is detectable already after a few minutes. After 2 h the spectrum shows signals at 3615, 3590, and 3530 cm^{-1}, together with broad bands at 3100 and 2500 cm^{-1}, and an increase in the baseline over the whole spectral range. The ν(C=O) and fingerprint regions are also affected by the reaction, even though they are dominated by the characteristic absorptions of EP. New peaks, which are not associated with CD or EP, grow with time at 1780, 1610, 1210, 1095, and 1054 cm^{-1} (not shown).

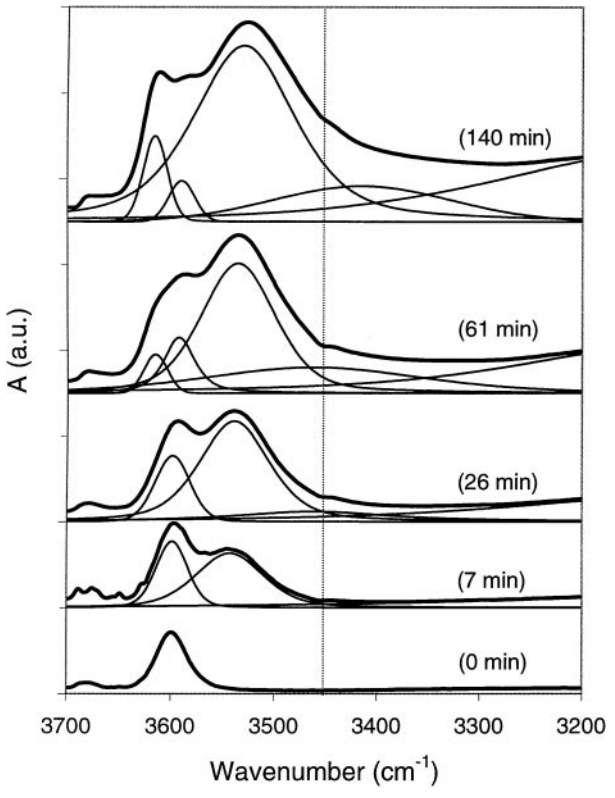


FIG. 1. IR spectra of the ν(O–H) region of a CD–EP solution as a function of time after the solution was prepared. Difference spectra are displayed, which are obtained by subtracting the EP spectrum (i.e., 0 time corresponds to pure CD). Bold and regular lines are real spectra and fitting curves, respectively. The dotted line represents the position of the $2 \cdot \nu$(C=O) overtone of EP. Conditions: CD, 0.005 M; EP, 0.5 M; CH_2Cl_2 solvent.

To reveal the individual role of the secondary OH group and the quinuclidine N of CD in the observed transformation, the influence of these functions of CD were mimicked by using 2-propanol and quinuclidine, respectively. Weak hydrogen-bonding interactions could be detected between EP and 2-propanol but the changes were not time dependent. However, on the basis of IR analysis, the same reaction occurred between quinuclidine and EP as observed with CD and EP, indicating the importance of the (basic) quinuclidine N of CD.

Figure 2 shows the influence of CD concentration on the rate of the observed reaction. The peak at 1210 cm^{-1}, which is associated with the formation of the new compound, was used for the kinetic experiments and the intensity was measured 15 min after the solutions were prepared. There is a good linear correlation between the amount of CD and that of the new compound.

On the basis of early work on aldol reactions of α-ketoesters including EP (14–19), we assumed that CD and quinuclidine act as base catalysts of this condensation reaction. Several control experiments have been made to support this assumption.

The dimer, formed by the aldol reaction and subsequent ethanol elimination and cyclization (Scheme 2), was synthesized using CD or Et_3N as the base catalyst. The product **1** is present in two tautomers. The IR spectrum in CH_2Cl_2 showed two strong carbonyl bands (1781 and 1749 cm^{-1}) together with an overtone at 3492 cm^{-1}. The ν(O–H) band of the enol form of **1** was found at 3228 cm^{-1}. The carbonyl band at unusually high wavenumber is typical for lactones. The other carbonyl band was assigned to the ester group (21). A signal at 1672 cm^{-1} was assigned to ν(C=C). Similar bands were found for species of the same family of lactones (22, 23). Notably, virtually the same IR and NMR spectra were obtained for **1**, independent of the base (CD or triethylamine) used as the catalyst. However, the CD-catalyzed reaction was enantioselective, as indicated by the remarkably high specific rotation of the purified product. Unfortunately, the ee could not be determined since the specific rotation of **1** is unknown.

