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# Why are $\alpha$-hydroxycarboxylic acids poor chiral modifiers for Pt in the hydrogenation of ketones?

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**Abstract**

Mandelic acid (**1**) and its derivatives and 1-naphthylglycolic acid (**8**) were used as modifiers for the asymmetric hydrogenation of ketopantolactone to pantolactone on supported Pt, Ru, and Rh catalysts. A systematic variation of the modifier structure showed that **8** was the best modifier, affording up to 28% ee on Pt; the other metals were barely efficient. The catalytic studies were completed with FTIR spectroscopic analysis of the modifier–modifier and modifier–substrate interactions in solution. Attenuated total reflection infrared spectroscopy was applied to study the adsorption of the $\alpha$-hydroxy-carboxylic acid type modifiers on a $Pt/Al_2O_3$ model catalyst in the presence of hydrogen. The study indicates that the modifiers are present on the metal surface as monomers with an internal hydrogen bond between the hydroxyl group and the carboxyl carbonyl group, and the phenyl or naphthalene rings are in a tilted position relative to the surface. The moderate enantioselection is attributed to a hydrogen bond interaction between the carboxylic OH group of the modifier and the carbonyl O atom of the substrate. The poor enantioselectivities attained in ketopantolactone hydrogenation may be explained by the overly weak adsorption of the modifiers on Pt and by the weakness of the O–H–O-type H bond between the substrate and the modifiers. It seems that the carboxyl group has a double role, allowing interaction with the substrate and the Pt surface.



*Keywords:* Ketopantolactone; Asymmetric; Enantioselective; Hydrogenation; (*R*)-Mandelic acid; (*S*)-Naphthylglycolic acid; FTIR; ATR-IR; Hydrogen bonding; Pt; Rh; Ru

## 1. Introduction

The two chirally modified metal catalysts most effective in the hydrogenation of ketones are Ni modified with tartaric acid [1–4] and Pt modified with cinchona alkaloids [5–12]. Not only the modifiers, but also the application ranges are very specific for the metals; Ni is used for the hydrogenation of $\beta$-functionalized and unfunctionalized ketones, whereas Pt is outstanding in the hydrogenation of activated ($\alpha$-functionalized) ketones to the corresponding chiral alcohols. In case of the Ni/tartaric acid system, substitution of more than one of the hydroxyl groups or one of the carboxyl groups of the modifier leads to an almost complete loss of enantioselection [2,3,13]. It was suggested that in the hydrogenation of a $\beta$-ketoester (e.g., methylacetoacetate), the two carboxyl groups are necessary to anchor the modifier onto the Ni surface, whereas the OH functions can interact via hydrogen bonds with the carbonyl groups of the reactant.

Mechanistic studies of cinchona-modified Pt, including the systematic variation of the structure of cinchonidine [14] and some other chiral amine modifiers and their derivatives [15–22], have revealed that the crucial structural parts of the modifiers, besides the stereogenic center(s), are the flat aromatic ring for anchoring onto the Pt surface and the basic aliphatic nitrogen function for interacting with the substrate. Beside amines and amino alcohols, several other types of chiral compounds have been tested as modifiers in the Pt-catalyzed hydrogenation of ketones, but none of them could compete with cinchonidine or its *O*-methyl derivative [23–26].

One reaction of special interest for industry is the hydrogenation of ketopantolactone (KPL) to (*R*)-pantolactone ((*R*)-PL), which is an intermediate in the production of vitamin B5 and a constituent of co-enzyme A [27]. Cinchonidine-modified

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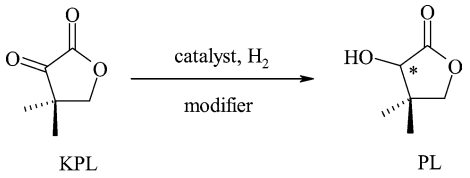


Scheme 1. Enantioselective hydrogenation of ketopantolactone (KPL) to pantolactone (PL), on supported Pt, Rh and Ru catalysts, modified by α-hydroxycarboxylic acids and derivatives.

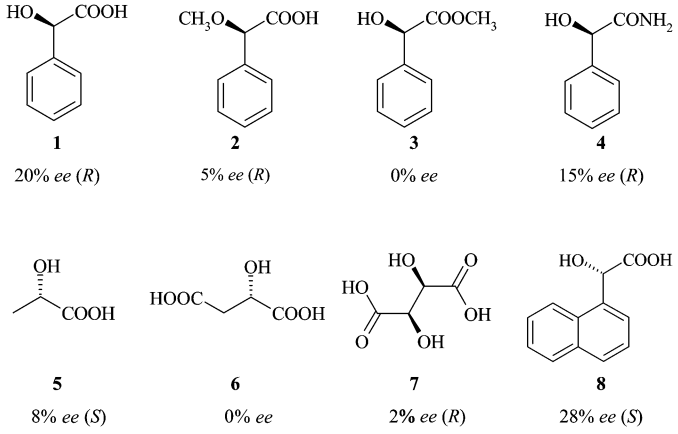


Fig. 1. Structure of the chiral modifiers and the best ee's achieved at full conversion, on $Pt/Al_2O_3$.

