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A combined experimental and theoretical study of 1-phenylpropane-1,2-dione hydrogenation over heterogeneous cinchonidine-modified Pt catalyst

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Abstract

The enantioselective hydrogenation of vicinal diketones over cinchonidine-modified Pt resulted in enantiomeric excess of structurally similar (*R*)-enantiomers. Furthermore, the kinetic resolution was caused due to faster reaction of (*S*)-hydroxyketone further to diols, resulting in an increase of ee. The diastereoselectivities in diols were similar. The (*R*,*S*) or (*S*,*R*) diols were always the main products whereas considerably less (*R*,*R*) of (*S*,*S*) were formed. For the first time in 1-phenylpropane-1,2-dione (**A**) hydrogenation enantiomeric excesses of both C1=O1 and C2=O2 group have been reported. The $ee_{1\text{-OH}}$ and $ee_{2\text{-OH}}$ were 50 and 25%, respectively, at 50% conversion of **A**. Based on batch and continuous reactor experiments it could be concluded that the source of enantioselectivity is an increased formation rate of (*R*)-enantiomer and decreased formation rate of (*S*)-enantiomer. Theoretical calculations revealed that in the substrate-modifier diastereomeric complex the reactant forms a nonplanar s-*cis* conformation and bonds to the protonated cinchonidine either via a bifurcated hydrogen bond or with two hydrogen bonds where the OH group is involved also. Optimized diastereomeric complexes were equal in energy. The calculated proton affinity of CD was high, 1000 kJ mol^{-1}, indicating that protonation is feasible under typical experimental conditions.

Keywords: Diketone; Cinchonidine; Enantioselective hydrogenation; Ab initio calculations

1. Introduction

The use of chiral modifiers, which adsorb on the metal surface, has proven to be one of the most effective ways to transfer chirality by utilizing solid, heterogeneous catalysts. Pt dispersed on a high surface area material (e.g., Al_2O_3 or SiO_2) is an effective catalyst for the hydrogenation of a carbonyl group (C=O) to a corresponding alcohol. Prochiral carbonyl compounds are hydrogenated to racemic product mixtures, 50% (*R*)- and 50% (*S*)-enantiomers, over a conventional supported Pt catalysts. However, when a chiral auxiliary, e.g., a natural alkaloid, is added the situation changes and, e.g., α-keto esters can be hydrogenated to α-hydroxy esters with up to 98% enantiomeric excess (ee) [1]. This example represents one of the most intensively investigated modified heterogeneous catalytic systems, i.e., Pt modified with cinchona alkaloids, which were discovered in the late 1970s by Orito et al. [2–5]. Nowadays the enantiodifferentiating mechanism of α-keto esters is fairly well understood [6–9].

Hydrogenation of vicinal diketones including butane-2,3-dione [10,11], hexane-3,4-dione [11], cyclohexane-1,2-dione [12], 1,2-diphenyl-1,2-dione [13], hexane-2,3-dione [11], and 1-phenylpropane-1,2-dione [14,15] can be carried out enantioselectively over the Pt-cinchona alkaloid catalytic system (Fig. 1). Although the reaction mechanism has not been studied extensively, as is the situation with α-keto esters, there are evident mechanistic analogies between vicinal diketone and α-keto ester hydrogenations. The dependence on, e.g., catalyst properties (pretreatment, activation, structural properties), solvent, and modifier concentration is in some cases very similar. The hydrogenation products of vicinal diketones, optically active hydroxy ketones and di-

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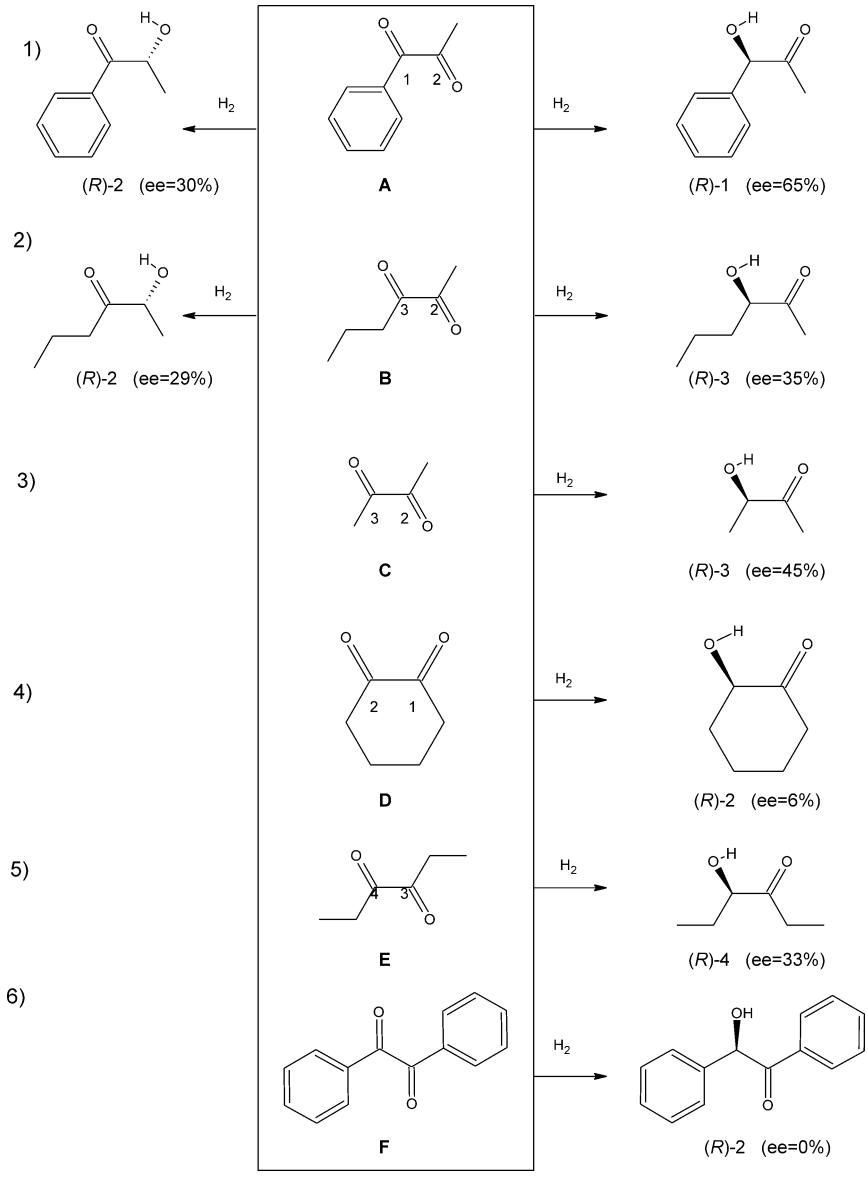

Fig. 1. Vicinal diketones and excess enantiomer (ee in brackets) in hydrogenation over cinchonidine-modified Pt catalyst.

ols, are utilized in the synthesis of pharmaceuticals; e.g., ephedrine [16] is synthesized from **(*R*)-1** (Fig. 2).

In mechanistic studies of asymmetric heterogeneous metal catalysts the crucial questions are: what is the nature of a chiral site, and how does the enantiodifferentiation take place on the metal surface? These questions are particularly difficult to answer when three-phase systems are involved. The interplay of all participating elements can be very complex involving solid catalyst, the liquid phase (solvent, dissolved reactants and products, chiral catalyst modifier), and the gas phase. Surface-sensitive spectroscopic techniques, theoretical calculations, and traditional kinetics each have their own disadvantages. However, when used in combination, these methods can yield valuable mechanistic information.

The aim of this study is to develop an enantiodifferentiation model for the hydrogenation of vicinal diketones over cinchona alkaloid-modified Pt catalysts. 1-Phenyl-1,2-propanedione is used as a model molecule because it comprises all the aspects of the inherently complex vicinal diketone hydrogenation reaction network. Extensive kinetic experiments in continuous and batch reactors are utilized in parallel with theoretical calculations and in connection with the available spectroscopic data on the Pt/cinchona alkaloid system to develop an enantiodifferentiation model.

