Solvent Effects in the Enantioselective Hydrogenation of Ethyl Benzoylformate

Gerson Martin · Päivi Mäki-Arvela · Dmitry Yu. Murzin · Tapio Salmi

Received: 24 May 2013/Accepted: 5 July 2013 © Springer Science+Business Media New York 2013

Abstract Solvent effects in the enantioselective hydrogenation of ethyl benzoylformate (EBF) to (R)-ethyl mandelate over (-)-cinchonidine (CD)-modified Pt/Al₂O₃ catalyst were studied in a semi-batch reactor. Solvents of different nature were used: protic (2-propanol, 1-propanol, 1-octanol and ethanol), aprotic polar (methyl acetate, acetone, ethyl acetate and tetrahydrofuran) and apolar solvents (methyl cyclohexane and toluene). The effects of pure solvents and binary solvent mixtures on hydrogenation rates and enantioselectivity were investigated. The highest enantiomeric excess (ee) of 72 % was obtained in ethyl acetate, decreasing nonlinearly with increasing dielectric constant (ɛ) being close to 20 % in ethanol. The highest value of the initial hydrogenation rate was obtained in the apolar solvents $(21 \text{ mmol dm}^{-3} \text{ min}^{-1}\text{g}_{cat}^{-1})$ while the lowest one was observed in tetrahydrofuran (2 mmol dm⁻³ min⁻¹ g⁻¹_{cat}). A kinetic model was proposed for the enantioselectivity dependence on dielectric constant based on Kirkwood treatment. The non-linear dependence of ee on (ϵ) was included in the model to describe quantitatively the variation of ee in different solvents. The results showed a good fit for *ee* as a function of ε .

Keywords Enantioselective hydrogenation · Solvent effect · Pt catalyst · Transition state theory · Dielectric constant

Published online: 25 July 2013

1 Introduction

The hydrogenation of α -ketoesters on supported Pt catalysts modified with cinchona alkaloids was discovered by Orito et al. [1] in 1979 and, since then, detailed studies have been conducted and different substrates have been investigated using Pt-cinchona alkaloid catalytic systems. In case of the hydrogenation of ethyl benzoylformate, only few papers have been recently published. For instance, Bartók et al. [2] studied the effect of different alkaloids (cinchonidine, cinchonine, quinine, quinidine, α -isocinchonine, α -isocinchonidine and δ -isoquinidine) in the hydrogenation of EBF; Sutyinszki et al. [3] found extremely high enantioselectivity (98 %) using Pt/Al_2O_3 as a catalyst at 25 bar of pressure; Diezi et al. [4] studied the steric effects in the Pt-catalyzed asymmetric hydrogenation of nine different α -ketoesters by variation of the bulkiness at the keto and ester side of the substrates and Szőllősi et al. [5] studied the origin of rate enhancement using methyl benzoylformate as raw material in a continuous-flow-fixed-bed reactor.

Solvents have a crucial effect in the production of fine chemicals. Although the presence of solvents in the reaction mixture increases the process costs, the use of solvents in liquid-phase reactions is required to accomplish at least one of the following functions: (1) to dissolve solid reactants and products; (2) to control the reactant rate in the case of very rapid chemical reactions; (3) to dissipate the heat generated in highly exothermic reactions. The choice of suitable solvents is frequently critical and an unfortunate choice can lead to a loss of activity and/or selectivity. Therefore, the selection of solvents is extremely important to understand how solvents interact with the reaction components.

The selective hydrogenation of aromatic ketones into the corresponding alcohols on metal-based catalysts in the

G. Martin · P. Mäki-Arvela · D. Yu. Murzin (⊠) · T. Salmi Process Chemistry Centre, Åbo Akademi University, 20500 Turku, Finland e-mail: dmurzin@abo.fi

presence of different solvents has been widely studied for the synthesis of flavors, fragrances, additives and pharmaceuticals [6]. Solvents can lead to variations in the activity, selectivity and stereoselectivity in hydrogenation reactions [7]. However, the factors responsible for such variations could be several, e.g. solubilities of liquid and gaseous reactants and their adsorption on the catalyst surface, competitive adsorption of solvent molecules, interaction between the solvent and the reactant(s) either in the liquid phase or on the catalyst surface as well as catalyst deactivation caused by the solvent [8]. Furthermore, complex organic molecules commonly coexist in various conformations and the apparent population of different conformers can vary as a function of the solvent dielectric constant and thus affect the selectivity [9]. It is for that reason that the phenomena known as solvent effects are a combination of several physical and chemical factors which makes it difficult to predict and rationalize performance of solvents in a particular reaction.