Pt afforded 91.6% ee [28]; other amine-type modifiers were less effective [17,29,30]. A new chiral non–amine-type modifier, 1-naphthyl-1,2-ethandiol gave only 30% ee [26]. The probable mechanism involves O–H–O-type hydrogen bonds between the two OH groups and the keto-carbonyl group of KPL. Because the OH groups are weak hydrogen bond donors, the low enantioselectivity might be due to the weak interaction between the modifier and the substrate. We assumed that the more protic α-hydroxy carboxylic acids that function excellently with Ni may offer better enantioselectivities in the hydrogenation of KPL as well.

Here we report the study of this reaction (Scheme 1) on supported Pt, Rh, and Ru catalysts modified by mandelic acid and its derivatives (Fig. 1). The catalytic experiments have been completed with IR spectroscopic measurements to aid in understanding the function of these modifiers.

## 2. Experimental

### 2.1. Materials

Ketopantolactone (KPL; 4,4-dimethyldihydrofuran-2,3-dione; F. Hoffmann–La Roche AG), (*R*)-(–)-α-hydroxyphenylacetic acid (**1**; (*R*)-mandelic acid; Aldrich, 99%), (*R*)-(–)-α-methoxyphenylacetic acid (**2**; Fluka, 99.5%), (*R*)-(–)-α-hydroxyphenylacetic acid methyl ester (**3**; Aldrich, 99%), (*S*)-(+)-2-hydroxypropanoic acid (**5**; (*S*)-lactic acid; Lancaster, 99%), (*S*)-(–)-hydroxysuccinic acid (**6**; Sigma, 98–100%), and L-(+)-dihydroxysuccinic acid (**7**; L-tartaric acid; Across, 99%) were used as received.

(*R*)-α-hydroxybenzeneacetamide (**4**) was synthesized from methyl (*R*)-mandelate and ammonia, as reported elsewhere [31]; its structure was confirmed by NMR. (*S*)-1-Naphthylglycolic acid (**8**) was synthesized from bromoform, 1-naphthylaldehyde, and potassium hydroxide with lithium chloride as a catalyst [32,33]. The (*S*)-1-naphthyl glycolic acid enantiomer was separated by crystallization, after refluxing a saturated solution of the racemic mixture with cinchonine in ethanol. Its structure was identified by NMR, and its enantiomeric purity was verified by HPLC, using a CHIRALCEL OD column. The NMR analyses were performed using a Bruker Avance 500 spectrometer.

Dichloromethane (Baker, 99.5%) was dried and stored over activated molecular sieves. All other solvents were used as received. The additive 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, Aldrich) was used as received.

### 2.2. Catalytic hydrogenation

The 5% $Pt/Al_2O_3$ catalyst (Engelhard 4759) was prereduced at 400 °C for 1 h as described in detail previously [34]. The same procedure was applied to the 5% $Pt/SiO_2$ (Engelhard, EscatTM 2351), Pt/C (Fluka), $Rh/Al_2O_3$ (Engelhard 8001 ESCAT 34), and $Ru/Al_2O_3$ (Degussa AG H213 B/D 5%) catalysts.

Hydrogenations under standard conditions were carried out in a parallel pressure reactor system (Endeavor$^{TM}$) with eight mechanically stirred 15-mL stainless steel reactors [22]. Hydrogenations at 60 bar were performed in a 100-mL autoclave with a 50-mL glass liner and PTFE cover and magnetic stirrer [29]. Total pressure and $H_2$ uptake were controlled by a computerized constant-volume, constant-pressure device (Büchi BPC 9901). For hydrogenation at 15 °C, the system was cooled with a Julabo F25 cryostat.

Under standard conditions, 10 mg of prereduced catalyst, 0.437 mmol of KPL, 19.7 μmol of modifier, and 5 mL of solvent were stirred (500 rpm) at 10 bar and room temperature (23–25 °C), if not otherwise stated. In case of difficulties in dissolving the modifier, the slurry was sonicated before the catalyst was added.

Conversion and enantioselectivity were determined by an HP 6890 gas chromatograph, using a Chirasil-DEX CB (Chrompack 7502; 25 m × 0.25 mm × 250 nm) capillary column. Conditions were split injection (250 °C; 20:1), He carrier gas (42 cm/s), FID detector (250 °C), and 80–180 °C column temperature. The reproducibility of ee was within ±0.5%.

