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Journal of Catalysis 219 (2003) 41–51

JOURNAL OF CATALYSIS

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Palladium-catalyzed enantioselective hydrogenation of 2-pyrones: evidence for competing reaction mechanisms

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Received 10 February 2003; revised 31 March 2003; accepted 3 April 2003

Abstract

The enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone (**1a**), 3,6-dimethyl-4-hydroxy-2-pyrone (**2a**), 4-methoxy-6-methyl-2-pyrone (**3a**), and 4,6-dimethyl-2-pyrone (**4a**) was studied over a 5 wt% Pd/TiO_2 catalyst. Various cinchona alkaloids and their O- and N-methyl derivatives were applied as chiral modifiers. The catalytic experiments combined with FTIR, NMR, and NOESY-NMR spectroscopic analysis and ab initio calculations revealed an interesting feature of the reactions: the ee is determined by competing reactant–modifier interactions. These interactions may involve the OH function and the quinuclidine N of the alkaloid modifier. When the reactant possesses an acidic OH group (**1a** and **2a**), the reaction via the energetically most stable bidentate complex controls the enantioselectivity. Protic or basic solvents diminish the ee in these reactions by stabilizing a single-bonded (acid–base type) interaction. Different mechanisms are proposed for the hydrogenation of the nonacidic pyrones **3a** and **4a**. These models can well interpret the catalytic results but require further confirmation. Besides, the studies provided the first experimental evidence for an intrinsic rate acceleration coupled with the enantiodifferentiating process over chirally modified Pd.

Keywords: Asymmetric; Hydrogenation; Cinchonidine; Cinchonine; Palladium; 2-Pyrone

1. Introduction

Enantioselective hydrogenation of carbon–carbon double bonds with homogeneous chiral metal complex catalysts is a thoroughly investigated and highly efficient method, providing the desired enantiomer with 99% and higher enantiomeric excess (ee) [1,2]. Supported Pd catalysts in the presence of a cinchona or vinca alkaloid modifier (both simply added to the reaction mixture) are the best heterogeneous catalyst systems for the enantioselective hydrogenation of α,β-unsaturated carboxylic acids (up to 72% ee [3–10] and ketones (up to 55% ee [11–14]).

Hydrogenation of substituted 2-pyrones has recently become a subject of great interest as the partial hydrogenation products possess various biological activities [15] and can be used as chiral intermediates in the synthesis of pharmaceuticals [16]. Consiglio and co-workers [17,18] described a cationic Ru complex that catalyst afforded 98% ee and good chemoselectivities to 5,6-dihydropyrones. Hydrogenation of 4-alkyl-2-pyrones, and 4-hydroxy-2-pyrones, which are not substituted at the C^3 position, did not stop at the dihydropyrone stage and afforded only a mixture of *cis* and *trans* tetrahydropyrones.

The importance of chiral pyrone derivatives and the obvious technical advantages of heterogeneous catalysis prompted us to explore the enantioselective synthesis of dihydropyrones over chirally modified metals. The Pd/TiO_2–cinchona system afforded 85% ee in the transformation of the hydroxypyrone **1a** to **1b** [19] and 94% ee in the hydrogenation of **3a** to **3b** [20] (Scheme 1). Special advantages of the method are the very mild conditions (1 bar, room temperature), the high chemoselectivity (up to 95%) to dihydropyrones even in the absence of a C^3 substituent, and that the tetrahydro-derivatives are produced in 98–99% diastereomeric excess (de) to the *cis* isomers.

In a former report we proposed a mechanistic model for the enantioselective hydrogenation of **1a** (Fig. 1) [21]. The model rationalized the preferential formation of (*S*)-product on Pd in the presence of cinchonidine (CD, Fig. 2) as chiral modifier under optimum conditions, in acetonitrile. The protonated quinuclidine N of CD ($pK_a = 10.0$ [22]) is bound to

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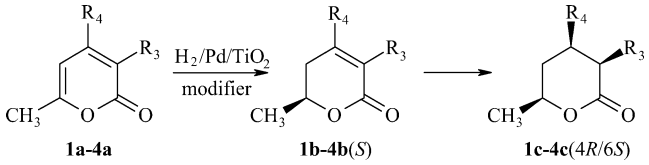
0021-9517/$ – see front matter
doi:10.1016/S0021-9517(03)00166-0



	R_3	R_4
1a	H	OH
2a	CH_3	OH
3a	H	OCH_3
4a	H	CH_3

Scheme 1. Consecutive reaction steps in the hydrogenation of 2-pyrones (**1a**–**4a**) over cinchona-modified Pd.

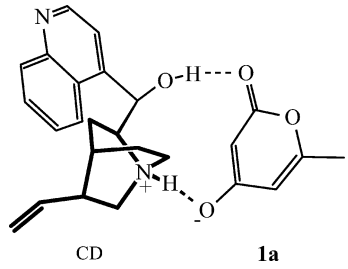


Fig. 1. Cinchonidine (CD)–**1a** interaction controlling the enantiodifferentiation over Pd; schematic top view over the Pd surface.

the deprotonated OH group of **1a** ($pK_a = 4.73$ [18]), and a second H-bonding interaction involves the OH group of CD and the carbonyl group of **1a**. Here we show that the validity of this model is limited to certain conditions and that the mechanisms of enantiodifferentiation of nonacidic 4-alkoxy and 4-methyl-pyrones **3a** and **4a** are remarkably different.

In an enantioselective reaction formation of one enantiomer in excess is usually attributed to the dominance of either the energetically favored or the more reactive chiral transition complex {pro-(*R*) or pro-(*S*)} [23–25]. Beside the thermodynamic and kinetic control there is a third, less common possibility when two (or more) reaction mechanisms or reaction pathways are feasible and the stereochemical outcome of the reaction is determined by a competition between them. The first example in heterogeneous catalysis is the highly enantioselective hydrogenation of a trifluoromethyl ketone over cinchona-modified Pt/Al_2O_3 [26]. In primary alcoholic solvents or in the presence of small amounts of water, hydrogenation of the ketone (minor but most reactive species) shifts to the hydrogenolysis of the hemiketal or hydrate intermediates affording either a racemic mixture or even the opposite enantiomer in excess, respectively. Hydrogenation of 2-pyrones over cinchona-modified Pd/TiO_2 provides another example in this category as the product distribution is determined by competing reaction mechanisms.

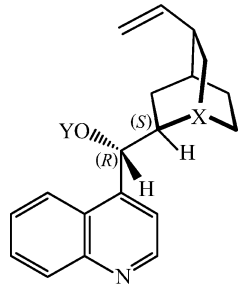
2. Experimental

2.1. Materials

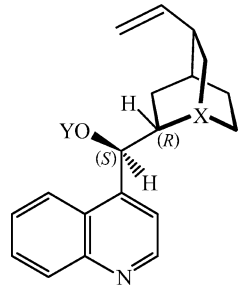
All solvents were distilled before use. It must to be emphasized that even traces of impurities in the reaction mixture can lead to significant variations in ee.