2. Experimental

2.1. Catalyst and chemicals

Commercial 5 wt% Pt/Al_2O_3 catalyst (Strem Chemicals, 78-1660) was used in the hydrogenations (BET specific surface area 95 $m^2\,g^{-1}$, the mean metal particle size 8.3 nm (XRD), dispersion 40% (H_2 chemisorption), and the mean

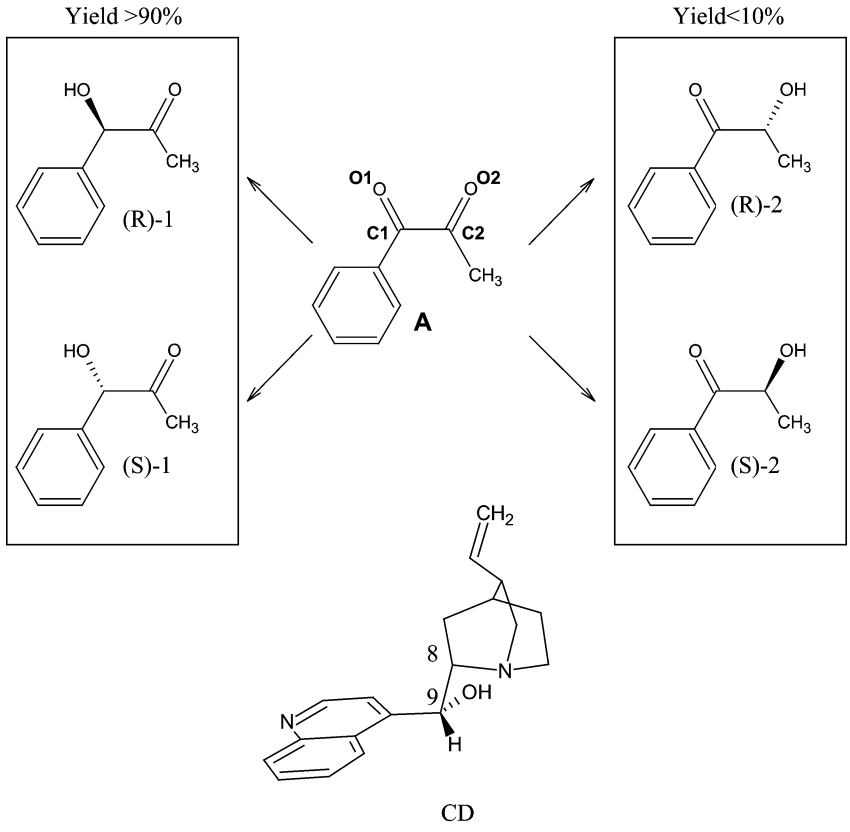

Fig. 2. Simplified reaction scheme of 1-phenylpropane-1,2-dione (**A**) hydrogenation and cinchonidine (**CD**).

catalyst particle size 18.2 μm (Malvern). Catalyst characterization has been described in detail previously [14,17].

The chemicals, 1-phenylpropane-1,2-dione (Aldrich, 22303-4, 99%), toluene (J.T. Baker, 8077, > 99.5%), ethyl acetate (Lab-Scan, A3511, 99.8%), and (−)-cinchonidine (Fluka, 27350, 98%), were used as received.

2.2. Hydrogenation experiments

1-Phenylpropane-1,2-dione (**A**) was hydrogenated in a pressurized batch reactor (Parr, 300 cm^3) under kinetic control. The hydrogen (AGA, 99.999%) pressure and temperature were 6.5 bar and 15 °C, respectively. Typically, in the kinetic experiments, the catalyst mass and liquid volume were 0.15 g and 150 cm^3, respectively, and the stirring velocity was 1950 rpm. The catalyst was activated prior to the reaction under hydrogen flow (100 $cm^3\,min^{-1}$) for 2 h at 400 °C and cooled down to the reaction temperature. An in situ modification procedure was utilized; i.e., the hydrogen degassed reactant solution containing reactant, modifier, and solvent was injected into the reactor and the reaction was commenced immediately by starting agitation. The initial concentrations of 1-phenylpropane-1,2-dione and cinchonidine (**CD**) were 0.025 and 0–2.7 × 10^{-3} mol dm^{-3}, respectively.

Continuous hydrogenation was carried out in a fixed-bed reactor (10 cm length and 0.9 cm internal diameter) at 25 °C and 5 bar hydrogen. The catalyst bed was composed of 25 mg catalyst (particle size 45–90 μm) diluted with 200 mg of Al_2O_3 (JM, EN AL4174P), resulting in the catalyst bed thickness of 1.0 cm. Prior to the reaction, the catalyst was reduced in situ under flowing hydrogen at 400 °C and 1 bar for 2 h. The liquid phase containing the modifier, the solvent, and the reactant was bubbled with hydrogen for 25 min prior to commencing the reaction. Typically the experiments were carried out with concurrent downward gas (50 $cm^3\,min^{-1}$) and liquid flows (2.8 $cm^3\,min^{-1}$).

2.3. Definitions of selectivities and yield

Enantiomeric excess of (*R*)-1-hydroxy-1-phenyl-2-propanones and (*R*)-2-hydroxy-1-phenyl-1-propanones, **(*R*)-1** and **(*R*)-2**, respectively, are defined:

$$ee_{1\text{-OH}} = \frac{[(\boldsymbol{R})\text{-}\mathbf{1}] - [(\boldsymbol{S})\text{-}\mathbf{1}]}{[(\boldsymbol{R})\text{-}\mathbf{1}] + [(\boldsymbol{S})\text{-}\mathbf{1}]} \times 100\%,$$

$$ee_{2\text{-OH}} = \frac{[(\boldsymbol{R})\text{-}\mathbf{2}] - [(\boldsymbol{S})\text{-}\mathbf{2}]}{[(\boldsymbol{R})\text{-}\mathbf{2}] + [(\boldsymbol{S})\text{-}\mathbf{2}]} \times 100\%.$$

The yield of compound i has been defined accordingly

$$Y_i = \frac{[i]}{\sum[\text{products}]} \times 100\%.$$

The regioselectivity (rs) is defined as

$$\mathrm{rs} = \frac{[(\boldsymbol{R})\text{-}\mathbf{1}] + [(\boldsymbol{S})\text{-}\mathbf{1}]}{[(\boldsymbol{R})\text{-}\mathbf{2}] + [(\boldsymbol{S})\text{-}\mathbf{2}]}.$$

2.4. Analytical procedure

Samples were withdrawn from the reactor at different time intervals and analyzed with a Varian 3300 gas chromatograph (GC) equipped with a chiral column (β-Dex 225). A new (previously not used) chiral column that could separate (*R*)- and (*S*)-2-hydroxy-1-phenyl-1-propanones was utilized in the present work. With time the column's ability to separate (*R*)- and (*S*)-2-hydroxy-1-phenyl-1-propanones decreases rapidly and therefore in previous reports these enantiomers could not be separated with an aged column. Details of the analytical procedure, calibration, and GC standard synthesis can be found in [14].

2.5. Calculations

2.5.1. Protonated cinchonidine-1-phenylpropane-1,2-dione complexes

The source of enantiodifferentiation is the interaction between catalyst modifier and reactant. Therefore, different substrate-modifier complexes were evaluated by using ab initio calculations with Gaussian98 software [18]. Different starting geometries for the reactant, 1-phenylpropane-1,2-dione (**A**), having s-*cis* and s-*trans* conformations, were first preoptimized by using Hartree–Fock (HF) approximation with the 3-21G basis set. Modifier cinchonidine was assumed to be protonated having an Open(3) conformation in analogy with the previous calculations for methyl pyruvate [19]. These starting geometries of the cinchonidine-reactant complexes were fully optimized by using HF approximation with the 6-31G* basis set [20–22]. The effects of the complex formation on the relative energies of 1-phenylpropane-1,2-dione bonding and antibonding orbitals in the keto carbonyl moiety were evaluated.

2.5.2. Proton affinity of cinchonidine

In order to calculate the gas-phase proton affinity of cinchonidine, i.e., the negative of ΔH for the reaction $\mathrm{CD} + \mathrm{H}^+ \rightarrow \mathrm{CDH}^+$ in the standard conditions (at 298.15 K in pressure of 1 bar), the equilibrium structures and vibrational spectra of CD and CDH^+ were computed with density functional theory (DFT) using the resolution-of-the-identity (RI) approximation [23] and the analytic second derivative program AOFORCE [24] as implemented in the TURBOMOLE program package [25,26]. For these calculations the BP86 functional [27,28] and TZVP [29,30] basis set were used. The frequencies were scaled by a factor of 0.95. The single-point energies of the DFT-BP86/TZVP-optimized structures were calculated with Gaussian98 using second-order Møller–Plesset perturbation theory (MP2) [31] with the standard 6-31G* basis set.

3. Results

The pertinent kinetic observations for vicinal diketones are presented. The main focus is on factors which affect enantioselectivity and reaction rate.