The most widely studied model compound in enantioselective hydrogenation has been ethyl pyruvate [10, 11]. In contrast to ethyl pyruvate, hydrogenation of ethyl benzoylformate (EBF) has been scarcely studied. Although the reaction was originally described by Orito et al. [1] at the time of the discovery of the catalytic enantioselective hydrogenation of α -ketoesters and these authors achieved an enantiomeric excess of 84 % for the production of ethyl-(R)-mandelate (EM), only few papers have recently been published on the hydrogenation of EBF. For instance, Bartók et al. [2] investigated the effect of different alkaloids (cinchonidine, cinchonine, quinine, quinidine, α -isocinchonine, α -isocinchonidine and δ -isoquinidine) in the hydrogenation of EBF and Sutyinszki et al. [3] found extremely high ee (98 %) using Pt/Al₂O₃ as a catalyst under 25 bar hydrogen pressure. Hydrogenation of EBF yields very valuable building blocks, ethyl-(R)- and ethyl-(S)-mandalate (EM). Indeed, mandelate derivatives are important synthetic building blocks in preparative organic chemistry owing to their versatile functional groups, which may be easily transformed into other functionalities, for example, diols, halo or amino derivatives and epoxides.

Generally, high enantioselectivities in the hydrogenation of ethyl and methyl pyruvates can be obtained in solvents with dielectric constants between 2 and 10 [12]. Consequently, acetic acid [13] and toluene are known to be among the best solvents. It was proposed that the dependence of the enantioselectivity on the dielectric constant correlates with the population of the Open(3) conformer of the modifier (CD) in the liquid phase [14]. This offers a plausible explanation for the dependence of the enantioselectivity on the dielectric constant. The dependence of the Open(3) conformer population on the dielectric constant of the solvent is non-linear, resembling the shape of the Onsager function [15]. However, the effect of the reactant conformation in α -ketoesters hydrogenation over analogous systems is not totally clear.

Quantum chemical methods HF and B3LYP have been used to study the effect of conformation of 1-phenyl-1, 2-propanedione, and similar results in different media were obtained. The effect of a polar solvent gave only a slight decrease in the torsion angle τ_2 and thus, the dipole moment of the molecule increased in polar media. In general, the solvent effect on the reactant conformation can be considered relatively minor. This was the case also with ethyl benzoylformate, for which the potential energy surface over τ_2 has a similar shape [16].

The maximum enantiomeric excess found in the literature for different substrates is reported in Table 1. Substrates, such as 1-phenyl-1,2-propanedione, ethyl pyruvate [12], methyl pyruvate [17], ketopantolactone [18], ethyl benzoylformate [17] and 2,3-butanedione [19] showed interesting differences regarding the influence of the solvent dielectric coefficient dependence on *ee*. It became clear that ketopantolactone, 1-phenyl-1,2-propanedione and ethyl benzoylformate [16, 20] exhibit pronounced solvent dependencies (i.e. decline in *ee* with increasing solvent dielectric constant), whereas, the others are less solvent dependent. Therefore, some reactant specific factors (solubility of hydrogen, iterations between the solvent and reactant(s), etc.) should be involved in the explanation of solvent effects.

In the present paper, the three-phase hydrogenation of ethyl benzoylformate in the presence of Pt/Al_2O_3 and a dissolved catalyst modifier (CD) in different solvents is studied. The reaction scheme for the hydrogenation of EBF is displayed in Fig. 1. As shown in the Figure, the complete reaction scheme comprised three components. The reactant, ethyl benzoylformate (**A**), is hydrogenated on Pt catalyst to produce two enantiomers (*R*)- and (*S*)-ethyl mandelate, (**B**) and (**C**), respectively.

Typically the enantiomeric excess (*ee*) is defined as $ee = [C_B - C_C]/[C_B + C_C]$. Hydrogenation of **A** has been studied previously both in batch [3] and continuous reactors [22]. The highest reported *ee* has been 98 % (reaction

 Table 1
 Maximum enantiomeric excess reported for different substrates [21]

Raw material	ee (%)
Methyl pyruvate	87
Ethyl pyruvate	87
Ethyl benzoylformate	84
Butane-2,3-dione	46
1-Phenyl-1,2-propanedione	65
Ketopantolactone	91





(S)-Ethyl mandelate (C)

Cinchonidine (M)

conditions: 24 °C, acetic acid as a solvent, 25 bar, 10 mmol L^{-1} dihydrocinchonidine and 50 mg of 5 % w/w Pt/Al₂O₃ Engelhard 4759).

The hydrogenation kinetics was carefully investigated using ten different solvents. The solvents were chosen to provide a wide range of different properties and polarities: (1) polar protic (*n*-propanol, ethanol and 1-octanol); (2) aprotic polar (tetrahydrofuran, ethyl acetate, methyl acetate and acetone); (3) non-polar aromatic (toluene) and (4) naphthenic (methylcyclohexane) compounds. The relative solvent–catalyst, solvent–reactant and reactant–catalyst interactions and their influence on the activity pattern were considered in the analysis. The influence of hydrogen solubility in each solvent was considered too. An explanation of the solvent influence on the catalytic activity is given on the basis of the solvent properties and the different types of interactions existing in the three-phase hydrogenation of EBF.