4-Hydroxy-6-methyl-2-pyrone (**1a**, Fluka, 98%) was purified prior to use by column chromatography (silica gel, dry hexane:ethyl acetate 1:1), followed by recrystallization from ethyl acetate. 4,6-Dimethyl-2-pyrone (**4a**, Aldrich) was sublimated (380 K, 0.1 mbar) and recrystallized twice from hexane. 3,6-Dimethyl-4-hydroxy-2-pyrone (**2a**) [27] and 4-methoxy-6-methyl-2-pyrone (**3a**) [28] were synthesized according to known methods. They were purified by sublimation followed by recrystallization twice from hexane (3,6-dimethyl-4-hydroxy-2-pyrone (**2a**) from dioxane). NMR spectroscopic data and molecular mass were in good agreement with the structures.

Cinchonidine (CD, Fluka), cinchonidine hydrochloride (CD·HCl, Aldrich) and cinchonine (CN, Fluka) were used as received. *O*-Methylcinchonidine (MeOCD) [29] and *N*-methylcinchonidine chloride (MeNCDCl) [30] were prepared according to published methods. Elementary analysis and NMR spectroscopic data were in good agreement with the structures.



X	Y	
N	H	Cinchonine (CN)



X	Y	
N	H	Cinchonidine (CN)
N^+HCl^-	H	Cinchonidinium hydrochloride (CD·HCl)
N^+MeCl^-	H	*N*-Methylcinchonidinium chloride (MeNCDCl)
N	Me	*O*-Methylcinchonidinium (MeOCD)

Fig. 2. Structures and abbreviations of cinchona alkaloids and their simple derivatives used as chiral modifiers.

A 5 wt% Pd/TiO_2 (metal dispersion: $D = 0.18$, determined by H_2 chemisorption) was prepared as follows. 0.97 g $PdCl_2$ was dissolved in 50 ml water and 2 ml concentrated HCl. Then 11.16 g TiO_2 (P25, Degussa, 55 m^2/g) was added to the solution and the pH was set to 10 by dropping aqueous Na_2CO_3 to the stirred suspension at room temperature. After filtration the catalyst was washed to neutral, dried at 350 K in vacuum, and reduced in a hydrogen flow at room temperature for 30 min.

2.2. Catalytic hydrogenation

The reactions were carried out in a magnetically stirred 100-ml glass reactor. In a standard procedure, 20 mg catalyst was rereduced in 10 ml solvent with H_2 for 5 min, at 1 bar and room temperature, under intensive stirring. Then the appropriate amount of modifier and 5 min later 50 mg substrate were added, and the reaction started.

The conversion, chemo-, and enantioselectivity of hydrogenation products **3a** and **4a** were determined by a HP 6890 gas chromatograph using a Chirasil-DEX CB column (Chrompack). Conversion of **1a** and **2a** and chemoselectivity to **1b** and **2b** were analyzed with a HP-5 column. Before determination of enantioselectivity in **1b** and **2b**, they were methylated to **3b** and 5,6-dihydro-3,6-dimethyl-4-methoxy-2-pyrone, respectively. Enantioselectivity of 5,6-dihydro-3,6-dimethyl-4-methoxy-2-pyrone was determined on a Cyclosil B column (J+W). The experimental error (SD: ±1%) was about double the usual value due to the low conversion and the derivatization process. Derivatization was carried out in 3 ml methanol with 0.1 to 0.01 mmol hydrogenation product and 10 mg trimethylorthoformate in the presence of an acidic ion-exchange resin (Diaion RCP1 60H).

The turnover frequency (TOF°, mol/(mol Pd_s h); SD: ±8–10%) was calculated from the initial reaction rate and the number of surface Pd atoms (Pd_s).

2.3. Spectroscopic analysis

IR spectra were recorded on a Bruker IFS-66 spectrometer at a resolution of 4 cm^{-1} by coaddition of 200 scans. Spectra were taken in transmission mode using a cell equipped with CaF_2 windows with a path length of 1 mm. $CDCl_3$ was used as solvent and the pure solvent served as the reference. ^1H and ^{13}C NMR spectra were measured using a Bruker DPX 300 spectrometer.

2.4. Theoretical calculations

Intermolecular interactions between **1a** and CD were studied by quantum chemical calculations using GAUSSIAN98 [31]. The B3LYP [32] density functional hybrid method was applied together with a 6-31G* basis set. For geometry optimization all intra- and intermolecular degrees of freedom were completely relaxed. Several structures were chosen as initial geometries in the optimization runs. CD was assumed to be in its open(3) conformation (Fig. 3), which is the most stable conformation when the alkaloid is protonated at the quinuclidine N [33,34].

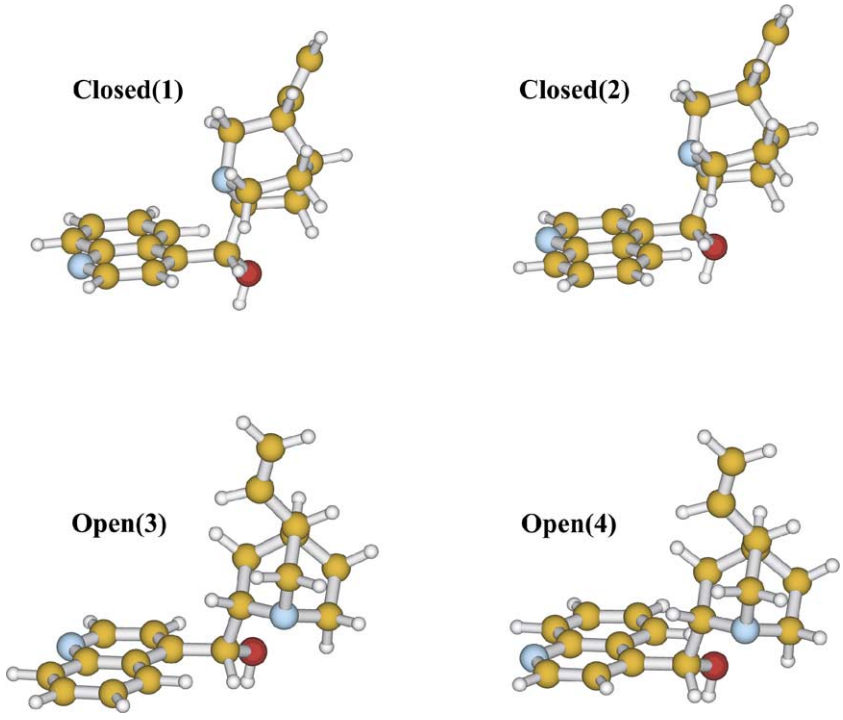


Fig. 3. Four stable conformations of CD based on NMR measurements and theoretical calculations [33,47–49].