3.1. Influence of solvent

Solvent plays an important role and affects the reaction rate and enantioselectivities considerably. Bad choice of solvent can lead, for instance, to almost racemic reaction. The $\mathrm{ee}_{1\text{-OH}}$ depends strongly on solvent polarity [32] in the hydrogenation of **A**. Toluene, $\mathrm{ee}_{1\text{-OH}} = 65\%$, and ethyl acetate, $\mathrm{ee}_{1\text{-OH}} = 62\%$, give the highest $\mathrm{ee}_{1\text{-OH}}$ at maximum yield. In preliminary experiments with **A** in acetic acid the $\mathrm{ee}_{1\text{-OH}} = 6\%$ and activity decreased considerably. Application of alcohols, e.g., ethanol ($\mathrm{ee}_{1\text{-OH}} = 12\%$) and methanol ($\mathrm{ee}_{1\text{-OH}} = 4\%$), resulted in low $\mathrm{ee}_{1\text{-OH}}$, although the reaction rate was about the same as in ethyl acetate.

In other vicinal diketone hydrogenation experiments, similar observations have been reported. For butane-2,3-dione (**C**) the ee decreased in acidified toluene (1 M AcOH in toluene) with respect to neat toluene from 45 to 28% [33] and alcohols reduced the ee from the highest value obtained in toluene. Cyclohexane-1,2-dione (**D**) hydrogenation [12] gave high 81% ee of (1*R*,2*R*)-cyclohexane-1,2-diol in toluene whereas in acetic acid, tetrahydrofurane, 2-propanol, and acetonitirle, reduced ee and a lowered activity was observed (the ee in this context is the ee of final product diol and not the (*R*)-2 hydroxyketone).

In conclusion relatively nonpolar solvents such as toluene are the best ones for achieving high enantioselectivity in vicinal diketone hydrogenation. The utilization of acetic acid, which is commonly known as the best solvent for α-keto esters, particularly for ethyl pyruvate, leads to decreased ee and activity in hydrogenation of **A**, **C**, and **D**. However, ketopantolactone (KPL), also an α-keto ester which has a fixed s-*cis* conformation, has a very similar dependence on solvent polarity [34,35] as **A** [32]. Namely, toluene is clearly the best solvent for KPL hydrogenation, and acetic acid and alcohols lead to considerably reduced ee. Although the reason for the negative effect of acetic acid and alcohols as solvents is not understood completely, it seems to be characteristic of vicinal diketones.

3.2. Rate acceleration

It has been reported that an *overall rate acceleration* is a general feature of the Pt/cinchona system (the Orito reaction) for α-functionalized ketones [6–8]. In principle this means that in the presence of a catalyst modifier, e.g., cinchonidine, the overall reaction rate is considerably higher than in the absence of modifier. For ethyl pyruvate up to 100-fold increase of reaction rate has been reported [36]. Furthermore, Wells and co-workers [37] stated that the rate

acceleration is always observed for both of the enantiomers with respect to racemic hydrogenation.

In this light a noteworthy observation is that cinchonidine induces ee but not necessarily overall rate acceleration in vicinal diketone hydrogenation. With **A,** e.g., no rate acceleration could be observed in the presence of **CD** over 5% Pt/Al_2O_3 (Strem) catalyst [15]. Analogous results were reported [12] for **D** for which the **CD** resulted in considerably reduced reaction rate in the first reaction step to hydroxyketone over a 5% Pt/Al_2O_3 (Engelhard 4759) catalyst. For **C** differing observations have been reported. When 6.3% Pt/SiO_2 catalyst was used no rate acceleration was reported [11]. However, over 5% Pt/Al_2O_3 (JM94) catalyst considerable rate acceleration could be observed [10]. Noteworthy is that in both cases similar ee values were obtained (ee = 40–45%). Furthermore, in **C** hydrogenation when codeine was used as the catalyst modifier in dichloromethane or ethanol as solvent up to fivefold rate acceleration could be observed with zero enantioselectivity [38]. This suggests that in vicinal diketone hydrogenation the *overall rate acceleration,* although observable in some cases, is not a prerequisite for an enantioselective reaction.

3.3. Enantioselectivity in vicinal diketone hydrogenation

In the previously reported studies [14,15,17,32,39,44] in hydrogenation of **A** over cinchona alkaloid-modified Pt catalyst the (*R*)- and (*S*)-2-hydroxy-1-phenyl-1-propanones (**(*R*)-2** and **(*S*)-2** in Fig. 2) could not be separated making the reaction network incomplete (Fig. 2). However, in the present work, the unused chiral column that was employed allowed such a separation (see experimental section for details) and in Fig. 3 for the first time both the $ee_{1\text{-OH}}$ and $ee_{2\text{-OH}}$ are illustrated as a function of conversion of **A**. The $ee_{1\text{-OH}}$ and $ee_{2\text{-OH}}$ increase slightly with conversion of reactant **A** from 20 to 80% after which the increase is more steep. The $ee_{1\text{-OH}}$ has been maximally 65% in the first reaction step under optimized conditions at maximum yield. The $ee_{1\text{-OH}}$ can be increased to nearly 100% by kinetic resolution of **(*R*)-1** and **(*S*)-1**, which is represented by the steeply increasing $ee_{1\text{-OH}}$ at high reactant conversion (Fig. 3). **(*S*)-1** reacts faster to diols than **(*R*)-1** and therefore, the $ee_{1\text{-OH}}$ increases. In the hydrogenation of the second carbonyl group (C2=O2) the (*R*)-enantiomer was also formed in excess, although the $ee_{2\text{-OH}}$ was notably lower. Not surprisingly, analogous kinetic resolution was observed also for $ee_{2\text{-OH}}$. The **(*S*)-2** reacted faster to diols than **(*R*)-2** and therefore, $ee_{2\text{-OH}}$ increases from 25 to 50% at high reactant conversions. Increase of ee by kinetic resolution is achieved at the cost of reduced yield of main product as illustrated in Fig. 4.

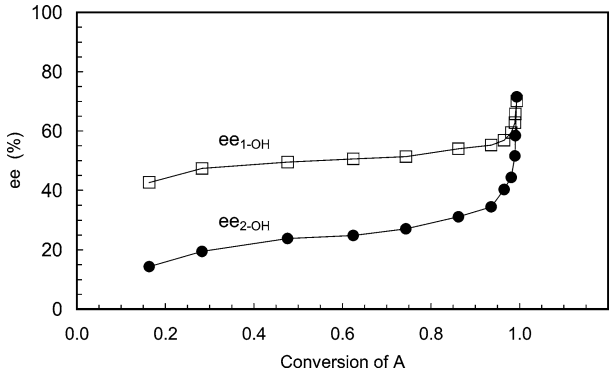

Fig. 3. The enantiomeric excesses in hydrogenation of 1-phenylpropane-1,2-dione over a 5% Pt/Al_2O_3 catalyst at 15 °C in toluene.

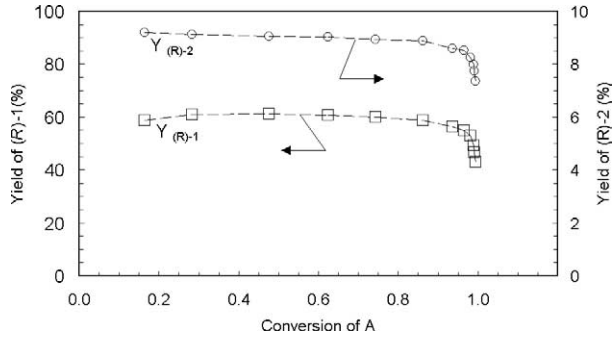

Fig. 4. The yield of excess enantiomers (*R*)-1 and (*R*)-2 in hydrogenation of 1-phenylpropane-1,2-dione (**A**) at 15 °C in toluene.

Interestingly, with asymmetrical hexane-2,3-dione (**B**, Fig. 1) the stereochemical outcome was analogous to the hydrogenation of **A** [11]. Structurally analogous (*R*)-2 and (*R*)-3 were obtained in 29 and 35% enantiomeric excess, respectively (Reaction 2 in Fig. 1).

Studer et al. [10] used 5% Pt/Al_2O_3 and an in situ catalyst modification procedure, whereas Slipszenko et al. [11] utilized 6.3% Pt/SiO_2 (EUROPT-1) catalyst and ex situ aerobic modification for the hydrogenation of **C**. In both investigations the (*R*)-3 was obtained in excess (ee = 45% at maximum yield). The ee of (*R*)-3 could be increased up to 85–90% by kinetic resolution. In analogy to hydrogenation of **A** the (*S*)-3 reacted much faster to diols, resulting in improved ee of the remaining (*R*)-3.

In hydrogenation of hexane-3,4-dione (**E**, Fig. 1) Slipszenko et al. [11] applied a 6.3% Pt/SiO_2 (EUROPT-1) catalyst and obtained the (*R*)-4 in 33% excess.

In hydrogenation of **D** the first hydrogenation step is almost racemic, the (*R*)-2 was obtained with only marginal 6% ee (calculated from the rate constants) [12]. Regardless of the low ee, the configuration of the excess enantiomer was the same as with all other vicinal diketones.

