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Asymmetric hydrogenation of cyclohexane-1,2-dione over cinchonidine-modified platinum

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Abstract

The asymmetric hydrogenation of cyclohexane-1,2-dione over cinchonidine-modified platinum was investigated. Despite the fact that the first hydrogenation step is close to nonenantioselective, a high enantiomeric excess is obtained for the (*R*)-α-hydroxyketone due to kinetic resolution. In the second hydrogenation step one out of the four reactions of the network is substantially accelerated with respect to the others and with respect to the reaction in the absence of modifier, leading to an enantiomeric excess of (1*R*, 2*R*)-*trans*-cyclohexane-1,2-diol of over 80%. Comparison with recently reported asymmetric hydrogenation of α-hydroxyethers indicates striking similarities, which hint at similar reactant–modifier interaction in both cases. The importance of *cis* versus *trans* conformation of the reactant for the reactant–modifier interaction emerges from a comparison of suggested reaction intermediates for cyclohexane-1,2-dione and butane-2,3-dione hydrogenation, respectively.

Keywords: Cyclohexane-1,2-dione; Cyclohexane-1,2-diol; Asymmetric; Enantioselective; Hydrogenation; Cinchonidine; Platinum

1. Introduction

Heterogeneous enantioselective hydrogenation using chirally modified metal catalysts is a promising route for the synthesis of optically pure compounds using a heterogeneous process. One of the most investigated catalysts for such reactions is the platinum cinchona alkaloid system [1–7], and the mechanism of enantiodifferentiation is the target of ongoing research in several laboratories. The scope of the reaction is steadily increasing, although it is still rather limited to α-keto acid derivatives and "activated" ketones.

Here we investigate the heterogeneous enantioselective hydrogenation of a cyclic vicinal diketone, cyclohexane-1,2-dione. The enantioselective hydrogenation of vicinal diketones on Pt with cinchonidine as modifier has been in the focus of several studies. Investigated diketones include butane-2,3-dione [8], hexane-3,4-dione [9], and 1-phenylpropane-1,2-dione [10]. The reduction of diketones can be a helpful tool in deducing the stereochemical requirements for fast reaction, since several reaction pathways compete, as shown in the reaction network in Fig. 1. The vicinal diketones investigated so far show considerable structural flexibility. In particular they can exist in *cis* and *trans* conformation, which makes analysis of stereochemical requirement difficult. We therefore decided to investigate cyclohexane-1,2-dione (**1**), which has a fixed *cis* conformation of the keto groups.

Several applications of the chiral hydrogenation product cyclohexane-1,2-diol (**3**) have been reported. (*R*, *R*)-cyclohexane-1,2-diol is used in organic synthesis as a chiral auxiliary. The conjugate addition of organocuprate reagents and Grignard reagents to α,β-unsatured esters of chiral (*R*, *R*)-cyclohexane-1,2-diol proceed with high diastereoselectivity [11,12]. For instance, it is used as an auxiliary for the enantio- and diastereoselective synthesis of β-substituted five-, or six-membered cyclohexanecarboxylates [13]. It is further used as a photocrosslinkable chiral doping agent in liquid-crystal mixtures and in optical devices [14] and in the preparation of carbohydrate mimetics having anti-adhesive properties [15,16].

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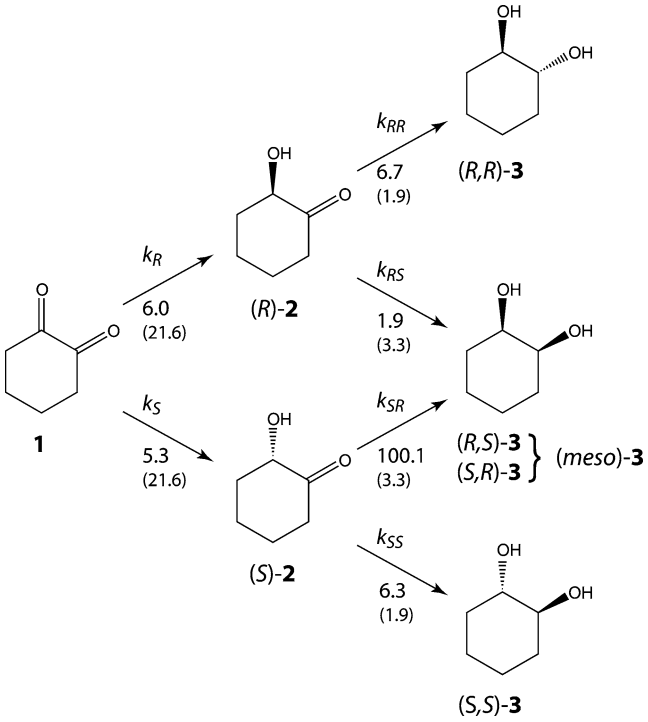