Table 1
Enantioselective hydrogenation of 2-pyrone-derivatives in various solvents over cinchonidine (CD)-modified Pd[a]

Reactant	Product	Acetonitrile		2-Propanol		3-Pentanone		Acetic acid	
		TOF°	ee (%)	TOF°	ee (%)	TOF°	ee (%)	TOF°	ee (%)
1a	**1b**	3.1	72 (*S*)	7.9	33 (*S*)	7.5	50 (*S*)	12	27 (*S*)
2a[b]	**2b**	0.1	33 (*S*)	–	–	0.2	53 (*S*)	0.3	32 (*S*)
3a	**3b**	4.2	41 (*S*)	67	75 (*S*)	8.4	48 (*S*)	1.0	34 (*S*)
4a[c]	**4b**	49	44 (*S*)	500	61 (*S*)	71	43 (*S*)	7	8 (*S*)

[a] Conditions: 50 mg reactant, 40 mg 5 wt% Pd/TiO_2, 10 ml solvent, 17 μmol CD, 1 bar, 298 K, reaction time 1 h, chemoselectivity > 90% to **1b**–**3b**.
[b] Reaction time 8 h.
[c] Reaction time 10 min, chemoselectivity 50–60% to **4b** due to further hydrogenation to **4c**.

3. Results

We have shown recently that hydrogenation of **1a** over CD-modified Pd is complicated by a slow hydrogenation of the aromatic rings of the chiral modifier [35]. A further disturbing side reaction is the C–N bond hydrogenolysis in case of *N*-methylated CD (MeNCDCl) [29]. In order to minimize these effects and avoid distortion of the results in the following mechanistic study, the catalytic experiments were interrupted after a short time period and the product distribution was analyzed at relatively low conversions (in the hydrogenation of **1a** and **2a** usually below 5% conversion).

3.1. Hydrogenation of 2-pyrone derivatives

The validity of the mechanistic model suggested for the enantioselective hydrogenation of the hydroxypyrone **1a** (Fig. 1) has been tested by variation of the structure of 2-pyrones according to Scheme 1. The experiments in various solvents (Table 1) show the complexity of reactant–modifier interactions. It was proposed earlier [21] that in the hydrogenation of **1a** good ee could be achieved in strongly polar solvents that are poor hydrogen bond donors and acceptors, with an optimum in acetonitrile. On the basis of the model in Fig. 1, some steric repulsion is expected between CD and H^3 of **1a** (atom labeling in Fig. 4). Replacing this hydrogen by a methyl group leading to compound **2a** should suppress this

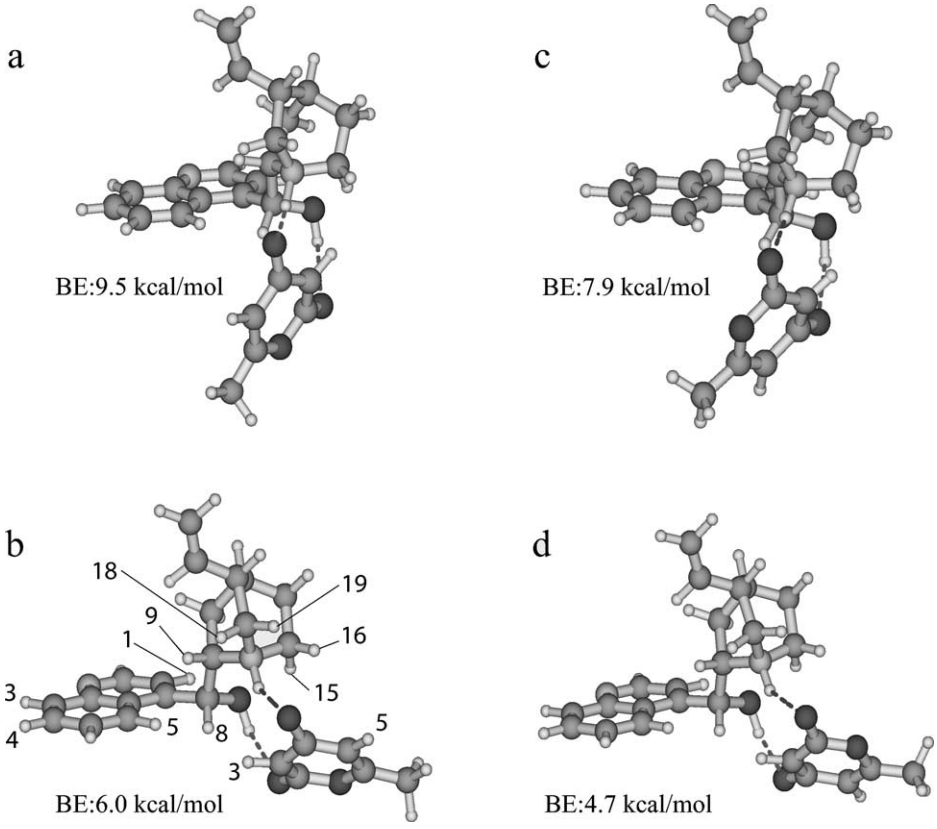


Fig. 4. Calculated structures of possible CD–**1a** complexes. All structures were fully optimized at the B3LYP level using a 6-31G* basis set. For details see the original publication [21].

interaction and diminish the ee. Indeed, in acetonitrile the ee dropped to less than half but no decrease was observed in 3-pentanone and AcOH. Remarkable is the very low initial rate (TOF°) of the hydrogenation of **2a** in all solvents. The rate decrease by a factor of 30–40 compared to the hydrogenation of **1a** may indicate a sterically hindered adsorption of the CD–**2a** complex on the Pd surface.

The importance of the acid–base interaction between CD and **1a** (Fig. 1) has been tested by replacing the acidic 4-hydroxy group to 4-methoxy (**3a**) and 4-methyl groups (**4a**). Astonishingly, the ee's were unexpectedly high, particularly in 2-propanol—a poor solvent for the hydrogenation of **1a**. The reactivity of **4a** was outstanding in all solvents except AcOH where the ee was also low. Another characteristic feature of the latter reaction is the poor separation between the uptake of the first and second equivalents of hydrogen (Scheme 1). The fully hydrogenated *cis*-tetrahydropyrone **4c** was the major product at conversions higher than 50%, with 99% diastereoselectivity to the *cis*-isomer.