2 Experimental Section

2.1 Chemicals

Ethyl benzoylformate (Aldrich, 95 %, 25,891-1) was used as purchased. Hydrogen (AGA, 99.999 %), toluene (J. T. Baker, 8077, >99.5 %), ethyl acetate (LAB-SCAN, 99.8 %), methyl acetate (Acros, 99 %), tetrahydrofuran (LAB-SCAN, 99.8 %), 1-pentanol (Fluka, 98 %), 1-propanol (Sigma-Aldrich, 99.5 %, 402893) 2-propanol (LAB-SCAN, 99.7 %), ethanol (Primalco, 99.5 %), methyl cyclohexane (Fluka, >98 %, 66295), 1-octanol (Riedel-de Haën, 99.5 %, 24134), acetone (J. T. Baker, 99.5 %) and (–)-cinchonidine (Fluka, 27350, 98 %) were used as received.

2.2 Hydrogenation of Ethyl Benzoylformate

Experiments were performed in a glass reactor at atmospheric pressure under a flow of molecular H_2 with a

volumetric flow rate of 295 mL min⁻¹. The reaction temperature was 25 °C and the solvents with dielectric constants (ϵ) in the range of 2–25 were investigated. In order to obtain a more detailed insight into the influence of ε , two solvents (2-propanol and ethyl acetate) were mixed in different proportions (25-75, 50-50 and 75-25 %) and subsequently tested. The dielectric constants and hydrogen solubility in different solvents have been previously measured [21]. The hydrogenation catalyst (220 mg of 5 % (w/w) Pt/Al₂O₃ Aldrich, Strem, 78-1660) was pre-reduced under flowing hydrogen at 400 °C for 2 h. To avoid interactions between the catalyst and oxygen, the reaction media was bubbled with Ar for 10 min before putting it in contact with the catalyst. The stirring rate and catalyst particle size was 500 rpm and $< 90 \mu$ m, respectively. Calculations of the rates of mass transfer confirmed that such conditions are sufficient to perform experiments in the kinetic regime. The liquid phase volume and the initial concentration of the substrate were 150 mL and 0.006 mol L^{-1} , respectively. (–)-Cinchonidine was used as a catalyst modifier with a concentration of $2 \times 10^{-5} \text{ mol } \text{L}^{-1}$.

The catalyst characterization has been previously reported [23]. The main results are summarized here. The metal (Pt) dispersion was 34 %. The specific surface area and the pore volume of the fresh catalyst determined by nitrogen adsorption were 95 m² g⁻¹_{cat} and 0.319 cm³ g⁻¹_{cat}, respectively.

2.3 Analytical Procedure

Samples were withdrawn from the reactor at different time intervals and analyzed with a gas chromatograph (GC) (Varian 3300) equipped with a chiral capillary column (Silica Chiralsil-DEX; length 25 m, diameter 0.25 mm, film thickness 0.25 μ m). Helium was used as a carrier gas with a split ratio of 33. The detector (FI) and injector temperatures were 270 and 240 °C, respectively. The temperature program of the GC was 120 °C (25 min)–



Fig. 2 Hydrogenation kinetics of ethyl benzoylformate. Reaction conditions: 0.923 mmol of ethyl benzoylformate, 0.054 n (CD)/n (surface Pt), 220 mg of 5 wt% Pt/Al₂O₃ (<90 μ m), 150 mL of toluene, 25 °C and atmospheric pressure

20 °C min⁻¹–190 °C (6 min). The GC analysis was calibrated with ethyl benzoylformate (Aldrich, 95 %, 25,891-1), (*R*)-ethyl mandelate (Aldrich, 99 %, 30,998-2) and (*S*)-ethyl mandelate (Aldrich, 99 %, 30,997-4).

3 Results and Discussion

All reaction components **A**, **B**, and **C** in the scheme (Fig. 1) were distinguishable by chromatographic analysis. In the presence of the chiral modifier, (-)-cinchonidine, (R)-ethyl mandelate is formed in excess. The typical hydrogenation kinetics of ethyl benzoylformate (used as received) in

toluene and using (-)-cinchonidine as a catalyst modifier is displayed in Fig. 2.

3.1 Initial Reaction Rate and Conversion

The initial hydrogenation rate varied in different solvents, the highest values were observed in toluene and methyl cyclohexane and the lowest ones in ethyl acetate and tetrahydrofuran, while relatively high rates were obtained in the other studied solvents (Table 2). The activity pattern with the protic solvents was: 2-propanol > 1-propanol > 1-octanol > ethanol. In case of aprotic polar solvents, the activity followed the pattern: methyl acetate > acetone > ethyl acetate > tetrahydrofuran. In general, protic solvents showed higher initial hydrogenation rates compared to aprotic polar solvents. Protic solvents can act as H-bond donors and give an extra amount of hydrogen for the reaction, whereas aprotic polar solvents have a low capability to act as H-bond donors, since their C–H bonds are not sufficiently polarized [8].