### 2.3. Infrared measurements

All infrared measurements were performed on a Bruker Optics IFS66 spectrometer after co-addition of 200 scans at a resolution of 4 $cm^{-1}$. FTIR transmission spectra were recorded using a liquid cell of 1 mm path length equipped with KBr windows. (*R*)-(–)-α-hydroxyphenylacetic acid (**1**) and (*R*)-(–)-α-methoxyphenylacetic acid (**2**) were analyzed at the same concentrations as those in the reaction mixture (19.7 μmol modifier in 5 mL $CH_2Cl_2$). Additional spectra of (*S*)-(+)-2-hydroxypropanoic acid (**5**) and acetic acid were recorded for

comparison. Two series of KPL/**1** mixtures at molar ratios ranging from 0.25 to 2 were analyzed in $CH_2Cl_2$ at constant substrate concentration and constant acid concentration. The neat solvent served as the reference for the spectra of the solutes.

Adsorption of **1**, **5**, and **8** on $Pt/Al_2O_3$ was monitored in situ using attenuated total reflection infrared (ATR-IR) spectroscopy. The $Pt/Al_2O_3$ model films (1 nm Pt, 100 nm $Al_2O_3$) were prepared and characterized as reported elsewhere [35]. The experimental procedure for adsorption studies is analogous to that used for other chiral modifiers [36]. Briefly, the metal surface was cleaned using $H_2$-saturated solvent before solute adsorption. A spectrum was recorded after 10 min on stream, which served as background for the next spectra. Then a solution of the acid was admitted to the thermostatted stainless steel cell, and ATR-IR spectra were recorded as a function of time. The solute was replaced by $H_2$-saturated solvent after about 50 min on stream to remove weakly adsorbed and dissolved species. All measurements were carried out at a temperature of 20 °C, a flow rate of 1 mL/min, and an acid concentration of 1 mM (if not otherwise specified).

## 3. Results

### 3.1. Enantioselective hydrogenation on mandelic acid-modified Pt-group metals

The hydrogenation of KPL to (*R*)-PL was investigated on supported Pt, Rh, and Ru catalysts modified with **1**; the important results of these experiments are summarized in Table 1. Pt afforded the highest ee (about 20%) in dichloromethane (Table 1, entries 1, 8, and 14); the type of support had only a minor effect on ee. More significant differences were obtained when using the catalysts without reductive treatment at elevated temperatures (Table 1, entries 2, 9, and 15). Note that the positive effect of reductive catalyst treatment frequently observed since the first report by Orito et al. [8] is probably due to cleaning or restructuring of the metal surface [34,37–39].

Addition of the chiral modifier **1** diminished the reaction rate. For example, the conversion was 39% after 5 min in the reaction quoted in Table 1, entry 1, and it increased to 91.5% in the absence of **1**. The lower rate in the presence of **1** is analogous to the slower hydrogenation of activated ketones on Pt in the presence of strong acid additives, such as trifluoroacetic acid [21,40,41].

The enantioselectivity dropped below 10% when replacing $Pt/Al_2O_3$ by $Rh/Al_2O_3$ and $Ru/Al_2O_3$ which performed even worse. Only racemic PL was formed in very slow reactions (Table 1).

Next, improvement of the enantioselectivity of $Pt/Al_2O_3$ was attempted by varying the conditions. A "chiral" restructuring of the catalyst by prestirring the slurry containing the prereduced $Pt/Al_2O_3$ and **1** in dichloromethane for 1 h under $N_2$ or $H_2$ did not result in the expected improvement [37], but the ee decreased to 18 and 13%, respectively.

Hydrogenation of KPL in the presence of **1** was strongly solvent-dependent. Enantioselectivity was induced only in halogenated solvents and toluene, as shown in Table 1. It is important that dichloromethane is carefully dried before use; otherwise, even traces of water diminish the enantioselectivity. For example, addition of 10 µL water to the reaction mixture in dichloromethane resulted in a decrease of ee from 20% (Table 1, entry 1) to 5% under otherwise standard conditions. Attempts to hydrogenate KPL on $Pt/Al_2O_3$ in polar solvents, including ethanol, tetrahydrofuran, dioxane, water, and acetic acid, resulted in the complete loss of enantioselectivity. Only racemic product was formed also on $Rh/Al_2O_3$ when the reaction was carried out in nonchlorinated solvents.

