Heterogeneous asymmetric reactions 20. Effect of ultrasonic variables on the enantiodifferentiation in cinchona-modified platinum-catalyzed sonochemical hydrogenations

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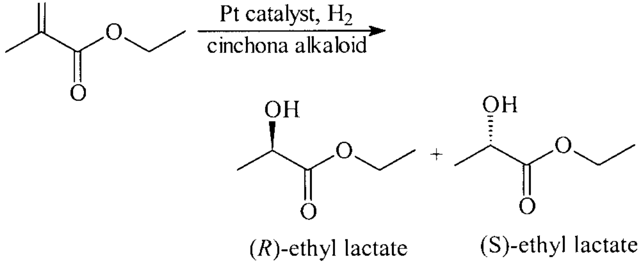
The effect of sonochemical variables on a cinchona alkaloid modified Pt/Al_2O_3 catalyst system and its application in α-ketoester hydrogenation are described. The sonochemical pretreatment of these commercial Pt/Al_2O_3–cinchonidine catalysts resulted in excellent ee values (up to 92–98% ee) under mild experimental conditions. To gain more insight into the nature of the ultrasonic effect the reactions were screened under widely varied conditions (ultrasound source, frequency, insonation time). Besides investigating the reactions, the catalyst–modifier system was also studied. The changes in metal particle size were determined by transmission electron microscopy, while the alteration of modifier concentration in the solvent upon sonication was followed by UV–vis spectroscopy. The transformation of the modifier during the pretreatment was detected by GC-MS and verified by NMR. Summarizing the results, the major effects of the sonochemical activation on the cinchona-modified supported Pt catalyst system can be described. The ultrasonic pretreatment increased the quantity of adsorbed cinchona and blocked its hydrogenation to provide more and highly stable chiral active sites for enantioselection.

KEY WORDS: enantioselective hydrogenation; Pt/Al_2O_3; cinchona alkaloids; ultrasounds; α-ketoesters.

1. Introduction

The increasing number of chiral pharmaceuticals and agrochemicals provides actuality and potential for asymmetric synthesis including enantioselective hydrogenations [1]. Since Orito's discovery [2] the asymmetric hydrogenation of α-ketoesters over platinum catalysts has received significant attention and has been reviewed extensively [3]. The most popular model reaction in this field, the chiral hydrogenation of ethyl pyruvate, provides excellent enantioselectivity using cinchona alkaloids (mainly cinchonidine) and platinum catalysts (up to 98% ee) [4]. The topic has been reviewed again very recently [5], indicating high interest and extensive research activities.



Two of the most frequently studied problems related to the Pt–cinchona catalytic system are (i) to further clarify the present mechanistic explanations and (ii) to widen the application possibilities of this unique catalyst [3,5]. The recent research activity resulted in numerous really intriguing examples (90–97% ee) of practical importance [6].

Ultrasonic irradiation is one of the most promising techniques in chemistry [7], the sonochemical methods becoming widely used especially in organic synthesis [8]. Although the first steps in sonocatalysis were made over 30 years ago [9], this field is still not widely explored. Ultrasonic irradiation was extensively applied in the preparation of nanosize MoC, MoS_2 or Fe [10] or noble metal catalysts [11]. The sonication of a catalytic system is highly efficient for the rate and selectivity increase in the hydrogenation of a C=C double bond [12]. The application of ultrasounds in heterogeneous asymmetric hydrogenations was first described by Tai *et al.* [13] for the hydrogenation of β-diketones and β-ketoesters catalyzed by tartrate-modified Raney-Ni (up to 94% ee) [13,14]. The authors explained the increased enantioselectivity by the removal of the aluminum-enriched Ni domains thought to be non-enantiodifferentiating sites. More recently, we described the beneficial effect of ultrasounds on the enantioselective hydrogenation of ethyl pyruvate over SiO_2, C and K-10-supported cinchona-modified Pt catalysts (ee up to 50–70%) [15]. Later,

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however, really satisfactory enantiomeric excesses (up to 97 ± 1%) were obtained with an alumina-supported platinum catalyst of Engelhard type [16]. The pool of substrates was widened using the well-known Engelhard reference catalyst E4759 [17]. 9-*O*-methoxy-cinchonidine (MeOHCD) was found to be even more effective than cinchonidine after ultrasonic pretreatment and thus 98 ± 1% ee can be achieved, indicating almost complete enantiodifferentiation [4(b)]. Since all these studies were of a phenomenological nature, with the primary goal of increasing the optical yields, no detailed efforts were made to interpret the effect of ultrasonic irradiation on the catalytic system.