In 1,2-diphenylethane-1,2-dione (**F**, Fig. 1) hydrogenation, the lack of enantioselectivity over cinchonidine-modified 6.3% Pt/SiO_2 (EUROPT-1) was reported [13]. As an explanation the steric hindrance caused by the nonplanar molecule, as it adsorbs on flat Pt surface, was offered. An additional possibility for the 0% ee was, according to the author, the hot filtration method used for the product recovery, which might have racemized the product [13].

To summarize, in the hydrogenation of vicinal diketones, excluding **F**, structurally analogous (*R*)-enantiomers were obtained in excess with cinchonidine as the catalyst modifier.

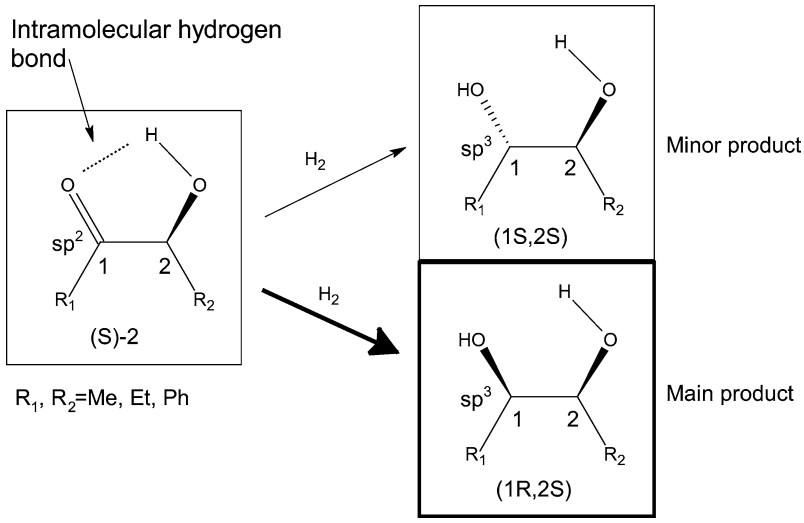

Fig. 5. The effect of steric repulsion on the product distribution of diols.

Furthermore, in all reported cases (reactions 1, 3, and 4 in Fig. 1) analogous kinetic resolution took place due to faster reactions of the (*S*)-enantiomer, thus increasing the ee of remaining (*R*)-enantiomer. The similarities indicate that the underlying reaction mechanism is similar for vicinal diketones.

3.4. Regioselectivity

Regioselectivity is an additional factor, which can be defined for reactions 1 and 2 (Fig. 1), where the carbonyl groups are distinguished from each other. In the case of symmetrical diones (**C**, **D**, **E**, and **F**) regioselectivity cannot be defined due to molecular symmetry.

Regioselectivity is rather high (rs = 10, in the absence of modifier rs = 4) in hydrogenation of **A**, indicating that the C1=O1 group adjacent to phenyl ring reacts mainly in the first step of the reaction yielding over 90% **(*R*)-1** + **(*S*)-1** (Figs. 2 and 4). In hydrogenation of **B**, regioselectivity equal to one was reported [11] demonstrating that there is no preference for different C=O group hydrogenation.

The source of high regioselectivity in **A** is probably the delocalization of electrons between the C1=O1 group and the phenyl ring [39], which makes the C1=O1 group more reactive that the C2=O2 group.

3.5. Diastereoselectivity and enantioselectivity of product diols

Three reactions (1, 3, and 4, Fig. 1) have been studied further [10,11,14,32] so that the product distribution among completely hydrogenated diols has been reported. The product distribution of diols and kinetic resolution (i.e., (*S*)-enantiomer reacts faster) in the second hydrogenation step are similar in these reactions, which indicate similar reaction mechanisms. The (1*S*,2*R*) and (1*R*,2*S*) diols in reaction 1 [32] or the meso diols (*S*,*R*) and (*R*,*S*) in reactions 3 and 4 were the major products [10,11]. Considerably less (*S*,*S*) and (*R*,*R*) enantiomers were formed. The contributing factor to the distribution of diols is evidently steric constraints induced by the Pt surface. In (*S*,*S*) and (*R*,*R*) one OH group points toward the Pt surface (when fixed in s-*cis* conformation, which is the most stable conformation of intermediate hydroxyketones [12] due to intramolecular hydrogen bonding) making their adsorption sterically hindered. The situation with (*S*,*R*) and (*R*,*S*) is different in such a way that both OH groups point away from the Pt surface making their adsorption sterically favored (Fig. 5). The evident similarities in the further reactions to diols support a proposal of a common reaction mechanism.

3.6. Kinetics of enantiodifferentiation

The origin of enantiodifferentiation was found to be the altered formation rate of product enantiomers **(*R*)-1** and **(*S*)-1** in the presence of cinchonidine [15] (Figs. 6 and 7a). The formation rate of **(*R*)-1** increased and exhibited a maximum as a function of cinchonidine concentration, whereas the formation rate of **(*S*)-1** continuously decreased with respect to racemic hydrogenation as cinchonidine concentration was increased (Fig. 7). A similar observation was made in continuous operation in a fixed-bed reactor as well, i.e., with increasing time-on-stream the amount of **(*R*)-1** increased and **(*S*)-1** decreased (Fig. 6). The overall activity remains nearly constant as the **(*R*)-1** increase is very much compensated by the **(*S*)-1** decrease. However, this is not qualitative compensation as catalyst deactivation contributes also to the overall activity.

A notable experimental fact is that the maximum in $ee_{1\text{-OH}}$ does not directly correspond to the maximum in formation rate of **(*R*)-1** nor to a clear minimum in **(*S*)-1** alone (Fig. 7a). However, if the formation rate of **(*S*)-1** is subtracted from the formation rate of **(*R*)-1** a very good correlation between the experimentally observed ee and

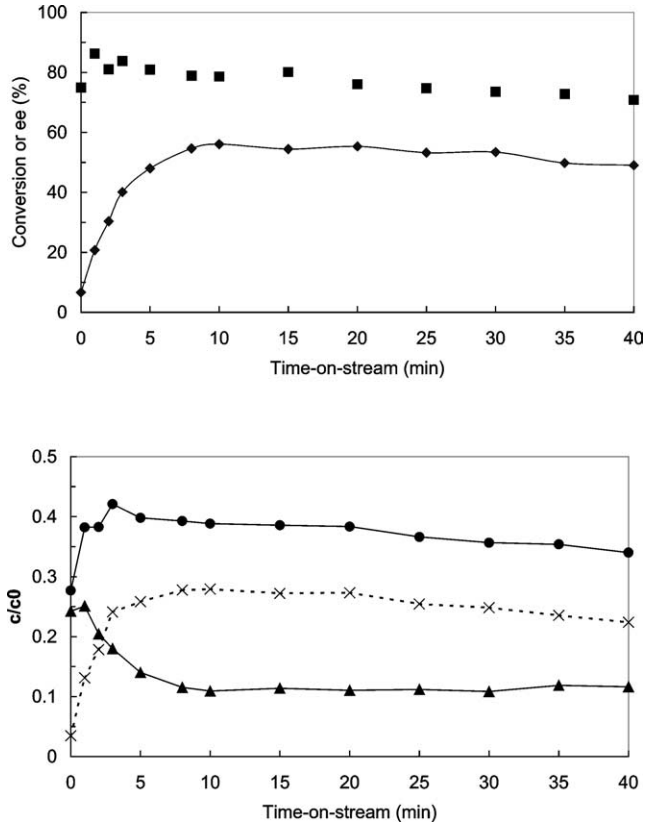

Fig. 6. Continuous hydrogenation of 1-phenylpropane-1,2-dione (**A**). Symbols: (◆) $ee_{1\text{-OH}}$, (■) conversion of **A**, (●) [(*R*)-1], (▲) [(*S*)-1], (×) [(*R*)-1] − [(*S*)-1]—product concentration in the reactor outlet, C_0—inlet concentration of A. The dashed line is obtained by subtraction of [(*S*)-1] from [(*R*)-1].

the remaining "enantioselective" formation rate **(*R*)-1** (see Fig. 7b) is obtained. This demonstrates that the apparent formation rate of **(*R*)-1** can well be divided into racemic (R_{racemic}) and enantioselective components ($R_{\text{enantioselective}}$) where the enantioselective component follows the experimental $ee_{1\text{-OH}}$:

$$R_{\text{apparent}} = R_{\text{enantioselective}(\boldsymbol{R})\text{-}\mathbf{1}} + R_{\text{racemic}(\boldsymbol{R})\text{-}\mathbf{1}}.$$

Even under optimum conditions the racemic reaction route contributes considerably to the apparent reaction rate. The ratio of $R_{\text{enantioselective}(\boldsymbol{R})\text{-}\mathbf{1}}$ to $R_{\text{racemic}(\boldsymbol{R})\text{-}\mathbf{1}}$ at maximum enantiomeric excess is 3.1.