Table 1
Hydrogenation of KPL to (*R*)-pantolactone in different solvents, using (*R*)-mandelic acid (**1**) as modifier, under standard conditions

| Entry | Catalyst | Solvent | Time (h) | Conversion (%) | ee% (*R*)-PL |
|---|---|---|---|---|---|
| 1 | $Pt/Al_2O_3$ | Dichloromethane | 0.6 | 100 | 20 |
| 2 | | Dichloromethane[a] | 1.5 | 100 | 10 |
| 3 | | Chloroform | 1 | 78 | 5 |
| 4 | | 1,2-Dichloroethane | 3 | 47 | 5 |
| 5 | | 1,2-Dichlorobenzene | 0.5 | 51 | 6 |
| 6 | | Trifluorotoluene[b] | 2 | 86 | 11 |
| 7 | | Toluene | 1 | 100 | 13 |
| 8 | $Pt/SiO_2$ | Dichloromethane | 3 | 100 | 19 |
| 9 | | Dichloromethane[a] | 3 | 100 | 20 |
| 10 | | Chloroform | 3 | 71 | 2 |
| 11 | | 1,2-Dichloroethane | 3 | 14 | 5 |
| 12 | | 1,2-Dichlorobenzene | 3 | 78 | 6 |
| 13 | | Toluene | 1 | 100 | 8 |
| 14 | Pt/C | Dichloromethane | 2 | 100 | 19 |
| 15 | | Dichloromethane[a] | 2 | 100 | 6 |
| 16 | | Chloroform | 2 | 99 | 1 |
| 17 | | 1,2-Dichloroethane | 2 | 87 | 5 |
| 18 | | 1,2-Dichlorobenzene | 2 | 95 | 2 |
| 19 | $Rh/Al_2O_3$ | Dichloromethane | 2 | 55 | 6 |
| 20 | | Dichloromethane[a] | 2 | 54 | 4 |
| 21 | | Chloroform | 2 | 4 | 2 |
| 22 | | 1,2-Dichloroethane | 4 | 13 | 8 |
| 23 | | Toluene | 1 | 100 | Racemic |
| 24 | $Ru/Al_2O_3$ | Dichloromethane | 8 | <1 | – |
| 25 | | Tetrahydrofuran | 8 | 7 | Racemic |

[a] Untreated catalyst.
[b] Partially dissolved modifer.

The pressure had only a marginal effect on catalyst performance. For example, the ee decreased from 20 to 18% (at full conversion) when the reaction in Table 1, entry 1 was carried out at 5 bar instead of 10 bar (standard conditions) and no change was detectable between 10 and 60 bar. Temperatures above room temperature (23–25 °C) had a negative effect on the enantioselectivity. In the same reaction, at 35 °C the ee dropped from 20 to 9% at full conversion, and no improvement could be achieved at lower temperatures (e.g., 18.5% ee at 15 °C). These experiments show that **1** is a poor modifier in the hydrogenation of KPL and its application is limited to Pt in weakly polar solvents.

### 3.2. Structural effects

Additional experiments were performed to explore the role of the three functions of modifier **1**—OH, COOH, and the

phenyl ring—in the interaction with the substrate and the metal surface. In this study several $\alpha$-hydroxycarboxylic acids and derivatives were used as modifiers of Pt in the hydrogenation of KPL; their structures are presented in Fig. 1. The experiment shown in Table 1, entry 1 was used as reference reaction. Note also that (*R*)-**1** and its derivatives afforded always (*R*)-PL as the major enantiomer, whereas (*S*)-PL was produced in excess when Pt was modified by (*S*)-**1** and its derivatives.

Protection of the –OH group of **1** by methylation in modifier **2** resulted in a drop in enantioselectivity from 20 to 5% ee. The effect of protecting the carboxyl group by methylation was even more detrimental; a racemic mixture was obtained when Pt was modified by (*R*)-(–)-$\alpha$-hydroxyphenylacetic acid methyl ester (**3**). Obviously, the free carboxyl group is crucial for enantioselection. This conclusion is supported by the complete loss of enantioselectivity when the reference reaction was carried out in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 5 µL). The strong bulky base deprotonates **1** and presumably prevents the interaction of the carboxylate with the substrate. In contrast, replacement of the carboxyl group by an amido group in **4** decreased the ee only to 15%. The likely explanation for this finding is that the amido group of **4** can still interact with the substrate via H-bonding. Similar to **1**, the $\alpha$-hydroxyamide type modifier **4** was effective only in dichloromethane; a racemic mixture was formed in any other solvent.

Next we investigated the importance of the phenyl group of **1** as the potential "anchoring moiety" of the modifier. After replacement of the phenyl ring by a methyl group ((*S*)-lactic acid, **5**), the ee dropped to less than half. Modifier **5** may adsorb via the carboxyl group, and this adsorption mode is sufficient to provide a small ee.

Replacement of the phenyl group with a carboxymethyl group in (*S*)-(–)-hydroxysuccinic acid (**6**) resulted in the loss of enantioselectivity. The hydrogenation was repeated under standard conditions in other solvents, such as 2-propanol, tetrahydrofuran, dioxane, and water, that dissolve **6** better than dichloromethane, but no enantioselection was obtained.