The major thrust of the present work is to investigate the effect of ultrasonic irradiation on the enantioselective hydrogenation of α-ketoesters over $Pt/A1_2O_3$–cinchonidine catalysts and propose an interpretation for this effect. Systematic experimental results will be shown and the sonochemical effect on this unique system will be analyzed.

2. Experimental

2.1. Materials

Ethyl pyruvate (EtPy), ethyl benzoylformate (EtBF) and ethyl 2-oxo-4-phenylbutyrate (EtPhB) were of analytical grade (Fluka), while solvents (purity $\geq$99.5%) were Reanal and Fluka products. Cinchonidine (CD) and cinchonine (CN) (purity >98%) were purchased from Fluka, while 9-*O*-methoxy-10,11-dihydrocinchonidine (MeOHCD) was kindly donated by Dr. Martin Studer (Solvias AG, Basel, Switzerland). 5% Pt/Al_2O_3 (Engelhard, denoted as E4759 and E40655) catalysts were used in hydrogenations. 5% Pt/C (Engelhard, E46,476), 5% Pt/K-10 [18], 3% Pt/SiO_2 [19] and 5% Pt/Al_2O_3 (Aldrich) were used in transmission electron microscopy studies for comparison. E4759 catalyst was usually subjected to a reductive heat treatment (400 °C, H_2 flow) prior to use [3,5].

2.2. Ultrasonic pretreatments

The presonication of the catalyst was carried out at 20 °C in a 20 ml Schlenk-type glass vessel equipped with a hydrogen inlet and a rubber septum. To maintain the homogeneity of the ultrasonic field [20], the same vessel was always used. Before sonication the solvent was added to the catalyst–cinchonidine system and flushed with high purity hydrogen (99.995%) for 15 min; then the irradiation proceeded for the required time (usually 30 min) in a closed hydrogen atmosphere. The reactor used for pretreatment was immersed in the center position of the ultrasonic bath, and the solvent level was 2 cm below the water bath level.

The activated catalysts were transferred into the autoclave under an inert atmosphere and then the reactant was introduced. Both hydrogen and nitrogen atmospheres were applied, respectively, in order to check the effect of different gases. However, no differences were found in catalyst performances. As a result, for safety reasons, nitrogen was used in each experiment during catalyst transfer.

2.2.1. Ultrasonic baths

Three ultrasonic baths, namely a Realsonic 40SF (20 kHz, 30 W), a Donau-Lab-Sonic DLS-310-T (35 kHz, 30 W) and a Cole-Palmer 8892 (47 kHz, 105 W), were used for the presonication.

2.2.2. Ultrasonic probe

A Sonics&Materials VC 50 ultrasonic processor with a titanium alloy (Ti-6Al-4V) probe (3–138 mm) was immersed directly into the reaction mixture.

2.3. Enantioselective hydrogenations

The hydrogenations were performed in a glass reactor or in a Berghof Bar 45 autoclave with a Teflon liner at room temperature (25 °C). The catalytic system (standard conditions: 50 mg of catalyst, 5 mg of cinchonidine and 5 ml of solvent) was activated (1 bar or the reaction hydrogen pressure) and the reactant (2.15 mmol) was introduced. After that the autoclave was flushed with hydrogen several times, filled to the desired pressure and stirred (1300 rpm) for the required time. The product identification and the determination of enantiomeric excesses ($ee\% = (|[R]-[S]|) \times 100/([R]+[S])$) were made by gas chromatography (HP 5890 GC-FID, 30 m Cyclodex-B and Lipodex-A capillary columns). The ee values were reproducible within 2%.

2.4. Transmission electron microscopy (TEM)

Measurements were performed with a Philips CM10 electron microscope by the usual methodology [16].