Fig. 1. Reaction network for the hydrogenation of cyclohexane-1,2-dione (**1**). The values indicate the rate constants $k_i' = k_i/V$ [$g^{-1}h^{-1}$]. Note that k_i' is used to be consistent with previously reported rate constants [26]. The values in parentheses are rate constants for the corresponding racemic reaction. See text for details.

2. Experimental

A 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced in flowing hydrogen for 90 min at 400 °C. The platinum dispersion after heat treatment was 0.27 as determined by TEM measurements. Toluene and cinchonidine were used as received (Baker, Fluka). The reactant cyclohexane-1,2-dione (**1**) (Avocado > 98%) was distilled before use. The hydrogenation reactions were carried out in a 100-ml stainless-steel autoclave equipped with a 50-ml glass liner and PTFE cover. The reactor was magnetically stirred ($n = 500\ \text{min}^{-1}$). The pressure was held at a constant value by computerized constant-volume–constant-pressure equipment (Büchi BPC 9901), which allowed following the hydrogen uptake. Under standard conditions, 42 ± 2 mg prereduced catalyst, 1.84 mmol substrate, 6.8 µmol modifier, and 10 ml solvent were used and the reaction was carried out at 30 bar and 15 °C.

Conversion, enantiomeric excess (ee), and diastereomeric excess (de) were determined using an HP 6890 gas chromatograph (GC) and a Chirasil-DEX CB (ChromPack) capillary column. The injector temperature was 150 °C. We noticed that the measured enantiomeric excess of 2-hydroxycyclohexanone (**2**) strongly depended on the injector temperature of the GC. At an injector temperature of 250 °C the ee was significantly lower (about 25%) than at lower temperature, likely due to fast keto–enol tautomerism. At 200 °C the effect was much smaller (about 2% lower ee) and at 150 °C it was negligible. The peaks in the chromatogram were identified by comparison with commercial racemic compounds **2** (Aldrich) and cyclohexane-1,2-diol (**3**) (Acros 98%). The absolute configuration of the preferentially formed enantiomer was determined by comparison with (R,R)-**3** from Fluka ($\geqslant$ 99%). The GC was calibrated by injecting mixtures of **1**, **2**, and **3** of known composition. To follow the time dependence of the reaction 100-µl samples were withdrawn from the reactor at defined times using a syringe. Enantiomeric excess is expressed as ee (%) $= 100 \times (|R - S|)/(R + S)$. Diastereomeric excess is expressed as de (%) $= 100 \times (|cis - trans|)/(cis + trans)$. The relative concentration of **1**, **2** (sum of (R) and (S)) and **3** (sum of (R,R), (S,S) and (*meso*)), as well as the ratio of the enantiomers of **2**, were determined in one GC run and the relative concentrations of (R,R)-**3**, (S,S)-**3**, and (*meso*)-**3** in a second run using a different temperature program.

3. Results

3.1. General features of the reaction

The enantioselective hydrogenation of cyclohexane-1,2-dione(**1**) resulted in an 81.3% enantiomeric excess (ee) in favor of $(1R,2R)$-*trans*-cyclohexane-1,2-diol ((R,R)-**3**) at full conversion under standard conditions. The diastereomeric excess (de) of the *cis*-cyclohexane-1,2-diol ((R,S)-**3**,(S,R)-*3*)) was 22.9% at complete conversion. Due to kinetic resolution the ee of the (R)-intermediate (R)-**2** reached very high values, close to 100%, toward the end of the reaction. We found that the purity of the reactant and the water content in the reaction mixture strongly affected the ee. Addition of 1‰ of water resulted in a decrease of ee to 29.2%. Addition of 5‰ of water gave an ee of 18.4%. We also noticed that distillation of the reactant was necessary to obtain high ee and that the residue contained some polymerized reactant. Thus purification of the reactant seems to be a necessary prerequisite to avoid catalyst deactivation.

