Journal of Catalysis **187,** 160–166 (1999)
Article ID jcat.1999.2584, available online at http://www.idealibrary.com on IDEAL®

Enantioselective Hydrogenation of α,β-Unsaturated Carboxylic Acids over Cinchonidine Modified Palladium: Nature of Modifier–Reactant Interaction

K. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat, and A. Baiker[1]

Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich, Switzerland

Received March 8, 1999; revised June 4, 1999; accepted June 4, 1999

The mechanism of enantiodifferentiation in the hydrogenation of alkenoic acids over cinchona-modified Pd has been investigated using the tiglic acid → 2-methyl-butanoic acid transformation as test reaction. Application of simple derivatives of cinchonidine, modified at the (C-9)–OH and/or the quinuclidine nitrogen, proved that both functional groups are involved in the enantiodiscriminating step. Addition of a strong base (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) to tiglic acid prior to hydrogenation revealed that one cinchonidine molecule interacts with a dimer of tiglic acid on the metal surface. *Ab initio* **calculations corroborate the existence of an energetically favored acid dimer–cinchonidine intermediate stabilized by hydrogen bonding, involving both the OH and the quinuclidine nitrogen of cinchonidine.**

Key Words: α,β**-unsaturated carboxylic acid; dimer; cinchonidine derivatives; hydrogenation; palladium-on-alumina;** *ab initio* **calculation.**

INTRODUCTION

Asymmetric catalysis has made enormous progress during the past decades fostered by a growing demand on chiral substances. An important target of research has been the enantioselective hydrogenation of α,β-unsaturated acids, affording useful building blocks for the synthesis of nonsteroidal anti-inflammatory agents (1, 2). Transition metal complexes with chiral ligands are the most powerful catalysts for the production of optically active carboxylic acids. In particular ruthenium(II) complexes with chiral diphosphine BINAP ligands received much attention (3). The development of new atropisomeric bis(triarylphosphine) ligands (H_8-BINAP) provided outstanding catalysts affording enantiomeric excess (ee) over 97% (4, 5).

Solid catalyzed enantioselective hydrogenation would be, however, preferable due to its technical and economic advantages (6). Presently, supported Pd catalysts in the presence of cinchona alkaloids as the source of chiral induction are the only useful solid catalysts for the enantioselective hydrogenation of alkenoic acids (7). The best enantioselectivities are around 50% for alkenoic acids (8) and over 70% for an aryl substituted derivative (9). Pd/silica modified by chiral silyl ethers (10) and Raney Ni modified by tartaric acid (11) were shown to be far less effective catalysts.

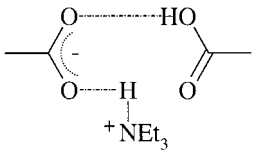
The advances made so far have been based exclusively on "trial and error" approaches. Understanding of the reaction mechanism could put the development of new and more efficient catalysts on a more rational basis. To date, only a few papers have reported on the possible interactions between reactant and chiral modifier, both adsorbed on the metal surface. We proposed first (12) that, analogous to the well studied triethylamine–acetic acid interaction (Scheme 1 (13)), the alkenoic acid dimer protonates the quinuclidine nitrogen of cinchonidine (CD) in apolar medium. This proposal could rationalize the observed loss of ee in polar medium, due to the shift of dimer–monomer equilibrium to the monomer side. Independently, Wells and coworkers (14) proposed an acid–base interaction between an alkenoic acid and a CD molecule. This 1 : 1 type interaction has been supported by simple calculations.

Recently, we provided spectroscopic evidence for the presence of alkenoic acids as dimers in apolar solutions (12), and we assumed that the dimer structure is preserved on the Pd surface during the enantiodifferentiating step. On the basis of this 2 : 1 reactant–modifier interaction we proposed a generally applicable empirical rule to predict the absolute configuration of the major enantiomer of the product. Besides, XRD analysis of a CD–α,β-unsaturated acid salt indicated a chain-like structure, stabilized by a hydrogen bonded network involving both amino and alcohol functional groups of the modifier. However, the possible role of the OH group in the enantiodiscriminating step remained unresolved.

Very recently, Nitta and Shibata (15) proposed that both the OH functional group and the quinuclidine nitrogen atom of cinchonidine are involved in hydrogen bonding with α-phenylcinnamic acid via 1 : 1 interaction. Note that in the strongly polar medium, used under optimized

[1] To whom correspondence should be addressed.

0021-9517/99 $30.00



SCHEME 1. Structure of triethylamine–acetic acid dimer species in apolar solvents (13).

conditions, α-phenylcinnamic acid may dominantly be present as monomer due to stabilization by substrate–solvent interactions. However, it is unclear whether in the enantiodiscriminating step CD interacts with a monomer or a dimer of acid on the metal surface.

Here we report results from our continued effort to understand the mechanism of enantiodifferentiation in the hydrogenation of alkenoic acids. Several CD derivatives, modified at the quinuclidine nitrogen and/or at the (C-9)–OH, have been synthesized and tested in the hydrogenation of *trans*-2-methyl-2-butenoic acid (tiglic acid). Beside the catalytic experiments, *ab initio* calculations were performed to confirm the possible structure of the diastereomeric transition complex formed between CD and the reactant carboxylic acid.