2.5. Ultraviolet–visible spectroscopy (UV–vis)

UV–vis spectra were recorded using a Hitachi UV-3000 spectrometer. A 1 mg ml^{-1} solution of cinchonidine in acetic acid was pretreated conventionally (1 h stirring) or by ultrasonic activation followed by 1 h stirring. The catalyst was then removed and the clear supernatant was subjected to UV–vis measurements.

2.6. Mass spectrometry

The analysis was carried out (including the gas chromatographic separation) using a Hewlett-Packard

5970 MS (70 eV EI ionization, 12 m long HP-1 column) coupled with a Hewlett-Packard 5890 GC.

2.7. ^{1}H-NMR spectroscopy

^{1}H-NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard on a Bruker AM 400 spectrometer.

3. Results and discussion

3.1. Effect of ultrasonic variables on the enantioselective hydrogenations

According to our previous findings [15–17], the enantioselective hydrogenation of ethyl pyruvate and two other α-ketoesters (EtBF and EtPhB) have been selected for test reactions. The reactions were carried out in acetic acid using 5% Pt/Al_2O_3 catalysts (E40655, E4759).

3.1.1. Type of ultrasound source

First, the effect of presonication with various types of ultrasound sources was studied on enantioselective hydrogenation of α-ketoesters. The reaction rates and ee values were determined with catalysts pretreated by different types of presonication. An ultrasonic bath and an immersed titanium probe were used under the same (20 kHz, 30 W) operating and experimental conditions. The collected results are tabulated in table 1. As shown, the sonochemical pretreatment with an ultrasonic bath increased the ee values. The immersed probe, however, does not significantly affect either the reaction rates or the optical yield. In addition to the increase in ee the use of an ultrasound bath resulted in remarkably higher reaction rates (up to 50% rate increase in the case of EtPhB). These observations are in accordance with earlier conclusions [7]; immersion probes usually show better performance in homogeneous systems, while baths are more effective under heterogeneous conditions.

Table 1
Effect of different ultrasound sources on the enantioselective hydrogenation of α-ketoesters over a 5% Pt/Al_2O_3 (E40655) catalyst in acetic acid (standard conditions, 1 bar H_2, frequency 20 kHz, power input 30 W, 30 min insonation time)

Ultrasound source	Substrate	r (mmol min^{-1} g_{cat}^{-1})	ee (%) (R)
–	EtPy	1.3	81
Probe	EtPy	1.2	81
Bath	EtPy	1.5	86
–	EtBF	0.4	75
Probe	EtBF	0.4	75
Bath	EtBF	0.5	80
–	EtPhB	0.7	76
Probe	EtPhB	0.8	78
Bath	EtPhB	1.1	85

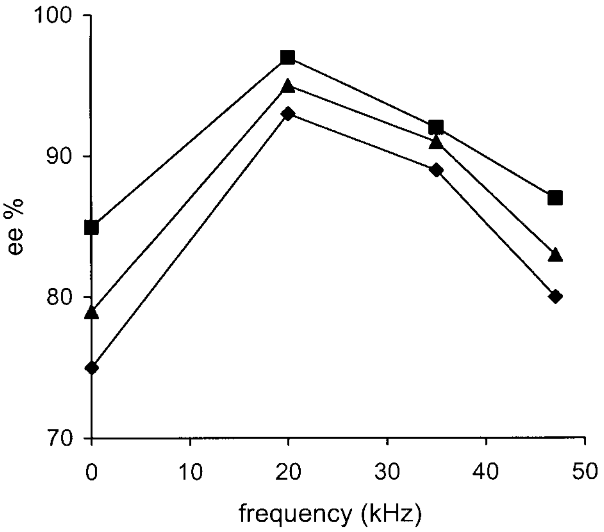


Figure 1. Effect of ultrasound frequency on the optical yield sonochemical hydrogenation of α-ketoesters over cinchonidine-modified Pt/Al_2O_3 catalysts in acetic acid under 10 bar hydrogen pressure. ■, EtPy, E40655; ◆, EtBF, E4759; ▲, EtPhB, E4759.