When evaluating the overall reaction rate, one should keep in mind that adsorption of the modifier decreases the fraction of free Pt surface available for hydrogenation [40]. Under optimum conditions with respect to **CD** concentration a considerable fraction of the Pt surface is covered by the modifier and therefore, one would expect to observe a reduced C=O group hydrogenation rate if no rate-accelerating (activation) effects are involved. This is actually the situation for the **(*S*)-1** in the hydrogenation of **A** (Fig. 7). However, for the **(*R*)-1** the formation rate increased from the racemic hydrogenation level (Fig. 7) with increasing cinchonidine amount. This indicates that **CD** has some activating effects for the formation rate of (*R*)-enantiomer. This activation is a key to the enantiodifferentiation and enantioselectivity.

3.7. Theoretical calculations

In order to understand the enantiodifferentiation mechanism the reactant–modifier interaction should be considered. According to current understanding a one-to-one reactant–modifier complex is the source of enantiodifferentiation [6–9] in the Orito reaction. In the following calculation catalytic Pt surface has not been taken into account. Because only little information about the effect of modifier structure in vicinal diketone hydrogenation is available, the analogies observed with well-studied α-keto ester hydrogenation are used as a basis for the calculations. Cinchonidine is a complex molecule and exhibits a rich conformational behavior. Based on detailed experimental and theoretical considerations Open(3) conformer [6–9,35] has been proposed to be the actor species in enantiodifferentiation. Therefore, in this work the Open(3) conformer is considered the actor species and has been used in theoretical calculations. However, one should keep in mind that the situation is more complex, as other cinchonidine conformations are present as well and only about 70% of cinchonidine adopts Open(3) conformation in toluene.

Previously, in theoretical calculations with methyl pyruvate [19], the O=C–C=O system of methyl pyruvate and the quinoline ring of cinchonidine were restricted to coplanarity in order to mimic steric constraints induced by a flat Pt surface. In case of **A** the constraining to planarity was not utilized, because the catalyst used in the hydrogenation had clearly spherical Pt particles. The particle morphology became evident when analyzing transmission electron microscopy (TEM) images by comparing the shape of the Pt particles at the edge and on the center of the catalyst particle.

The important reactant-modifier interaction takes place via a hydrogen bond (C=O···H^+···N) between carbonyl oxygen and proton bonded to quinuclidine nitrogen of the cinchonidine [6–9]. Recently this kind of hydrogen bond between ketopantolactone (an α-keto ester) and cinchonidine was observed experimentally by attenuated total reflection IR concentration modulation spectroscopy [41]. There exists mechanistic proposals for α-keto esters [6–9], which include both protonated and nonprotonated **CD**; however, in both cases the substrate-modifier interaction takes place via a hydrogen bond. In this work the protonated cinchonidine (**CDH^+**) is considered as the source for the hydrogen bond between **A** and **CD**. In the following, molecular level interactions between protonated **CD** (**CDH^+**) in Open(3) conformation and **A** are considered by means of ab initio calculations.

3.7.1. Geometries of the complexes

Five minima on the potential energy surface (PES) were found for the substrate-modifier complexes between pro-

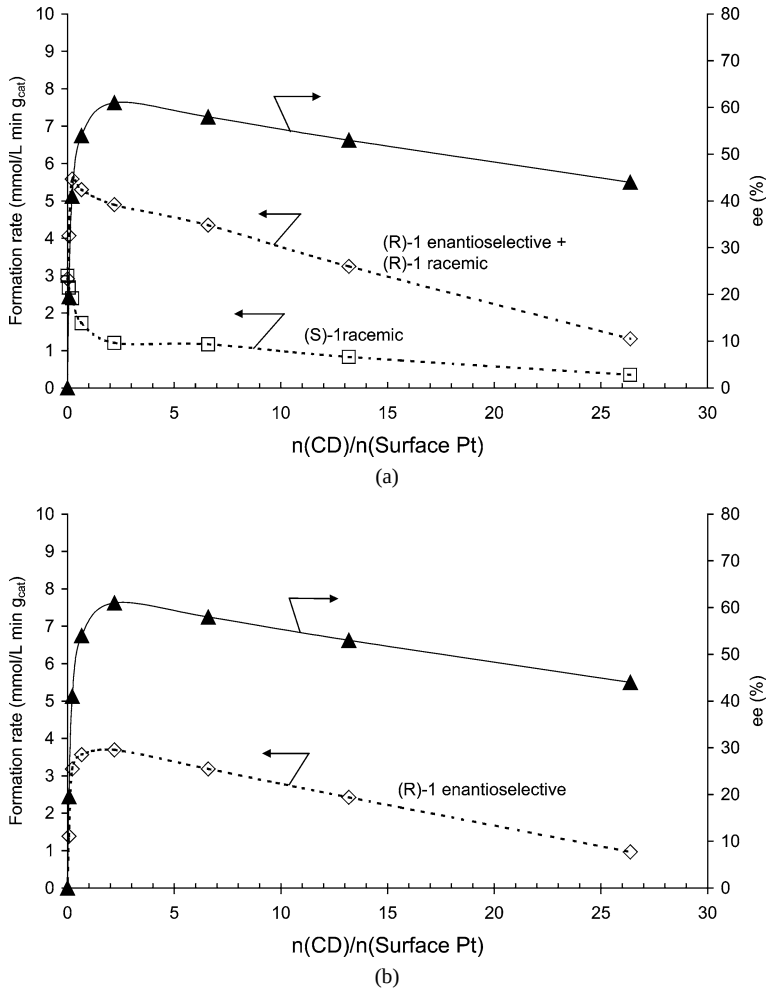

Fig. 7. The formation rates and enantiomeric excess (ee) in 1-phenylpropane-1,2-dione hydrogenation at different molar rations of cinchonidine-to-surface Pt in batch reactor. Symbols: $ee_{1\text{-OH}}$ (solid line), initial formation rates (dashed lines).

tonated cinchonidine (**CDH**$^+$) in Open(3) conformation and **A**, see Figs. 8 and 9. All optimized complexes were equal in stability, the largest relative energy difference being only 1.9 kJ mol^{-1} (Table 1). Two essentially different types of complexes were found, pro-R or pro-S (Fig. 8) and tilted ones (Fig. 9). In all complexes the reactant adopts an s-*cis* conformation, and especially no minimum on the PES for a complex, in which the reactant would have adopted s-*trans* conformation, was found. However, the PES is extremely flat and the existence of a complex with s-*trans* structure of the reactant cannot be completely ruled out. Based on the HF/3-21G preoptimized geometries, the complexes with the s-*trans* conformation of the reactant were ca. 16 kJ mol^{-1} less stable than the corresponding complexes with the s-*cis* conformation. Pro-S and pro-R complexes were stabilized by a bifurcated hydrogen bond between the proton and the two O=C groups of **A** (Fig. 8). Note that the isolated optimized reactant adopts s-*trans* conformation [39] (Table 1). The essential geometrical parameters are given in Tables 1 and 2. All pro complexes (Fig. 8) have a similar bifurcated hydrogen bond system, which defines the geometry. The aromatic ring of the modifier and the adjacent C=O group of the reactant are almost coplanar (see Fig. 8). In the tilted complex, (Fig. 9), the modifier's OH group is involved in the complexation. Two hydrogen bonds are formed: one between the modifier's OH hydrogen and the reactant's oxygen O2 and the second one between the modifier's NH^+ proton and the reactant's oxygen O1.

When evaluating the optimized modifier-reactant complexes one should keep in mind that the reactive C=O group should have an easy access to the adsorbed hydrogen on the spherical Pt surface. This limits the possible complex candidates to be considered as actor species in enantiodifferentiation as well. In the tilted complex (Fig. 9) the carbonyl groups are oriented in such a way that the addition of hydrogen from (below) the spherical Pt surface would not be possible. On the other hand, in pro-R1 and pro-S1 complexes the sterical criteria are fulfilled and the complexes can easily adsorb on a spherical Pt surface while both C=O groups have relatively easy access to adsorbed hydrogen. However, in pro-R2 and pro-S2 complexes the phenyl substituent sterically hinders their adsorption.