The ee of the product depended on the cinchonidine concentration as shown in Fig. 2. The increase in ee was significant at low cinchonidine concentration. At 1 mg cinchonidine, corresponding to a reactant/modifier ratio of 542, the ee of the product (R,R)-**3** amounted to 75.9% and increased only slightly at higher cinchonidine concentration. Such behavior is quite common for the Pt–cinchona system. It is likely due to the increasing adsorption of the modifier on the Pt catalyst, which is saturated already at low concentration [17,18].

The highest ee reached for the product (R,R)-**3** was 83.7% at full conversion (15 °C, 30 bar, 4 mg cinchonidine, **1**/cinchonidine ratio 135). A decrease in the amount of catalyst had a negative effect on the ee. Using 31 mg catalyst instead of 42 mg led to a decrease of the ee to 70.6%. Increasing the pressure to 90 bar also had a significant negative effect on the ee of (R,R)-**3**, which decreased to 67.5%,

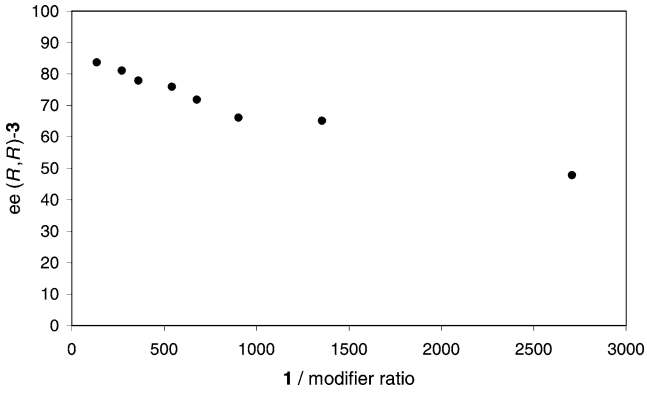

Fig. 2. Enantiomeric excess of (R,R)-**3** at full conversion as a function of the reactant **1**/cinchonidine ratio (mol/mol). The concentration of cinchonidine was varied. Other parameters are the same as under standard conditions (see text).

whereas decreasing the pressure to 10 bar lowered the ee only slightly to 78.5%. The ee was also quite sensitive to temperature in the following manner: 35 °C, 64% ee; 25 °C, 77.6% ee; 15 °C, 81.3% ee; 5 °C, 81.0% ee. Other solvents, which have been tested are acetic acid, tetrahydrofurane, 2-propanol, and acetonitrile, but the reaction rates and ee were significantly lower than for toluene. We also noted that the solubility of *trans*-**3** in toluene is higher than that of *cis*-**3**.

3.2. Kinetics

The hydrogenation of **1** can give useful information on the modified Pt catalyst, since several reactions compete. A prerequisite for such an analysis is, however, the examination of the reaction network depicted in Fig. 1. In order to perform this, the reaction was followed in time. The kinetic data shown in Figs. 3 and 4 for modified and unmodified catalyst (presence and absence of cinchonidine) were fit to a simple model corresponding to the reaction scheme depicted in Fig. 1. An analogous reaction scheme has been proposed for the hydrogenation of butane-2,3-dione [8]. The simple kinetic model is applied to analyze the connectivity between the different steps and their relative reaction rates. Each single reaction is considered as first order with respect to reactant and catalyst. The reaction rates for the different species i are defined as: $r_i\ [\mathrm{mol}/h\,\mathrm{g_{cat}}] = 1/m_{\mathrm{cat}}\ \mathrm{dN}_i/\mathrm{d}t = 1/(m_{\mathrm{cat}}/V)\ 1/V\ \mathrm{d}N_i/\mathrm{d}t$. Assuming constant volume, $r_i = V/m_{\mathrm{cat}}\ \mathrm{d}c_i/\mathrm{d}t$, where N_i corresponds to moles of species i, m_{cat} is the mass of the catalyst, and V is the volume of the reaction mixture. The rate equations derived for the reaction network (Fig. 1) are:

$$r_1 = -(k_R + k_S)[1],$$
$$r_{(R)-2} = k_R[1] - (k_{RR} + k_{RS})\big[(R) - 2\big],$$
$$r_{(S)-2} = k_S[1] - (k_{SS} + k_{SR})\big[(S) - 2\big],$$
$$r_{(R,R)-3} = k_{RR}\big[(R) - 2\big],$$
$$r_{(meso)-3} = k_{RS}\big[(R) - 2\big] + k_{SR}\big[(S) - 2\big],$$
$$r_{(S,S)-3} = k_{SS}\big[(S) - 2\big].$$