3.1.2. Frequency of ultrasonics

The previous section called attention to the crucial role of energy input. Ultrasonic frequency is also related to energy and its effect should be important. As a result, different ultrasonic baths have been used with increasing frequency, namely 20, 35 and 47 kHz. The enantioselectivity values obtained in the asymmetric hydrogenation of α-ketoesters are plotted in figure 1. As clearly shown, the ultrasonic irradiation of the catalytic system resulted in higher enantiomeric excesses. The best enantiomeric excesses were obtained in the order EtPy > EtPhB > EtBF. In each case, irradiation at 20 kHz provided the most characteristic increase; however, the results obtained after 35 and 47 kHz irradiation are still better than those obtained after silent pretreatment. Considering the energy–frequency relationship, we can conclude that, after an optimal energy input, the excess energy decreases the catalytic performance and enantioselectivity.

3.1.3. Sonication time

In addition, to gain better insight into the activation process, the ee values were determined as a function of insonation time. In light of the previous sections, an ultrasonic bath working at 20 kHz has been selected for these investigations. The results are shown in figure 2. As shown, the ee *versus* insonation time functions pass through a maximum for each substrate. The maxima were found at 30 min, clearly indicating that the prolonged sonication did not increase the performance of the catalytic system. This is in good correlation with the previous sections. It should be noted that the sonochemical pretreatment significantly increased the ee values, resulting in excellent enantioselectivities.

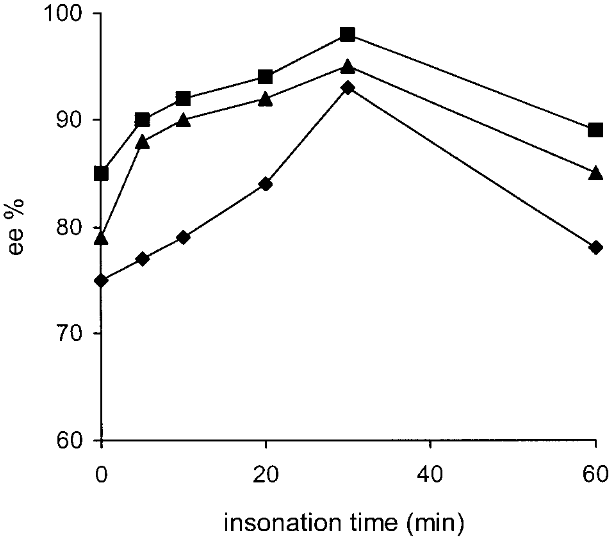


Figure 2. Enantiomeric excess *versus* insonation time functions of the sonochemical enantioselective hydrogenation of α-ketoesters over 5% Pt/ Al_2O_3–cinchonidine catalyst systems in acetic acid at 25 °C and under 10 bar hydrogen pressure. ■, EtPy, E40655; ◆, EtBF, E4759; ▲, EtPhB, E4759. Pretreatment: bath, 1 bar H_2, 20 kHz.

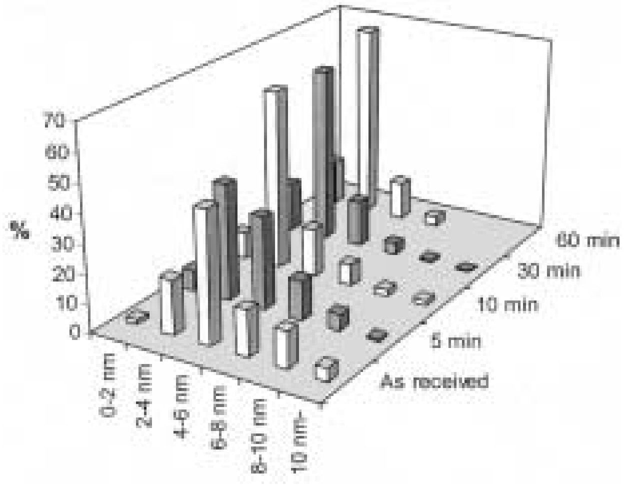


Figure 3. Metal particle size distribution of 5% Pt/Al_2O_3 reference catalysts (E4759) as received and after various presonication times without modifier.