In the presence of tartaric acid (**7**), which contains two additional functional groups (OH and COOH) relative to mandelic acid (**1**), a very small but significant ee of 2% was obtained in tetrahydrofuran. Other solvents, including 2-propanol, dioxane, and water, did not improve enantioselectivity.

Improved enantioselectivity was achieved only when the phenyl ring of **1** was replaced by a naphthyl group in (*S*)-1-naphthylglycolic acid (**8**). Under optimized conditions (0.86 mmol KPL, 19.8 µmol **8**, 20 mL dichlorobenzene, 20 mg reduced $Pt/Al_2O_3$, 20 bar, room temperature), (*S*)-PL was produced with 28% ee. More details on the role of solvent and catalyst composition are given in Table 2. Clearly, only Pt is useful in this reaction. The stronger adsorption of **8** on Pt compared to that of **1** is indicated by the enantioselection obtained in polar solvents, such as tetrahydrofuran and isopropanol, in which **1** was completely ineffective. The twofold slower conversion of KPL observed by replacing **1** with **8** is probably another indication of the stronger adsorption of the latter that leads to higher modifier coverage and fewer free surface sites available for the hydrogenation reaction.

Table 2
Hydrogenation of KPL to (*S*)-PL in different solvents, using (*S*)-1-naphthylglycolic acid (**8**) as modifier, under standard conditions (20 mg catalyst)

| Solvent | Catalyst | Time (h) | Conversion (%) | ee% (*S*)-PL |
|---|---|---|---|---|
| Dichloromethane | $Pt/Al_2O_3$ | 0.5 | 25 | 7 |
| Dichloromethane[a] | $Pt/Al_2O_3$ | 1 | 100 | 14 |
| 1,2-Dichlorobenzene | $Pt/Al_2O_3$ | 0.5 | 56 | 24 |
| 1,2-Dichloroethane | $Pt/Al_2O_3$ | 2 | 37 | 9 |
| Isopropanol | $Pt/Al_2O_3$ | 1.25 | 100 | 5.5 |
| Tetrahydrofuran | $Pt/Al_2O_3$ | 1.25 | 100 | 8 |
| Toluene[a] | $Pt/Al_2O_3$ | 1 | 100 | 14 |
| 1,2-Dichlorobenzene[a] | $Pt/SiO_2$ | 0.8 | 100 | 5.5 |
| Dichloromethane[a] | $Pt/SiO_2$ | 0.6 | 100 | Racemic |
| 1,2-Dichloromethane [a] | $Rh/Al_2O_3$ | 2.75 | 100 | Racemic |
| 1,2-Dichlorobenzene [a] | $Rh/Al_2O_3$ | 1 | 11 | Racemic |
| 1,2-Tetrahydrofuran | $Ru/Al_2O_3$ | 8 | 22 | Racemic |
| 1,2-Dichloromethane | $Ru/Al_2O_3$ | 8 | <1 | Racemic |
| 1,2-Dichlorobenzene | $Ru/Al_2O_3$ | 8 | <1 | Racemic |

[a] 20 bar, 20 mg catalyst.

Further evidence for the stronger adsorption of **8** on Pt was obtained by studying the nonlinear phenomenon [42–45]. When the hydrogenation of KPL was carried out with mixtures of the two modifiers (*R*)-**1** and (*S*)-**8**, in all cases **8** controlled the enantioselectivity. For example, under standard conditions in dichloromethane, a mixture of **1** and **8** containing only 1 mol% **8** afforded 2% (*S*)-PL in excess even though the calculated (theoretical) value was >19% ee to (*R*)-PL. This difference indicates that the naphthyl ring increased the adsorption strength of the modifier.

### 3.3. Infrared spectroscopy

Fig. 2 shows the IR spectra of **1**, **5**, and acetic acid in dichloromethane in the $\nu$(O–H) region. The weak band extending from 3300 to below 2700 $cm^{-1}$ in the spectra of acetic acid reveals the formation of intermolecular hydrogen bonds [46]. This band is very weak in **5** and is missing in **1**. Therefore, these spectra indicate that association via both intermolecular and intramolecular hydrogen bonds is possible, although not favored, in **5** [47], whereas **1** exists exclusively as monomer in solution with an internal hydrogen bond between the hydroxyl group and the carbonyl group of the acid function, in agreement with previously published data [48] (this part of the spectrum not shown). This structure could be retained on adsorption on Pt, as discussed below.

Titration of KPL with **1** did not reveal any significant change in the carbonyl and in the hydroxyl region, indicating that only a very weak substrate–modifier interaction exists in solution.