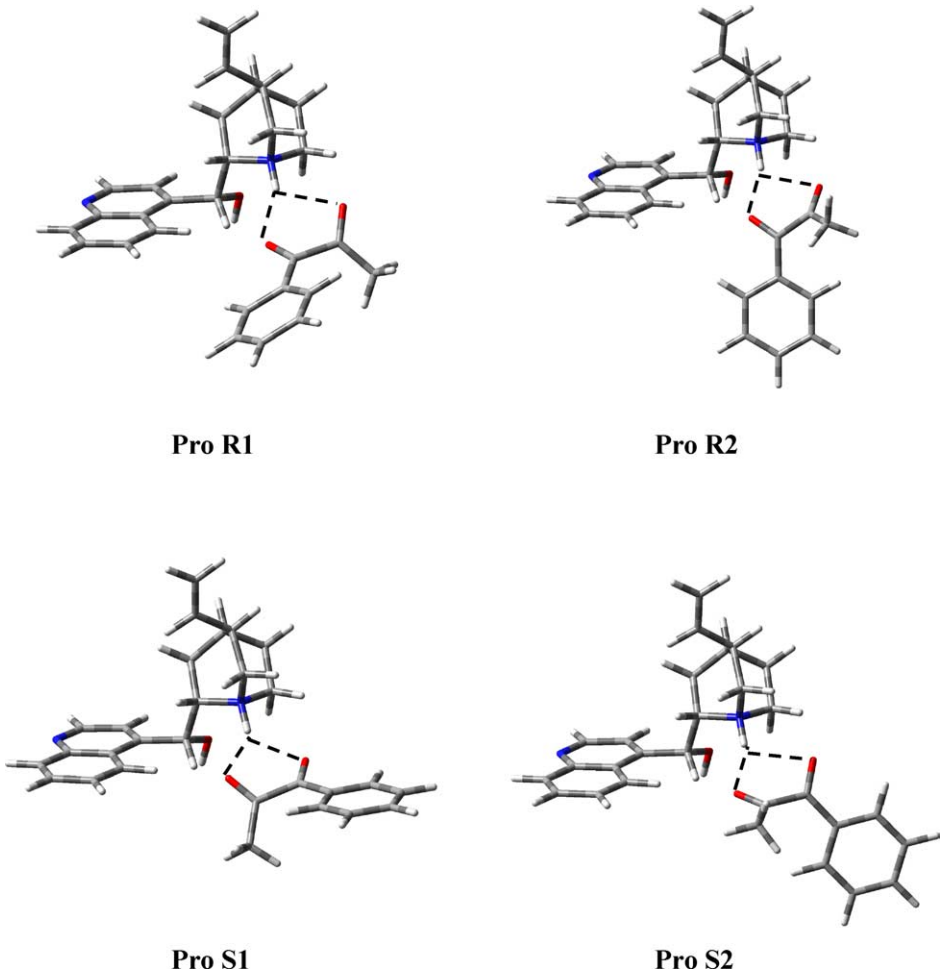

Fig. 8. CDH^+-**A** complexes having bifurcated hydrogen bond.

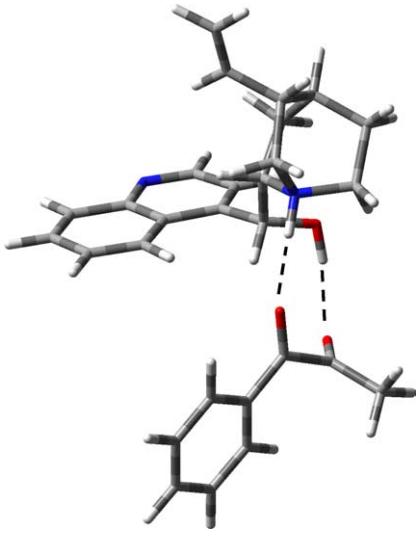

Fig. 9. The optimized tilted conformation of the modifier-reactant complex.

3.7.2. Proton affinity of cinchonidine

In theoretical calculations the protonated cinchonidine has been commonly utilized as a starting point [19]. The proton has a central role in the modifier-reactant interactions as it is involved in hydrogen bond formed between the cinchonidine and the reactant. The proton affinity (PA) was calculated in order to get information on how feasible the protonation of cinchonidine is. Calculation results demonstrate that cinchonidine has a very high proton affinity (987 and 1000 kJ mol^{-1} at the BP86/TZVP and MP2/6-31G*//BP86/TZVP level, respectively) and in case there are proton donors available the protonation of **CD** is probable.

3.7.3. Stability of 1-phenylpropane-1,2-dione keto carbonyl π orbitals

Recently, Vargas et al. [42] proposed that the stabilities of the bonding and antibonding keto carbonyl π (i.e., π and π^*) orbitals are a good measure for the reactivity of α-substituted ketones in racemic hydrogenation. Based on the frontier molecular orbital theory, the energy of the transition state can be extrapolated from the initial stage of the reaction to the activated complex. Activation, and consequently hydrogenation, would be correlated to the stabilization of the keto carbonyl orbitals. The stabilization (lowering of energy) of keto carbonyl orbitals would result in lowering of the transition-state energy and thus, decreasing the activa-

Table 1
The torsion angle D(O=C–C=O) (τ, °), complexation energies ($\Delta E_{\text{complex}}$, kJ mol^{-1}), and relative energies (kJ mol^{-1}) of the keto carbonyl antibonding π^* and the two keto carbonyl bonding π orbitals[a] in some complexes formed by 1-phenyl-1,2-propanedione (**A**) and protonated cinchonidine calculated at the HF/6-31G* level of theory

Complex	τ	$\Delta E_{\text{complex}}$	ΔE(A.B.)[b]	ΔE(B1)[c]	ΔE(B2)[d]	ΔE(sum)[e]
Pro-R1	44.2	−70.9[f]	0.0[g]	0.0[h]	0.0[i]	0.0
Pro-R2	−45.2	−70.7	−1.6	0.8	1.1	0.2
Pro-S1	−41.7	−69.5	2.7	8.0	1.8	12.5
Pro-S2	57.9	−71.4	27.9	9.1	12.1	49.2
Tilted	−74.4	−70.5	24.4	−1.0	7.5	31.0
Pure **A**	144.6	–	298.3	282.0	318.1	898.4

[a] Energies relative to the energies of the corresponding orbitals in the pro-R1 complex.
[b] Antibonding π^* orbital.
[c] Bonding π orbital 1.
[d] Bonding π orbital 2.
[e] $\Delta E_{\text{sum}} = \Delta E(\text{A.B.}) + \Delta E(\text{B1}) + \Delta E(\text{B2})$.
[f] $E_{\text{tot}}(\text{pro R1}) = -1411.6563301$ a.u., $E_{\text{tot}}(\mathbf{CD}\text{H}^+) = -916.4294386$ a.u., and $E_{\text{tot}}(\mathbf{A}) = -495.1998815$ a.u.
[g] $\varepsilon = -0.04739$ a.u.
[h] $\varepsilon = -0.60784$ a.u.
[i] $\varepsilon = -0.67770$ a.u.

Table 2
The distance (pm) between the carbonyl oxygens of the reactant and the NH^+ proton of the modifier in some complexes formed by 1-phenyl-1,2-propanedione and protonated cinchonidine and calculated at the HF/6-31G* level of theory

Complex	d ($NH^+\cdots$O1)	d ($NH^+\cdots$O2)
Pro-R1	203	255
Pro-R2	204	252
Pro-S1	226	221
Pro-S2	267	203
Tilted	196	228[a]

[a] The distance between O2 and the OH hydrogen of the modifier.

tion energy of the hydrogenation. This eventually leads to intrinsically higher hydrogenation rate.

The bonding π orbitals of 1-phenyl-1,2-propanedione and antibonding π^* (LUMO) are illustrated in Fig. 10. The first keto carbonyl-bonding orbital mixes with the π system of the aromatic ring and is split to two molecular orbitals, bonding 1 and bonding 2. The relative energies of LUMO, bonding 1, bonding 2, and sums of them for 1-phenyl-1,2-propanedione in optimized complexes with the modifier are reported in Table 1. Vargas et al. [42] proposed that the sum of orbital stabilization (HOMO + LUMO) is the most general parameter to be used as a measure for the reactivity. In the pro-R1 complex the differential orbital stabilization (ΔE_{sum}pro-S1 − ΔE_{sum} pro-R1, Table 1) is 12.5 kJ mol^{-1} compared to the pro-S1 complexes. This difference could explain the $ee_{1\text{-OH}}$ with kinetic control: in the pro-R1 complex **A** reacts faster to the (***R***)**-1** enantiomer than in the pro-S1 complex to the (***S***)**-1** enantiomer due to the stabilization of the keto carbonyl orbitals. This is in good agreement with the experimental observations for hydrogenation of **A**, where the formation rate of (***R***)**-1** enantiomer increased considerably in the presence of cinchonidine. However, the $ee_{2\text{-OH}}$ cannot be explained directly in an analogous manner, as the excess enantiomer (***R***)**-2** (upon hydrogenation of the C2=O2) is

