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Asymmetric Hydrogenation of 4-Hydroxy-6-methyl-2-pyrone: Role of Acid–Base Interactions in the Mechanism of Enantiodifferentiation

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Enantioselective hydrogenation of the pseudo-aromatic 4-hydroxy-6-methyl-2-pyrone to the corresponding 5,6-dihydropyrone has been studied over cinchonidine-modified Pd/Al_2O_3 and Pd/TiO_2 catalysts. A mechanistic model for enantiodifferentiation is proposed, involving two H-bond interactions (N–H · · ·O and O–H · · ·O) between the deprotonated reactant and the protonated chiral modifier. The model can rationalize (i) the sense of enantiodifferentiation, i.e., the formation of (*S*)-product in the presence of cinchonidine as modifier; (ii) the complete loss of enantioselectivity when the acidic OH group of the reactant is deprotonated by a base stronger than the quinuclidine N of the alkaloid; and (iii) the poor enantiomeric excesses obtained in good H-bond donor or acceptor solvents. NMR and FTIR investigations, and *ab initio* calculations, of reactant–modifier interactions support the suggested model. Several factors, such as catalyst prereduction conditions, trace amounts of water, presence of strong bases and acids, and competing hydrogenation of acetonitrile to ethylamines, were found to affect the efficiency of this catalytic system.

Key Words: **enantioselective; asymmetric; hydrogenation; cinchonidine; palladium; 4-hydroxy-6-methyl-2-pyrone; *ab initio* calculations; nuclear magnetic resonance; Fourier transform infrared spectroscopy.**

1. INTRODUCTION

The structure of 2-pyrone, and di- and tetrahydropyrones, is a frequent pattern in natural and synthetic compounds of pharmaceutical interest. For example, the partially hydrogenated derivatives of 2-pyrones have been used as chiral intermediates in the synthesis of a potent antiobesity drug and an HIV protease inhibitor (1–3). The enantioselective hydrogenation of substituted 2-pyrones with homogeneous chiral Ru complexes afforded enantiomeric excesses (ee's) up to 98% and good chemoselectivities to 5,6-dihydropyrones (4, 5). A limitation of this highly selective method is that hydroxymethylpyrone **1** (Scheme 1) and other pyrones, which are not substituted in the C-3 position, are too reactive and only a mixture of *cis*- and *trans*-tetrahydropyrones is produced.

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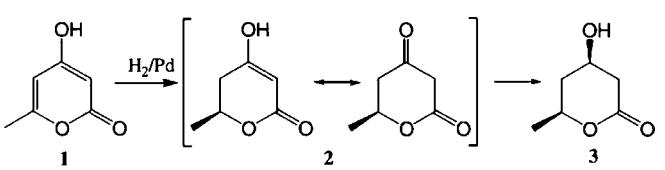
Seeing the topic from a broader perspective, enantioselective hydrogenation of prochiral C=C bonds with homogeneous chiral metal complex catalysts provides the desired enantiomer with ee's of 99% and above (6). Heterogenization of these complexes can result in good and recyclable catalysts for alkene hydrogenation, but the number of successful applications is limited (7). Using a conventional metal hydrogenation catalyst and trace amounts of a strongly adsorbing chiral modifier is another thoroughly investigated approach, offering relatively cheap and commercially available catalysts combined with easy catalyst separation and recycling (8). Supported palladium is the best choice for the enantioselective hydrogenation of functionalized olefins (9, 10) though the ee's are limited by the possible migration of the C=C bond in the reactant and the competing hydrogenation of the isomers on the metal surface (11). For example, hydrogenation of α, β-unsaturated carboxylic acids afforded only 10–53% ee (12–16), but 72% ee was reported for the hydrogenation of (*E*)-α-phenylcinnamic acid (10), in which reactant no double bond isomerization is possible. Other limitations of chirally modified Pd are the strong retardation of the hydrogenation reaction by the chiral modifier and the relatively high modifier/reactant ratio (up to 100 mol%) necessary to achieve good ee's (10, 17, 18).

The first attempt to hydrogenate **1** to the dihydro derivative **2** (Scheme 1) with a heterogeneous enantioselective catalyst was not promising: the Raney Ni–tartaric acid–NaBr system yielded the tetrahydro derivative **3** with only 17% ee (3). Recently we have reported that cinchona-modified Pd is able to reduce **1** selectively to **2** with ee's up to 85% (19). A drawback of the method is the strong rate deceleration induced by the presence of cinchonidine



SCHEME 1

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(CD). In addition, during the long reaction times the aromatic ring system of CD was also hydrogenated, leading to weaker adsorption of the modifier on the metal surface and partial or complete loss of enantiodifferentiation (19). Consumption of CD during hydrogenation of **1** was indicated by unprecedented rate acceleration with increasing conversion, and was confirmed by NMR analysis (20). The limited stability of CD could be overcome and the high initial ee maintained by feeding of small amounts of modifier during the reaction (19).

It seems to be important for understanding the reactant–modifier interaction(s) that the acidity of the enolic OH group of **1** [$pK_a = 4.73$ in aqueous medium (5)] is similar to that of acetic acid. On the other hand, the quinuclidine N and quinoline N atoms of CD are medium and weakly basic [$pK_a = 10.0$ and 5.8, respectively (21)]. The aim of the present work is to reveal the role of acid–base interactions during the enantioselective hydrogenation of **1** to **2** and to propose a feasible mechanism for enantiodifferentiation.