Fig. 3 shows the ATR-IR spectra of **5**, **1**, and **8** in solutions in contact with the $Pt/Al_2O_3$ model film. Similar features can be found in the transmission spectra of the acid modifiers, which are shown for **1** and **8** in Fig. 3e and f. The signal at ca. 2000 $cm^{-1}$ indicates the formation of CO adsorbed on top, probably originating from decomposition of the acid or of impurities of solvent and solute. An intense signal at 1450 $cm^{-1}$

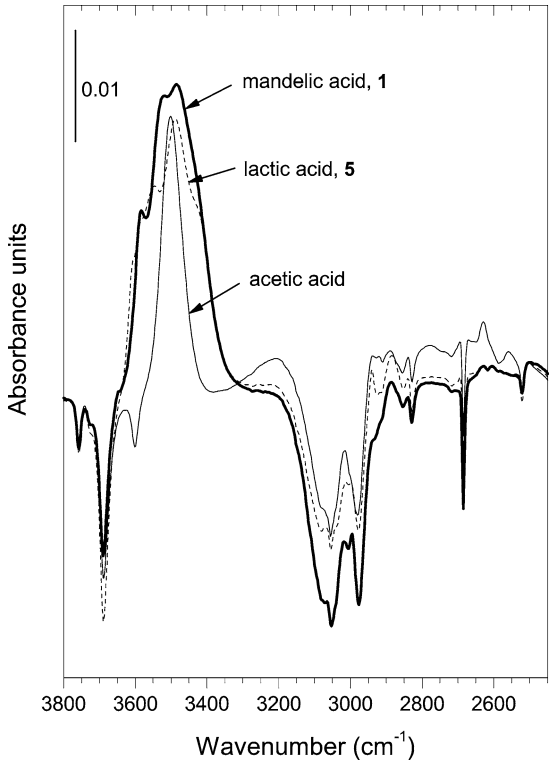


Fig. 2. Transmission IR spectra of (*R*)-mandelic acid (**1**) (—), (*S*)-lactic acid (**5**) (- - -) and acetic acid (—) in $CH_2Cl_2$ in the OH region. The concentration (3.94 mM) is equivalent to that used in the hydrogenation reactions. The negative bands are due to incomplete solvent compensation.

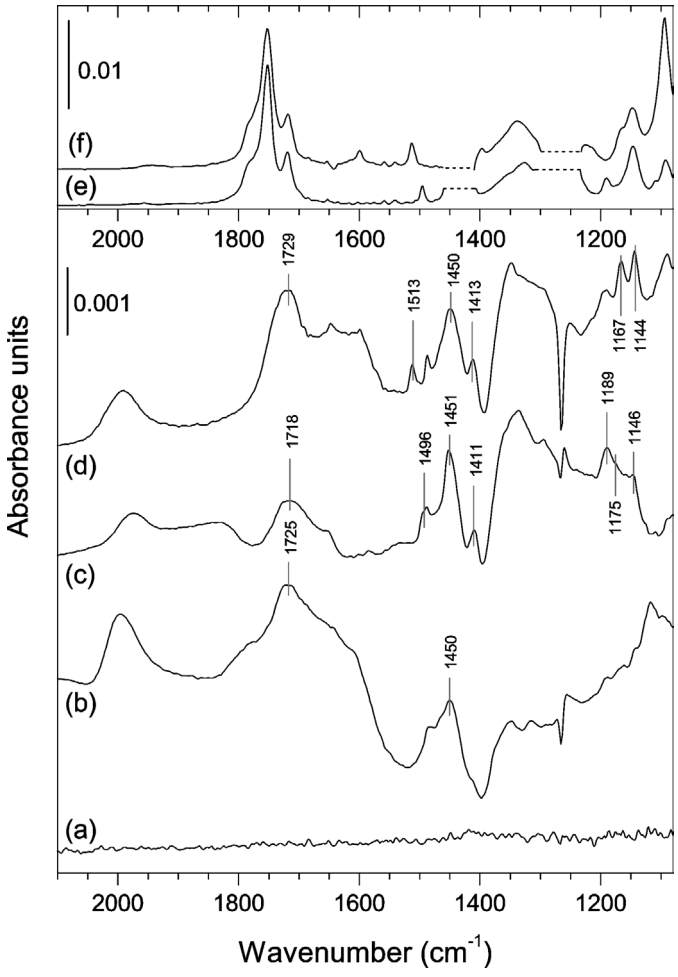


Fig. 3. In situ ATR-IR spectra of (b) (*S*)-lactic acid (**5**), (c) (*R*)-mandelic acid (**1**) and (d) (*S*)-naphthylglycolic acid (**8**) adsorbed on $Pt/Al_2O_3$ in the presence of $H_2$ and $CH_2Cl_2$ solvent. Spectrum (a) represents the state of the Pt surface before adsorption. Spectra (e) an (f) are the transmission IR spectra of a solution of **1** and **8** in $CH_2Cl_2$, respectively. Conditions: $C_{acid} = 1$ mM, 20 °C.