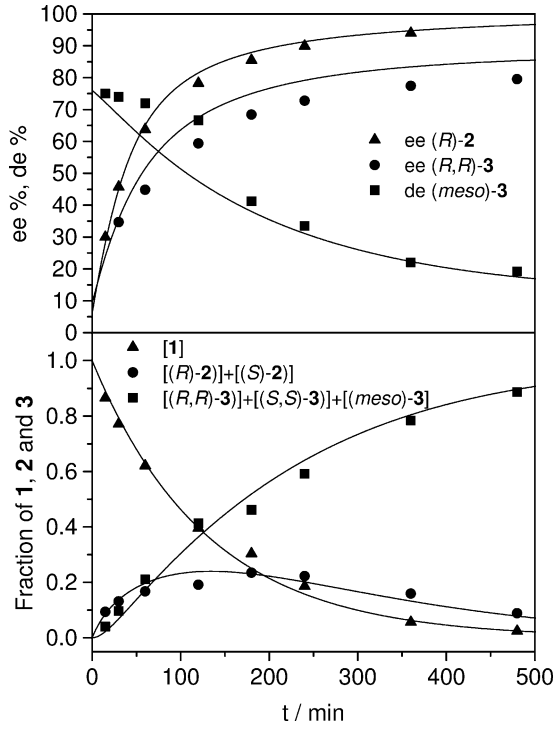

Fig. 3. Kinetic behavior of the enantioselective hydrogenation of cyclohexane-1,2-dione (**1**) over cinchonidine-modified Pt. Solid lines are obtained from the fit of the model depicted in Fig. 1 to the experimental data. Standard conditions as specified in the experimental part. Bottom: Fraction of **1**, **2** (sum of (R)-**2** and (S)-**2**), and **3** (sum of (R,R)-**3**, (S,S)-**3** and (*meso*)-**3**) as a function of time. Top: Enantiomeric excesses of intermediate (ee-**2**) and final product (ee-**3**) and diastereomeric excess of final product de-**3**.

These equations were solved numerically. The experimental data were fit using a least squares procedure, which is a nonlinear χ^2 fitting routine based on the Levenberg–Marquardt method. The concentrations of all six involved species, **1**, (R)-**2**, (S)-**2**, (R,R)-**3** *meso*-**3** ((R,S)-**3** plus (S,R)-**3**), and (S,S)-**3**, at any time were calculated by integrating the above rate laws taking into account the known initial concentrations and initial guesses for the rate constants k. The six rate constants k_R, k_S, k_{RR}, k_{RS}, k_{SR}, and k_{SS} were simultaneously fit to the following time-dependent experimental values. The concentration of **1**, the concentration of intermediate product **2** (sum of (R)-**2** and (S)-**2**), the concentration of product **3** (sum of (R,R)-**3**, *meso*-**3**, and (S,S)-**3**), the ee of **2**, the ee of **3**, and the de of **3**. A total of 48 data points (32 for the racemic reaction) were used for the fit. For the racemic reaction (without cinchonidine addition) the three rate constants $k_R = k_S$, $k_{RR} = k_{SS}$, and $k_{SR} = k_{RS}$ were fit to the concentration of **1**, the concentration of intermediate product **2** (sum of (R)-**2** and (S)-**2**), the concentration of product **3** (sum of (R,R)-**3**, *meso*-**3** and (S,S)-**3**), and the de of **3**. The initial guess for the rate constants was varied in order to search for local minima, but all initial guesses converged to the same set of rate constants. The fitting was implemented in a Fortran program using standard numerical procedures [19].