3.2. *Effect of ultrasonics on the catalyst–modifier system*

As is well known and widely accepted, the recent mechanistic interpretation of the cinchona-modified Pt-catalyzed enantioselective hydrogenations is based on the so-called *modified catalyst* model [3,5]. Numerous research groups contributed to the development of this model. Unfortunately, despite the extensive efforts, direct evidence concerning the adsorption in these liquid–solid systems using high-performance instrumental techniques (*e.g.* STM, AFM) [21] cannot be obtained yet. As a consequence, the catalyst–modifier system was studied in an indirect way by transmission electron microscopy (TEM) and UV–vis spectroscopy. In addition, the transformation of the modifier during the different pretreatments was followed by GC-MS and ^{1}H-NMR.

3.2.1. *Transmission electron microscopy*

The results of hydrogenation reactions indicated an important contribution of ultrasounds to the formation of a more effective Pt–cinchonidine catalytic system. Since it is known that ultrasonic irradiation strongly affects the particle size of solids [22], it was an obvious choice to study the catalyst as well. The metal particle size of the catalysts was determined by TEM. On the basis of TEM images (not shown) the summarized metal particle size distribution of a Pt/Al_2O_3 catalyst as a representative example is displayed in figure 3 (E4759) as received and after ultrasonic irradiation.

As an additional characteristic, the mean metal particle diameters were determined as a function of presonication time and plotted in figure 4. For comparison, this feature of other catalysts previously used in these hydrogenations is also shown.

In accordance with the literature [22] a mean metal particle size decrease was expected. This is exactly what we observed by TEM. In the case of each catalyst the metal particle size monotonically decreased as a function of irradiation time. The reductive heat treatment used for E4759 resulted in particle aggregation and higher metal particle size. The presence of the modifier during sonication reduces the particle size decrease. In addition, as a general observation, the irradiation produced more homogeneous metal particle size distribution (figure 3). The change in metal particle size most likely plays an important role in these catalytic systems, taking into account the structure-sensitive character of the reaction [3,5]. One clear advantage of the ultrasonic pretreatment,

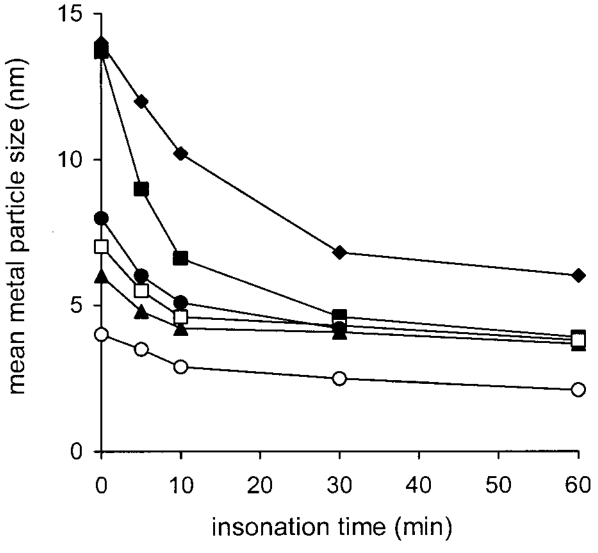


Figure 4. Effect of presonication at 20 kHz on the mean metal particle size of some supported Pt catalysts as a function of irradiation time. ■, E40655; ●, E4759; □, E4759 red; ◆, Pt/Al_2O_3 (A); ○, Pt/C; ▲, Pt/SiO_2.

Table 2
Effect of the presence of the modifier on the enantioselectivity in the enantioselective hydrogenation of EtPy over 5% Pt/Al_2O_3 catalyst (E40655)–cinchonidine system (standard conditions)

Hydrogen pressure (bar)	Presonication	Modifier during presonication	Optical yield (ee%)
1	No	–	80
1	20 kHz, 30 W, 30 min	No	81
1	20 kHz, 30 W, 30 min	Yes	85
10	No	–	85
10	20 kHz, 30 W, 30 min	No	88
10	20 kHz, 30 W, 30 min	Yes	97

however, is that in this way one can prepare catalysts with substantially different particle size but the same origin (reduction method, precursor, etc.). It makes the process an even more useful and promising tool for other heterogeneous catalytic applications.