*3.2. Variation of the modifier structure—hydrogenation of **1a***

The efficiency of some simple CD derivatives is illustrated in Table 2 by the hydrogenation of **1a** in acetonitrile, which is the best solvent for this reaction [21]. The highest ee was achieved with CD·HCl. The positive effect of HCl is specific to the reaction in acetonitrile, and has been attributed to neutralization of ethylamines resulting from the hydrogenation of the solvent during catalyst prehydrogenation (i.e., in the absence of **1a** and modifier) [21]. The basicity of ethylamines is similar to that of the quinuclidine N of CD; thus, ethylamines can compete with the modifier for interacting with **1a**. In other solvents the rate and ee were always considerably smaller with CD·HCl. For example, in 3-pentanone the ee and TOF values were 35% and 1.1 with CD·HCl, compared to 49% and 9.5 with CD.

Methylation of the quinuclidine N of CD resulted in a complete loss of ee and very slow reactions in all solvents. The loss of ee by blocking the quinuclidine N of CD is in agreement with the model in Fig. 1. As concerns the reaction rate, we have shown earlier [35] that hydrogenation of **1a** over Pd/TiO_2 is relatively fast even under ambient conditions but addition of the modifier slows down the reaction by a factor of 60, depending on the modifier/Pd ratio. The slow reaction is a general feature of enantioselective hydrogenations over chirally modified Pd [3,36–38] and is attributed to the coverage of a considerable fraction of surface active sites by the modifier. It is commonly assumed that adsorption of the alkaloid occurs via the quinoline ring system ("anchoring" moiety) and the quinuclidine part is not in direct contact with the metal surface [25,39,40]. This assumption has been evidenced recently by ATR-IR spectroscopic analysis of CD adsorption in the presence of hydrogen on Pd/Al_2O_3 [41] and Pt/Al_2O_3 [42,43]. Hence, adsorption of CD·HCl and MeNCDCl on Pd should be similar and the higher hydrogenation rate by a factor of ca. 7 with the former modifier (Table 2) may be an indication of an intrinsic rate acceleration coupled with the enantiodifferentiating process. This is the first experimental evidence for such an effect over chirally modified Pd.

Table 2
The efficiency of cinchona modifiers in the enantioselective hydrogenation of **1a** to **1b** in acetonitrile[a]

Modifier	TOF°	ee (%)
CD	3.2	73(*S*)
MeNCDCl[b]	0.5	0
MeOCD	9.5	2 (*R*)
CD·HCl	3.4	76 (*S*)

[a] Conditions: 50 mg **1a**, 20 mg 5 wt% Pd/TiO_2, 10 ml acetonitrile, 17 μmol modifier, 1 bar, 298 K, reaction time 1 h, chemoselectivity better than 90%.
[b] Reaction time: 2 h.

On the basis of the model in Fig. 1, MeOCD was expected to be an inefficient modifier as the H-bonding interaction of the OH group of CD with the carbonyl group of **1a** is hindered. Indeed, the ee was close to zero in acetonitrile but in other solvents, such as 2-propanol, AcOH, and 3-pentanone, the opposite enantiomer (*R*)-**1b** formed with 10, 12, and 14% ee, respectively (determined at 5–7% conversion). The small but significant ee to the opposite enantiomer is an indication of some changes in the mechanism in the latter solvents.

*3.3. The effect of modifier structure—hydrogenation of **3a** and **4a***

The efficiency of CD derivatives depends also on the structure of 2-pyrones, as illustrated by the hydrogenation of **3a** and **4a** in THF and 2-propanol (Table 3). Hydrogenation in the presence of MeOCD afforded medium ee's and the highest reaction rates. Obviously, the OH group of CD is not indispensible for enantiodifferentiation in these reactions and blocking of this functional group accelerates the reaction.

Blocking of the quinuclidine N of CD in MeNCDCl led to less clear results. In aprotic solvents as, for example, THF the ee's were close to zero at around 1% conversion but 24 and 15% ee, respectively, were achieved in 2-propanol. The reactions were very slow in all tested solvents (0.3–2% conversion in 1 h) and the ee's increased with time. The most probable explanation is that MeNCDCl is ineffective as chiral modifier of Pd and the ee measured at 1% conversion but after a long reaction time is due to hydrogenolysis of the C–N bond (demethylation) of the modifier. This side reaction is much faster in 2-propanol which solvent facilitates demethylation. We have already observed this complication in the hydrogenation of alkenoic acids where the acidic reactant accelerated the C–N bond hydrogenolysis [29]. A further support to this interpretation is that demethylation of MeNCDCl results in CD·HCl and the efficiency of this modifier is similar to that of MeNCDCl in all solvents (Table 3).

Table 3
Influence of cinchona modifiers and solvents on the enantioselective hydrogenation of **3a** and **4a**[a]

Modifier	**3a**				**4a**			
	Tetrahydrofuran		2-Propanol		Tetrahydrofuran		2-Propanol	
	TOF°	ee (%)	TOF°	ee (%)	TOF°	ee (%)	TOF°	ee (%)
CD	47	61 (*S*)	77	74 (*S*)	310	61 (*S*)	550	60 (*S*)
MeNCDCl	0.2	< 2[b]	2.4	24 (*S*)	2	< 2[b]	110	15 (*S*)
MeOCD	110	32 (*S*)	130	45 (*S*)	420	32 (*S*)	670	22 (*S*)
CD·HCl	0.7	1 (*S*)	2.6	33 (*S*)	9	1 (*S*)	180	17 (*S*)

[a] Conditions: 50 mg reactant, 20 mg 5 wt% Pd/TiO_2, 10 ml solvent, 4 μmol modifier, 1 bar, 298 K, reaction time 30 min, chemoselectivity better than 90%.
[b] Reaction time: 2 h.

Thus, after an induction period not MeNCDCl but CD·HCl was the actual modifier of Pd.

3.4. Theoretical calculations—steric hindrance by the C^3-methyl group of 2-pyrones

On the basis of the model calculated for the CD–**1a** interaction (Fig. 1) [21] a considerable steric hindrance is expected in the CD–**2a** complex due to the presence of the 3-methyl group. To support this assumption, we carried out quantum chemical calculations with the possible bidentate complexes between CD (Fig. 5) and **2a**, and the structures were compared to the CD–**1a** complexes proposed earlier (Fig. 4) [21].

The most important stable conformations of CD are shown in Fig. 3. CD in its closed(1) conformation cannot form bidentate complexes with **1a** and **2a** for steric reasons. Attempts to find bidentate CD–**1a** complexes involving the closed(2) conformation were not successful and resulted in a single bonded complex with no H bond between the carbonyl group of **1a** and the OH group of CD. For the open(3) conformation the relative arrangement of the quinuclidine N and the OH function of CD is ideally suited to bind **1a** or **2a** via a double H bonding interaction (Figs. 4 and 5). The structures resemble the CD–carboxylic acid interactions suggested previously using spectroscopic methods and calculations [29,44].