2. EXPERIMENTAL

Materials

The 5 wt% Pd/Al_2O_3 catalyst (Engelhard 40692, metal dispersion: 0.21, determined by TEM) was used as received. A 5 wt% Pd/TiO_2 (metal dispersion: 0.18, determined by H_2 chemisorption) was prepared as follows. $PdCl_2$ 0.97 g was dissolved in 100 ml water and 1 ml concentrated HCl. TiO_2 11.16 g (P25, Degussa, 55 m^2/g) was added to the solution and the pH was set to 10 by dropping an aqueous Na_2CO_3 solution to the stirred slurry at room temperature. After filtration the catalyst was washed to neutral and dried at 80°C *in vacuo* for 24 h. The catalyst was reduced by hydrogen *in situ* before use.

4-Hydroxy-6-methyl-2-pyrone (**1**, Fluka 98%) was purified by column chromatography (silica gel, dry hexane: ethyl acetate 1 : 1), followed by recrystallization from ethyl acetate. Cinchonidine (Fluka, 99% alkaloid by titration) and trifluoroacetic acid (Fluka) were used as received. Acetonitrile (Fluka, >99.5%, stored over molecular sieve) and all other solvents and basic additives were distilled before use. It must be emphasized that even traces of impurities in the reaction mixture can lead to significant variations in ee.

Catalytic Hydrogenation

The reactions were carried out in a magnetically stirred 100-ml glass reactor. In a standard procedure, 20 mg catalyst in 10 ml solvent was pretreated with H_2 for 5 min, at 1 bar and room temperature. Then the appropriate amount of modifier and 100 mg **1** were added, and the stirring was started. Hydrogenation of cyclohexene under standard conditions in isopropanol was 300 times faster than hydrogenation of **1** under standard conditions, in the presence of 1.5 mg CD. This is an indication that hydrogen supply to the active sites is not rate limiting during the enantioselective hydrogenation of **1**.

Conversion and chemoselectivity were determined with a HP 6890 gas chromatograph using a HP-5 column. The chemoselectivity to **2** (Scheme 1) was better than 95%. In the presence of some organic base additives it was not possible to obtain exact conversion and chemoselectivity values by GC analysis, due to overlapping signals. Separation of **1** and **2** by extraction was also not quantitative because of the poor solubility of **1** in apolar solvents.

The enantiomeric excess [ee $= |R(\%) - S(\%)|$] in the product was determined on a Chiralsil-DEX CB column (Chrompack) after methylation. Derivatization was carried out in 3 ml methanol with 10 mg trimethyl orthoformate in the presence of acidic ion-exchange resin (Diaion RCP1 60H) and 0.1 to 0.01 mmol hydrogenation product. The product, after isolation by flash chromatography (silica gel, hexane : ethyl acetate 1 : 1), was identified by NMR and GC-MS analysis and by optical rotation. With CD as chiral modifier the (*S*)-enantiomer formed in excess in all solvents. The reproducibility of the experiments was better than ±1% in ee in most solvents. In acetonitrile the error was somewhat higher due to hydrogenation of the solvent itself, which led to the formation of ethylamines formed mainly during catalyst prereduction.

The amount of water in the reaction solution was determined by NMR. For these experiments the water content of each NMR tube with 1 ml benzene-d_6 was measured and then 0.1 ml of the reaction solution was added. The difference in water signals, normalized by the methyl signal of the reactant, gave the absolute quantity of water. The experiments with basic and acid additives in acetonitrile were carried out with additional 0.5 vol% water (resulting in an increase of the amount of water in the reaction solution from about 0.5 to 2 mol%).

Spectroscopic Analysis

IR spectra were recorded on a Bruker IFS-66 spectrometer at a resolution of 4 cm^{-1} by co-addition of 200 scans. Spectra were recorded in transmission mode using a cell with a path length of 1 mm and equipped with CaF_2 windows. The pure solvent $CDCl_3$ served as the reference.

NMR spectra were recorded on a DPX 300 spectrometer. A solution of 2.5 mg CD in acetone-d_6 was titrated with different amounts of **1**, AcOH or TFA.

Theoretical Calculations

Intermolecular interactions between **1** and CD were studied by quantum chemical calculations using GAUSSIAN98 (22). The B3LYP (23) density functional hybrid method was used together with a 6-31G* basis set. For geometry optimizations all intra- and intermolecular degrees of

freedom were completely relaxed. Several structures were chosen as initial geometries in optimization runs. CD was assumed to be in its Open(3) conformation, which is the most stable when CD is protonated at the quinuclidine N (24).

3. RESULTS

Influence of Catalyst Prereduction

Preliminary experiments revealed that the oxidation state of Pd before contact with the reactant played an important role. The unreduced catalyst containing hydrated palladium oxide afforded low ee in a relatively fast reaction (Table 1). Prehydrogenation of the catalyst in the solvent for 5 min, or prereduction of the dry catalyst in flowing H_2 at 80°C and addition of the catalyst to the reaction mixture under exclusion of air, afforded around 60% ee. Prereduction in a hydrogen flow at temperatures higher or lower than 80°C, or applying longer reduction times, did not improve the ee. The temperature 80°C was chosen to remove the main part of water produced during prereduction. Reoxidizing the metal surface by exposing the catalyst to air lowered the ee considerably but the oxidation–reduction cycles were reversible (Table 1, methods C and D). The lower ee achieved when Pd was in an oxidized state may be connected with the acidic properties of **1** leading to surface restructuring by dissolution of some palladium oxide species and redeposition during hydrogenation. In the following experiments method D was used for catalyst prereduction (standard procedure).