The IR bands characteristic of **1**, such as the high-frequency lactone ν(C=O) signal, were also observed during study of the CD–EP interaction in CH_2Cl_2. Furthermore, the new band at 3615 cm^{-1} (Fig. 1) is assigned to ν(O–H) of ethanol, which is released during the formation of **1** (Scheme 2). Assignment of other signals in the 3600- to 3200-cm^{-1} region is complicated by the fact that CD, EP, ethanol, and **1** mutually interact via hydrogen bonds, giving rise to a variety of signals.

The intensity of the strong ν(C=O) band at 1780 cm^{-1} was used for a semiquantitative estimate of the rate of formation of **1** during the CD–EP interaction in CH_2Cl_2. Solutions with known concentrations of **1** were used for calibration. After about 80 min the concentration of **1** roughly equaled the concentration of CD. More accurate measurements were not possible due to the poor stability of **1**. Further transformation of **1** could be clearly observed by thin

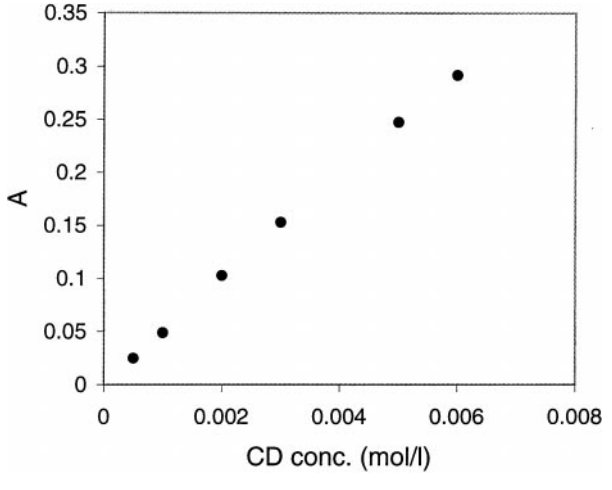


FIG. 2. Absorbance of the signal at 1210 cm^{-1} as a function of CD concentration.

layer chromatography and IR spectroscopy. Most prominent was the appearance of a sharp peak at 2337 cm^{-1}, which is not associated with **1**.

^{1}H-NMR spectroscopy

NMR spectra of CD–EP mixtures in $CDCl_3$ were measured using the same concentrations as those used for the IR experiment shown in Fig. 1 (0.005 M CD, 0.5 M EP). The spectral region below 4.5 ppm is very crowded due to the large excess of EP and therefore difficult to interpret. On the other hand, the spectrum above 4.5 ppm, the region which mostly contains the aromatic and vinyl protons and H_8 (for atom numbering, see Scheme 1) of CD, provides sufficient information. First of all, the spectrum changes with time: several CD resonances shift and new resonances appear which are not associated with CD. This behavior indicates a chemical reaction, thus confirming the IR experiments. Important new information is that the CD resonances only *shift* without being split. At any time we could only detect one set of resonances associated with CD. This is a clear indication that CD catalyzes the transformation of EP but the chiral base itself is not a reactant.