EXPERIMENTAL

Tiglic acid (98%, Aldrich), DBU (1,8-diazabicyclo[5.4.0] undec-7-ene, >99%, Fluka), and toluene (99.7%, Riedel-deHaën) were used as received. Tetrahydrofurane (>99.5%, Scharlau) and *n*-pentane (>99.5%, Fluka) were purified over sodium wire and distilled prior to use.

Cinchonidine Derivatives

Cinchonidine hydrochloride (**1**, Sigma) and *N*-benzyl cinchonidine chloride (**4**, Fluka) were used as received. The other chiral modifiers were readily prepared from CD. These compounds were identified by elemental analysis, NMR, and mass spectroscopy. The results of the spectroscopic methods are not shown here. ^{1}H NMR spectra were recorded on a Bruker Advance DPX 300 operating at 300 and 75 MHz. Mass spectra were recorded on Hitachi-Perkin-Elmer RMU-6M for EI; VG-ZAB2-SEQ for FAB in 3-nitrobenzyl alcohol matrix (3-NOBA).

*Cinchonidine hydrobromide (**2**).* CD (1.18 g, 4 mmol) was dissolved in methylene chloride (50 ml) and cooled in an ice bath. Hydrobromic acid (48%, 0.67 g, 4 mmol) was added dropwise with continuous stirring and the resulting mixture was stirred for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2 : MeOH = 10 : 1) to afford **2** as white colorless crystal (1.36 g, 91%). Anal. Calcd for $C_{19}H_{23}BrN_2O$ (**2**): C, 60.8; H, 6.2; N, 7.5. Found: C, 60,7; H, 6.2; N, 7.4.

*N-allyl cinchonidine chloride (**3**) and N-benzyl cinchonidine bromide (**5**): General procedure.* Allyl chloride (0.60 g, 8 mmol) (benzyl bromide 0.68 g, 4 mmol) was added dropwise to a solution of CD (1.18 g, 4 mmol) in THF (50 ml) under continuous stirring. After refluxing the mixture for 1 week (12 h for benzyl bromide) the solvent was evaporated *in vacuo* and the crude solid was purified by flash chromatography using CH_2Cl_2 : MeOH = 7 : 1 as eluent (CH_2Cl_2 : MeOH = 18 : 1 for **5**) (**3**, 0.20 g, 13%; **5**, 1.4 g, 75%). Anal. Calcd for $C_{22}H_{27}ClN_2O$ (**3**): C, 71.2; H, 7.3; N, 7.6. Found: C, 70.7; H, 7.6; N, 7.1. Anal. Calcd for $C_{26}H_{29}BrN_2O$ (**5**): C, 67.1; H, 6.3; N, 6.0. Found: C, 66.7; H, 6.4; N, 5.9.

*N-methyl cinchonidine chloride (**6**).* CD (6 g, 20.4 mmol) was dissolved in methanol (110 ml), and methyl iodide (5 g, 35.6 mmol) in methanol (50 ml) was added dropwise under an argon atmosphere, at room temperature with continuous stirring and the resulting mixture was stirred for 24 h. The solvent was evaporated and the residue was recrystallized twice from ethyl acetate : methanol = 5 : 8 to afford *N*-methyl cinchonidine iodide as white colorless crystal (6.75 g, 76%). Ion exchange using 1.3 eq of AgCl (Fluka) in MeOH : water = 1 : 1 afforded **6**. The modifier contained 8.5% iodide on the basis of elementary analysis. Anal. Calcd for $C_{20}H_{25}ClN_2O$ (**6**): C, 69.7; H, 7.3; N, 8.1. Found: C, 68.4; H, 7.52; N, 8.0.

*N,O-dibenzyl- (**7**), N,O-diallyl- (**8**), and N-benzyl O-allyl cinchonidine bromide (**9**): General procedure.* Modifier **5** (0.93 g, 2 mmol) (*N*-allyl cinchonidine bromide for **8**, which was synthesized by the same method as **3** using allyl bromide) was dissolved in methylene chloride (20 ml). Benzyl or allyl bromide (6 mmol) was then added to the solution followed by 50% aqueous NaOH (3.2 g, 40 mmol). After 4 h reaction time the organic phase was separated and the aqueous phase was washed with methylene chloride (3 × 10 ml). The combined methylene chloride extract was dried over $MgSO_4$. The solvent was evaporated and the crude product was suspended in ether (30 ml), stirred for an additional 4 h, and filtered. Purification by column chromatography (CH_2Cl_2 : MeOH = 10 : 1) afforded the title compounds (**7**, 0.64 g, 58%; **8**, 0.65 g, 71%; **9**, 0.599 g, 61%). Anal. Calcd for $C_{33}H_{35}BrN_2O$ (**7**): C, 71.4; H, 6.4; N, 5.04. Found: C, 69.2; H, 6.2; N, 5.0. Anal. Calcd for $C_{25}H_{31}BrN_2O$ (**8**): C, 65.9; H, 6.9; N, 6.2. Found: C, 66.2; H, 7.0; N, 6.4. Anal. Calcd for $C_{29}H_{33}BrN_2O$ (**9**): C, 68.9; H, 6.6; N, 5.5. Found: C, 67.2; H, 6.8; N, 5.7.