Prereduction in acetonitrile decreased the reaction rate by a factor of 2 compared with prereduction of the dry catalyst (Table 1). The rate deceleration was even more pronounced when applying prereduction times longer than 5 min. This effect is likely due to the hydrogenation of the solvent to ethylamines, as will be discussed later. For comparison, when hydrogenation of **1** was carried out in 2-propanol, the initial reaction rates were almost independent of whether the catalyst prereduction was carried out in the presence or absence of solvent.

TABLE 1

Influence of Catalyst Prereduction with H_2 in Acetonitrile[a]

Prereduction method	Conversion (%)	Time (h)	ee (%)
None	1	0.3	35
(A) In solvent (5 min/26°C)	1	1	64
(B) Dry (1 h/80°C)	1	0.5	58
(C) B, then stored under air (24 h, 26°C)	1	0.5	44
(D) C, then A	1	1	62

[a] Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 1.5 mg CD, 10 ml acetonitrile, 1 bar H_2, 26°C.

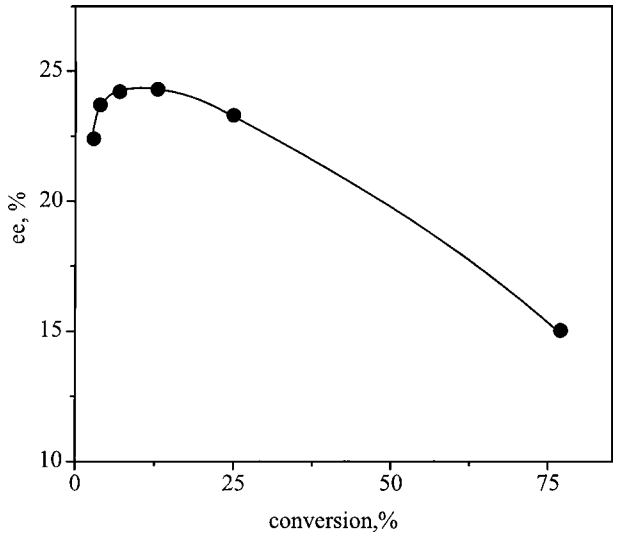


FIG. 1. Influence of conversion on enantioselectivity in the hydrogenation of **1** in acetic acid. Standard conditions, 5 wt% Pd/TiO_2, 3 mg CD, and reaction time 1–24 h.

Solvent Effect

It has been shown before that the ee strongly depends on the reaction time (or conversion of **1**), mainly due to the competing hydrogenation of CD (19, 20). A general dependence of ee on conversion is shown in Fig. 1, using the reaction in acetic acid as an example. The small but significant initial increase in ee is characteristic of experiments carried out with moderate amounts of CD (20). In Fig. 1 the initial amount of CD corresponds to a reactant/modifier molar ratio of 80. The maximum in ee likely corrresponds to the optimum in the reactant/modifier ratio developed with time by the competing hydrogenation of CD and **1**.

The maxima in ee, which were reached in most solvents after around 2 h reaction under standard conditions, are plotted in Fig. 2 as a function of the empirical solvent parameter E_N^T (25). At first sight there is no correlation between ee and solvent polarity, but a closer inspection of the data reveals that in aprotic solvents, ee increases with increasing solvent polarity (up to $E_N^T \cong 0.5$) while an inverse trend is valid for protic polar solvents. Toluene seems to be an exception but this solvent barely dissolves **1** and the very low actual concentration of **1** can distort the result.

Some important features of the solvents applied have been collected in Table 2. Apparently, good ee can be achieved in those solvents that are poor H-bond donors and acceptors; i.e., both Kamlet–Taft solvent parameters α and β (26–28), respectively, are small. Among these solvents acetonitrile is the most polar, characterized by the empirical solvent parameter E_N^T and the relative permittivity ε_r, and the ee is the highest in this solvent. The second best solvent is dimethylformamide, which is strongly polar but also a good H-bond acceptor and the latter feature seems to have a negative impact on ee.

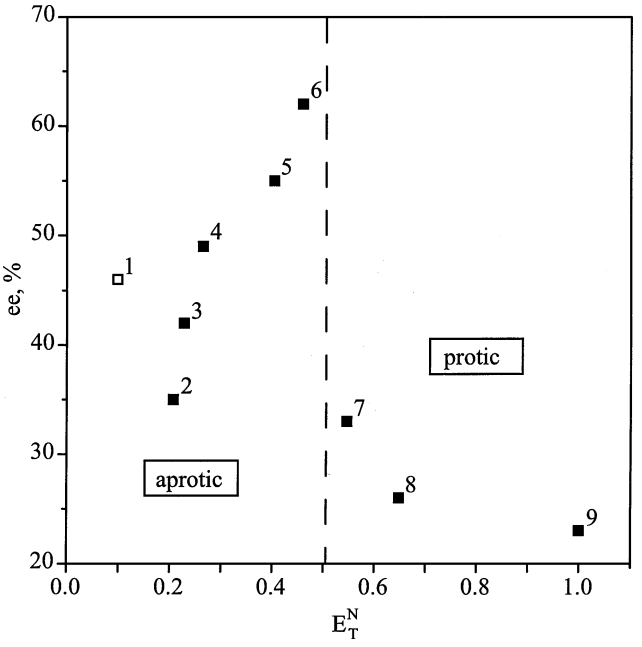


FIG. 2. Variation of ee as a function of solvent polarity characterized by the empirical solvent parameter E_T^N. Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 1.5 mg CD, 10 ml solvent, 24°C, 1 bar, reaction time 2 h. Conversion are given in Table 2. Solvents: (1) toluene, (2) tetrahydrofuran, (3) ethyl acetate, (4) diethylketone, (5) dimethylformamide, (6) acetonitrile, (7) 2-propanol, (8) acetic acid, (9) water.

