The solvent effect in the enantioselective hydrogenation of (E)-2-methyl-2-butenoic acid with cinchonidine doped Pd/Al$_2$O$_3$

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Abstract

The hydrogenation of (E)-2-methyl-2-butenoic acid (tiglic acid), using a commercial 5 wt% Pd/Al$_2$O$_3$ catalyst (Engelhard) doped with cinchonidine (CD) ($P = 4.0$ MPa, $T = 298$ K) was investigated in depth to evidence the nature of the interaction CD:acid and the specific role of the solvent polarity on the enantiomeric excess (e.e.). Previous results reported in the literature on the same substrate or on similar unsaturated short chain acids have been verified for a feasible industrial application. A linear correlation between the dielectric constant of the solvent (ε) and the e.e. was observed, with a decrease in e.e. by increasing ε. The highest enantiomeric excess (e.e. = 48%) was obtained with *n*-hexane.
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1. Introduction

The enantioselective hydrogenation of short chain aliphatic α,β-unsaturated carboxylic acids is a subject of high potential industrial relevance in the pharmaceutical, fragrances and agrochemical sectors and a few optically pure R-CH(R')COOH are key intermediates or final active ingredients already on the market or under active development (Fig. 1). Enantioselective heterogeneous catalysts, although they usually display a lower enantioselectivity than homogeneous catalysts, would be industrially preferable on account of their lower cost and easy handling and separation properties. More details on the general aspects of the enantioselective catalysts may be found in the recent reviews [1–4].

Some papers of different research groups [5–14] have already been dedicated to this reaction, to identify a possible mechanism and underline the relevance of some reaction parameters. A medium–low enantioselectivity has nowadays

been evidenced. We decided to check these previous results with the aim, if possible, of shedding new light upon the enantioselective hydrogenation of short chain α,β-unsaturated acids, in particular of (E)-2-methyl-2-butenoic acid (tiglic acid). Commercially available noble-metal based heterogeneous catalysts have been used, to obtain data of the widest interest, evidencing the specific role of solvent properties and analyze the interaction between unsaturated acid and cinchonidine (CD). Maximum enantiomeric excess (38%) had been reported for the hydrogenation of tiglic acid [8] using a commercial Pd/Al$_2$O$_3$ catalyst (Engelhard) doped with CD and using toluene as solvent. In this paper, three possible interactions have been reported between CD and the unsaturated acid in solution, the latter being present in dimeric or monomeric form. The authors underlined that the interaction between dimeric acid and CD was favored energetically in solution and that the alcoholic OH group as well as the quinuclidine nitrogen of CD were hydrogen bonded to the reactant alkenoic acid in the enantiodifferentiating step. These authors proposed a CD:acid = 1:2 adduct absorbed on the Pd surface, in contrast with the hypothesis by other authors [5,14].

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Arundic acid (Phase II; ONO)
stroke; anti-Parkinson

ZD-3523 intermediate
(Phase II, Mitsubishi)
anti-asthma

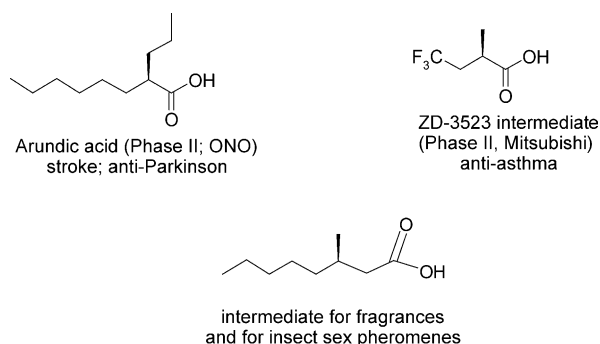intermediate for fragrances
and for insect sex pheromenes

Fig. 1. A few optically pure acids as key intermediates or final active ingredients already on the market or under active development.

However, although the described interaction is feasible in solution, we doubt that it can also happen on the metallic surface of the catalyst. In any case, some experiments (see the obtained results below) to verify the effect of the dilution on the enantiomeric excess (e.e.) would have been able to support, in our opinion, the alternative hypothesis of a CD:acid = 1:1 adduct absorbed on the Pd surface.

Another important parameter is the choice of solvent that affects the activity and the enantioselectivity of the reaction. The factors that give rise to differences may be several: solubility of the liquid and gas reactants, competitive adsorption of the solvent molecules and interaction of the solvent with the reactant(s). Furthermore, CD commonly coexists in different conformers and the presence of these conformers depends on the dielectric constant of the solvent.

As regards the CD conformations, it has in fact been showed that the most stable one depends on the solvent polarity [7,15–18]. Bürgi and Baiker [7] investigated the different CD conformations in different solvents showing that the "open" conformers were more stable in non-polar solvents, while the stability of the "closed" conformers increased on raising the solvent polarity. The aim of this study was to check these previous results, identifying the best experimental conditions intended for a possible industrial application.