that is not seen in the spectrum of the neat acids (top panel of Fig. 2) is assigned to the symmetric stretch mode of a carboxylate group [$\nu_S$(OCO)], suggesting that the acids adsorb partly as anion on Pt. The broad feature extending between 1800 and 1600 $cm^{-1}$ is probably due to an overlap of a weak signal of CO adsorbed in the bridged geometry, which is more evident toward higher frequencies in **5** and signals of unprotonated acid molecules, in comparison with the transmission spectra. The presence of these entities is corroborated by the signal at ca. 1145 $cm^{-1}$ [$\delta$(O–H)$_{acid}$], which should be silent if only deprotonated species were present on Pt. Other signals in the 1600–1400 $cm^{-1}$ spectral region indicate that the phenyl and naphthyl rings are tilted with respect to the metal surface, either adsorbed or hanging toward the solution. The signal at ca. 1340 $cm^{-1}$ belongs to the deformation mode of the alcoholic –OH, which is coupled with C–H in plane deformation modes of the ring in the aromatic acids. The signal indicates that the intramolecular hydrogen bond characteristic of **1** is retained on adsorption.

All of the aforementioned signals display little loss of intensity on replacement of the solute with neat solvent. Thus the spectra shown in Fig. 3 are characteristic of adsorbed species. Inspecting these spectra reveals that at least two adsorption modes are feasible through interaction of the carboxyl group with the surface, thus affording carboxyl and carboxylate species, as mentioned earlier. This group could be the dominant anchoring point to the surface in the carboxylate species. The spectra suggest that orientation of the aromatic moiety is not parallel to Pt, although signals of an absolutely parallel ring would not be allowed by the surface selection rule [49]. This suggests the presence of species with the aromatic moiety adsorbed tilted or pendant. The variety of adsorption modes is likely given by the high surface coverage [50] obtained with the relatively high concentration used in the ATR-IR measurements. However, experiments at tenfold-lower concentrations released equivalent spectra with less contribution from those below 1300 $cm^{-1}$ due to solution-like species (carboxylic acid).

Additional information can be extracted from the spectra shown in Fig. 3. In contrast to the ATR-IR spectra of strongly adsorbing chiral modifiers, such as the cinchona alkaloids [36,51], the present spectra do not display any significant negative signal at ca. 1400 $cm^{-1}$. This signal is likely indicative of the adsorption strength of the adsorbate because it is assigned to the removal of other hydrocarbon surface species resulting from decomposition of dichloromethane (solvent) on Pt during the 10-min cleaning of the $Pt/Al_2O_3$ film in hydrogen [36]. In the case of cinchona alkaloids, adsorption is dictated primarily by the nearly “flat” adsorbing quinoline moiety and secondarily by the quinuclidine moiety [52], with a strong negative

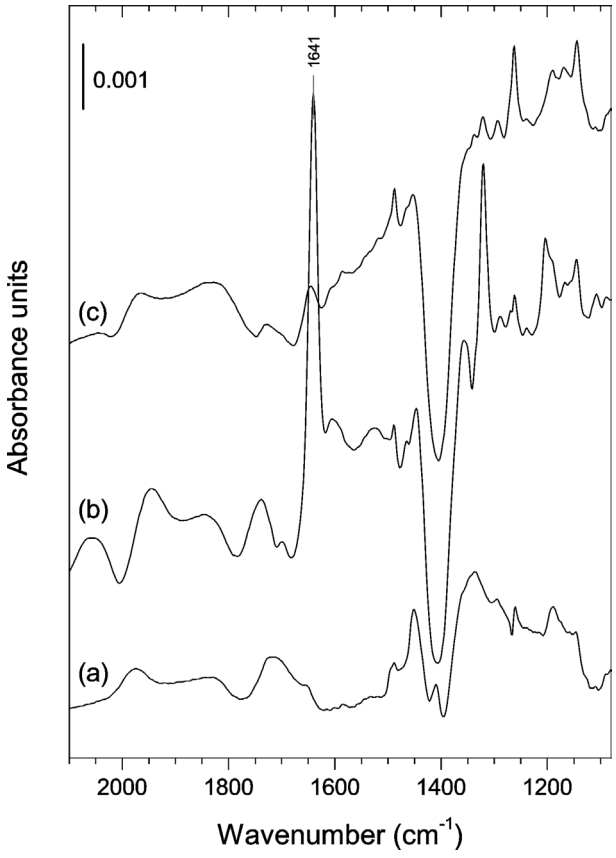


Fig. 4. In situ ATR-IR spectra of (a) (*R*)-mandelic acid (**1**) adsorbed on Pt and (b) of a solution containing excess DBU in contact with the same pre-equilibrated Pt surface. Spectrum (c) corresponds to the state of the surface after removing the solution containing DBU. Conditions: $C_{acid} = 1$ mM, 20 °C.

signal observed at 1400 $cm^{-1}$. Similarly, adsorption of (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE) predominantly via the naphthyl ring at a concentration 100 times lower than that in the present study afforded the same band without further signal attributable to ring modes [53], thus indicating that the naphthyl ring of PNE adsorbs strongly on Pt parallel to the surface. In contrast, the spectra shown in Fig. 3 suggest that despite the aromatic ring, the chiral acids do not adsorb strongly on Pt.