*9-Deoxy cinchonidine (**10**).* 9-Deoxy cinchonidine was prepared according to a previously reported method (16). CD (3.00 g, 0.01 mol) was dissolved in a 2-propanol–2 M aqueous HCl mixture (700 ml, 23% v/v for HCl) and irradiated with a medium pressure UV lamp equipped with a Pyrex filter and cooled by tap water. The solution was flushed with nitrogen for 20–30 min prior to and during

irradiation. After 24 h stirring the solvent was evaporated under reduced pressure. The residue was treated with 6 M aqueous NaOH and then extracted with chloroform and purified by flash chromatography (*n*-hexane : acetone : diethylamine = 30 : 18 : 1) to afford **11** as an oily product (320 mg, 11.5%). Anal. Calcd for $C_{19}H_{22}N_2$ (**10**): C, 81.9; H, 7.9; N, 10.0. Found: C, 80.0; H, 7.8; N, 10.2.

*O-methyl cinchonidine (**11**).* Under nitrogen atmosphere, 0.53 g KH (0.013 mol, 20% suspended in oil) was washed three times with *n*-pentane, suspended in dry THF (40 ml), and cooled to 0°C. CD (3.24 g, 0.011 mol) was added to the slurry in small portions. The reaction mixture was stirred for 30 min at 0°C and then 30 min at 50°C. To the cooled reaction mixture methyl iodide (2.41 g, 0.017 mol) was added gradually and stirred for 1 h at room temperature. The mixture was then cooled to 0°C and carefully quenched with 50 ml water. The aqueous phase was extracted with ethyl acetate (3 × 15 ml). The organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent under reduced pressure, the residue was purified by flash chromatography using a *n*-hexane : acetone : diethylamine = 40 : 18 : 1 solvent mixture. Recrystallization from *n*-hexane gave **11** as colorless crystal (2.0 g, 65%). Anal. Calcd for $C_{20}H_{24}N_2O$ (**11**): C, 77.9; H, 7.8; N, 9.0. Found: C, 77.7; H, 8.1; N, 9.3.

Hydrogenation of Tiglic Acid

The reactions were performed in a 100-ml stainless steel autoclave equipped with magnetic mixing. A 50-ml glass inlet with a Teflon cap and stirrer was used to keep the system inert. Hydrogen consumption was followed by a constant pressure–constant volume apparatus (Büchi Pressflow Gas Controller). A 5 wt% Pd/Al_2O_3 catalyst (Engelhard 40692, D = 0.21 as determined by TEM, BET = 200 $m^2\ g^{-1}$) was used for hydrogenations. In reactions using CD derivatives the conditions were as follows: 500 mg tiglic acid, 20 mg catalyst (without pretreatment), 2 mg modifier, 15 ml toluene, 15°C, and 40 bar hydrogen pressure.

The standard conditions for experiments with base additive were as follows: 100 mg tiglic acid, 10 mg catalyst, 3 mg CD, 14 ml toluene, 15°C, and 60 bar. The catalyst was reduced in the presence of CD in 12 ml toluene at 30 bar hydrogen pressure in the autoclave, resulting in the formation of 10,11-dihydrocinchonidine. Then tiglic acid and the appropriate amount of base (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) were added in 2 ml toluene. After reaction the catalyst was filtered off, the filtrate acidified with 5 M aqueous HCl and the organic layer analyzed.

The reaction mixtures were analyzed by gas chromatography using a chiral column coated with CP-cyclodextrin-2,3,6-M-19 (Chrompack). Enantiomeric excess is expressed as ee (%) = 100 × |(R − S)|/(R + S), with a reproducibility of ±0.5%.

Theoretical Calculations

The intermolecular interaction between CD and acrylic acid (the simplest model of an α,β-unsaturated carboxylic acid) has been investigated by *ab initio* calculations at Hartree Fock level of theory using a 4-31G standard basis set. Complete geometry optimizations were performed by relaxing all intra- and intermolecular degrees of freedom. To mimic flat adsorption of the acid as well as the quinoline moiety of CD on the Pd surface, some restricted calculations were performed where the quinoline moiety and the acid were kept coplanar relaxing all other degrees of freedom. For the calculations only CD protonated at the quinuclidine nitrogen was considered. The calculations were performed using GAUSSIAN94 (17) on a HP/Convex Exemplar SPP2000/X-32 and a HP Model 735 workstation.