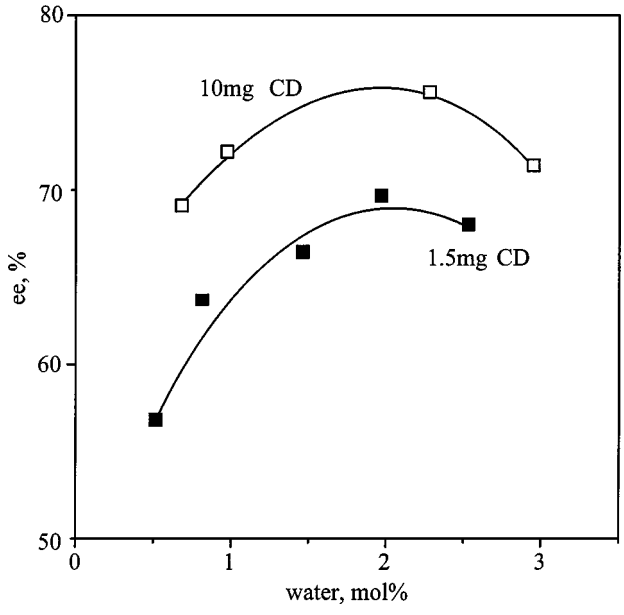


FIG. 3. Hydrogenation in acetonitrile–water solvent mixtures. Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 10 ml acetonitrile, 32°C, 1 bar, reaction time 1 h for 1.5 mg CD and 3 h for 10 mg CD, conversions in the range 3–4% (Table 3).

Role of Water in the Solvent

When searching for the reason for some irreproducibility during preliminary experiments we found that the ee depended on the quality (supplier) of acetonitrile. It turned out that the crucial difference was the water content. The correlation between the water content in the solvent, the amount of modifier, and the ee obtained after 1 h reaction time is illustrated in Fig. 3. Water addition increased ee by up to 14%. The highest ee was obtained in the presence of about 2 mol% water. Above the optimum, ee decreased as water is a poor (strongly polar and protic) solvent for the reaction. The positive effect of water addition is limited to acetonitrile as solvent: in any other solvent, such as 2-propanol, dimethylformamide, and acetic acid, ee barely changed, or rather decreased, by addition of small amounts of water.

The small differences in ee achieved with various catalyst prereduction methods (Table 1) can also be explained by the different amounts of water that formed during the treatment and remained on the catalyst surface. The smallest amount of water is expected when the catalyst is prereduced in a hydrogen flow at 80°C, and this catalyst provided the lowest ee (58%, method B). When the catalyst containing hydrated palladium oxide was hydrogenated *in situ* at room temperature according to method A, the co-product water mainly remained in the slurry. This method led to the largest amount of water in the system and also to the highest ee of 64%.

TABLE 2

Influence of Solvent Properties on Enantioselectivity[a]

Solvent	E_T^N	ε_r	α (Taft)	β (Taft)	Conversion (%)	ee (%)
Toluene	0.099	2.38	0	0.0	1	46
Tetrahydrofuran	0.207	7.58	0	0.55	4	35
Ethyl acetate	0.268	6.02	0	0.45	6	42
Diethylketone	0.265	17	0.08	0.48	6	49
Dimethylformamide	0.404	36.71	0	0.69	4	55
Acetonitrile	0.460	35.94	0.15	0.31	2	62
Isopropanol	0.546	19.92	0.78	0.95	8	33
Acetic acid	0.648	6.17	1.11	—	10	25
Water	1	78.3	1.13	0.18	12	23

[a] Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 1.5 mg CD, 10 ml solvent, 1 bar, 26°C, reaction time 2 h.

Evidence for Competing Hydrogenation of Acetonitrile

GC-MS analysis revealed that the positive effect of water on enantioselection is connected to the slow hydrogenation of the solvent acetonitrile during reduction of **1**. The main product was triethylamine, and even traces of acetaldehyde, formed by hydrolysis of the intermediate aldimine (29), could be detected. The amount of Et_3N was small but approximately equivalent to that of CD on a molar basis. Addition of water decreased the amount of Et_3N produced during reaction by a factor of up to 2.5 (Table 3).

TABLE 3

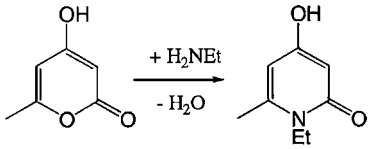
Effect of Water on the Hydrogenation of Acetonitrile during Reduction of 1[a]

Water content in acetonitrile (mol%)	Conversion (%)	ee (%)	Et_3N/CD (mol/mol)
0.6	3	71	1
2	4	78	0.4

[a] Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 10 mg CD, 10 ml acetonitrile, 1 bar, 32°C, reaction time 3 h.

In control experiments Et_2NH and Et_3N were added to the reaction mixture. Table 4 shows the results when applying larger amounts of amines (1 eq related to **1**). The ee decreased considerably in the presence of amines in acetonitrile (and also in acetic acid). The reaction rate was lower by a factor of about 10 compared with the reactions without amine additives, based on a semiquantitative estimation of product formation by GC analysis. The influence of $EtNH_2$ was also investigated, but the results are not interpretable unambiguously. Under the reaction conditions monoalkylamines easily form the corresponding pyridone **4** with the reactant **1**, as shown in Scheme 2 (30). The pyridone **4** itself is inert to hydrogenation even under rigorous conditions (high pressure), with or without CD.