3.2.2. *Modifier–catalyst interaction*

TEM studies indicated differences between metal particle size after ultrasonic pretreatment done with or without modifier. As a result, the hydrogenation of EtPy was tested when the catalyst was pretreated with ultrasonics both in the presence and in the absence of cinchonidine. The results are summarized in table 2. The data unambiguously show that the presence of the modifier during the sonochemical pretreatment is of principal importance. If the pretreatment was carried out without cinchonidine the ee values increased only slightly (up to 3%), while pretreatments with CD resulted in a significant increase in ee (up to 12%). This observation obviously indicates that the change in metal particle size and distribution, although being an important feature, does not interpret the phenomenon.

As a result, the catalytic system was studied by UV–vis spectroscopy, while the transformation of the modifier was determined by mass spectrometry combined with effective gas chromatographic separation. First, the catalyst–modifier system was pretreated and then the catalyst was removed. The clear supernatants were subjected to UV–vis studies. The spectra are plotted in figure 5. As shown, the spectra gradually change as a function of pretreatment. The spectrum obtained after 10 min insonation and 1 h stirring (figure 5, trace B) corresponds to the original spectrum of CD in acetic acid [23]. After prolonged irradiation the spectrum does not change significantly in shape, and only a continuous decrease in the integrated absorbance can be observed. This indicates a modifier concentration decrease in the solution. Stirring with no ultrasonic pretreatment, however, resulted in remarkable changes in the shape of the spectrum (figure 5, trace A). The original signals (~300 nm) decreased, while a band at 250 nm highly developed (figure 5, trace A), indicating the saturation of the N-containing aromatic ring. Since the reaction mixture contains several compounds and their UV bands overlap, it is very difficult to calculate their exact concentration from the spectra. As a result, integrated absorbances were determined and used for a semiquantitative comparison. It was found that increasing insonation time resulted in a decreasing amount of cinchona in the supernatant. As a consequence, the ultrasonic pretreatment increased the amount of cinchona adsorbed on the catalyst, most likely on both metal and support (figure 6). As can be seen, the modifier

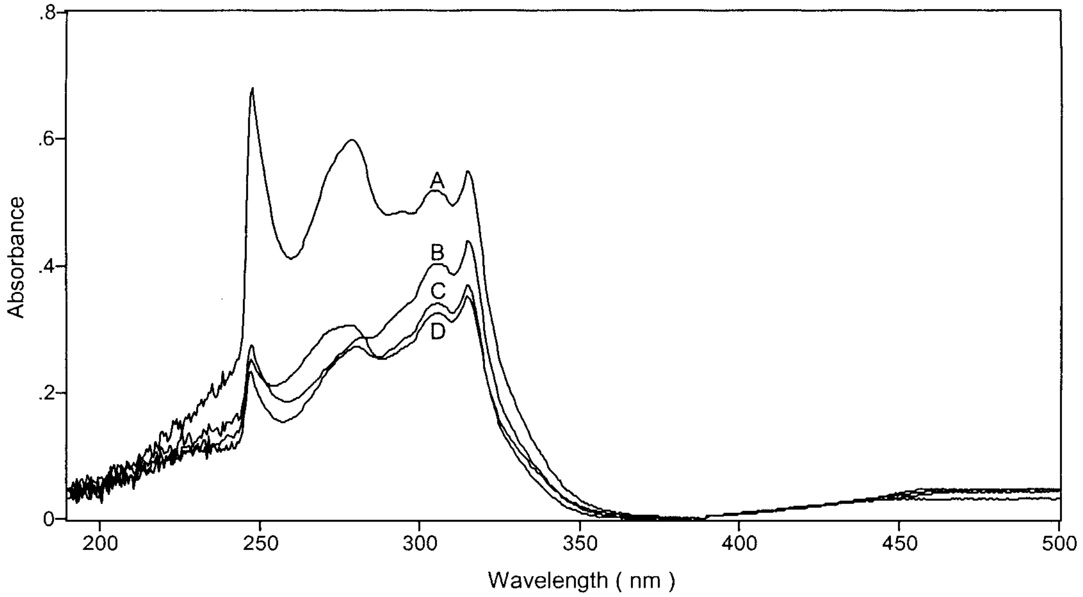


Figure 5. UV–vis spectra of cinchonidine in acetic acid (1 mg ml^{-1}) treated with 5% Pt/Al_2O_3 catalyst under hydrogen pressure at 25 °C (A) after 1 h stirring, (B) after 10 min insonation and 1 h stirring, (C) after 30 min insonation and 1 h stirring, (D) after 60 min insonation and 1 h stirring.