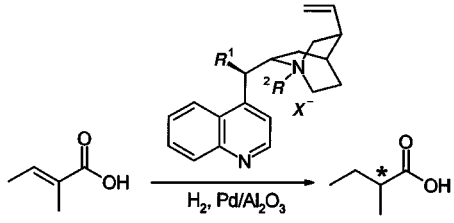
RESULTS

Hydrogenation of Tiglic Acid over Pd/Alumina, Modified by CD Derivatives

The efficiency of CD and its derivatives as chiral modifiers has been tested in the enantioselective hydrogenation of tiglic acid to 2-methyl-2-butanoic acid over a 5 wt% Pd/alumina catalyst. Conversions and enantioselectivities achieved in 1.5 h are shown in Table 1. In this time period full conversion could not be reached when the modifier contained a halide anion (**1**–**9**). Modifiers with bromide anion had a stronger inhibitory effect on the catalyst than the

TABLE 1

Conversion and Enantioselectivity in the Hydrogenation of Tiglic Acid over 5 wt% Pd/Alumina Modified with CD Derivatives

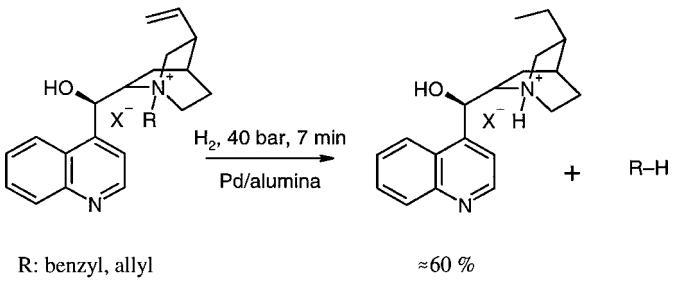


Modifier	R^1	R^2	X^-	Conversion (%)	ee (%) (*S*)
CD	OH	—	—	100	38
1	OH	H	Cl	47	26
2	OH	H	Br	21	29
3	OH	Allyl	Cl	29	17
4	OH	Benzyl	Cl	40	18
5	OH	Benzyl	Br	23	24
6	OH	CH_3	Cl	35	1
7	*O*-benzyl	Benzyl	Br	27	1.5
8	*O*-allyl	Allyl	Br	25	2
9	*O*-allyl	Benzyl	Br	7	2
10	—	—	—	100	1
11	OCH_3	—	—	100	2

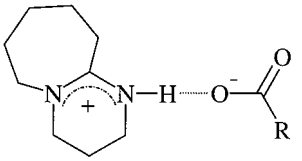
chloride salts. Incomplete reactions in the presence of different CD halide salts (**1**–**9**) can be explained by the general observation that strongly adsorbing halogen ions (adsorption strength: $I^- > Br^- > Cl^- > F^-$) can result in deactivation of platinum metal catalysts (18).

Beside the poisoning effect of these modifiers, also the enantioselectivities were lower compared to that induced by CD. When applying CD-hydrohalide salts (**1** and **2**) the ee decreased by approximately 10%. Modifiers (**3**–**5**), in which the quinuclidine nitrogen was quaternerized by an allyl or a benzyl group, still induced a moderate ee. However, the N-methylated derivative (**6**) was inefficient as a chiral modifier for Pd. Similar results were obtained when either a benzyl or an allyl group was attached to the quinuclidine nitrogen as well as to the alcoholic OH of CD (**7**–**9**). Derivatives of CD, in which the quinuclidine nitrogen was not modified but the OH group was either removed (**10**) or methylated (**11**), did not inhibit the hydrogenation reaction, but provided essentially a racemic mixture of 2-methyl butanoic acid. Apparently, protection by an allyl or a benzyl group, or elimination of the (C-9)–OH group of CD, destroys the enantiodifferentiating ability of modifiers.

The purpose of quaternarization of the quinuclidine nitrogen was to prevent the protonation of this nitrogen atom by the reactant alkenoic acid. Moderate enantioselectivities were still achieved with modifiers **3**–**5**, which would suggest that the quinuclidine nitrogen–tiglic acid interaction via hydrogen bonding is not of vital importance in the enantiodiscriminating step. In a control experiment the hydrogenation of tiglic acid in the presence of *N*-benzyl cinchonidine chloride (**4**) was interrupted in the early stage of the reaction (after 7 min) and the filtrate was analyzed by NMR spectroscopy. It was found that already 60% of **4** underwent hydrogenolytic debenzylation (Scheme 2). Note that Pd is the most active catalyst for debenzylation (19), and the ease of hydrogenolysis of amines at room temperature and atmospheric pressure follows the following order: quaternary ammonium salts > tertiary > secondary > primary amines (20). At higher pressure and elevated temperature this sequence is reversed (21). It is assumed that hydrogenolysis of the



SCHEME 2. Partial hydrogenation of *N*-benzyl- and allyl CD derivatives (**3**–**5**) over Pd/alumina during tiglic acid hydrogenation.



SCHEME 3. Protonation of DBU.

N-allyl derivative (**3**) occurs similarly. We can conclude that when using modifiers **3**–**5** the actual effective modifier which affords enantiodifferentiation is (dihydro)-CD hydrochloride, which explains the unexpectedly high ee. On the contrary, hydrogenolysis of the *N*-methyl group was not detectable by NMR, which explains the very low final ee (1%). The *O*-allyl and *O*-aryl derivatives **7**–**9** are more resistant to hydrogenolysis under the conditions applied, as indicated by the very low ees. These results suggest that both the quinuclidine nitrogen and the OH group of CD are involved in the interaction with the reactant in the enantiodifferentiating step.