The role of the basic character of ethylamines in the negative impact on ee is confirmed by addition of a strong acid, trifluoroacetic acid [$pK_a = 0.3$ (21)] to the reaction mixture before hydrogenation. Enhancement of ee by 5% in the presence of 0.5 eq trifluoroacetic acid is attributed to the neutralization of ethylamines formed by hydrogenation of the solvent acetonitrile (Table 5). When the time of catalyst prereduction was increased from 5 to 10 min, the optimum amount of trifluoroacetic acid also doubled (trifluoroacetic acid/CD = 1 eq). A feasible explanation is that small amounts of the strong acid improve ee by neutralizing the ethylamine by-products. This interpretation is in accordance with our former observation (19) that the highest ee of 85% in the hydrogenation of **1** was achieved using CD hydrochloride, instead of CD.



1 **4**

SCHEME 2

Effect of a Strong Base Additive

The negative impact of Et_2NH and Et_3N on enantioselectivity (Table 4) may be attributed to competition between these amines and the quinuclidine N of CD during enantiodifferentiation. To confirm this assumption we applied an organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene [DBU, $pK_a = 23.9$ (31)], which is much stronger than the quinuclidine N [$pK_a = 10.0$ (21)]. The enantioselectivities obtained in the presence of increasing amounts of DBU are shown in Fig. 4. The ee dropped almost linearly from about 80% without additive to close to zero with 1 eq DBU related to the reactant. Similar to the experiments with ethylamines shown in Table 4, the reaction rate decreased markedly in the presence of 1 eq DBU.

NMR Experiments

The acid–base-type interactions between CD and **1**, and some other acids, have been studied by NMR. Most of the hydrogen signals of CD are shifted when an acid is added. This shift is due mainly to protonation of the quinuclidine nitrogen of CD and the resulting rotation around the $C^{4'}$–C^9 and C^9–C^8 bonds (Scheme 3) (24). Additional steric and ionic interactions are also probable which render the quantitative interpretation ambiguous. Figure 5 shows the shifts of a representative aromatic and a nonaromatic hydrogen signal of CD during titration with trifluoroacetic acid, acetic acid, and **1** in acetone. The shift of

TABLE 4

Influence of Amine Additives on Enantioselectivity[a]

Amine	pK_a	ee (%) Acetonitrile[b]	ee (%) Acetic acid
None	—	74	30
Diethylamine	11.1	65	24
Triethylamine	10.6	58	26

[a] Conditions: 100 mg (0.8 mmol) **1**, 0.8 mmol basic additive, 20 mg 5 wt% Pd/TiO_2 (5 wt% Pd/Al_2O_3 in AcOH), 5 mg CD, 10 ml solvent, 1 bar, 26°C, reaction time 2 h.

[b] Containing 2 mol% water.

TABLE 5

Effect of Trifluoroacetic Acid (TFA) on Enantioselectivity in Acetonitrile[a]

Catalyst prereduction (min)	TFA/CD (mol/mol)	Conversion (%)	ee (%)
5	0	2	76
5	0.5	2	81
10	0	1	74
10	1	1	80

[a] Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 10 mg CD, 10 ml acetonitrile containing 2 mol% water, 32°C, 1 bar, reaction time 3 h.

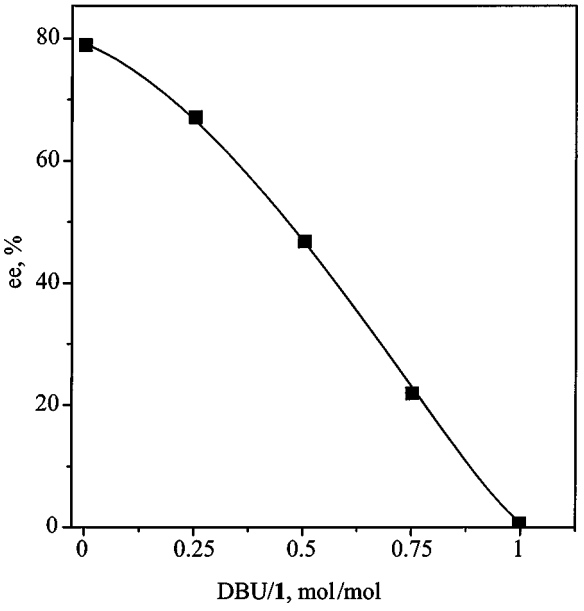


FIG. 4. Influence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) additive on enantioselectivity in acetonitrile. Conditions: 100 mg **1**, 20 mg 5 wt% Pd/TiO_2, 3 mg CD, 10 ml acetonitrile, 2 mol% water, 26°C, 1 bar, reaction time 2 h.

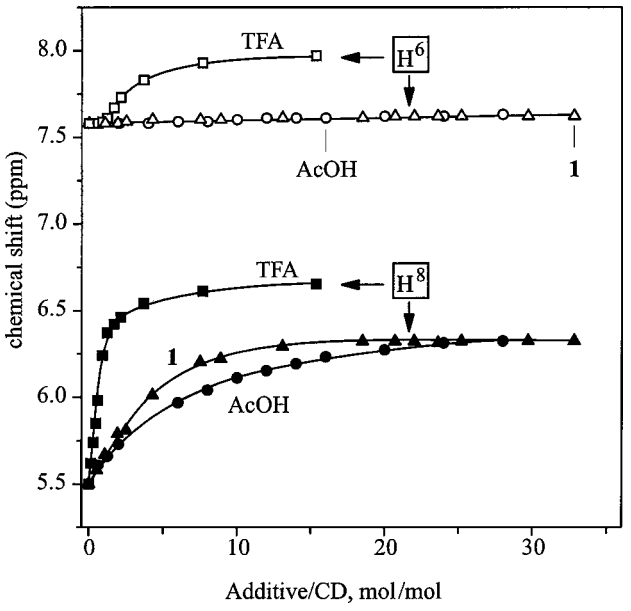
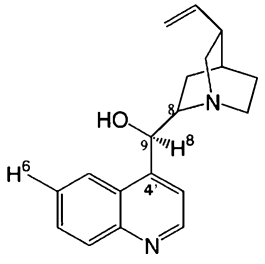