One of the questions to be answered was whether the initial hydrogenation rate correlated with the hydrogen solubilities or with the dielectric coefficients. As it can be seen from Table 2, neither the hydrogen solubility nor dielectric coefficient of the solvent correlated with the initial hydrogenation rate. The hydrogen solubility decreased as the dielectric coefficient increased (Table 2). It has been found that the reaction order with respect to hydrogen is close to zero in the hydrogenation of EBF in the detailed kinetic experiments [24] carried out in ethyl acetate. Therefore, it is understandable that the differences in the hydrogenation rate

Table 2 Dielectric coefficients (ϵ), hydrogen solubility given as mol fraction (X_{H2}), initial hydrogenation rate and conversion in the hydrogenation of ethyl benzoylformate

Solvent	ε at 25 °C	X _{H2} (10 ⁻⁴)	Initial reaction rate (mmol dm ⁻³ min ⁻¹ g_{cat}^{-1})	Conversion (%) after 24 h	Enantiomeric excess (%)
Methyl cyclohexane	2.02		21	100	27
Toluene	2.37	3.2	21	100	48
Ethyl acetate	6.02	3.5	5	99	72
Methyl acetate	6.68	3.0	11	77	59
Ethyl acetate (x = 0.75) - 2-propanol (x = 0.25) mixture	7.30		15	100	66
Tetrahydrofuran	7.43	2.9	2	28	59
Ethyl acetate (x = 0.50) - 2-propanol (x = 0.50) mixture	9.25		14	100	55
1-Octanol	9.90		12	100	41
Ethyl acetate (x = 0.25) - 2-propanol (x = 0.75) mixture	12.20		11	98	51
2-Propanol	18.30	2.7	17	100	39
1-Propanol	20.10		16	100	37
Acetone	20.70		9	90	48
Ethanol	24.30	2.1	12	100	21

and enantioselectivity. However, other effects coming from different solvents play a much more remarkable role in the hydrogenation of ethyl benzoylformate.

The high hydrogenation rate in 2-propanol (17 mmol dm⁻³ min⁻¹ g_{cat}) can partly be a result of the hydrogen donating properties and the inertness of 2-propanol towards the Pt surface in the presence of hydrogen [25, 26]. In toluene, the hydrogenation rate was the highest among all the solvents (21 mmol dm⁻³ min⁻¹ g_{cat}). This result corresponds with the previous studies, in which a high initial hydrogenation rate has been achieved in the hydrogenation of α -ketoester using toluene is in line with non-dissociative adsorption of toluene on Pt(111) surface below 300 K [27], i.e. toluene is not decomposed on the Pt surface at this temperature and evidently the adsorption strength is not as high as for tetrahydrofuran. In ethanol, the initial hydrogenation rate was relatively high (12 mmol dm⁻³ min⁻¹ g_{cat}) however, the *ee* remained low.

Two kinds of interactions between solvents and catalysts can occur, adsorptive and reactive (solvent decomposition



or hydrogenation). These interactions may strongly influence the activity of Pt/Al_2O_3 for the EBF hydrogenation. When both the solvent and the reactant possess the same adsorption strength, competitive adsorption takes place and due to the high solvent concentration, the majority of available sites are occupied by the solvent inhibiting the



Fig. 3 Influence of the solvent dielectric constant (ϵ) on the enantioselective hydrogenation of ethyl benzoylfomate: **a** rate and **b** enantiomeric excess dependencies. The reaction conditions: 0.923 mmol of ethyl benzoylformate, 0.054 n (CD)/n (surface Pt), 220 mg of 5 wt% Pt/Al₂O₃ (<90 µm), 150 mL of solvent, 25 °C and atmospheric pressure

Fig. 4 Relation between enantiomeric excess and conversion for a aprotic b protic and c non-polar solvents. Reaction conditions: 0.923 mmol of ethyl benzoylformate, 0.054 n (CD)/n (surface Pt), 220 mg of 5 wt% Pt/Al₂O₃ (<90 μ m), 150 mL of solvent, 25 °C and atmospheric pressure

adsorption of raw material. Moreover, solvent adsorption on the catalyst may modify the intrinsic activity of neighboring metal active sites and/or the reaction intermediate complex leading to a change in apparent activation energy of the catalytic reaction.

Some solvents such as tetrahydrofuran (THF) are known to have a strong interaction with the catalyst surface due to oxygen lone pair orbital bonding [25, 28]. Competition of the solvent and the reactant could explain a low initial hydrogenation rate (2 mmol dm⁻³ min⁻¹ g_{cat}^{-1}) and conversion (28 % after 24 h) obtained in THF.

3.2 Enantioselectivity

The enantiomeric excess in the hydrogenation of ethyl benzoylformate depends on the solvent properties. In this paper, the main effort was focused on the understanding of



Fig. 5 Influence of binary solvent mixture in the enantioselective hydrogenation of ethyl benzoylformate. Reaction conditions: 0.923 mmol of ethyl benzoylformate, 0.054 n (CD)/n (surface Pt), 220 mg of 5 wt% Pt/Al₂O₃ (< 0 μ m), 150 mL of solvent, 25 °C and atmospheric pressure



Fig. 6 Relation between ee and conversion for binary solvents in the enantioselective hydrogenation of ethyl benzoylformate. Reaction conditions: see Fig. 5

such behavior. The highest *ee* was obtained in ethyl acetate (72 %) while the lowest one was observed for ethanol (21 %) (Table 2). In general, aprotic polar solvents showed higher enantiomeric excess compared to protic solvents (Fig. 4).