Hydrogenation of Tiglic Acid in the Presence of Strong Base Additive

In order to gain more information on the interaction between the alkenoic acid and CD we studied the effect of a strong base on the enantioselective hydrogenation of tiglic acid. The bulky, strong N-base, 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU, $pK_a = 23.9$ (22)), was chosen for this purpose. Note that the pK_a value of the quinuclidine nitrogen of CD is only 10 (23). DBU is a sterically hindered bicyclic amidin base which reacts with carboxylic acids to form a relatively large delocalized cation (Scheme 3) (24). Besides, DBU was resistant against hydrogenation under the reaction conditions applied. The base was added to the reaction mixture prior to hydrogenation in an apolar medium. The influence of DBU/tiglic acid molar ratio on the ee is depicted in Fig. 1. Till about 0.5 eq of DBU the

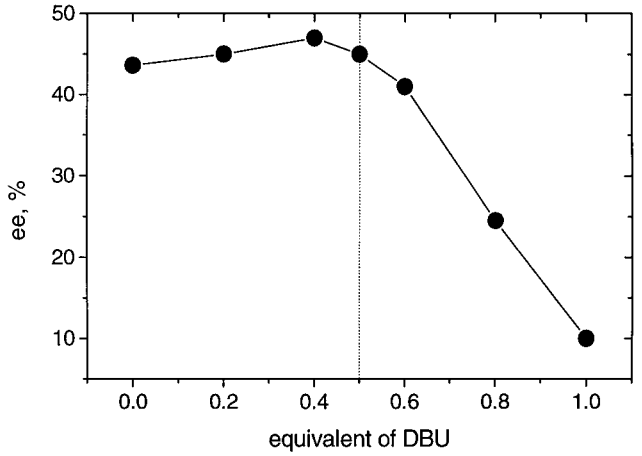


FIG. 1. Effect of DBU on ee in the hydrogenation of tiglic acid in toluene over Pd/alumina modified with CD.

ee barely changed, while an abrupt decrease was observed when this amount was exceeded. The base had only a minor effect on the rate of hydrogenation: the initial rate varied between 1.8 and 2.5×10^{-4} mol H_2 g^{-1} (cat.) s^{-1}, independent of the amount of base additive.

In the concentration range where the variation of ee is small (Fig. 1), there are two major species present in equilibrium: the acid dimer and DBU–$(acid)_2$ (dimer) salt. Above 0.5 eq of DBU the dominant species in the liquid phase are expected to be the DBU–$(acid)_2$ (1 : 2) and DBU–acid (1 : 1) salts. Apparently, the ee diminishes with increasing amounts of 1 : 1 salt, but is barely influenced by the presence of 1 : 2 salt.

Theoretical Calculations

Ab initio calculations were performed to gain some insight into the possible structure of the CD–alkenoic acid activated complex. At first the structure of a CD–$(acid)_2$ species was optimized. For this purpose the simplest unsaturated carboxylic acid, acrylic acid was used. As starting geometry conformation Open(3) was chosen for CD, since it has been shown by NMR experiments that CD adopts this conformation in the presence of acids (25–27). A possible geometry of a CD–(acrylic $acid)_2$ intermediate has been calculated in which both the {CD}NH···O{acid} and {CD}OH···O{acid} hydrogen bonds are involved, as shown in Fig. 2. This adduct exhibits strong stabilization with respect to species where only one acid molecule is interacting with CD. The analogous activated intermediate was obtained when the two acid molecules were fixed coplanar

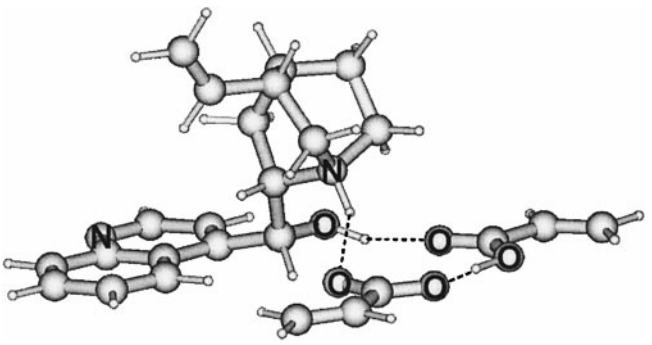


FIG. 3. Coplanar arrangement of acrylic acid dimer–CD species.

to the quinoline moiety of CD, as shown in Fig. 3. The geometrical arrangement of the (C-9)–OH and the N–H of protonated CD is ideally suited to form a hydrogen bonded network (27).