FIG. 5. Shift of the representative NMR signals H^6 and H^8 of CD (Scheme 3) during titration with trifluoroacetic acid (TFA), acetic acid (AcOH), and **1** in acetone; 2.5 mg CD, 1 ml acetone-d_6.

the H^8 (nonaromatic) signal is due to protonation of the quinuclidine N atom. Complete protonation requires 14 eq **1** or 24 eq acetic acid. Interestingly, in water the two acids have almost identical acid strength [$pK_a \cong 4.7$ (5)] but in acetone **1** is considerably stronger. With 1 eq trifluoroacetic acid the shift of the H^8 signal is similar to the value of the plateau reached with acetic acid and **1**. The further shift obtained by increasing the trifluoroacetic acid/CD ratio is attributed mainly to protonation of the quinoline N. The same conclusion can be drawn from analysis of other nonaromatic H signals.

The H^6 signal is shown as an example of the aromatic protons. A considerable shift is achieved by addition of a second equivalent of trifluoroacetic acid. This shift is attributed to protonation of the quinoline N, which occurs after full protonation of the more basic quinuclidine N. Protonation of the aromatic N by **1** or acetic acid is barely detectable even above an acid/CD molar ratio of 30.



SCHEME 3. Designation of hydrogen and carbon atoms used in NMR studies (cf. Fig. 5).

We can conclude that both **1** and acetic acid protonate the quinuclidine N of CD when the acid is present in large excess but cannot protonate to a significant extent the quinoline N of CD. These results are in agreement with our former observations by NMR and FTIR spectroscopy concerning the CD–acetic acid interaction in polar and apolar solvents (24, 33). Contrary to our observations it has been proposed very recently, without showing details of the NMR analysis, that protonation of the quinuclidine N of CD is not complete in acetic acid, and trifluoroacetic acid is not sufficiently strong for double protonation of CD (34).

IR Study of Reactant–Modifier Interaction

Figure 6 shows the IR spectra of the ν(O–H) region for mixtures of **1** and CD in $CDCl_3$. Addition of **1** in increasing concentrations results in considerable development of a broadband in the range 3500 cm^{-1} to about 1800 cm^{-1}. Such broad absorption bands are associated with proton polarization (35). In our case the appearance of this intensive band indicates the formation of $N–H^+\cdots O$ hydrogen bonds between CD and **1**, and thus confirms the protonation of CD by **1** observed by NMR (Fig. 5). The spectra are very similar to those found for solutions of CD and acetic acid (32).

Additional information on the interaction between CD and **1** can be extracted from the behavior of the free (i.e., not hydrogen bonded) OH group of CD (Fig. 6). The intensity of the ν(O–H) signals at around 3600 cm^{-1} decreases markedly with increasing concentration of **1**. This is a clear indication that on protonation of CD by **1** the OH group

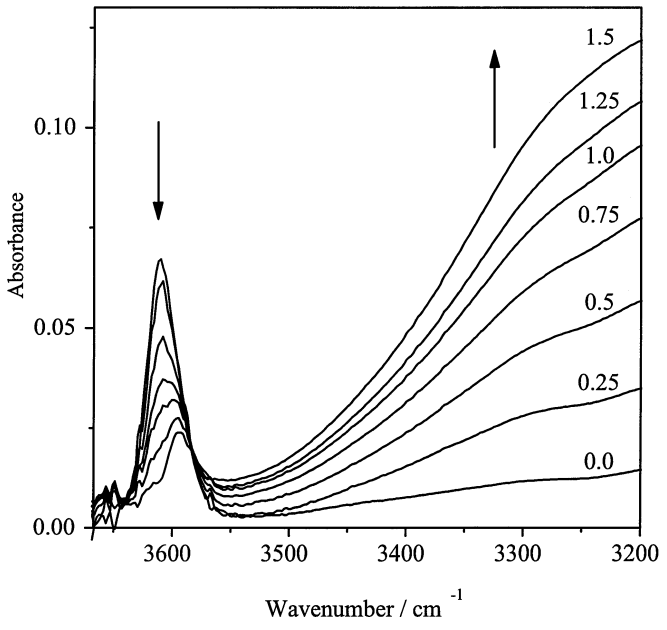


FIG. 6. IR spectra of $CDCl_3$ solutions of **1**–CD mixtures. The CD concentration was 0.01 M in all cases. The **1**:CD ratios are 0, 0.25, 0.5, 0.75, 1.0, 1.25, and 1.5. The arrows indicate the development of the signals on increasing the **1**:CD ratio.

of CD is also involved in the reactant–modifier interaction via hydrogen bonding. At an equimolar ratio of CD and **1** a considerable fraction of OH groups of CD are still not involved in hydrogen bonding, but in the catalytic reactions (Figs. 1, 3, and 4) the reactant was present in a large excess (**1**:CD molar ratio always higher than 70).