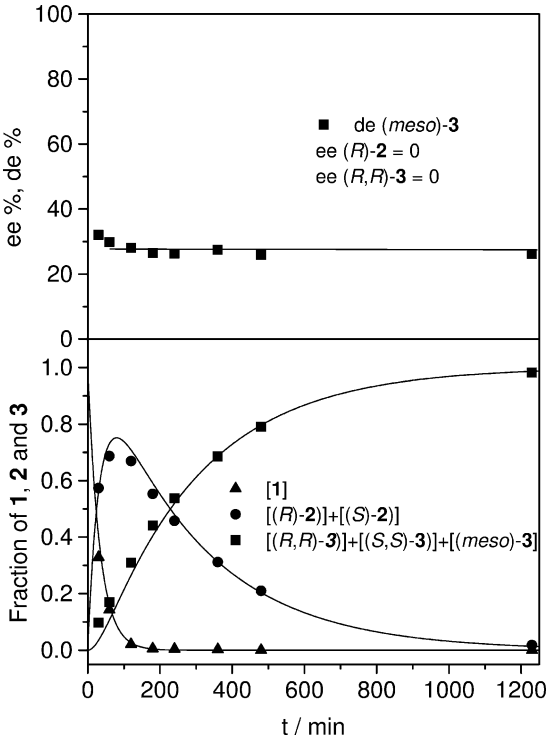

Fig. 4. Kinetic behavior of the racemic hydrogenation of cyclohexane-1,2-dione (**1**) over cinchonidine-modified Pt. Bottom: fraction of **1**, **2**, and **3** as a function of time. Solid lines are obtained from the fit of the model depicted in Fig. 1 to the experimental data, considering that $k_R = k_S$, $k_{RR} = k_{SS}$ and $k_{SR} = k_{RS}$ for the racemic reaction. Top: diastereomeric excess de-**3**. The experimental data were measured under standard conditions except that no cinchonidine was added to the reaction mixture.

Figs. 3 and 4 show that the simple kinetic model based on the scheme depicted in Fig. 1 fits the data well. The resulting rate constants for the individual reactions are given in Fig. 1 In the presence of cinchonidine the first step **1** → **2** is only slightly enantioselective. From the values of k_R and k_S an enantiomeric excess ee of less than 10% is obtained. The reaction (*S*)-**2** → (*meso*)-**3** is an order of magnitude faster than any of the other individual reactions, which has the following consequences: (i) (*R*)-**2** is much more abundant than (*S*)-**2** (except for very low conversion), leading to high ee of **2** even though both enantiomers are formed at similar rates (kinetic resolution), (ii) **2** is never present at high concentration (about 20% at most), (iii) (*R*,*R*)-**3** is much more abundant than (*S*,*S*)-**3** (high ee-**3**), although the rate constants k_{RR} and k_{SS} for their formation are very similar, and (iv) the *meso* form of **3** is formed preferentially. A comparison with the racemic reaction reveals that the first reaction, **1** → **2**, slows down in the presence of cinchonidine, whereas the second, **2** → **3**, is accelerated. As a consequence the maximum concentration of the intermediate is relatively low. Fig. 5 shows experimental data obtained for the enantioselective hydrogenation of racemic **2** under standard conditions. The observation that similar values of ee and de are obtained as

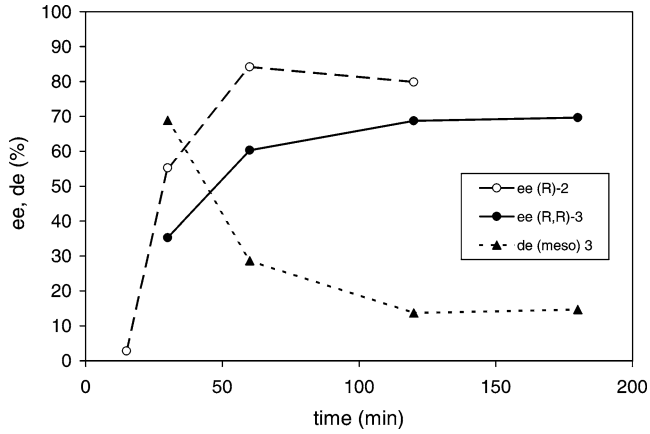

Fig. 5. Kinetic behavior of the hydrogenation of racemic α-2-hydroxycyclohexanone (**2**) under standard conditions. Lines are only to guide the eyes.

for the reaction starting from the diketone **1** confirms the kinetic analysis given above.