A maximum enantiomeric excess in the hydrogenation of EBF is visible when plotting *ee* as a function of the solvent dielectric constant (Fig. 3). This kind of behavior has also been found in the hydrogenation of ethyl pyruvate [12] and ketopantolactone [18] over cinchonidine-modified Pt catalysts.

Additionally, by plotting the enantiomeric excess versus the reactant conversion (Fig. 4) interesting results were obtained. In non-polar solvents, no enantiodifferenciation was observed until 30 % of conversion, which implies that product-modifier interactions are present in the system for these solvents. However, when the conversion had reached a certain value (in this case around 30 %) for aprotic polar solvents, the optical yield becomes dependent of conversion. This behavior has been observed before in ethyl pyruvate hydrogenation, where interactions between (R)lactate and the modifier in the liquid phase were proposed to explain the *ee* dependence on the conversion [29]. Lately, it was suggested that the enantiomer of the product interacts with the alkaloid–substrate complex during enantioselection, inducing a shift of *ee* with conversion [30].

3.3 Influence of Ethyl Acetate and 2-Propanol Mixtures in the Hydrogenation of EBF

In order to understand the interplay of binary solvent mixtures in the hydrogenation of ethyl benzoylformate, ethyl acetate and 2-propanol were selected. The dielectic constant range varied from 6.2 (ethyl acetate) to 18.3 (2-propanol). The values of dielectric constants of the ethyl acetate—2-propanol mixtures used in hydrogenation are reported in Table 2 [21]. The dependence of the *ee* on the dielectric constant is illustrated in Fig. 5. The initial hydrogenation rates in solvent mixtures varied between the boundary values observed in pure ethyl acetate and 2-propanol and the *ee* decreased with increasing dielectric constant.

Regarding the influence of conversion on ee (Fig. 6), it was observed that after 30 % of conversion, the optical yield became independent of the conversion. This result followed the same pattern discussed in Sect. 3.2, as it was demonstrated that the product-modifier complex plays an important role in the enantiodifferentiation.

As a general comment it should be noted that although solvent mixtures allow a reliable investigation of dielectric constant influence on *ee*, the selection of solvents for a binary or ternary mixture should be done carefully, in order to avoid chemical reactions between the solvents and the catalyst. The dielectric constants as a function of the solvent mole fractions showed a non-linear dependence, thus the determination of ε has to be done either by complex models or experimentally [21].

3.4 Solvation of the Modifier

Solvation can affect directly the adsorption equilibria during the hydrogenation, influencing the activation energy and the reaction rate. Previous studies have revealed that polar organic compounds remain solvated in polar media in a stronger way than in non-polar ones, leading to an inhibition of the reactant and modifier adsorption [31, 32].

Previous studies of (-)-cinchonidine adsorption on Pt/ Al₂O₃ using different solvents have demonstrated that higher amounts of (-)-cinchonidine can be adsorbed on the catalyst in toluene than in methanol [33]. Table 2 shows that in non-polar solvents (toluene and methyl cyclohexane), higher initial hydrogenation rates were achieved compared to the ones obtained in protic and aprotic polar solvents. These results are in agreement with the previous studies (1-phenyl-1,2-propanedione [21] and ethyl pyruvate [34]) and proved that the enantioselective hydrogenation of α -ketoesters is affected by solvation. However, enantiomeric excess did not follow the same trend, achieving higher values for protic and aprotic polar than for non-polar solvents. In the present case, rather high modifier concentrations were used, and therefore, the effect of modifier solvation can be considered negligible.

3.5 Side Reactions Between the Reactant and Alcoholic Solvents

The enantiomeric excess for alcohols as solvents were lower compared to other solvents (Table 2). One explanation of such behavior could be the formation of acetals during the reaction. Previous studies have shown that formation of hemiketals is relevant if there is a strong electron-withdrawing group in the α -position to the ketocarbonyl group [35]. This interaction has not, however, been studied for the hydrogenation of ethyl benzoylformate. The results from the hydrogenation of ethyl pyruvate have shown hemiketals to play a minor role [35, 36] leading to an assumption that in the case of ethyl benzoylformate the hydrogenation via hemiketals formation can be also considered negligible.

Alcohols are prone to hydrogen bonding and this may interfere in the formation of the weak complex between the modifier and the substrate in the liquid phase. However, other hypotheses suggest that the influence of the reaction product on the evolution of enantiomeric excess is unclear. In fact, Baiker and co-workers [37] assumed that in alcohols, the inversion of the major product relative to that formed in toluene is (partly) due to the formation of hemiketals. It should be noted that during the hydrogenation, the hemiketal formation is efficiently catalyzed by the basic alkaloid modifier. The importance of this side reaction has been demonstrated more than a decade ago for hydrogenation of ethyl-4,4,4-trifluoroacetoacetate in various alcohols by a detailed kinetic and NMR study [35]. Additional examples of the hydrogenation of α -fluorinated ketones in alcohol solvents show an analogous inversion of *ee* [38, 39].