For CD–**2a** (Fig. 5), four different double H-bonded complexes have been found which correspond to (local) minima on the potential energy surface. In the hydrogenation of **1a** and **2a** the (*S*) enantiomers form in excess when CD is used as modifier. In the pro-(*S*) complexes (Figs. 4a and 4b and Figs. 5a and 5b) the N–H group of protonated CD binds to the deprotonated OH group of **1a** and **2a**, and the OH group of CD to the carbonyl O of **1a** and **2a**, respectively. Exchange of the two H-bond acceptor groups of **1a** and **2a** leads to the pro-(*R*) complexes (Figs. 4c and 4d and Figs. 5c and 5d). This exchange is energetically feasible as the anion of deprotonated **1a** exists in two mesomeric structures (Fig. 6).

The two different pro-(*S*) and pro-(*R*) complexes for both **1a** and **2a** differ in the relative orientation of the quinoline moiety of CD and the pseudo-aromatic ring of **1a** and **2a**. In Figs. 4 and 5 the binding energies for the various complexes, with respect to the separated neutral molecules, are also given. The complexes involving CD and **2a** were less stable by 4.3–7.9 kcal/mol than the ones calculated for CD and **1a**. The main reason for this deviation is, as expected, the large repulsion between the methyl-group in the C^3 position of **2a** and the quinuclidine part of CD.

The calculations predict that the pro-(*S*) structures are more stable than the corresponding pro-(*R*) complexes, offering a feasible explanation for the experimentally observed product distribution. The energy difference is 1.3 kcal/mol for the nearly parallel (Figs. 4b and 4d) and 1.6 kcal/mol for the nearly perpendicular complexes (Figs. 4a and 4c) between CD and **1a**. The corresponding energy differences are 0.2 kcal/mol (Figs. 5b and 5d) and 3.6 kcal (Figs. 5a and 5c) for complexes with CD and **2a**.

The complexes with nearly perpendicular orientation of the quinoline moiety of CD and the ring of **1a** (**2a**) are remarkably more stable than the nearly parallel arrangements, but cannot easily adsorb on an approximately flat Pd surface. Adsorption and hydrogenation of these complexes would require special sites (e.g., steps or terraces) on the Pd particles, but the amount of these surface structures on moderately dispersed Pd is low (average metal particle size: 5–6 nm). The angle between the two molecules in structures Figs. 5a and 5c are even smaller than 90° and this angle cannot increase during adsorption on a step or terrace due to strong steric hindrance by the methyl group. Hence, the surface concentration of these complexes should be very low and their contribution to the overall reaction may be negligible. Even the adsorption of the nearly parallel CD–**2a** complexes in Figs. 5b and 5d is sterically disfavored that can explain the low rate of this reaction (Table 1). In contrast, the nearly parallel complexes of CD–**1a** in Figs. 4b and 4c are more stable than the corresponding CD–**2a** complexes. Adsorption of the nearly parallel complexes of CD–**1a** is favored on low-dispersed Pd and allows fast hydrogenation.

3.5. IR spectroscopic analysis of modifier–reactant interactions

The IR spectra of CD–**1a**, CD–**2a**, and CD–**3a** mixtures and CD alone in $CDCl_3$ are shown in Fig. 7. The molar ratio of 2-pyrones to CD was always 1:1. Addition of **3a** to CD had no significant effect on the spectrum in the ν(O–H) range providing no evidence for any interaction. Note, that

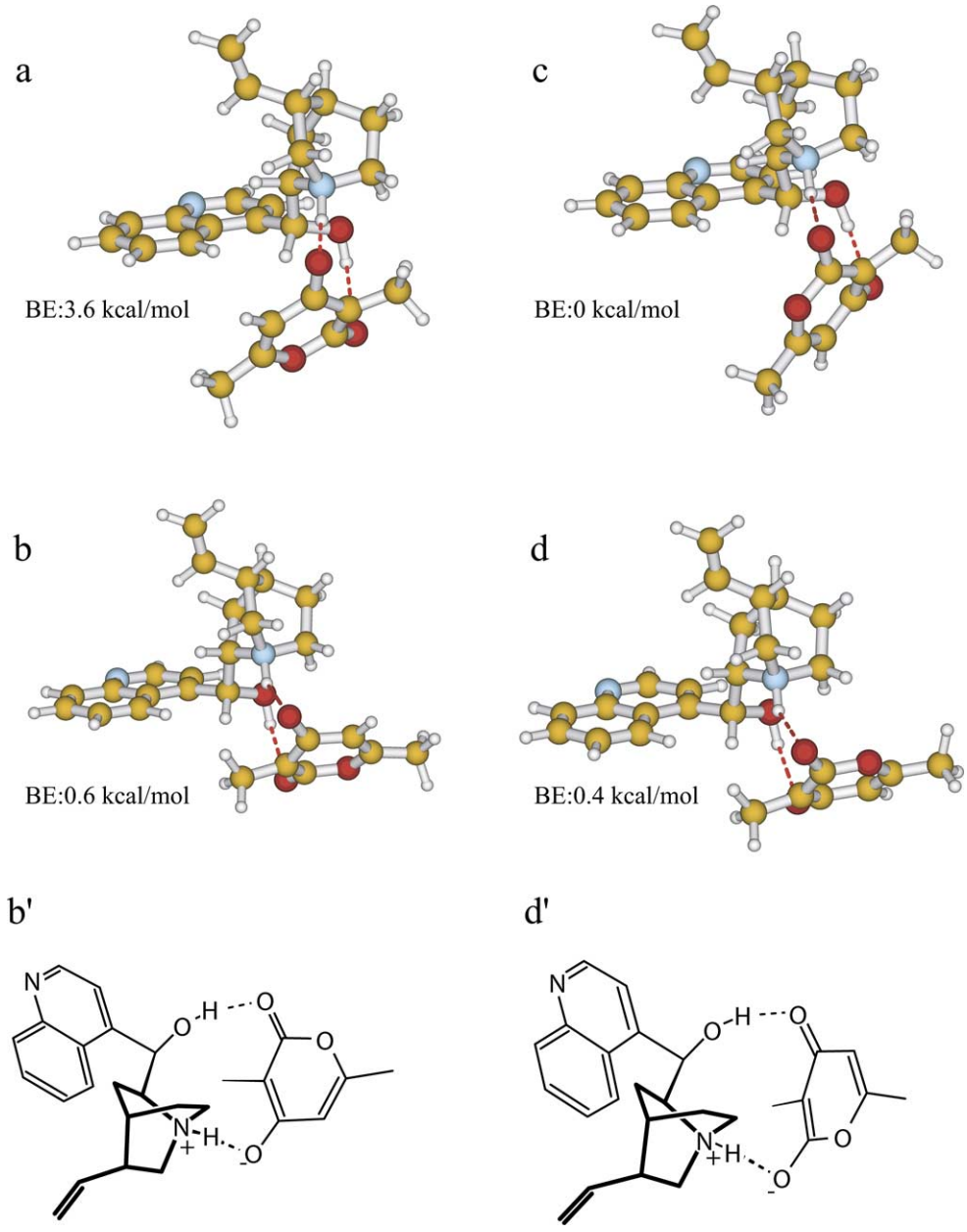
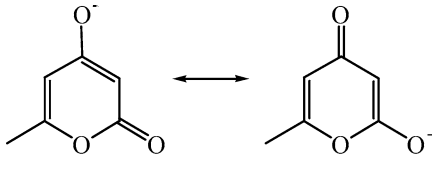