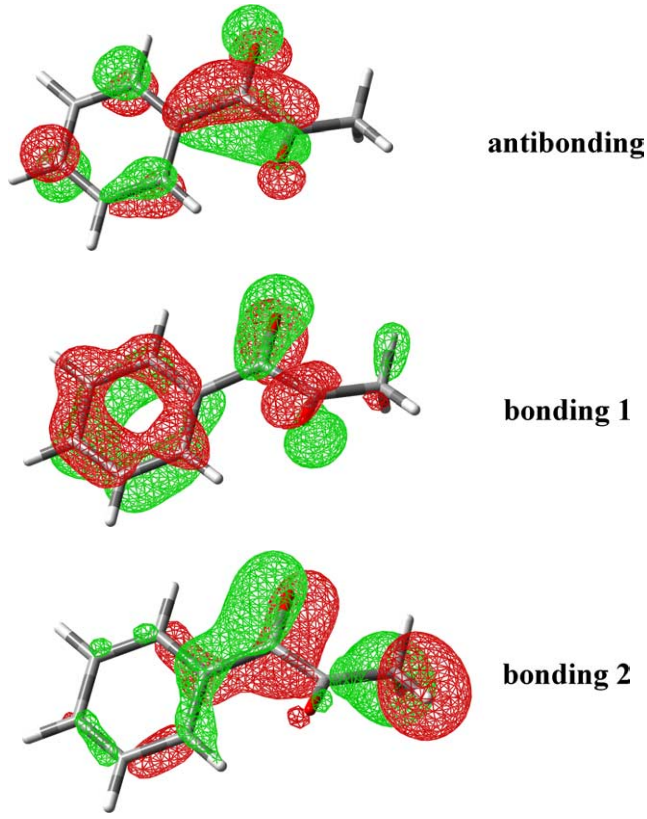

Fig. 10. Keto carbonyl antibonding π^* and bonding π orbitals of 1-phenyl-propane-1,2-dione.

evidently formed from the less stabilized pro-S1 complex upon hydrogenation. Calculations are currently in progress to evaluate alternative substrate-modifier complexes involving, e.g., interactions of **A** with the OH group of cinchonidine.

In order to further verify the observed keto carbonyl π orbital stabilization effect, additional optimization was carried using protonated cinchonine and **A** in order to see if analo-

gous orbital energy stabilization would be observed as well. Not surprisingly, analogous mirror image complexes could be optimized with a similar stabilization of the keto carbonyl π in the pro-S. This is in line with the kinetic experiments cinchonine yielded the major product **(*S*)-1** in excess [43]. Consequently, the observed keto carbonyl π orbital stabilization effect does not contradict with experimental observations.

3.7.4. Summary of theoretical calculations

The **CDH**$^+$**-A** interaction involves s-*cis* conformation of the reactant. Both carbonyl groups were involved in hydrogen bonding with the protonated **CD**. The hydrogen bond was either bifurcated (Fig. 8) or involved the hydroxyl group of cinchonidine (Fig. 9). In the present work complexes involving a bifurcated hydrogen bond were mainly considered; however, the possible involvement of the OH group of **CD** in enantiodifferentiation should not be totally forgotten. The optimized complexes were energetically identical and, therefore, enantioselectivity cannot be accounted by the stability of the different diastereomeric complexes (thermodynamic control) considered in this work.

The **CDH**$^+$**-A** interaction led to 12.5 kJ mol^{-1} keto carbonyl group stabilization of pro-R1 compared to the pro-S1 (Table 1). Analogous keto carbonyl molecular orbital stabilization has been observed in substituted acetophenones [42] and it could be linked to the hydrogenation activity; i.e., more profound stabilization means higher hydrogenation rate, as the energy levels of adsorbed hydrogen and reacting carbonyl group become closer to each other. This could be a contributing factor in enantiodifferentiation and in the enhancement of formation rate of (*R*)-enantiomer. However, the fact that two carbonyl groups of **A** can react complicates the situation.

The proton affinity of **CD** was around 1000 kJ mol^{-1}. Based on the high proton affinity of **CD** one can conclude that under typical experimental conditions the protonation of the modifier is feasible as long as proton donors are present (e.g., water or adsorbed hydrogen on Pt).

4. Discussion

In the sequel, central mechanistic aspects, which are relevant for the present work, are considered in detail for vicinal diketones.

4.1. Cinchonidine protonation

The vicinal diketones can be successfully hydrogenated in nonprotic solvents like toluene and under such conditions the protonation of **CD** has been questioned [6]. However, cinchonidine has a very high proton affinity and in case there are proton donors available the protonation of **CD** is probable. It should be noted that the optimum **CD** concentration is very low ($c = 10^{-5}$ mol dm^{-3}) and, therefore, the amount of proton donors needed is also small. **CD** protonation in nonprotic media could well take place either in the liquid phase by the residual water, always present to some extent or alternatively on the catalyst surface, which is covered by hydrogen. The adsorbed hydrogen as a source of proton has been proposed recently for ketopantolactone hydrogenation in dichloromethane [41] as the residual water and the solvent could be excluded as proton sources. Normally it is assumed that the hydrogen resides on the Pt surface in form of hydrogen atoms ($H^\bullet$) as a result of homolytic cleavage of a hydrogen molecule (H_2). In order for the adsorbed hydrogen atom to protonate **CD** it has to lose an electron, and where would this additional electron go and could the acid sites of alumina support be involved in the CD protonation are still open questions. However, regardless on the mechanism of the CD protonation on the catalyst surface (acid sites of alumina or dissociatively adsorbed hydrogen on Pt) there is experimental evidence [41], which supports CD protonation on the catalyst surface.

4.2. Hydrogen addition mechanism

The hydrogen addition mechanism has not been addressed considerably in the literature. However, in enantioselective hydrogenation one can question mechanisms which assume that the proton in protonated **CD** would be involved in the actual hydrogenation step [6]. This is due to the fact that proton abstraction from **CDH**$^+$ by the reactant would require passing over a high-energy barrier, thus making this reaction route less probable at least at room temperature, which is predominantly used in asymmetric heterogeneous catalysis. Mechanisms, which involve a nonprotonated **CD** [6–9], are also questionable, as **CD** protonates readily under typical experimental conditions.

An alternative possibility is that the protonation of the cinchonidine is an activation step for the reactant-modifier interactions that occur via a hydrogen bond. Protonated cinchonidine **CDH**$^+$ and **A** have attractive interactions whereas **CD** and **A** have negligible ones. After the **CDH**$^+$**-A** complex is formed it is hydrogenated on a Pt surface releasing the hydrogenation product and creating a free **CDH**$^+$. In this mechanism the proton in **CDH**$^+$ is not involved in the hydrogenation cycle.

4.3. The role of s-cis conformation and bifurcated hydrogen bond

It has been proposed [11,12] that vicinal diketones would require the s-*trans* conformation to react enantioselectively to hydroxyketones. This is a reasonable assumption when results for **C** and **D** are compared. The latter has a fixed nearly planar s-*cis* structure (ee of (*R*)-enantiomer only 6%) (Fig. 1), whereas the former has an s-*trans* conformation (ee in the first step is 45%) (Fig. 1). A mechanism for hydrogenation of **C** has been proposed, which is based on adsorption of the reactant in planar s-*trans* conformation [11] as illustrated in Fig. 11a. The cinchonidine is in Open (3)