4 Modeling of Solvent Effects

4.1 Kinetic Model for the Enantioselective Hydrogenation of Ethyl Benzoylformate

The general principle of kinetic modeling used in this work was based on a model developed by Toukoniitty et al. [24] for enantioselective hydrogenation of ethyl 1-phenyl-1, 2-propanedione, which takes into account parallel enantioselective and racemic hydrogenation routes in the presence of the modifier. The reactions taking place on unmodified sites produce racemic mixtures of products, while the reactions occurring on the modified sites result in the selective formation of the *R*-enantiomer (Fig. 7), although S-enantiomer can be also formed. The reversible reactant and modifier adsorption is assumed to be rapid or quasi-equilibrated, whereas, the irreversible addition of noncompetitively adsorbed hydrogen is rate determining according to the model. The details of hydrogen addition could not be equivocally revealed in the present work, since experiments were done at a constant hydrogen pressure. It should be noted that other assumptions regarding hydrogen involvement would lead essentially to the same equations relating enantioselectivity and the initial reaction rates with the dielectric constant of various solvents.



Fig. 7 Schematic representation of the reaction network model for combined racemic and enantioselective hydrogenation

Generally, the rates on modified and unmodified sites can be written according to Eqs. (1)–(3)

$$r = r_{\text{mod}} + r_{un\text{mod}}$$
(1)
$$r_{\text{mod}} = k'_{\text{mod}} \frac{C_{H_2} C_A C_M C_B}{D(1 + K_{H_2} C_{H_2})}; k'_{\text{mod}} = k_{\text{mod}} K_{H_2} K_A K_M K_B$$
(2)

$$r_{unmod} = k'_{unmod} \frac{C_{H_2} C_A}{D(1 + K_{H_2} C_{H_2})}; k'_{unmod} = k_{unmod} K_{H_2} K_A$$
(3)

where K_i is the adsorption equilibrium constant of a particular compound, C_{H2} is the concentration of dissolved hydrogen and D is the adsorption term equal to $1 + K_M C_M + K_A C_A + K_M K_B C_M C_B + K_M K_C C_M C_C$. It is important to note that the model described here considers the enantioselective reaction from substrate-modifier-product complexes following [27], since enantioselectivity clearly increases with conversion.

4.2 Solvent Effect Extension

The target in the modeling was to include the solvent effects on the catalytic hydrogenation. For this reason, the transition state theory was used as a tool to get a better understanding of the reaction path. Keeping in mind that the enantio-differentiating transition state includes both the reactant and the modifier, it can be treated as a dipoledipole interaction. The Kirkwood treatment [40] for the case when the reactants are not charged leads to

$$\ln k_{\text{mod}} = \ln k_{\text{mod}}^{0} - k'' \frac{(\mu^{\neq})^{2} - (\mu_{A})^{2} - (\mu_{B})^{2} - (\mu_{M})^{2}}{\epsilon}; \ln k_{un\text{mod}} = \ln k_{un\text{mod}}^{0} - k''' \frac{(\mu^{\neq})^{2} - (\mu_{A})^{2}}{\epsilon}$$
(4)

where ε is the dielectric constant, μ denotes the dipole moments and k'' and k''' are temperature dependent constants.

If the reaction occurs with the formation of an activated complex, which is less polar than the reactants (i.e. $(\mu^{\neq})^2 < ((\mu_A)^2 + (\mu_B)^2 + (\mu_M)^2)$ and $(\mu^{\neq})^2 < (\mu_A)^2$, the rate constants decrease with increasing dielectric constant. Hence, the rate constants sites can be expressed in the following way:

$$k_{unmod} = k_{unmod}^0 e^{\alpha_1/\varepsilon} \tag{5}$$

$$k_{\rm mod} = k_{\rm mod}^0 e^{\alpha_2/\varepsilon} \tag{6}$$

$$k_{\rm mod}/k_{\rm mod}^0 = k_{\rm mod}^0/k_{unmod}^0 e^{(\alpha_2 - \alpha_1)/\varepsilon} = k_{\rm mod}^0/k_{unmod}^0 e^{\alpha/\varepsilon} \qquad (7)$$

where α_1 and α_2 are constants, which demonstrate how strongly the rate constant depends on the solvent polarity.

Taking Eqs. (1)–(3) and (5)–(6) into account the generation rates of **B** in the batch reactor are given by

$$\frac{1}{\rho_{bulk}} \frac{dC_B}{dt} = r_{B,\text{mod}} + 0.5 r_{B,unmod}
= k_{B,\text{mod}} \frac{C_{H_2} C_A C_M C_B}{D(1 + K_{H_2} C_{H_2})}
+ 0.5 k_{unmod} \frac{C_{H_2} C_A}{D(1 + K_{H_2} C_{H_2})};$$
(8)

where ρ_{bulk} is the catalyst bulk density $(\rho_B = \frac{m_{cat}}{V_I})$ and $k_{B,\text{mod}}$, $k_{un\text{mod}}$ are lumped constants including adsorption coefficients.