Among the most significant changes in the spectrum are the increasing chemical shift of H_8 accompanied with a drop in the $^3J H_8H_9$ coupling constant and the decreasing chemical shift of the characteristic vinyl H_{20} signal. After several hours of reaction time in $CDCl_3$ the chemical shift of H_8 changed from 5.6 to 6.3 ppm and that of H_{20} from 5.7 to 5.55 ppm. Similar spectral changes were observed when the synthesized compound **1** was added to a CD solution in C_6D_6 (0.007 M CD, 0.03 M **1**). In benzene the $^3J H_8H_9$ coupling constant dropped from 5.0 Hz without **1** to below 2 Hz after addition of **1**. This change corresponds to an increase of the population of conformer Open (3) of CD from 58% in pure benzene to about 100% after addition of **1** (24). At last, for solutions of EP and CD (100 : 1 ratio) in $CDCl_3$ a signal at δ 6.2 ppm appeared after some time, which is not associated with CD. This signal is characteristic of the olefinic H of **1**, corroborating its formation during CD–EP interaction and thus supporting the IR experiments.

Catalytic Hydrogenation

Catalytic tests were carried out to clarify whether the aldol condensation of EP affects the enantioselectivity of the hydrogenation reaction. The influence of aldol product(s) was tested by (i) storing the reaction mixture in the autoclave for 2 h under N_2 before the hydrogenation reaction was started or (ii) adding small amounts of **1** to the reaction mixture in the presence or absence of CD. These results are compared to experiments carried out under standard conditions (Table 1).

When the reaction mixture was stored for 2 h before the start of the hydrogenation reaction to provide sufficient time for the aldol reaction, an enhancement in ee by ca. 2.5% was observed. This increase is relatively small but significant, as corroborated by repetitive experiments which resulted in a standard deviation of 0.5% for ee. The addition of **1** to a reaction mixture containing CD resulted in an enhancement in ee by ca. 4% under standard reaction conditions, while the use of **1** alone without CD did not induce any enantiodifferentiation. Note that **1** was used in considerably larger concentrations than CD.

TABLE 1

Enantioselective Hydrogenation of Ethyl Pyruvate over Modified Pt/Al_2O_3

Modifier (mg)	Solvent	Enantiomeric excess (%)	
		Standard conditions	After 2 h of storing under N_2
CD (2.3)	CH_2Cl_2	80.6	82.7
CD (2.2)	Toluene	85.3	87.7
CD (2.2) + **1** (15.8)	Toluene	89.2	—
MeOCD (2.1)	Toluene	77.2	—
MeOCD (2.1) + **1** (22.0)	Toluene	81.7	—

Note. Experiments were carried out according to the standard procedure or after the reaction mixture was stored for 2 h under nitrogen before hydrogen was introduced into the autoclave.

The initial rate of the hydrogenation reaction under standard conditions was 2.3 mol h^{-1} g^{-1}, based on hydrogen consumption. Repeating the experiments under the same conditions but after the reaction mixture was stored for 2 h under nitrogen before hydrogen was introduced resulted in an almost identical hydrogen consumption curve. The calculated initial rate was 2.2 mol h^{-1} g^{-1}. The rate difference caused by the formation of **1** is clearly insignificant, when compared to the estimated standard deviation of initial rates (±5–10%).

To reveal the role of the OH group of CD in a possible interaction with **1**, hydrogenation of EP was repeated with MeOCD as a modifier and with both MeOCD and **1**. The presence of **1** resulted again in an enhancement in ee by 4.5%.

DISCUSSION

*Evidence for Protonation of CD by the Cyclic Aldol Dimer **1***

Both IR and NMR experiments demonstrate reaction(s) in apolar solutions of CD and EP. The fact that at any time only one set of lines for CD was observed by NMR indicates that on the NMR time scale ($\ll$1 s) only one CD species exists. For comparison, the chemical reaction observed by IR and NMR takes place on the time scale of minutes to hours. This difference shows that CD itself does not react, apart from being protonated. On the other hand, without CD the reaction does not occur. Hence, CD is assumed to act as a catalyst for the observed reaction. The experiments

with 2-propanol and quinuclidine revealed that the quinuclidine N of CD is involved in the catalytic transformation of EP. Furthermore, the major reaction product could be identified as **1**, indicating that the observed transformation is an aldol reaction catalyzed by CD. Separate synthesis of **1** proved that the aldol reaction catalyzed by the chiral base CD is enantioselective. Note that the product of an aldol reaction is still highly active (e.g., in further condensation and dehydration). Accordingly, **1** was the major but not the only aldol product from EP.