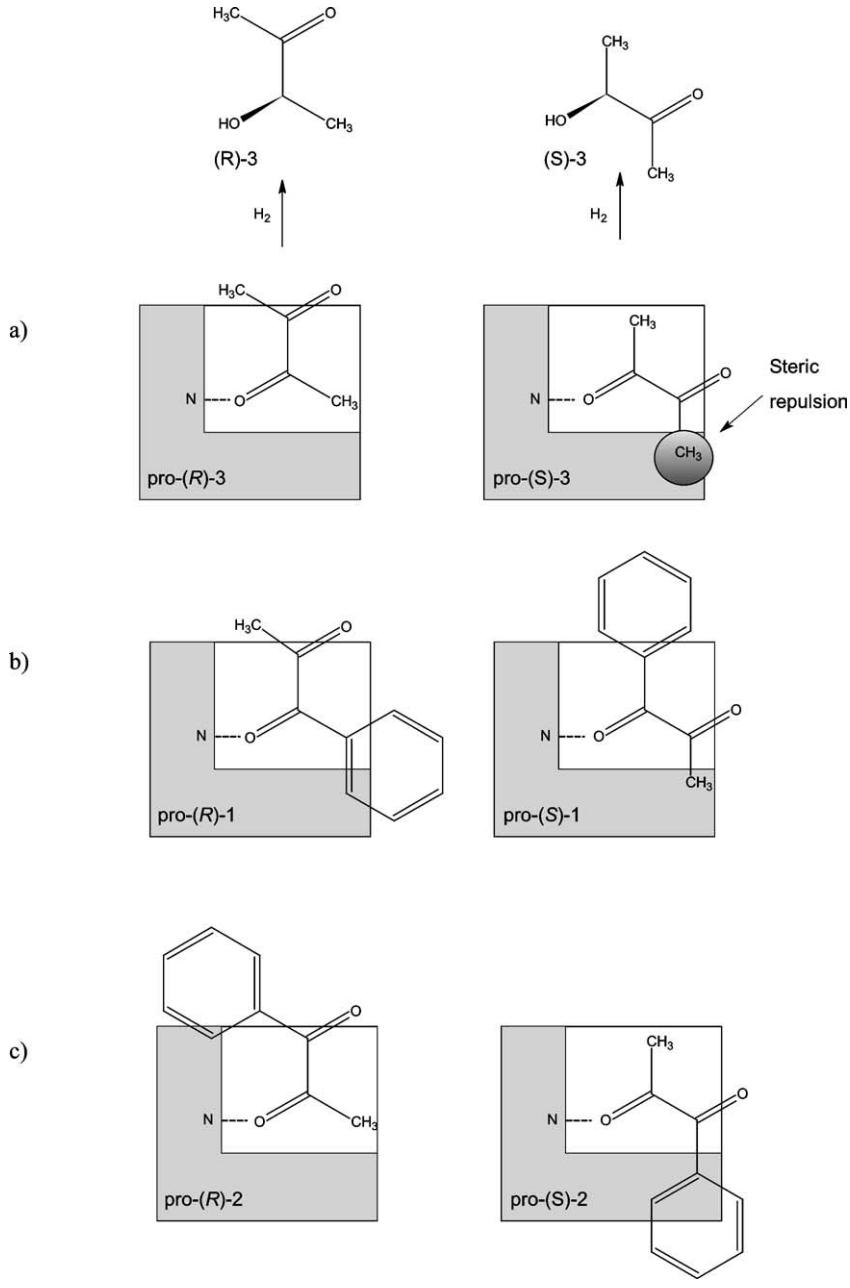

Fig. 11. s-*trans* model for diketones.

conformation (the L-shaped ensemble in Fig. 11) and the one-to-one substrate-modifier interaction occurs via a hydrogen bond between the quinuclidine nitrogen (illustrated as N in Fig. 11) and the carbonyl group. The adsorption in pro-(*R*)-3 arrangement is not sterically hindered by the methyl group-quinoline ring repulsion as is the case in pro-(*S*)-3 and therefore, the pro-(*R*)-3 complex results in the formation of the excess of (*R*)-enantiomer (thermodynamic control). As a source of enantiodifferentiation the steric repulsion induced by methyl group of **C** predicts the major enantiomer correctly as illustrated in Fig. 11a.

Despite the success of the s-*trans* approach to **C** and **D**, this concept applied for **A** reveals that by utilizing the steric repulsion model one cannot explain the observed enantioselectivities. As can be seen from Fig. 11b for the pro-(*R*)-1 and pro-(*S*)-1 the steric repulsion is similar, nevertheless **(*R*)-1** is obtained in 65% excess (Fig. 2). For the other case (Fig. 11c) one would expect greater ee in excess of **(*R*)-2** as the steric repulsion induced by phenyl ring in pro-(*S*)-2 is very large; however, experimental results indicate that about 50% lower ee is obtained for the **(*R*)-2** (Fig. 11c) with respect to **(*R*)-1** (Fig. 11b). One can conclude that the steric factors alone cannot be used a basis for a general model. By applying this steric repulsion concept to hydrogenation of **A** one would arrive in a negligible $ee_{1\text{-OH}}$ and considerably high $ee_{2\text{-OH}}$.

The protonated modifier stabilized the s-*cis* conformer of **A** to such extent that no s-*trans* conformers as an energy minimum on PES were found. The importance of s-*cis* conformation can be demonstrated by comparing **A** and acetophenone, which is structurally similar to **A**. The reactions of the C1=O1 carbonyl group of **A** are expected to be similar to that of acetophenone (note that the two carbonyl groups of **A** are not conjugated). However, it is the C2=O2 carbonyl group in **A** that makes the hydrogenation of C1=O1 of **A** ($ee_{1\text{-}OH} = 65\%$) very different from acetophenone (ee = 5%) in the presence of **CD**.

An explanation for these differences in enantioselectivities can be the s-*cis* conformation and bifurcated hydrogen bond (or two separate hydrogen bonds involving –OH of **CD**). In acetophenone (ee = 5%) this kind of complex with **CD** is not possible, while the C2=O2 group of **A** participates in stabilization of the s-*cis* conformation with the protonated cinchonidine and contributes to high enantioselectivity.

It has been proposed [44] that an electron-withdrawing substituent in α-position to C=O group is needed for enantioselective reaction. A plausible explanation for this "substrate specificity" based on our calculations is that the "electron-rich α-substituent" is needed for the stabilization of the s-*cis* conformation. Stabilization occurs via a bifurcated hydrogen bond (Fig. 8) or alternatively with two hydrogen bonds where the OH of **CD** (Fig. 9) is included in hydrogen bonding. There are several model substrates, which follow this criteria [7,8], e.g., acetophenone (ee = 5%) vs trifluoroacetophenone (ee = 92%) or **A** ($ee_{1\text{-}OH} = 65\%$).

4.4. Source of enantiodifferentiation

In principle there are two contributing factors in enantioselectivity [42], namely stability of the diastereomeric cinchonidine-reactant complexes (thermodynamic control) and the activation energy barrier for the hydrogenation (kinetic control). Both of these factors can either work in favor or disfavor of the apparent enantioselectivity.

The diastereomeric complexes (Figs. 8 and 9) are almost equal in energy, which implies that enantioselectivity cannot be explained solely by *thermodynamic control*. The geometry of **A** in complexes pro-R1 and pro-S1 is such that C1=O1 has optimal access to adsorbed hydrogen on the catalyst surface, whereas for the other complexes the orientation of **A** is nonoptimal. However, regardless on the assumed geometry of the Pt surface (spherical of planar) one cannot explain enantioselectivities by steric factors. The experimentally observed increase of **(*R*)-1** formation rate (Figs. 6 and 7) could be due to the 12.5 $kJ\,mol^{-1}$ stabilization of the reactant's keto carbonyl π-orbitals [42] in complex pro-R1 (Table 1). This would explain enantioselectivity in the hydrogenation of the C1=O1 group by means of kinetic control. An example of kinetically controlled enantioselectivity has been presented in the classical work of Landis and Halpern [45] and later on elaborated by Boudart [46] who demonstrated that the less stable diastereomeric complex yielded the major enantiomer as a result of a faster reaction. However, based on the present work one cannot explain unequivocally the enantiodifferentiation mechanism.

5. Conclusions

The available data on six vicinal diketones revealed that the reactions exhibit many similarities. In all cases the enantiomeric excess of structurally similar (*R*)-enantiomer was obtained with cinchonidine as catalyst modifier. Toluene gave the highest enantioselectivity whereas acetic acid resulted in considerably reduced enantioselectivity and reaction rate. Furthermore, the kinetic resolution was caused due to faster reaction of (*S*)-hydroxyketone further to diols, resulting in an increase of ee. The diastereoselectivies in diols were similar, the (*R,S*) or (*S,R*) diols were always the main products whereas considerably less (*R,R*) of (*S,S*) were formed. The overall rate acceleration could not be linked to enantioselective reaction in vicinal diketone hydrogenation.

For the first time enantiomeric excesses for both C=O group hydrogenation of 1-phenylpropane-1,2-dione (**A**) hydrogenation have been reported, making the reaction network complete. The $ee_{1\text{-}OH}$ and $ee_{2\text{-}OH}$ were 50 and 25%, respectively, at 50% conversion of **A**. From both batch and continuous reactor experiments it could be concluded that the source of enantioselectivity is increased formation rate of (*R*)-enantiomer and decreased formation rate of (*S*)-enantiomer. The reaction exhibits a high regioselectivity (rs = 10). The C1=O1 group adjacent to the phenyl ring hydrogenates faster probably due to delocalization of electrons between the C1=O1 and the phenyl ring.

Theoretical calculation revealed that in the substrate-modifier diastereomeric complex the reactant forms a nonplanar s-*cis* conformation and bond to the protonated cinchonidine either via a bifurcated hydrogen bond or with two hydrogen bonds where the OH group is involved also. All diastereomeric complexes were equal in energy, an indication that enantioselectivity cannot be explained directly by thermodynamic control. The keto carbonyl π-orbitals stabilization could be an explanation for the increased formation rate of **(*R*)-1**. The calculated proton affinity of CD was high, indicating that protonation is feasible under experimental conditions.

Acknowledgments

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