2. Experimental

The commercial 5% Pd supported on γ-Al$_2$O$_3$ catalyst was supplied by Engelhard (cod. 40692), being the same catalyst used by Baiker and co-workers [6,8], and was used without pre-treatment. (E)-2-Methyl-2-butenoic acid (tiglic acid), cinchonidine, undecane and n-hexane, toluene, methanol, heptane, methyl acetate, cyclohexanone, cyclohexane were purchased from Aldrich Chemicals (purity ≥98%). Unless stated otherwise, the following standard conditions for the experiments in a 300 mL stainless steel Parr autoclave with mechanic stirring were used: 54 μmol of Pd, 25 mmol of tiglic acid, 170 μmol of CD, 75 mL of solvent, 4.0 MPa of H$_2$ and 298 K. The reaction time was 2 h. The metal surface was doped during a preliminary 1 h step under stir-

ring and air atmosphere, using CD in 75 mL of the solvent; then the autoclave was purged three times with He at 0.3 MPa before H$_2$ and tiglic acid were introduced at the set pressure. Two milliliters was periodically sampled, 100 μL of undecane added as internal standard and the mixture diluted to 10 mL with the solvent. The products were analyzed using a Perkin-Elmer Autosystem XL gas chromatograph, equipped with FID and a wide bore PS086 chiral column (DEtTbuSililBETACDX 25 m × 0.25 mm, film width 0.25 μm). The enantiomeric excess was expressed as: e.e.% = [(S − R)/(S + R)] × 100.

3. Results and discussion

As already reported in the literature mainly on the basis of IR and Raman analyses [19], the dimeric form of the carboxylic acid is more favored in apolar solvents, although the situation might be different on the thin layer adsorbed on the catalyst surface. To analyze the mechanism of the reaction and understand the nature of the interaction between alkenoic acid (either the dimeric or monomeric form) and CD, the tiglic acid was hydrogenated with the CD doped-Pd/Al$_2$O$_3$ catalyst diluted in four different amounts of solvent: 38, 75, 150 and 250 mL. If the substrate–CD interaction in the enantioselective step on the metal surface had been that between the dimeric form of the acid and the dopant, a change in the e.e. of the reaction depending on the dilution had to be expected. In Table 1, the comparison between the four reaction conditions shows that the different dilutions did not influence the e.e. in a significant measure; therefore, it may be suggested that a 1:1 substrate–CD interaction is present in the adsorbed layer on the catalyst surface.

Table 1
Tiglic acid hydrogenation [5 wt% Pd/Al$_2$O$_3$ Engelhard 40692 modified with CD, T = 298 K; P$_{H_2}$ = 4.0 MPa; reaction time = 120 min]: quantity of used n-hexane: 38, 75, 150 or 250 mL

Substrate concentration (mol/L)	Time (min)	Conversion (%)	Yield (%)	e.e. (%)
0.66	30	76	74	42
	60	90	85	44
	90	>99	>99	46
	120	>99	>99	46
0.33	30	76	74	40
	60	>99	>99	43
	90	>99	>99	45
	120	>99	>99	48
0.16	30	87	70	46
	60	93	90	47
	90	>99	>99	48
	120	>99	>99	48
0.10	30	76	75	46
	60	92	90	47
	90	>99	>99	48
	120	>99	>99	48

Table 2
Tiglic acid hydrogenation [5 wt% Pd/Al$_2$O$_3$ Engelhard 40692, $T = 298$ K; $P_{H_2} = 4.0$ MPa; reaction time = 120 min]: without and in the presence of CD

Cinchonidine	Time (min)	Conversion (%)	Yield (%)	e.e. (%)
No	15	93	70	–
	30	99	90	–
	45	97	99	–
	60	>99	>99	–
	90	>99	>99	–
	120	>99	>99	
Yes	15	40	40	39
	30	76	74	40
	45	93	90	42
	60	>99	>99	43
	90	>99	>99	45
	120	>99	>99	48

In Table 2, the kinetics of the hydrogenation reaction in the presence and in the absence of the dopant were compared, thus evidencing a slight poisoning effect of CD on the Pd activity and confirming that the alkaloid was adsorbed on the catalyst surface.

The fact that a slight increase in e.e. of the product was always observed apparently nearly at the end of the reaction is unclear; in this moment we exclude an analytical artefact even if there are no sufficient elements to distinguish between two possible explanations:

(a) a preferential decomposition of the enantiomeric R-form of the hydrogenated molecules;
(b) a very high enantioselectivity in the hydrogenation of the last molecules of α,β-unsaturated substrate.

