Enantioselective hydrogenation of 2-methyl-2-pentenoic acid over cinchonidine-modified Pd/alumina

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A chiral alkanoic acid was prepared with up to 52% excess of the (S) enantiomer by hydrogenating an α,β-unsaturated carboxylic acid with a cinchonidine–Pd/Al_2O_3 catalyst system. Favourable conditions are: high surface hydrogen concentration ($\geq$60 bar hydrogen pressure, low catalyst concentration and apolar solvents), near ambient temperature and a cinchonidine/reactant molar ratio of at least 0.4 mol%. It is proposed that high hydrogen solubility and the presence of 2-methyl-2-pentenoic acid reactant as dimers are advantageous for enantiodifferentiation.

Keywords: enantioselective; hydrogenation; cinchonidine; Pd/alumina; methylpentenoic acid

1. Introduction

The enantioselective hydrogenation of α,β-unsaturated carboxylic acids has received great attention due to pharmaceutical importance of some chiral carboxylic acids, such as naproxen and ibuprofen [1–4]. Homogeneous ruthenium and rhodium complex catalysts can produce the desired enantiomer with an enantiomeric excess (ee) of 99% or even higher.

Heterogenization of transition metal complexes can provide excellent, recyclable catalysts for alkene hydrogenation, but the number of successful applications is very limited [5]. Another possibility is the application of conventional metal hydrogenation catalysts and a strongly adsorbing chiral auxiliary, termed modifier. Outstanding examples are the hydrogenation of substituted carbonyl compounds over the Ni–tartaric acid–NaBr system [6,7] and supported Pt modified with cinchona alkaloids or some other chiral amines [8–10].

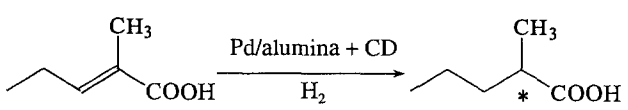
Unfortunately, there are no useful chirally modified metal catalysts with synthetic potential available for the enantioselective hydrogenation of C=C bonds. There are a few attempts to hydrogenate E and Z α-phenylcinnamic acid over cinchonidine-modified Pd catalysts [11–13]. The highest ee of (S)-2,3-diphenylpropionic acid (53%) was obtained in a strongly polar solvent mixture using a 5 wt% Pd/titania catalyst [13]. When substituting cinchonidine (CD) to other cinchona alkaloids (cinchonine (CN), quinidine and quinine), or Pd to Ni, the ee is considerably lower [11,14].

Enantioselectivities achieved in the hydrogenation of other types of alkenes are sometimes disappointing. Only 0.5–4.5% ee was obtained in the hydrogenation of α-acetamidoacrylic and α-acetamidocinnamic acid over Pd/C modified with sparteine or ephedrine [15]. Pt/C modified with CD is also a poor catalyst for the enantioselective hydrogenation of this type of substituted C=C bonds [9]. A careful choice of reaction parameters and catalyst structure afforded 38% ee in the hydrogenation of isophorone in AcOH : MeOH = 1 : 100 mixture at 40 bar [16]. The best catalytic system for this reaction is Pd black modified with dihydrovinpocetine.

These studies indicate that the enantioselective hydrogenation of acrylic acid derivatives is a promising model reaction when using CD-modified Pd, but there is hardly any information available to help in the development of a mechanistic model for the reactant–modifier–Pd interactions [16]. The aim of our work is to contribute to the understanding of this type of stereoselective reactions. We have chosen a relatively simple model reaction, the reduction of 2-methyl-2-pentenoic acid (MPA), shown in scheme 1. The effect of important reaction parameters was studied using CD-modified Pd/alumina.

2. Experimental

5 wt% Pd/alumina (Engelhard 40692, $D = 0.21$ as determined by TEM) and 2-methyl-2-pentenoic acid (MPA, Aldrich, 99% E isomer) were used as received.



Scheme 1.

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Hydrogenations were carried out in a 100 ml stainless steel autoclave equipped with magnetic mixing (1250 rpm). A 50 ml glass liner with teflon cap and stirrer was used to keep the system inert. If not otherwise stated, the following standard conditions were used: 1 g (8.7 mmol) MPA, 50 mg catalyst, 10 mg (34 μmol) CD (Fluka) and 25 ml cyclohexane, at room temperature (20–23°C) and 50 bar. A Chirasil-DEX CB (Chrompack) capillary column was used for GC analysis. Enantiomeric excess is expressed as ee (%) = $100 \times |(R - S)|/(R + S)$, with a reproducibility of $\pm 1\%$. Initial rates were determined from the hydrogen consumption.