4. Discussion

Rate constants for the enantioselective hydrogenation of butane-2,3-dione, based on the same reaction network as the one in Fig. 1, have previously been reported [8], which allows a comparison of the reactions of the two diones. There are similarities but also important differences. A striking similarity is the finding that for the second reaction **2** → **3** the rate constant k_{SR} is the largest, i.e., the (*S*)-**2** → (*S*,*R*)-**3** reaction is the fastest. k_{SR} is less than four times larger than the other rate constants of the **2** → **3** reactions in the case of butane-2,3-dione. In contrast, it is 15 times larger for cyclohexane-1,2-dione. An important difference concerns the relative rates of the **1** → **2** and **2** → **3** reactions. The dominant pathway (*S*)-**2** → (*meso*)-**3** for the second reaction **2** → **3** is about an order of magnitude faster than the first reaction **1** → **2** in the case of cyclohexane-1,2-dione, whereas it is about an order of magnitude slower for butane-2,3-dione. Also, for butane-2,3-dione the first hydrogenation step shows some enantioselectivity (42% as calculated from the rate constants k_R and k_S) [8], whereas for cyclohexane-1,2-dione the first hydrogenation step shows almost no enantioselectivity (ee < 10%).

In the racemic reaction (Fig. 4) the hydrogenation rate constants k_{RS} and k_{SR} for the reactions leading to the *cis* product are larger than k_{RR} and k_{SS} for the reactions resulting in *trans* product. This can be rationalized if one assumes that (i) the hydrogen approaches the carbonyl bond from the surface side, and that (ii) **2** prefers an adsorption on the enantioface that is opposite to the O–H group such that the O–H group points away from rather than towards the surface. Note that for the hydrogenation of the corresponding 2-hydroxy-3-butanone the opposite was found ($k_{RS} = k_{SR} < k_{RR} = k_{SS}$).

The most important structural difference between cyclohexane-1,2-dione (**1**) and butane-2,3-dione is the greater rigidity of the former. Considering this fact, the finding is not surprising that for the former the first hydrogenation step is close to racemic, whereas for the latter moderate enantioselectivity was observed. For butane-2,3-dione the *trans* is much more stable than the *cis* conformation. In fact, ab initio calculations (Hartree–Fock, 6-31G(d,p) basis set) [20] reveal that *trans* is more stable than *cis* by about 8 kcal/mol and that the *cis* conformer is a saddle point rather than a minimum on the potential energy surface. Mechanistic models for the enantiodifferentiation in the ethyl pyruvate reaction propose a hydrogen-bonding interaction between the quinuclidine N of the modifier and the carbonyl group being hydrogenated. This hydrogen bond can be formed either between the protonated quinuclidine N and the keto oxygen [21] or between the quinuclidine N and the half-hydrogenated state of the keto group, in case the quinuclidine N is not protonated [22,23]. It was furthermore proposed that the quinoline part of the modifier plays an important role for enantiodifferentiation because of repulsive interactions with the reactant [24,25]. Due to this repulsion one would expect that in the presence of cinchonidine, adsorption on the one enantioface is favored if the butane-2,3-dione adopts *trans* conformation. This is schematically shown in Fig. 6. Note that this view of enantiodifferentiation predicts the correct absolute configuration of the major reaction product (*R*)-2-hydroxy-3-butanone. Adsorption, which would lead to the (*S*)-product, is less favored due to repulsive interactions. For the *cis* conformation adsorption on the two enantiofaces is identical also in the presence of cinchonidine (see Fig. 6c). Cyclohexane-1,2-dione (**1**) is fixed in the *cis* conformation. Hence, according to the view of enantiodifferentiation outlined above, one would not expect enantioselection for the reaction yielding **2**, in good agreement with observation. We should, however, note that for **1** the two carbonyl groups are not exactly oriented coplanar due to the six-membered ring.

As concerns the second reaction **2** → **3**, the relative arrangement of O–H and keto group may be similar for the 2-hydroxy-3-butanone and the 2-hydroxycyclohexanone (**2**), since here the former is more likely to adopt a *cis* conformation, due to intramolecular hydrogen-bonding. This is also confirmed by ab initio calculations, which show that the *cis* conformation is more stable by about 2 kcal/mol (Hartree–Fock, 6-31G(d,p) basis set). In this light it is not surprising that for both the 2-hydroxy-3-butanone and the 2-hydroxycyclohexanone (**2**) the same reaction among the four possible (see Fig. 1) dominates. Due to the presence of cinchonidine, k_{SR} is larger than k_{RS}. For 2-hydroxycyclohexanone (**2**) the determined ratio of the rate constants k_{SR}/k_{RS} is 53, whereas it is 3–4 for 2-hydroxy-3-butanone. The lower value for the latter may indicate that structural rigidity is favorable for discrimination between (*R*)-**2** and (*S*)-**2**. Since (*R*)-**2** and (*S*)-**2** are electronically identical, their vastly different reaction rate can be traced to the steric