The stability of adsorbed **1** is greatly affected by adding a strong base, such as DBU, as indicated by the catalytic data. Fig. 4b shows that admission of an $H_2$-saturated solution of DBU in large excess with respect to the chiral acid to an acid pre-equilibrated metal surface induces desorption of a major fraction of **1**. This is best seen in the spectrum obtained after changing again to $H_2$-saturated solvent to remove dissolved and weakly adsorbed species [Fig. 4c]. The strong signal at 1641 $cm^{-1}$ indicates protonation of DBU [54], occurring only due to adsorbed acid. DBU not only displaces the chiral acid from the metal surface, but also adsorbs strongly and thus removes the hydrocarbon fragments present on Pt, as indicated by the negative signal at 1400 $cm^{-1}$.

## 4. Discussion

The two best modifiers among the various $\alpha$-hydroxy-carboxylic acids and derivatives tested here are mandelic acid **1** and naphthylglycolic acid **8**. Under optimized conditions, KPL was hydrogenated on $Pt/Al_2O_3$ with only 20 and 28% ee, respectively. Structural variations in the modifiers revealed that the carboxyl group is fundamental for enantioselection and adsorption. We assume that this function is responsible for the substrate–modifier interaction, presumably via a weak O–H–O-type H-bond toward the keto-carbonyl O atom of KPL.

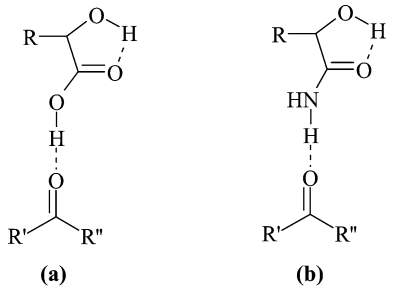


Fig. 5. Probable interaction of ketopantolactone (a) with **1** and **8**, and (b) with **4**.

Catalytic and spectroscopic measurements showed that adsorption of **1** on Pt was weak, and that replacing the phenyl ring with a naphthyl ring in **8** led to stronger adsorption. Hence, the better ee achieved with **8** may be attributed to its stronger adsorption, although the increasing steric hindrance induced by the extended aromatic system may also contribute to the difference. ATR-IR analysis showed that the aromatic rings of **1** and **8** adopted a tilted position relative to the Pt surface and that even **8** adsorbed weakly on Pt compared with the most effective modifier cinchonidine. On the basis of the ATR-IR spectra and a comparison with effective chiral amine-type modifiers, adsorption of **1** and **8** via the carboxyl (or carboxylate) function likely is more important than that via the aromatic rings.

We assume that another major reason for the poor performance of $\alpha$-hydroxy-carboxylic acids as modifiers of Pt is their weak interaction with the ketone substrate. This weak interaction is the likely reason for the complete loss of enantioselectivity when Pt was modified by **1** in polar solvents that allow H-bond interactions and can compete with the substrate. (Another feasible explanation for this is related to their stronger adsorption on Pt.) Mandelic acid, which is present exclusively as intramolecular hydrogen bonded species in solution (with this structure probably retained on adsorption on Pt), interacts very weakly with the substrate. A feasible modifier–substrate interaction is depicted schematically in Fig. 5. The H-bond type interaction is supported by the observation that deprotonation of the carboxyl group of **1** by DBU or transformation to an ester group (**3**) hindered the enantioselection, but that replacement of the carboxyl group by an amido group (still amenable to H bonding) had only a small negative effect on ee.

## 5. Conclusion

Various $\alpha$-hydroxy-carboxylic acids and their derivatives were tested as chiral modifiers of Pt in the hydrogenation of ketopantolactone to pantolactone. The <30% ee's achieved after a limited optimization are far below those values attainable by chiral amine-type modifiers. The probable reason for the low

efficiency is that in $\alpha$-hydroxy-carboxylic acids the "anchoring" and "interacting" functions are not separated; that is, the carboxyl group plays a dual role in adsorption on Pt and interaction with the substrate. This is a fundamental difference between these modifiers and the known good amine and amino alcohol-type chiral modifiers of ketone hydrogenation, such as cinchona alkaloids and 1-(1-naphthyl)ethylamine derivatives, in which the aromatic ring is responsible for adsorption and the amine function is responsible for interacting with the ketone.

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