Another adduct which could be located on the potential energy surface is depicted in Fig. 4. Here, both the quinuclidine nitrogen and the OH group of CD form hydrogen bonds to the O atoms of the acrylic acid monomer. Several unsuccessful attempts were made to locate a structure with both N–H···O and O–H···O hydrogen bonds by fixing the quinoline part of CD and the C=C double bond of acrylic acid in one plane. It seemed that while fixed in one plane the hydrogen bonded network is too stressed, leading to rupture at the O–H···O hydrogen bond which is the weakest connection. The N–H···O bond is much stronger than the O–H···O bond since the most important contribution to the bonding is ion–ion interaction in the former and ion–dipole interaction in the latter. The binding energies of the optimized species and acrylic acid dimer are shown in Table 2. Note the high stability of the 2 : 1 species, and the significant binding energy of the acid dimer.

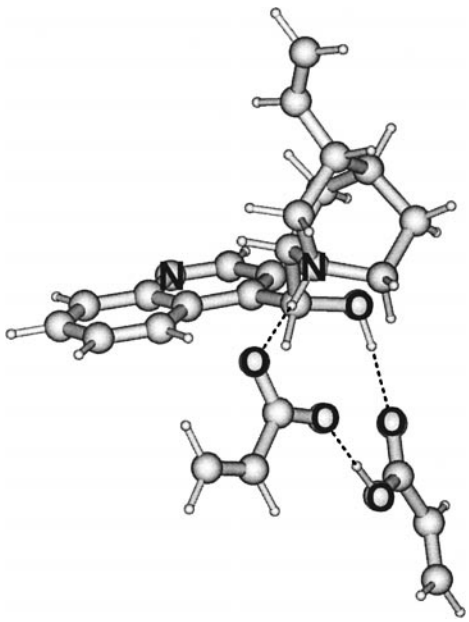


FIG. 2. Hydrogen bonding in the energetically most stable acrylic acid dimer–CD species.

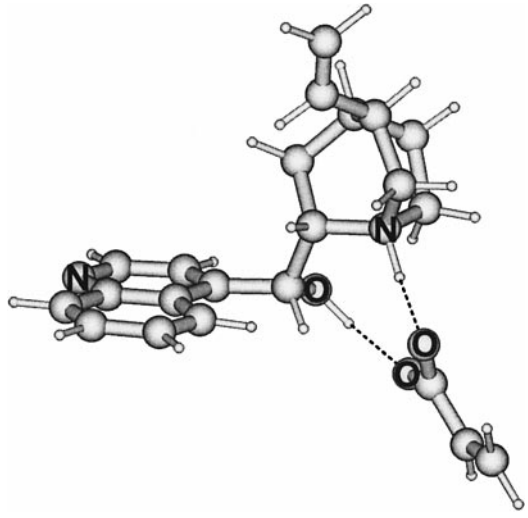


FIG. 4. Acrylic acid monomer–CD species.

TABLE 2

Binding Energies of Acrylic Acid Dimer and CD-Acrylic Acid Species

Species	ΔE (kcal/mol)
Acid dimer	20.8
CD–acrylic acid	19.2
CD–(acrylic acid)$_2$	40.7
CD–(acrylic acid)$_2$ planar	27.1

DISCUSSION

Developing a mechanistic model for the enantiodifferentiation in alkenoic acid hydrogenation over the Pd–CD system requires clarification (i) whether in the enantiodiscriminating step the reactant and the chiral modifier are anchored via single or double "docking" (H-bonding and ionic interaction), and (ii) of the stoichiometry of the transition complex. These questions have been addressed in some recent papers (12, 14, 15) but the conclusions of various research groups are contradictory. The experimental results and theoretical calculations presented above suggest that none of the former models (including our proposal (12)) are really correct.

Application of N- and O-derivatized CD as chiral modifiers (**3**–**11**) demonstrated that both the quinuclidine nitrogen and the (C-9)–OH functional group of CD are involved in the interaction with the alkenoic acid in the enantiodifferentiating step over the Pd surface. *N*-methylation of CD and alkylation or removal of the OH group resulted in an almost complete loss of enantioselectivity. HCl and HBr salts of CD (**1** and **2**) were less efficient than CD, but here the drop in rate and ee is likely due to the poisoning effect of halide ions, rather than protonation of the N-atom.

Application of *N*-allyl and *N*-benzyl CD (**3**–**5**) afforded misleading results: hydrogenolysis of the C–N bonds of the protecting groups was found to be faster than hydrogenation of the alkenoic acid, and the unexpectedly "high" ee is attributed to the enantiodifferentiation induced by 10,11-dihydrocinchonidine hydrochloride formed in the rapid, undesired reaction. (Note that saturation of the vinyl group at 10,11 position of CD is always fast even at atmospheric pressure.) In case of *N*-methyl CD (**6**) hydrogenolysis of the alkyl group could be excluded by NMR analysis. As the quaternarized quinuclidine nitrogen of **6** could not take part in H-bonding with tiglic acid, the ee approached zero indicating that an N–H$\cdots$O interaction between tiglic acid and CD is essential for enantiodifferentiation.