4. DISCUSSION

Acid–Base-Type Interactions

There are some important acid–base-type interactions that can influence the rate and enantioselectivity in the hydrogenation of **1** over cinchona-modified Pd. Analysis of these interactions is crucial to understanding the nature of substrate–modifier interaction and the enantiodifferentiation process. Important findings are addressed in sequence.

(a) The ee changes markedly depending on whether Pd is in an oxidized or reduced state before contacting with the (acidic) reactant **1** (Table 1). When **1** was added to an oxidized Pd catalyst before replacing the atmosphere to hydrogen, the selectivity was only 35–44%, depending on the extent of oxidation of Pd, while prereduced Pd afforded 62–64% ee under otherwise identical conditions. A possible explanation is the partial dissolution of oxidized Pd by the good chelating agent **1**, and the subsequent redeposition of metallic Pd at the early stage of the hydrogenation reaction. A deeper understanding of this structure sensitivity may offer the possibility of improving enantioselectivity in the hydrogenation of **1**. The observed effect should be distinguished from the structure sensitivity of the Pt–cinchona system in the enantioselective hydrogenation of activated ketones. In the latter reactions only prehydrogenation at elevated temperature, typically at 400°C, was effective in enhancing the ee; prereduction at ambient temperature was inefficient (36).

(b) We have shown earlier that hydrogenation of **1** is complicated by the competing hydrogenation of the aromatic ring system of CD, leading to successive loss of enantiodifferentiation (19, 20). In the present work we uncovered a further interfering side reaction: hydrogenation of the best solvent acetonitrile to ethylamines, mainly to Et_3N (Table 3). Ethylamines have basicities comparable to that of quinuclidine ($pK_a = 10.0$); thus they can compete with the modifier in interacting with **1** in the enantiodiscriminating step and diminish the ee (Table 4). Furthermore, under reaction conditions $EtNH_2$ can easily condense with **1** to form the corresponding pyridone **4** (Scheme 2). Compound **4** is not hydrogenated by the catalyst but it can block some active sites and contribute to the observed strong catalyst deactivation (19, 20). A consequence of this observation is that good ee can be achieved only when the ethylamines are neutralized. This is why the highest ee of 85% was achieved using cinchonidine hydrochloride (19), instead of CD (conditions: 26 mg CD · HCl, 40 mg Pd/TiO_2, in acetonitrile containing about 2 mol% water, at 1 bar and 31°C).

(c) The study of solvent effect (Fig. 2 and Table 2) showed that polar solvents favor interactions leading to enantio-differentiation, but strong hydrogen bond donors and acceptors (acidic and basic solvents) should be avoided. The highest ee was achieved in acetonitrile, a solvent that best matches these requirements. Apparently, acidic and basic solvents disturb the (acid–base-type) interactions between modifier and reactant.

(d) The negative impact of strong base (DBU) additive on ee (Fig. 4) suggests that the interaction between the modifier as a base and the reactant as an acid is crucial to enantio-discrimination. When the reactant is completely deprotonated by DBU, no interaction with CD is possible.

(e) NMR analysis demonstrated that there is an acid–base-type interaction between the quinuclidine N of CD and the acidic OH function of **1**. The same conclusion can be drawn from the IR study. The broad absorption band appearing during titration of CD with **1** is unambiguously attributed to an $N–H^+\cdots O$ hydrogen bond. Hence, protonation of quinuclidine N by **1** should be a crucial part of the reactant–modifier interaction.

(f) IR analysis provided a strong indication of a second type of interaction between reactant and modifier involving the OH group of CD. This interaction, similarly to the protonation of the quinuclidine N of CD by **1**, is dominant at **1**:CD > 1 molar ratios, a condition that is always fulfilled during the catalytic hydrogenation reactions.