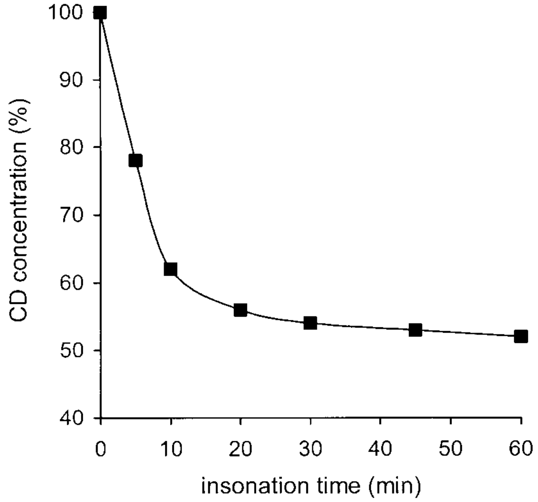


Figure 6. Effect of insonation time on the relative concentration of cinchonidine in the supernatant of the Pt/Al_2O_3-CD catalytic system in acetic acid calculated from the integrated absorbances.

concentration monotonically decreases as a function of insonation time. However, after 30 min only a slight decrease can be observed.

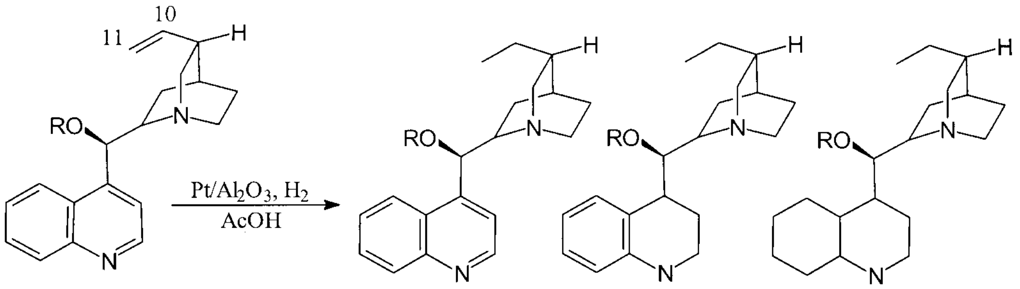
The UV–vis spectra (figure 5) clearly indicated that the modifier structure changed especially during the silent pretreatments; however, the UV spectra are not satisfactory to determine these transformations. Thus, the aliquot of the catalytic system was studied after evaporation by GC-MS spectrometry and ^1H-NMR spectra. As the results showed, the partial hydrogenation of cinchonidine readily took place during silent stirring under hydrogen. It was found, as expected [24], that besides the obvious vinyl group hydrogenation the N-containing aromatic ring of CD was saturated to a large extent. The hydrogenation of the benzenoid ring was also observed to a smaller extent. It is interesting to note that, using MeOHCD as a modifier, the hydrogenation of the N-containing aromatic ring occurred to a smaller extent than with CD. Benzenoid ring saturation, however, is completely missing, indicating that the MeOHCD is more resistant to hydrogenation. In contrast to silent pretreatments, the presonicated samples also show the transformation of the modifier, but to a smaller extent. These clearly prove that the ultrasonic pretreatment results in the adsorption of more cinchonidine on the surface and blocks, at least in part, the hydrogenation of the modifier (scheme 1). Since hydrogenated cinchona derivatives are not efficient modifiers in these hydrogenations, the mentioned blocking effect has great importance.