Interestingly, *N*-benzyl cinchonidine (**4**) was already tested in the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid over Pd/TiO_2 (15). The authors reported 57% ee, as compared to 61% achieved with CD under otherwise identical conditions. Though this observation clearly contradicts their final conclusion concerning the crucial role of the basic quinuclidine nitrogen in the reactant–modifier interaction, no explanation was given for this discrepancy. We propose that under the conditions applied (prehydrogenation of catalyst and modifier for 20 min prior to hydrogenation of (*E*)-α-phenylcinnamic acid) a facile debenzylation of **4** should occur, which results in CD hydrochloride as the actual modifier.

None of the CD derivatives protected at both the quinuclidine nitrogen and (C-9)–O atoms (**7**–**9**) were efficient as chiral modifiers (Table 1). Two other modifiers, 9-methoxy-CD (**11**) and deoxy-CD (**10**), were also tested in tiglic acid hydrogenation. The very low ee achieved with these compounds confirm that also the alcoholic OH of CD plays a crucial role in enantiodifferentiation. Moreover, the inefficiency of **11** indicates that the chiral modifier should be able to act as a donor in a hydrogen bonding interaction.

On the basis of these experimental observations, completed with theoretical calculations at the *ab initio* level, we propose that in the transition complex CD interacts with an acid dimer via two hydrogen bonds. The quinuclidine nitrogen is protonated by the acid dimer and the OH of CD acts as a hydrogen donor. Possible structures of this adduct are shown in Figs. 2 and 3. In the latter case the adduct was optimized assuming a parallel adsorption on an ideal flat Pd surface. However, as Fig. 2 demonstrates, a nonflat surface would not hinder the appropriate interactions between Pd, CD and alkenoic acid. If we assume that the addition of hydrogen occurs from the catalyst side ("bottom-side" *syn* addition (28)) then one of the C=C double bonds in the acid dimer should point toward the quinoline ring of CD. As we pointed out earlier (12), only this geometry affords the (*S*) product as the major enantiomer, assuming that the reactant acid molecules in the dimer are present in the thermodynamically more stable *trans* position.

In order to get further confirmation concerning the nature of interaction between CD and alkenoic acid, we designed a series of hydrogenation experiments in the presence of a bulky N-base (Fig. 1). This base (DBU) is orders of magnitude stronger than the quinuclidine nitrogen of CD, a feature which together with the steric hindrance imposed by its bulkiness, prevents any interaction between the quinuclidine nitrogen of CD and the tiglic acid salt. However, up to a DBU : tiglic acid = 1 : 2 molar ratio neither the reaction rate nor the ee decreased. In this concentration range tiglic acid is present as free dimers and DBU : tiglic acid = 1 : 2 salt in varying ratio as dominant species. The almost constant initial rate and ee, observed with increasing amounts of the 1 : 2 salt, indicate that this species does not disturb the enantiodifferentiation. A feasible explanation is that CD can replace the much stronger base DBU due to the stronger interaction between CD and the dimer, as compared to the interaction between DBU and tiglic acid dimer (Scheme 4).

$$[DBUH]^+[A]_2^- + CD \rightarrow [CDH]^+[A]_2^- + DBU$$

$$2[DBUH]^+[A]^- + CD \not\rightarrow [CDH]^+[A]_2^- + 2DBU$$

Where: A - alkenoic acid
$[A]_2$ - alkenoic acid dimer

SCHEME 4. Favored and unfavorable exchange between CD and DBU in DBU–(tiglic acid)$_2$ and DBU–tiglic acid salts, respectively.

This behavior corroborates that not only a base–acid interaction exists between CD and the acid dimer (8, 12, 14), but the H-bonding between the OH group of CD and the acid dimer also contributes to the total interaction energy in the adduct (15).

Above a DBU : tiglic acid = 1 : 2 molar ratio the ee dropped linearly with increasing amount of base. The most feasible explanation for the loss of ee is the presence of an increasing amount of DBU : tiglic acid = 1 : 1 salt in this concentration range. The interaction with CD would require then the breaking of hydrogen bonds in two DBU : tiglic acid 1 : 1 salt in order to form a CD–(tiglic acid)$_2$ intermediate. This is thermodynamically unfavorable compared to the substitution of DBU in the DBU–(tiglic acid)$_2$ species (Scheme 4). Thus the hydrogenation in the presence of 1 eq DBU results in drastic loss of ee (10% ee). Note that the same low ee was obtained recently in the hydrogenation of sodium (*E*)-α-phenylcinnamate (15).

On the basis of a wealth of literature data (29) and our IR study, we proposed earlier (12, 27) that the alkenoic acid reactant is dominantly present as dimers in an apolar medium, and this structure is preserved during interaction with CD on the Pd surface. As no direct (spectroscopic) confirmation is available yet for this assumption, the results obtained in the presence of DBU in toluene provide important indirect evidence for the proposed mechanistic model.