Fig. 5. Calculated structures of possible CD–**2a** complexes. All structures were fully optimized at the B3LYP level using a 6-31G* basis set.



1a

Fig. 6. Mesomeric structures of deprotonated 4-hydroxy-6-methyl-2-pyrone **1a**.

also no evidence for a CD–**3a** interaction was found by UV and NMR spectroscopy.

In contrast, the IR spectra of solutions of CD with **1a** and **2a** are characterized by strong absorption in the range of 3400–2800 cm^{-1}, which is associated with proton polarization due to protonation of the quinuclidine N of CD. Protonation of CD by these acidic compounds is indeed expected. A simultaneous decrease in the intensity of the stretching vibration ν(O–H) associated with the free (i.e., not H-bonded) OH group of CD at around 3600 cm^{-1} [44] indicates that the OH group of CD interacts with the hydroxypyrones [21]. This observation strongly supports the existence of the calculated complexes in Figs. 4 and 5.

From the intensity of the free ν(O–H) vibration in the 1:1 mixtures of CD and **1a** or **2a**, it was calculated that about 70% of the OH groups of the alkaloid is H-bonded. The remaining free OH groups of CD may be attributed to free CD or single-bonded complexes (only acid–base inter-

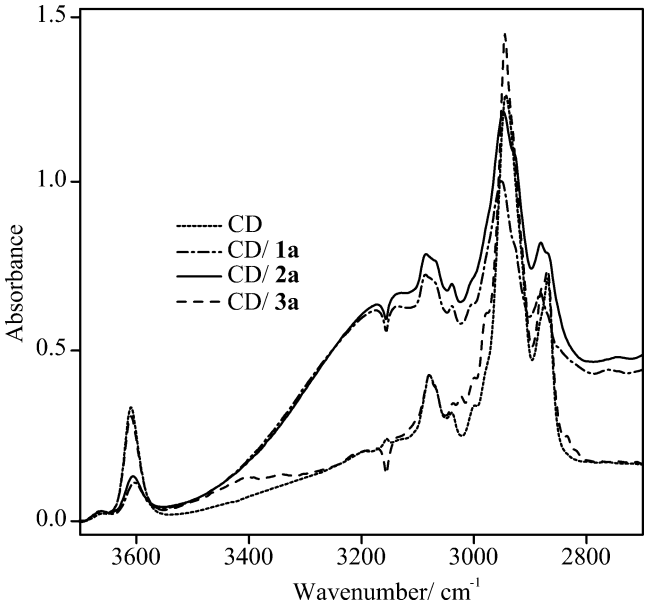


Fig. 7. IR spectra of 2-pyrone derivatives–CD mixtures. The CD concentration in $CDCl_3$ was 0.01 M in all cases. The 2-pyrone/CD molar ratios are 1.0.

action), as illustrated in Fig. 8. This calculation is supported by a former NMR study of the interaction of CD with **1a** and trifluoroacetic acid in $CDCl_3$ [21]. The shift of the H^8 signal of CD, due to protonation of CD by 1 eq of **1a**, corresponded to that of 0.6 eq trifluoroacetic acid. Independently, it has been shown that 1 eq of TFA completely protonates the quinuclidine N of CD [21]. We conclude that 60% of CD was protonated by **1a** in the equimolar $CDCl_3$ solution, in good agreement with the present results by IR.

3.6. NMR analysis of CD–hydroxypyrone interactions

Similar to the IR study, NMR analysis of CD–**1a** and CD–**2a** solutions in $CDCl_3$ revealed two H-bonding interactions. Two broad H signals with integrals of one proton for each associated with H bonds were detected below −10 °C. Below −30 °C chemical shifts of 14 and 8 ppm were found for both CD–**1a** and CD–**2a**. At room temperature the two signals merged to one single signal at 9.3 ppm for CD–**1a** and 8.3 ppm for CD–**2a** with integrals of 2 protons for each.

Table 4
Intermolecular NOEs between cinchonidine and **1a** measured by a two-dimensional NMR-NOESY experiment in $CDCl_3$ (s, strong; w, weak)

CD	**1a**		
	H^3	H^5	H^{Me}
H^1	s	w	–
$(H^3)/H^5$	s	s	–
H^8	s	w	s
$H^9/(H^{19})$	s	s	–
$H^{15}/(H^{18})$	s	–	–
H^{16}	s	w	–

With NOESY-NMR spectroscopy the geometry of the structures of CD–**1a** complexes was confirmed (Table 4) and evidence was found for the coexistence of different CD conformations. Unfortunately, the CD signals of H^3 and H^5 (doublet, atom labeling in Fig. 4b), H^9 and H^{19} (multiplet), and H^{15} and H^{18} (multiplet) were not separated. H^3 can be excluded from the discussion for geometrical reasons and for the missing intermolecular NOEs involving H^4. However, intramolecular NOE's involving H^{18} and H^{19} cannot completely be excluded and may be attributed to single bonded complexes (Fig. 8).