Analogously, the generation rate of C is expressed by

$$\frac{1}{\rho_{bulk}} \frac{dC_C}{dt} = r_{C,\text{mod}} + 0.5 r_{C,u\text{mod}}
= k_{C,\text{mod}} \frac{C_{H_2} C_A C_M C_C}{D(1 + K_{H_2} C_{H_2})}
+ 0.5 k_{u\text{nmod}} \frac{C_{H_2} C_A}{D(1 + K_{H_2} C_{H_2})};$$
(9)

In Eqs. (8) and (9) it is assumed that corresponding optically active products are involved in the respective modifier-product interactions leading to the same enantiomer.In order to obtain an expression for enantioselectivity (es), Eq. (8) is divided by Eq. (9), leading to:

$$es = \frac{dC_B}{dC_C} = \frac{1 + 2\frac{k_{B,\text{mod}}}{k_{\mu\text{mod}}}C_M C_B}{1 + 2\frac{k_{C,\text{mod}}}{k_{\mu\text{mod}}}C_M C_C}$$
(10)

The end-of-experiment values of enantioselectivity are thus given as:

$$es = \frac{1 + \beta_B e^{a_B/\varepsilon}}{1 + \beta_C e^{a_C/\varepsilon}} \tag{11}$$

where

(1)

$$\beta_B = 2 \frac{k_{B,\text{mod}}^o}{k_{un\text{mod}}^0} C_M C_B^{final}, \ \beta_C = 2 \frac{k_{C,\text{mod}}^o}{k_{un\text{mod}}^0} C_M C_C^{final},$$

$$\alpha_B = \alpha_{2B} - \alpha_1, \ \alpha_C = \alpha_{2C} - \alpha_1$$
(12)

Equation (11) was used to describe the dependence of enantioselectivity values at full conversion as a function of the dielectric constant (Fig. 8). The model was able to describe the main trend with reasonable accuracy although the values of parameter β are not well defined. The results of the calculations made using nonlinear regressions analysis implemented in Origin 7.5 demonstrated, that the model fitted the experimental data very well. Some outliers were presented in the experimental data such as the ee showed by 1-octanol and acetone. These were not taken into consideration for the calculations. The impact of solvent polarity on the hydrogenation rate can be evaluated from Eqs. (8)–(9).



Fig. 8 Dependence of enantioselectivity on solvent dielectric constant. *Points* experimental, *line* calculated

Since initial hydrogenation is almost racemic the initial hydrogenation rate is expressed by



Fig. 9 Dependence of the initial reaction rates (data in Table 2) on solvent dielectric constant. *Points* experimental, *line* calculated

solvents and binary solvent mixtures with different solvent dielectric constants on the enantioselectivity as well as on

$$-\frac{1}{\rho_{bulk}}\frac{dC_A}{dt} = \frac{k_{\mu\nu}^0 e^{\alpha_1/\varepsilon} K_{H_2} K_A C_{H_2} C_A}{(1 + K_M C_M + K_A C_A + K_M K_B C_M C_B + K_M K_C C_M C_C)(1 + K_{H_2} C_{H_2})}$$
(13)

Or

$$r = k e^{\alpha_1/\varepsilon} \tag{14}$$

According to Eq. (14), the reaction rate decreases with increasing solvent dielectric constant, if hydrogen solubility is taken as constant. The exceptions (Fig. 3) are ethyl acetate and tetrahydrofuran and such protic solvents as 1and 2-propanol. The behavior of THF was somewhat exceptional, the reaction rate was low and the catalyst deactivated the reason being strong interactions of the solvent with the catalyst surface due to the oxygen lone pair orbital bonding. A strong competition between the solvent and the reactant could explain therefore low initial hydrogenation rates and conversions obtained in this solvent. Protic solvents can act as efficient hydrogen donors thus increasing the reaction rates. Without these solvents the model (14) correctly captures the main trend in the dependence of the initial rates on solvent polarity (Fig. 9).

5 Conclusions

Solvent effects in the hydrogenation of ethyl benzoylformate were investigated in a batch reactor at atmospheric pressure over Pt/Al₂O₃ catalyst at 25 °C. The influence of the initial hydrogenation rate was studied. The initial hydrogenation rates correlates with the solvent dielectric constants except some protic solvents and solvents strongly adsorbed on the surface. No correlation with hydrogen solubilities is mainly associated with the low reaction order with respect to hydrogen. The highest rates were observed in toluene and methyl cyclohexane while the lowest ones measured in ethyl acetate and tetrahydrofuran. The dependence of the enantiomeric excess on the productmodifier interactions in the liquid phase was proposed as a key factor for the enantiodifferentiation. The initial hydrogenation rates and ee in solvent mixtures varied between the boundary values observed in pure ethyl acetate and 2-propanol. Solvation of the modifier could be an explanation for the higher initial hydrogenation rates obtained for non-polar solvents compared to protic and aprotic solvents. The highest enantiomeric excess was obtained in ethyl acetate (72 %) while the lowest was observed for ethanol (21 %), whereas both solvents gave conversions exceeding over 99 %. The ee, after reaching a maximum value for ethyl acetate decreased with the increasing solvent dielectric constant.

The solvent effect was included in an advanced kinetic model in order to describe quantitatively the variation of enantioselectivity in different solvents. The dielectric constant dependence was taken into consideration by applying the transition state theory and the Kirkwood treatment, which accounts for the effects of the solvent dielectric constant on the rate constant. The model was able to account for the behavior of the system as a function of the solvent dielectric constant and a good description of the rates and enantioselectivity was obtained.