3. Results and discussion

3.1. Influence of reaction parameters

In studying the effect of reaction conditions, some of those parameters were selected which had been found to be influential in previous studies of enantioselective hydrogenation reactions [8,10,16], namely the pressure, temperature, nature of solvent and amount of modifier and catalyst. Fig. 1 illustrates the influence of hydrogen pressure on the enantioselection using Pd/alumina in cyclohexane at room temperature. ee increases considerably with ascending pressure up to about 60 bar; above this value the change is negligible. Note that in all experiments shown in figs. 1–5 the conversion was complete or close to it. The deviation of ee as a function of conversion between 15 and 100% was within the experimental error; at lower conversion the determination of ee by GC analysis was found to be ambiguous.

Fig. 2 represents the influence of catalyst loading on the initial rate of hydrogen consumption and ee. Applying the criterion known for distinction between mass transfer and surface reaction control in three-phase reactor systems [17], it was found that both regimes were covered depending on the conditions used. The dashed line in fig. 2 indicates the rate of reaction in the absence of mass transport influence, which has been calculated from the reciprocal rate–reciprocal catalyst amount correlation. We found an almost linear correlation between rate and catalyst amount up to 50 mg. Above this value the increasing influence of hydrogen transport limitation lowers the global rate (ml H_2/s, g catalyst). As a consequence of the increasing influence of the diffusional transport, the surface concentration of hydrogen becomes lower, which may explain the loss in ee observed. This is in line with the observation that lowering the hydrogen pressure decreases ee (fig. 1).

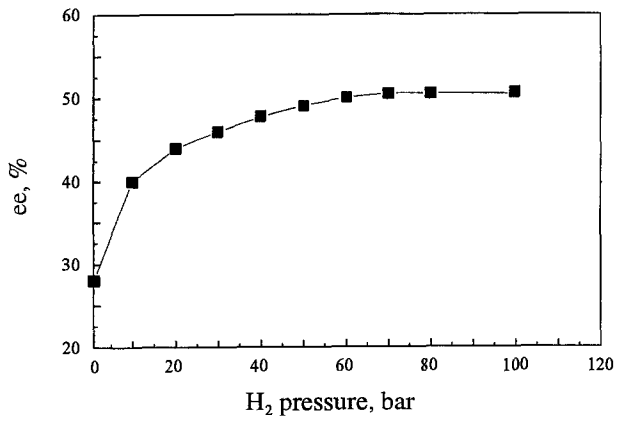


Fig. 1. Enantiomeric excess (ee) as a function of hydrogen pressure in cyclohexane under standard conditions, specified in the Experimental section.

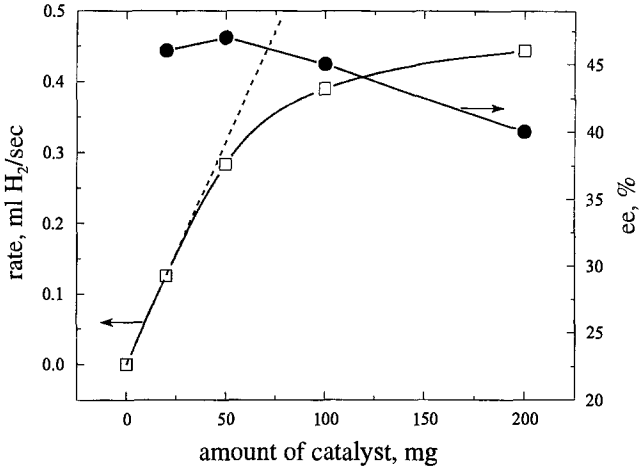


Fig. 2. Influence of catalyst amount on the initial rate (□) and enantiomeric excess (●) under standard conditions.

The enantioselectivity is strongly dependent on the solvent used (fig. 3). ee declines with increasing solvent polarity characterized by the most comprehensive empirical solvent parameter E_T^N [18]. Independent of the pressure applied (60 or 10 bar), the effect of polarity of the medium on ee is similar: ee decreases in polar solvents. Not only polar solvents but also mixtures of polar and apolar solvents afforded low ee. Note that water is a poor solvent of MPA and CD, and two phases were present during reaction.