NOEs between H^5–(CD) and H^3–(**1a**) and H^5–(**1a**) indicated that CD adopts open(3) conformation and thus confirm the structures in Figs. 4c, 4b, and 4d. NOE's of H^1–(CD) to H^3–(**1a**) and H^5–(**1a**) can be rationalized by CD in open(4) conformation, which is obtained by 180° rotation of the quinoline part of CD. NOEs of H^3–(**1a**) and H^5–(**1a**) with H^9–(CD) may be attributed to bidentate complexes of **1a** with CD being in a closed(2) conformation. Bidentate complexes with closed(1) conformation are not feasible, as for steric reasons the OH group can only point in the direction opposite to the quinuclidine part and thus it is not available for interaction with **1a** (Fig. 3). In general, complexes with CD in closed conformation are not important for the hydrogenation reaction. Accepting that CD is adsorbed on the metal surface via the quinoline moiety [41], interaction

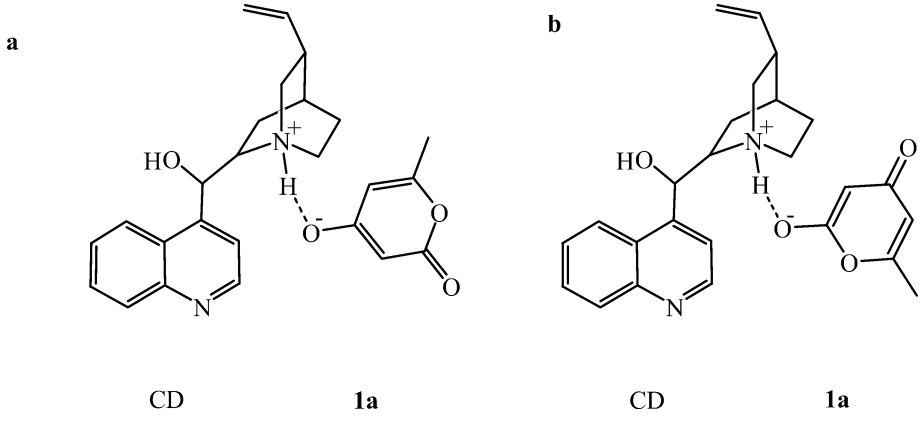


Fig. 8. Structures of possible single-bonded CD–**1a** complexes, not involving the OH group of CD.

of the reactant with CD in closed conformation results in a geometry in which the reactant overlaps with the quinoline rings of CD and can not be hydrogenated. In the solutions investigated, CD was mainly in open conformations, because the ^{3}J H^8–H^9-coupling constant was found to be very small (1.2 Hz) [33].

Most of the detected NOE's shown in Table 4 can be explained assuming bidentate complexes. In single-bonded CD–**1a** complexes H^3 and H^5 of **1a** should show weak NOEs with all H of CD in α-position to the quinuclidine N due to possible rotation of **1a** around the N–H–O bond. In fact, no cross-signal was observed between H^5 of **1a** and H^{18} of CD. Probably the interactions are distributed to all hydrogens in α-position to the quinuclidine-N and the cross-peaks are too weak to be detected. Note that a weakly polar solvent was chosen in order to minimize the interactions with the reactant, which explains the very low amount of single bonded CD–**1a** complexes.

Some very characteristic NOEs effects back up the feasibility of the calculated complexes of CD–**1a**. The cross-peaks of H$_3$–(**1a**) with H^{16}–(CD) and H^{15}–(CD) are characteristic for complexes shown in Figs. 4a and 4c, and the corresponding complexes with CD in open(4) conformation (not shown). The cross-signal between H^3–(**1a**) and H^8–(CD) can arise due to the very short distance of 0.184–0.186 nm found in complexes of Figs. 4b and 4d. A weak NOE between H^5–(**1a**) and H^{16}–(CD) supports the existence of the complex shown in Fig. 4d.

4. Discussion

4.1. Evidence for a bidentate reactant–modifier complex

We have proposed in a preliminary report [21] that in the hydrogenation of the hydroxypyrone **1a** in acetonitrile (optimum conditions) the enantioselectivity is controlled by a bidentate complex formed between the acidic reactant and the basic cinchona alkaloid modifier (Fig. 1). The crucial role of acid–base-type interactions was supported by the loss of ee in the presence of a base stronger than the quinuclidine N of CD, and by NMR and FTIR investigations. The importance of a second H-bond involving the OH group of CD was indicated by the poor ee achieved in good H-bond donor or acceptor solvents, ab initio calculations, and also by FTIR analysis.

In the present study the theoretical calculations, extended to another acidic hydroxypyrone **2a** (Fig. 5), confirm the model with two H-bonding interactions. A set of representative complexes for CD–**2a** was calculated (CD in open(3) conformation) and compared to the corresponding CD–**1a** complexes (Fig. 4). The calculations showed that the CD–**2a** complexes are feasible even with strong steric repulsion between the methyl group in the C^3 position of **2a** and the quinuclidine part of CD. Not surprisingly, the stabilization energies of these complexes were much lower compared to those of the corresponding CD–**1a** complexes. The complexes with a perpendicular arrangement, except the pro-(*R*) CD–**2a** complexes (Figs. 5c and 5d), were found to be more stable than those with a parallel orientation but the former cannot easily adsorb on an approximately flat metal surface (low Pd dispersion). The complexes with parallel arrangement (Figs. 4b and 4d; Figs. 5b and 5d) should be minor species in solution due to their lower stability. Interaction of CD with the pyrones on the Pd surface in this geometry is, however, more feasible than in a perpendicular arrangement of CD and the pyrones, due to strong steric repulsion between surface and substrate in the latter arrangement. Hydrogenation of pyrones in this arrangement is expected to be fast.

The calculated energetic discrimination of 1.3 kcal/mol for the parallel pro-(*R*) and pro-(*S*) CD–**1a** complexes (Figs. 4b and 4d) would lead to 70–80% ee at room temperature and this is in the range of the experimentally observed ee's (up to 85% ee in acetonitrile [19]). The ee in the hydrogenation of **2a** cannot be supported by the calculated energetic discrimination of the corresponding parallel CD–**2a** complexes (Figs. 5b and 5d). The very low reaction rate, however, can be attributed to an unfavorable adsorption of the CD–**2a** complexes (Figs. 5b and 5d) and to their very low energetic stability.

NMR analysis of CD–**1a** and CD–**2a** solutions corroborated the existence of two H-bonding interactions in apolar solution. NOESY-NMR spectroscopy confirmed the geometry of the calculated CD–**1a** complexes (Fig. 4) and the presence of CD in various conformations, though mainly in open(3).

4.2. Alternative reactant–modifier interactions

Hydrogenation of **1a** in the presence of CD derivatives (Table 2) provided the first indication of the limited applicability of the bidentate model shown in Fig. 1. Contrary to the expected loss of enantioselectivity, blocking of the OH group of CD in MeOCD led to small but significant ee's (2–14%) to the opposite enantiomer in various polar solvents. Furthermore, replacing the acidic C^4–OH function in **1a** by a methoxy (**3a**) or methyl group (**4a**) did not hinder the enantiodifferentiation with MeOCD: both **3b** and **4b** were obtained in fairly good ee, in the same range as those of **1b** and **2b** (Table 1). In the hydrogenation of **3a** MeOCD-modified Pd afforded more than half of the ee achieved with CD under otherwise identical conditions (Table 3). Obviously, in the latter reaction neither the H-bond involving the OH group of CD nor the acid–base-type interaction depicted in Fig. 1 exists.