As regards the effects of temperature (313 K versus 298 K) or pressure (2.0 MPa versus 4.0 MPa), a slight decrease in both cases was observed in comparison to the standard conditions: 37% e.e. (by decreasing the pressure) and 39% e.e. (by increasing the temperature) versus 48% e.e. (standard conditions).

Then the substrate–solvent interaction was studied to extend the study of the parameters that influence the e.e. As such, the tiglic acid was hydrogenated in the presence of solvents with different properties (Table 3). The choice of the reaction solvent was based either on its principal property descriptors [20] or simply on the dielectric constant value.

Table 3
Solvents used in the hydrogenation of tiglic acid: sector classification and dielectric constant values at 298 K [20]

Solvent	Sector (°)	Dielectric constant (ε)
Cyclohexanone	1	16.10
Methanol	2	32.66
Hexane	3	1.88
Heptane	3	1.92
Toluene	3	2.38
Methyl acetate	3	6.68
Cyclohexane	4	2.02

Furthermore, toxicity, commercial availability and price of the solvent were also considered.

In preliminary tests, solvents of four sectors (1–4) [20] were chosen: with cyclohexanone (first sector), methanol (second sector), hexane (third sector) and cyclohexane (fourth sector) e.e. = 30, 15, 48 and 46% were obtained, respectively. Since the highest e.e. had been obtained with a non-polar solvent of the third sector (*n*-hexane), three other solvents, heptane, toluene and methyl acetate, of the same sector were also tested, obtaining e.e. values between 46 and 38%.

Since descriptors analysis does not seem very useful for identifying the best solvent, we preferred to correlate the e.e. with a single solvent property, the dielectric constant (ε), finding a reasonably good linear relationship among the values of e.e. and ε (Fig. 2).

Previously Nitta et al. [14] reported different correlations between the solvent polarity and the e.e. were obtained in the hydrogenation of α,β-unsaturated acids, as a function of their backbone. For aliphatic unsaturated compounds the e.e. decreased increasing the solvent polarity, while when aromatic groups were present on the substrate, the trend was opposite, due probably a different way of absorption of the latter compounds on the catalyst surface for the presence of ring π electrons.

On the other hand, also Murzin and co-workers [15], investigating the hydrogenation of 1-phenyl-1,2-propanedione with CD modified Pt/Al$_2$O$_3$, observed that the e.e. decreased with an increasing solvent dielectric constant, but non-linearly. However, it must be noted they investigated a substrate very different from an unsaturated carboxylic acid, with the further presence of an aromatic group. No correlation with our research data could be therefore extrapolated.

Although it is not possible to extend the effect of the solvent in particular of its dielectric constant to the full kinds of alkenoic acids [14] and to foresee the e.e. value, being the enantioselectivity fine tuned by steric and electronic properties of the unsaturated acid [21], we believe that our results
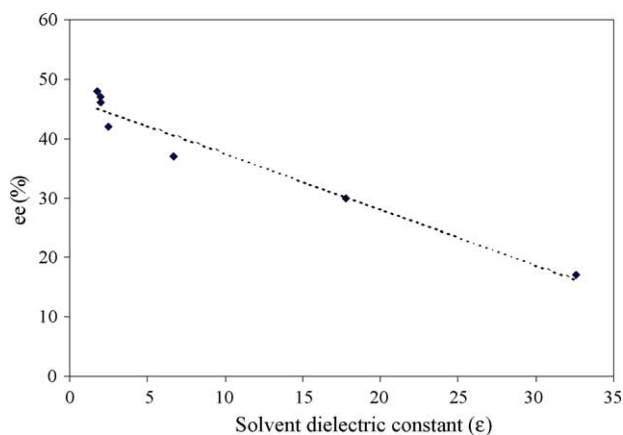

Fig. 2. Plot of experimentally found enantiomeric excesses (e.e.) in the hydrogenation of tiglic acid in different solvents as a function of ε. The other reaction conditions are standard.

may be useful for scaling-up some processes of asymmetric hydrogenation of short chain aliphatic alkenoic acids.

4. Conclusions

In this paper, the hydrogenation of the (*E*)-2-methyl-2-butenoic acid using a commercial Pd/Al$_2$O$_3$ catalyst doped with cinchonidine was investigated to evidence the nature of CD–substrate interaction the importance of the solvent polarity and to identify the best experimental conditions. The data collected in this work support the hypothesis that the interaction between CD and alkenoic acid on the adsorbed layer on the catalyst surface takes place by a 1:1 adduct, since the enantioselectivity is not affected by the dilution, in a large range of experimental conditions. Furthermore, a key role is played by the dielectric constant (ε) of the solvent with a linear correlation between ε and e.e. However, this observation is not general and must be limited to the hydrogenation of aliphatic alkenoic acids.

Acknowledgements

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