The solubilities of hydrogen in these solvents [19] expressed as hydrogen mole fractions are also plotted in fig. 3. The solubility of hydrogen in the liquid phase changes with the solvent polarity and shows a similar dependence as observed for the ee–E_T^N correlation. This is an indication that the positive effect of apolar solvents on the enantiodifferentiation is partly due to the resulting higher concentration of hydrogen on the Pd surface as a consequence of higher solubility. Contrary to our observation, polar solvents and solvent mixtures were found to be advantageous for the enantioselective hydrogenation of (E)-α-phenylcinnamic acid [13] and α-ketoacids [20].

The temperature dependence of enantiodifferentiation was investigated in *n*-hexane (fig. 4). The enantioselectivity is the highest at or below 0°C, but only ~ 2% less at room temperature. The loss of enantioselection at

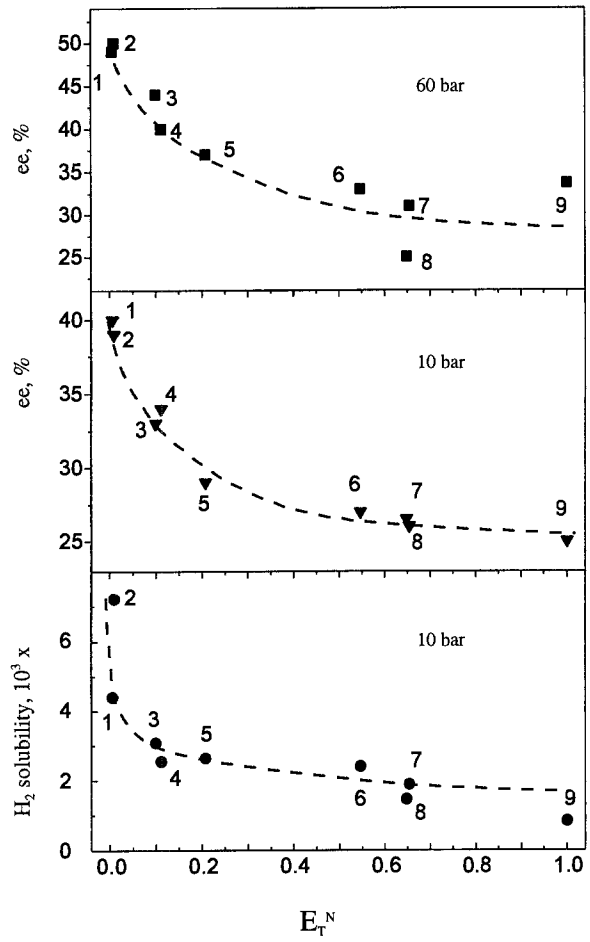


Fig. 3. Correlation between empirical solvent parameter (E_T^N) and hydrogen solubility (x, mol fraction of hydrogen at 10 bar partial pressure), and enantiomeric excesses (ee) at 10 and 60 bar hydrogen pressure measured in various solvents (other parameters standard condition): (1) *c*-hexane, (2) *n*-hexane, (3) toluene, (4) benzene, (5) tetrahydrofurane, (6) *i*-propanol, (7) acetic acid, (8) ethanol, (9) water.

higher temperature may partly be due to the suppressed solubility of hydrogen. The rate of hydrogen consumption increases with ascending temperature, as expected. For example, the initial rate is 0.018 ml H_2/s at 0°C and 0.74 ml H_2/s at 60°C.

An increase in ee is observed with raising amount of CD as depicted in fig. 5. Above a CD/MPA ratio of 0.35–0.4 mol% there is only a minor change in enantioselectivity. For comparison, a 3 mol% CD/reactant ratio was applied in the Pd-catalyzed enantioselective hydrogenation of α- and β-substituted cinnamic acid derivatives [11–13].

Besides, the modified reaction is slower than the unmodified (racemic) hydrogenation. For example, under standard conditions the initial rate of hydrogen consumption at 60 bar was lower by a factor of 1.9 compared to that of the unmodified reaction (0.28 ml H_2/s instead of 0.55 ml H_2/s). A similar retarding effect of the chiral modifier was observed in the enantioselective hydrogenation of (E)-α-phenylcinnamic acid [13] and isophorone [16].