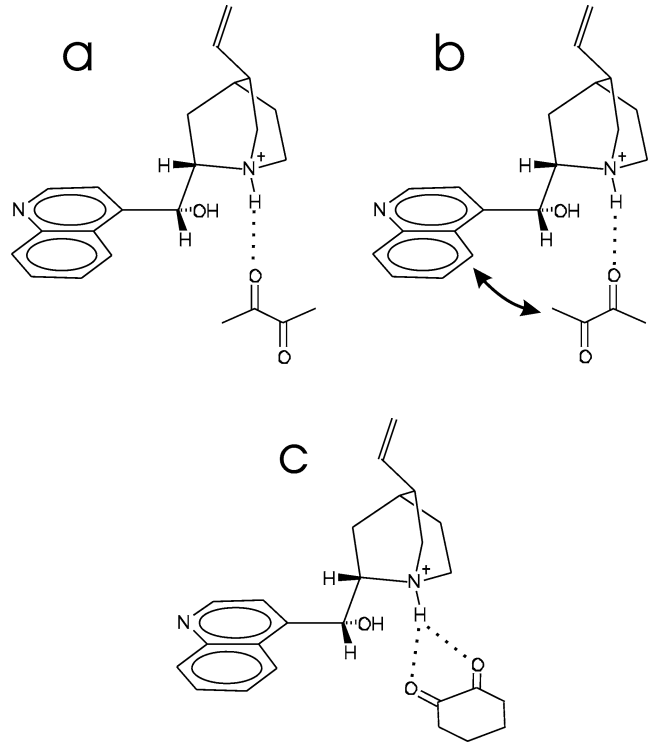

Fig. 6. Possible interaction of *trans* and *cis* diketones with cinchonidine modifier. In the presence of cinchonidine, adsorption on the two enantiofaces is different for the *trans* dione (a), (b), whereas this is not the case for the *cis* dione (c).

requirements of the chiral site. Very recently Studer et al. reported on the dynamic kinetic resolution of α-keto ethers, using cinchonidine modified Pt catalysts [26]. They found that the (*S*)-α-keto ether reacts faster than the (*R*)-α-keto ether and that the major product is the (*R*,*S*)-hydroxy ether. Depending on conditions the pseudo-first-order kinetic constant k_{SR} and k_{RS} differed by one to two orders of magnitude. This striking similarity between the behavior of α-keto ethers and α-hydroxy-ketone (**2**) strongly supports a similar mechanism for enantiodifferentiation for the two, which indicates that the second oxygen besides the keto O may act as a second hydrogen-bond acceptor, as has been proposed also for α-ketoester hydrogenation [25]. Furthermore the similarity shows that the O–H group of **2** is not involved in enantiodifferentiation and that it does not hinder the crucial modifier–reactant interaction.

5. Conclusions

The racemic and asymmetric hydrogenation of cyclohexane-1,2-dione (**1**) was investigated and the reaction network analyzed. In the absence of modifier the first hydrogenation step is considerably faster than the second, leading to a high intermediate concentration of the 2-hydroxycyclohexanone (**2**). In the presence of cinchonidine the latter is never present at high concentration due to rate acceleration of the second hydrogenation step in-

duced by the modifier. Kinetic analysis of the reaction network shows that one of the four possible reactions of 2-hydroxycyclohexanone (**2**) to cyclohexane-1,2-diol (**3**) is drastically accelerated. Comparison with the related hydrogenation of butane-2,3-dione shows that the same reaction is favored in the second hydrogenation step; however, discrimination is more pronounced for cyclohexane-1,2-dione (**1**), possibly due to its greater structural rigidity. In contrast to the asymmetric hydrogenation of butane-2,3-dione the hydrogenation of cyclohexane-1,2-dione (**1**) to 2-hydroxycyclohexanone (**2**) in the presence of cinchonidine shows almost no enantioselectivity. This finding can be explained by the fixed *cis* conformation of cyclohexane-1,2-dione (**1**). When interacting with the cinchonidine modifier butane-2,3-dione may be present partly in *trans* conformation, leading to different stability for adsorption on the two enantiofaces, as predicted by proposed modifier–reactant interaction models.

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