3.2.3. *Origin of the ultrasonic effect*

Considering the experimental results listed above, some important points can clearly be summarized as follows:

1. The beneficial effect of ultrasonics on these heterogeneous catalytic enantioselective hydrogenations is a definite phenomenon.
2. Ultrasonics decreased the main metal particle size of the catalysts and resulted in more homogeneous size distribution.
3. The characteristics of ultrasonics are of great importance; both frequency and insonation time functions are of maximum character.
4. The presence of the chiral modifier during presonication is important: ultrasonic pretreatments with modifier remarkably increased the ee values, unlike the modifier-free presonications.
5. The ultrasonic pretreatment results in decreasing modifier concentration in the solution and in part blocks the hydrogenation of the modifier.

Based on these major findings, the effect of ultrasonics on these catalytic systems can be interpreted by the synergism of the formation of a more uniform, favorable catalyst surface and the increase in the amount of adsorbed modifier.



	Conversion				
R = H	100%	strirring	20 %	65 %	15 %
	100%	presonicated	30 %	70 %	
R = Me	18%	strirring	82 %	18 %	
(10,11-dihydro)	1%	presonicated	99 %	1 %	

Scheme 1.

The TEM measurements indicated the transformation of the Pt particles. The mean metal particle size became smaller and the distribution turned out to be more homogeneous. The fact that highest enantiomeric excesses were obtained at ~4 nm Pt particle size is in agreement with earlier findings [25]. It is known that only catalysts with platinum possessing a mean metal particle size larger than 3–4 nm give good optical yields. The reason for this structure sensitivity is not clear yet; however, it seems that relatively flat low index planes of Pt are more suitable for the modifier adsorption [3]. In a virtual contrast, in a recent paper [4(a)] excellent ee values were reported in the presence of very small (~1 nm) Pt particles. However, the poly(vinyl-pyrrolidone) stabilized Pt colloid type catalyst is very different from alumina-supported Pt, and thus conclusions concerning the particle size effect in itself cannot be directly transferred to supported catalysts. The cinchona-free ultrasonic pretreatments (table 2), however, clearly revealed that the ee increases only when the modifier is present during presonication. As a result, the particle size decrease, although being an important factor, might not be the principal and exclusive reason for enhanced enantiodifferentiation.

During irradiation, the catalyst–modifier interaction became more pronounced. It is clearly shown by both cinchonidine concentration decrease in the bulk solution and the change in the ratio of hydrogenated *versus* original modifier after ultrasonic pretreatments. In our opinion, more cinchonidine adsorbs on the catalyst to cover the platinum surface and partially cover the support. In this way the metal–support interfaces may also become chirally modified to a large extent. In the light of our recent findings, the modifier immobilized only on the support can be effective in the reaction (ee up to 75%) [26]. Thus, the role of the metal–support interfaces seems of great importance. On the other hand, using MeOHCD as the modifier, almost complete enantiodifferentiation was obtained (up to 98% ee) after ultrasonic pretreatment [4(b)]. The decrease in the amount of partially ring-hydrogenated CD derivatives suggests that the adsorbed modifier is not released from the surface. Since these derivatives are less effective modifiers [3,5], suppressing these transformations is beneficial for the optical yields. As a possible explanation of this enhanced adsorption strength may be an additional contribution of the ultrasounds, namely, the displacement of the blocking surface moieties [27]. When this *in situ* surface cleaning occurs in the presence of the modifier, it can immediately adsorb on the clean platinum surface. Naturally, more adsorbed cinchona results in more chiral sites, increasing the rate of chiral hydrogenation and suppressing the formation of *racemic* product. This so-called surface cleaning effect may help prevent the catalyst deactivation as well. Finally, the blocking of the hydrogenation of the quinoline ring of the cinchona alkaloids keeps the modifier in the most effective form.

4. Conclusions

In conclusion, the sonochemical pretreatment of commercial Pt/Al_2O_3–cinchonidine catalytic systems resulted in enhanced enantioselectivity in the hydrogenation of α-ketoesters, providing excellent ee values (up to 98% ee) under mild and widely varied experimental conditions. This improved enantiodifferentiation was explained on the basis of the synergistic effect of the transformation and surface cleaning of metal particles and enhanced cinchona adsorption initiated by ultrasounds. The superposition of these separate phenomena results in the formation of more chiral active sites and suppresses the *racemic* hydrogenation, providing highly effective enantiodifferentiation. In this way the application of sonochemical methods may open new intriguing possibilities in asymmetric heterogeneous hydrogenations.

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