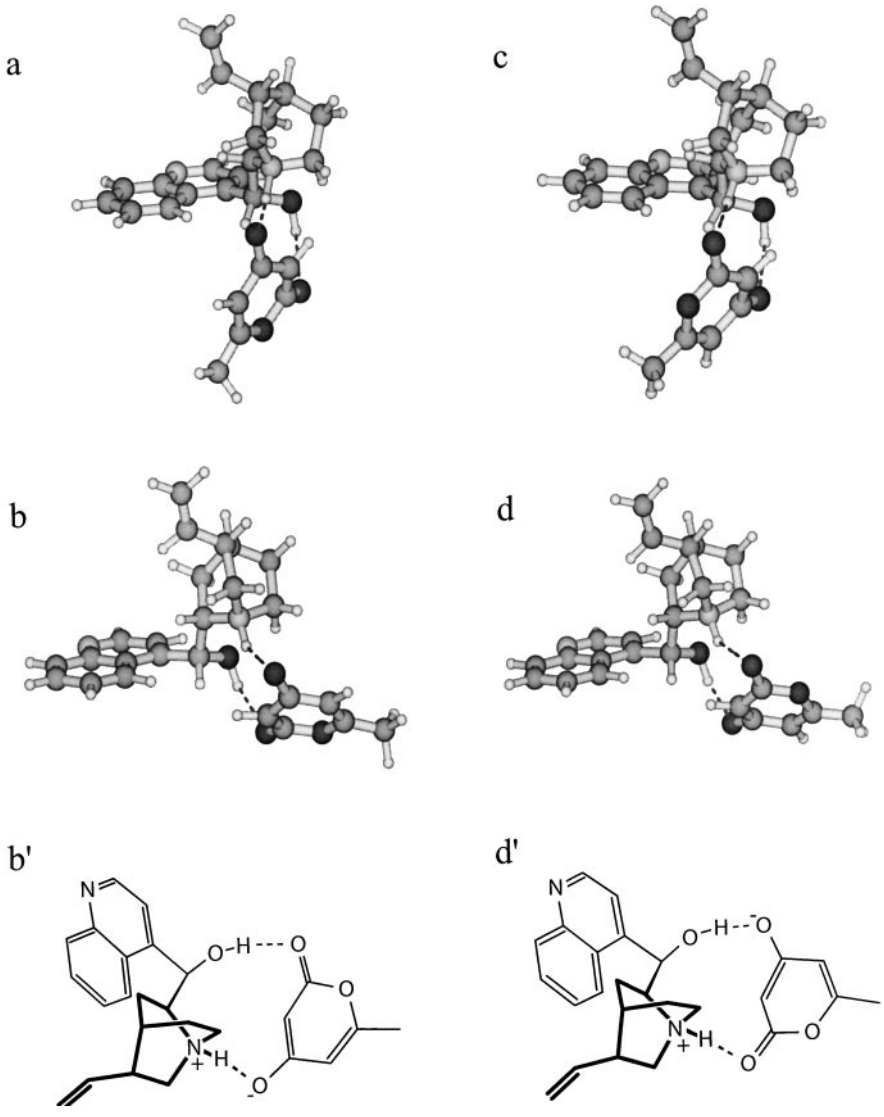


FIG. 7. Calculated structures of possible **1**–CD complexes. All structures were fully optimized at the B3LYP level using a 6-31G* basis set. The binding energy with respect to the separated neutral molecules is calculated as 9.5 kcal/mol for complex **a**. Structures **b**, **c**, and **d** are less stable by 3.5, 1.6, and 4.8 kcal/mol, respectively. Illustrations **b**′ and **d**′ show the corresponding structures **b** and **d**, respectively, from above assuming the metal surface being below.

Mechanistic Model for Enantiodifferentiation

On the basis of the above observations we propose the model shown in Fig. 7b as a working hypothesis for the enantioselective hydrogenation of **1** over the Pd–CD system. There are two H-bond interactions between CD and **1**. The quinuclidine N is connected to the OH group of **1** (medium strong base–medium strong acid interaction), and the C^9–OH group of CD is bound to the carbonyl O of **1** (weak acid–weak base interaction). NMR and FTIR spectroscopic analysis supports the suggested H-bond interactions. The model is in good agreement with the catalytic results obtained in the presence of DBU, and it can rationalize the unusual solvent effect: the poor enantioselectivity achieved in good H-bond donor or acceptor solvents.

To confirm the feasibility of the suggested acid–base-type interactions between CD and **1** we have performed quantum chemical calculations. Figure 7 shows four stable complexes identified as local maxima on the potential energy surface. In complexes a and b the O–H group of CD binds to the carbonyl O of **1**, and the N–H group of (protonated) CD to the deprotonated hydroxyl group of **1**. The structure is also plotted as a conventional formula (top view) in Fig. 7b′. Addition of hydrogen atoms from "below" (from the metal surface) leads to the dominant formation of the (*S*)-enantiomer, in agreement with experimental observations. Exchange of the two hydrogen bond acceptor groups

(O–H group of CD binds to the deprotonated hydroxyl group of **1**, and the N–H group to the carbonyl group of **1**) leads to complexes c and d (Fig. 7d′). Complexes a and b differ by the relative arrangement of the two planes defined by the quinoline part of CD and the semiaromatic ring of **1**. This arrangement is dictated largely by repulsive interactions between H in the C^3 position of **1** and the quinuclidine part of CD. According to the calculations, the most stable complex is **a** with a binding energy of 9.5 kcal/mol with respect to the separated neutral molecules. Exchange of the two hydrogen bond acceptor groups leads to destabilization by 1.6 kcal/mol (complex **c**).

In both complexes **a** and **c** the quinoline ring of CD and the ring plane of **1** are oriented nearly perpendicular to each other. For these complexes simultaneous adsorption of both CD and **1** on a (ideal) flat Pd surface is thus not possible. Hydrogenation of complexes **a** and **c** would require the presence of special steps or terraces on the Pd particles, which can accommodate the rather bulky complexes, but the expected concentration of such structures on a moderately dispersed Pd is very low. Complex **b** is less stable by 3.5 kcal/mol than complex **a** but can more easily adsorb on an approximately flat Pd surface. Analogously, complex **d** is less stable than **c** by 3.2 kcal/mol. Note that the complexes that would result in (*S*)-product on hydrogenation of **1** (**a** and **b**) are calculated to be more stable by 1.3–1.6 kcal/mol than the respective complexes yielding (*R*)-product (**c** and **d**).

Hence, *ab initio* calculations confirm the feasibility of the suggested complex between CD and **1** involving both N-H···O and C^9–O–H···O hydrogen bonds, and rationalize the formation of (*S*)–product as the major enantiomer in good excess (up to 85% ee).

5. CONCLUSIONS

The Pd-catalyzed hydrogenation of 4-hydroxy-6-methyl-2-pyrone afforded 77–85% excess to the (*S*)-enantiomer of 4-hydroxy-6-methyl-5,6-dihydro-2-pyrone, in the presence of CD or CD hydrochloride (19) as chiral modifier. The rate and enantioselectivity of the reaction are strongly affected by various acid–base-type interactions. These interactions are crucial to interpreting the unusual solvent effect, the role of catalyst prereduction under mild conditions, the negative impact of the competing hydrogenation of the solvent acetonitrile, and the selectivity enhancement by trace amounts of a strong acid. The suggested mechanistic model can serve as a basis for future studies of this important reaction.

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