The characteristic chemical shifts observed by ^{1}H-NMR in CD–EP solutions and after **1** was added to CD show that CD is protonated at the quinuclidine N. The drastic change in the $^3J_{H_8H_9}$ coupling constant and thus the conformational change in favor of Open(3) provide unambiguous evidence for protonation (24). Almost identical chemical shifts of CD resonances were observed when trifluoroacetic acid, a strong acid, was added to CD in $CDCl_3$, which fully protonates the quinuclidine N.

Protonation of CD by the acidic enol **1** can explain several characteristic features in the IR spectra. The continuous IR absorption over the whole spectrum that was formerly assigned to strong proton polarization (25) is typical for CD protonation. Such behavior was already observed for CD in acetic acid (26). The broad band near 2500 cm^{-1}, which increases with time, arises from the stretching mode of hydrogen-bonded N^+–H of CD. The band at 1610 cm^{-1}, which is observed in EP–CD solutions, is assigned to ν(C=C) of the enolate form of **1**, which shows that **1** is the source for protonation of CD. The acidity of **1** is unknown but the pK_a value of another cyclic enol-lactone, 4-hydroxy-6-methyl-pyran-2-one, is the same as that of acetic acid (4.7 (27)).

Implication of Competing Enantioselective Hydrogenation and Aldol Reactions of EP

The catalytic experiments presented in Table 1 demonstrate that the aldol product **1** alone is an inefficient chiral modifier for the enantioselective hydrogenation of EP, but protonation of CD by **1** results in a small but significant enhancement in ee. It has been shown earlier that protonation of the quinuclidine N of CD enhances the ee in the enantioselective hydrogenation of EP (7).

IR measurements indicated some H-bonding interactions involving the OH group of CD. Comparative experiments with MeOCD (Table 1) proved that these interactions are not important for the enhancement in ee.

When the relevance of aldol condensation as a competing side reaction is considered, the effect is assumed to be limited to reactions carried out in the absence of an acid. No aldol condensation is expected in acidic solvents or when a CD salt is used as a chiral modifier.

The influence of the relatively slow aldol condensation is expected to be more pronounced under low-pressure conditions when the hydrogenation reaction is slow. The aldol reaction is not assumed to depend on the hydrogen pressure, though removal (desorption) of high molecular weight aldol products from the catalyst surface may be facilitated by high surface hydrogen concentration.

Concerning the extension to the enantioselective hydrogenation of other activated ketones over Pt modified by chiral N bases, this side reaction is excluded for reactants possessing no H atom in the α position to the carbonyl group, such as ethyl benzoylformate (28), ketopantolactone (29), trifluoroacetophenone (30), and pyrrolidine-2,3,5-triones (31).

According to our present knowledge (2), the mechanism of EP hydrogenation depends on whether CD is protonated or unprotonated. The inevitable aldol condensation and successive protonation of the chiral modifier is expected to change the mechanism during hydrogenation in nonacidic solvents. This behavior complicates the interpretation of mechanistic studies in these solvents. On the other hand, under our conditions the influence of aldol products on the rate of enantioselective hydrogenation was marginal, including the initial period of EP hydrogenation. This behavior may be due to counteracting effects of several factors, e.g., a rate enhancement due to protonation of CD and catalyst poisoning by higher molecular weight, dehydrated aldol products. An example of the latter is the deactivation of Pt/Al_2O_3 by continuous formation of polymeric aldol products during oxidation of 1-methoxy-2-propanol to methoxyacetone (32).

CONCLUSIONS

Time-resolved IR and NMR analysis and catalytic experiments have shown that CD plays a double role during the enantioselective hydrogenation of EP. Beside the enantioselective hydrogen addition to the activated carbonyl group, a much slower enantioselective aldol condensation followed by cyclization is also catalyzed by the chiral N base. It seems that the most important effect of these side reactions is the protonation of CD by the cyclic enol product. Aldol condensation as a side reaction should be considered in mechanistic studies of the enantioselective hydrogenation of EP and other activated ketones that possess a H atom in the α position to the carbonyl group.

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