The IR and NMR are in line with the assumption that beside the bidentate complex shown in Fig. 1, single-bonded complexes may also exist in apolar solutions of CD and the acidic hydroxypyrones **1a** or **2a** (Fig. 8). Hydrogenation of **1a** via these complexes can rationalize the low but significant ee to (*R*)-**1b** achieved with MeOCD. The N–H–O-type

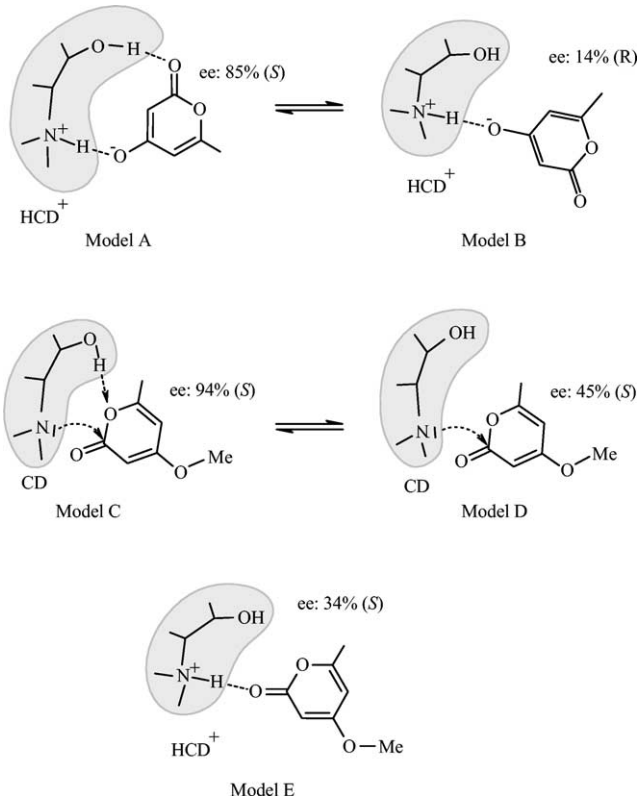


Fig. 9. Feasible mechanistic models for the enantioselective hydrogenation of 2-pyrones.

interaction alone is not enough to induce considerable enantiodifferentiation due to the weak steric discrimination between the O atoms connected to C^3 and C^5 in **1a** (see the mesomeric structures of deprotonated **1a** in Fig. 6).

To sum up, a survey of all feasible models based on different 2-pyrone–CD interactions is given in Fig. 9. Models A and B for the acidic reactants **1a** and **2a** are strongly supported by the catalytic and spectroscopic studies presented here and in a previous paper [21]. The bidentate interaction in model A affords up to 85% ee to the (*S*)-enantiomer [19]. When this interaction is disfavored by a basic or protic solvent or prevented by blocking the OH group of CD (in MeOCD), the interaction shifts to the monodentate model. The single attractive interaction in model B is poorly effective: it afforded at best only 14% ee to the (*R*)-enantiomer.

In the hydrogenation of nonacidic pyrones (4-methoxy- and 4-methyl-pyrones **3a** and **4a**, respectively) the nature of enantiodifferentiation seems to be completely different. The most selective among all reactions studied was the hydrogenation of **3a** to **3b** (94% ee [20,45]). Though no sign of interaction between the OH group of CD and **3a** could be detected by IR, UV, and NMR spectroscopy, blocking of the OH group reduced the ee by about 30% (Table 3). Thus, we propose again two possible models: a bidentate complex C for the CD–**3a** interaction and a monodentate complex D for the MeOCD–**3a** interaction (Fig. 9). Both modifiers provide (*S*)-**3b** in excess while cinchonine affords (*R*)-**3b** as the dominant enantiomer [20,45]. In model C we assume an interaction between the quinuclidine N of the modifier as electron pair donor and the carbonyl C atom of the pyrone, which is the only electrophilic atom present in the reactant. Further, it may be speculated that the high ee achieved in this reaction necessitates a second interaction to situate the reactant in a fixed position. This interaction may be a steric repulsion, similar to the hydrogenation of ethyl pyruvate on cinchona-modified Pt [46]. It is more likely, however, that there is a second attractive interaction involving the OH group of CD and the lactone O atom of **3a**. This assumption is supported by the good ee (73%) achieved in the hydrogenation of the 3-methyl derivative of **3a** (3,6-dimethyl-4-methoxy-2-pyrone [20]), indicating no steric hindrance against the reactant–modifier interaction proposed. When the OH function of CD is blocked (MeOCD), the interaction is shifted to the monodentate complex D (Fig. 9). The same models C and D may be applied for the hydrogenation of **4a** as we do not attribute any special role to the 4-methoxy group in **3a**.

The moderate ee's measured in the hydrogenation of **3a** and **4a** in AcOH (34 and 8%, respectively, Table 1) cannot be interpreted by model C or D. A possible explanation is model E (Fig. 9): an N–H–O type interaction between the protonated quinuclidine N and the carbonyl O atom of the pyrone. The validity of models C–E is currently under investigation in our laboratory.

5. Conclusions

The present study revealed the existence of different reaction mechanisms that can rationalize the enantiodiscrimination in the hydrogenation of the functionalized 2-pyrones **1a**–**4a** over a 5 wt% Pd/TiO_2 catalyst modified by CD or MeOCD. For the hydrogenation of the acidic hydroxy-pyrones **1a** and **2a** the energetically most favorable is a bidentate complex involving an acid–base-type interaction via the quinuclidine-N of the modifier and the OH group of the reactant, and a second H bond between the OH group of the modifier and the carbonyl-O of the reactant. In the same reactions, single bonded complexes involving only the stronger N–H–O interaction provide low ee to the opposite enantiomer. Obviously, this competing mechanism can diminish the ee. This is the case when the hydrogenation of **1a** or **2a** is carried out in a protic or basic medium, where the solvent can disturb the O–H–O interaction between the OH group of the alkaloid and the carbonyl O atom of the reactant. These two models (A and B in Fig. 9) are strongly supported by the catalytic and spectroscopic data and the ab initio calculations.

On the basis of the catalytic results we propose three other mechanisms for the hydrogenation of the nonacidic pyrones **3a** and **4a** (models C, D, and E in Fig. 9). These models are in agreement with the catalytic results using cinchona alkaloids or some of their simple derivatives as chiral modifiers and can interpret the big variations in enantioselectivity, de-

pending on the structure of reactant and modifier. Models C–E should be considered as working hypotheses that necessitate conformation.

Acknowledgments

We thank F. Bangerter for the NMR spectroscopic measurements and M. von Arx for the preparation of CD derivatives.

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