Acknowledgments This work is part of the activities at the Åbo Akademi Process Chemistry Centre (ÅA-PCC) within the Finnish Centre of Excellence Programme (2000–2011) appointed by the Academy of Finland.

References

- 1. Orito Y, Imai S, Niwa S (1979) Nippon Kagaku Kaishi 8:1118
- Bártok M, Felföldi K, Török B, Bártok T (1998) Chem Commun 23:2605
- 3. Sutyinszki M, Szöri K, Felföldi K, Bartók M (2002) Catal Commun 3:125
- 4. Diezi S, Reinmann S, Bonalumi N, Mallat T, Baiker A (2006) J Catal 239:255
- 5. Szőllősi G, Cserényi S, Füllöp F, Bartók M (2008) J Catal 260:245
- 6. Mäki-Arvela P, Hájek J, Salmi T, Murzin DYu (2005) Appl Catal A 292:1
- Santori GF, Moglioni AG, Vetere V, Moltrasio Iglesias GY, Casella ML, Ferretti OA (2004) Appl Catal A: Gen 269:215
- Bertero NM, Trasarti AF, Apesteguía CR, Marchi AJ (2011) Appl Catal A 394:228
- 9. Reichardt C (1990) Solvents and solvent effects in organic chemistry. VCH, Weinheim
- 10. Baiker A (1997) J Mol Catal A: Chem 115:473
- 11. Blaser H-U, Jalett H-P, Müller M, Studer M (1997) Catal Today 37:441
- 12. Wehrli J, Baiker A, Monti H-U, Jalett H (1989) J Mol Catal 57:245
- 13. Blaser H-U, Jalett H-P, Wiehl J (1991) J Mol Catal 68:215
- 14. Bürgi T, Baiker A (1998) J Am Chem Soc 120:12920
- 15. Onsager L (1936) J Am Chem Soc 58:1486

- 16. Ferri D, Bürgi T, Baiker A (2000) J Chem Soc Perkin Trans 2:221
- 17. Orito Y, Imai S, Niwa S (1980) J Chem Soc Jpn 37:670
- Schürch M, Schwalm O, Mallat T, Weber J, Baiker A (1997) J Catal 169:275
- 19. Zuo X, Liu H, Tian J (2000) J Mol Catal A: Chem 157:217
- Toukoniitty E, Mäki-Arvela P, Nieminen V, Hotokka M, Päivärinta J, Salm T, Murzin DYu (2002) In: Morrell DG (ed) Catalysis of organic reactions. CRC, Boca Raton
- Toukoniitty E, Mäki-Arvela P, Kuusisto J, Nieminen V, Päivärinta J, Hotokka M, Salmi T, Murzin DYu (2003) J Mol Catal A: Chem 192:135
- Toukoniitty E, Wärnå J, Murzin DYu, Salmi T (2010) Chem Eng Sci 65:1076
- Blaser H-U, Jalett HP, Monti DM, Baiker A, Wehrli JT (1991) In: Sleight A, Grasselli R (eds) Structure–activity and selectivity relationships in heterogeneous catalysis. Elsevier, Amsterdam, p 147
- Toukoniitty E, Ševčíková B, Mäki-Arvela P, Wärnå J, Salmi T, Murzin DYu (2003) J Catal 213:7
- 25. Augustine R, Warner R, Melnick M (1984) J Org Chem 49:4853
- 26. Vannice M, Erley W, Ibach H (1991) Surf Sci 254:12
- 27. Avery R (1988) J Chem Soc Commun 3:153
- 28. Sexton BA, Hughes AE (1984) Surf Sci 140:227
- 29. Murzin DYu (1997) Ind Eng Chem Res 36:4784
- Cakl Z, Reimann S, Schmidt E, Moreno A, Mallat T, Baiker A (2011) J Catal 280:104
- Koopman PGJ, Buurmans HMA, van Kieboom APG, Bekkum H, Recueil JR (1981) Neth Chem Soc 100:156
- 32. Wauquier JP, Jungers JC (1957) Bull Soc Chim Fr 10:1280
- Blaser H-U, Jalett H, Monti D, Reber J, Wehrli J (1988) In: Guisnet M et al (eds) Heterogeneous catalysis and fine chemicals. Elsevier, Amsterdam, p 153
- Bartók M, Sutyinszki M, Bucsi I, Felföldi K, Szöllösi G, Bartha F, Bartók T (2005) J Catal 231:33
- 35. Von Arx M, Mallat T, Baiker A (2001) J Catal 202:169
- 36. Minder B, Mallat T, Skrabal P, Baiker A (1994) Catal Lett 29:115
- Pereñigueza R, Santarossa G, Mallat T, Baiker A (2012) J Mol Catal A: Chem 365:39
- 38. Felföldi K, Varga T, Forgó P, Bartök M (2004) Catal Lett 97:65
- Vargas A, Hoxha F, Bonalumi N, Mallat T, Baiker A (2006) J Catal 240:203
- 40. Laidler KJ (1987) Chemical kinetics. Harper & Row, New York