3.2. Nature of reactant–modifier interaction

The study of the influence of reaction parameters on the enantioselection revealed that the Pd–CD catalyst system affords over 50% ee to (S)-2-methylpentanoic acid in the hydrogenation of 2-methyl-2-pentenoic acid (MPA). When substituting CD by its near enantiomer CN, the (R) enantiomer of the saturated acid is produced preferentially. Under standard conditions the ee's are 48% for CD and 45% for CN.

Contrary to the positive effect of polar solvents or solvent mixtures reported in the hydrogenation of α-phenylcinnamic acid [13], we found that the enantioselectivity is always higher in apolar solvents. It is known that simple alkanoic acids are present mainly as dimers in apolar medium (and in gas phase) [21]. We assume that also MPA forms dimers in an apolar medium.

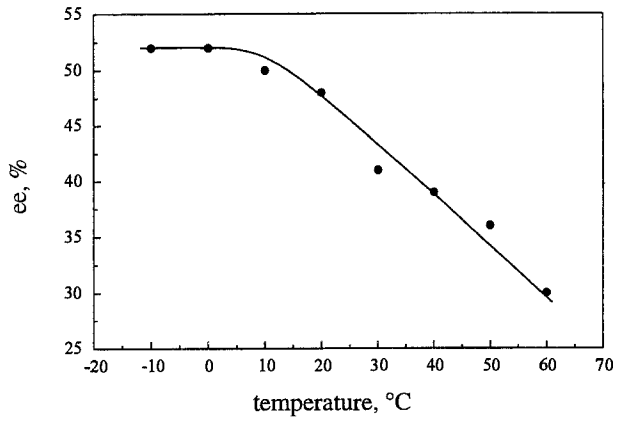


Fig. 4. Influence of reaction temperature on ee in *n*-hexane (60 bar, 50 mg catalyst, 1 g MPA, 20 mol *n*-hexane).

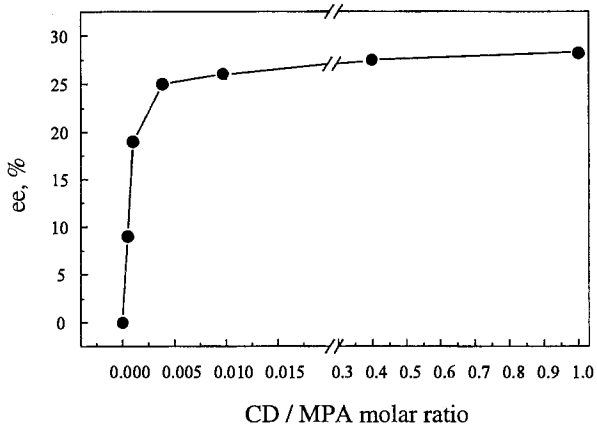
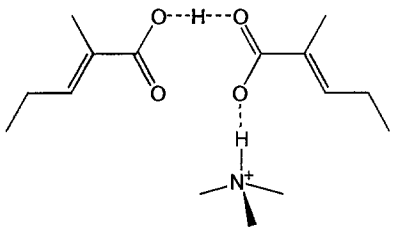


Fig. 5. Enantioselectivities as a function of cinchonidine/2-methyl-2-pentenoic acid (CD/MPA) molar ratio (room temperature, 1 bar, 100 mg catalyst, 0.4 g MPA, 40 ml toluene).



quinuclidine N of CD

Scheme 2.

Concerning the reactant–modifier interaction we propose that MPA dimers protonate the quinuclidine N of CD (scheme 2). This type of interaction is similar to that proposed in the triethylamine–acetic acid reaction [22]. Besides, protonation of CD by acetic acid in ethanol has been evidenced recently by NMR spectroscopy [23]. We assume that the loss of ee in polar medium is due to lower surface hydrogen concentration and the dimer–monomer equilibrium, which shifts to the monomer side as the monomer is stabilized by the polar solvent.

4. Conclusions

We have shown that over 50% ee can be achieved in the hydrogenation of 2-methyl-2-pentenoic acid (MPA) with cinchonidine-modified Pd/alumina. This value resembles the best ee obtained in the hydrogenation of C=C double bonds using chirally modified metal catalysts [9,13]. Apolar solvents are good reaction media, probably because of their good hydrogen dissolving properties and the presence of MPA as dimers.

Kinetic and spectroscopic experiments are presently carried out in our laboratory to evidence the dimer formation of MPA in apolar solvents.

Acknowledgement

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