CONCLUSIONS

Various CD derivatives modified at the quinuclidine nitrogen and/or at the (C-9)–OH group were synthesized and tested in the enantioselective hydrogenation of tiglic acid. The experiments confirmed a former proposal (15) that the alcoholic OH group as well as the quinuclidine nitrogen of cinchonidine are hydrogen bonded to the reactant alkenoic acid in the enantiodifferentiation step. Hydrogenation experiments in the presence of a strong and bulky base additive provided indirect evidence for our former assumption that cinchonidine interacts with an alkenoic acid dimer on the Pd surface. A feasible structure of the acid dimer–CD intermediate which can easily adsorb on the catalyst surface has been rationalized by *ab initio* calculation. The calculations indicated that formation of a CD : acid 1 : 1 adduct is unfavorable at high acid concentration and its adsorption on the palladium surface is sterically hindered. Formation of a CD : acid 1 : 2 transition complex is more feasible.

ACKNOWLEDGMENTS

We are thankful to M. von Arx for the synthesis of *N*-methyl cinchonidine chloride. Financial support from the Swiss National Science Foundation is gratefully acknowledged.

REFERENCES

1. Rieu, J. P., Boucherle, A., Cousse, H., and Mouzin, G., *Tetrahedron* **42**, 4095 (1986).
2. Shen, T. Y., *Angew. Chem. Int. Ed. Engl.* **11**, 460 (1972).
3. Noyori, R., and Takaya, H., *Acc. Chem. Res.* **23**, 345 (1990).
4. Zhang, X., Mashima, K., Koyano, K., Sayo, N., and Kumobayashi, H., *Tetrahedron Lett.* **32**, 7283 (1991).
5. Uemura, T., Zhang, X., Matsumura, K., Sayo, N., Kumobayashi, H., Ohta, T., Nozaki, K., and Takaya, H., *J. Org. Chem.* **61**, 5510 (1996).
6. Baiker, A., *Curr. Opin. Solid State Mater. Sci.* **3**, 86 (1998).
7. Wells, P. B., and Wilkinson, A. G., *Top. Catal.* **5**, 39 (1998).
8. Borszeky, K., Mallat, T., and Baiker, A., *Catal. Lett.* **41**, 199 (1996).
9. Nitta, Y., and Kobiro, K., *Chem. Lett.* 897 (1996).
10. Smith, G. V., Cheng, J., and Song, R., *Catal. Lett.* **45**, 73 (1997).
11. Bartók, M., Wittmann, G., Göndös, G., and Smith, G. V., *J. Org. Chem.* **52**, 1139 (1987).
12. Borszeky, K., Mallat, T., and Baiker, A., *Tetrahedron: Asymmetry* **8**, 3745 (1997).
13. Barrow, G. M., and Yerger, E. A., *J. Am. Chem. Soc.* **76**, 5211 (1954).
14. Hall, T. J., Johnston, P., Vermeer, W. A. H., Watson, S. R., and Wells, P. B., *Stud. Surf. Sci. Catal.* **101**, 221 (1996).
15. Nitta, Y., and Shibata, A., *Chem. Lett.* 161 (1998).
16. Stenberg and Travecedo, *J. Org. Chem.* **35**, 4131 (1970).
17. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Robb, M. A., Cheeseman, J. R., Keith, T., Petersson, G. A., Montgomery, J. A., Raghavachari, K., Al-Laham, M. A., Zakrzewski, V. G., Ortiz, J. V., Foresman, J. B., Cioslowski, J., Stefanov, B. B., Nanayakkara, A., Challacombe, M., Peng, C. Y., Ayala, P. Y., Chen, W., Wong, M. W., Andres, J. L., Replogle, E. S., Gomperts, R., Martin, R. L., Fox, D. J., Binkley, J. S., Defrees, D. J., Baker, J., Stewart, J. P., Head-Gordon, M., Gonzalez, C., and Pople, J. A., Gaussian Inc., Pittsburgh PA 1995.
18. Rylander, P. N., "Catalytic Hydrogenation over Platinum Metals." Academic Press, New York and London, 1967.
19. Prelog, V., *Helv. Chim. Acta* **36**, 308 (1953).
20. O'Murchu, C., *Tetrahedron Lett.* **1969**, 3231 (1969).
21. Mitsui, S., Kasahara, A., and Endo, N., *J. Chem. Soc. Jpn.* **75**, 234 (1954).
22. Galezowski, W., Jarczewski, A., Stanczyk, M., Brzezinski, B., Bartl, F., and Zundel, G., *J. Chem. Soc. Faraday Trans.* **93**, 2515 (1997).
23. Budavari, S., "The Merck Index," 11th ed. Merck, Rahway, NJ, 1989.
24. Ono, N., Yamada, T., Saito, T., Tanaka, K., and Kaji, A., *Bull. Chem. Soc. Jpn.* **51**, 2401 (1978).
25. Bürgi, T., and Baiker, A., *J. Am. Chem. Soc.* **120**, 12920 (1998).
26. Dijkstra, G. D. H., Kellogg, R. M., and Wynberg, H., *Recueil des Travaux Chimiques des Pays-Bas* **108**, 195 (1989).
27. Ferri, D., Bürgi, T., and Baiker, A., *J. Chem. Soc. Perkin Trans. 2.* 1305 (1999).
28. Siegel, S., *Adv. Catal.* **16**, 123 (1966).
29. Patai, S., "The Chemistry of Carboxylic Acids and Esters." Interscience, London, 1969.