

# Solvent effects in enantioselective hydrogenation of 1-phenyl-1,2-propanedione

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## Abstract

Solvent effects in enantioselective hydrogenation of 1-phenyl-1,2-propanedione (**A**) were investigated in a batch reactor over a cinchonidine modified Pt/Al<sub>2</sub>O<sub>3</sub> catalyst. The effect of different solvents, binary solvent mixtures and solvent dielectric constant on regio- and enantioselectivity as well as on the hydrogenation rate were studied. The hydrogen solubility in different solvents and the dielectric constants of solvent mixtures were measured. The highest enantiomeric excesses (ee) of (*R*)-1-hydroxy-1-phenylpropanone (**B**) (65%) were obtained in toluene. The ee decreased non-linearly with an increasing solvent dielectric constant being close to zero in methanol. The role of the reactant conformation in different solvents was evaluated by quantum chemical calculations and the role of the Open(3) conformer of the modifier, cinchonidine was discussed. The dependence of ee on the dielectric constant could not solely be attributed to the abundance of the Open(3) conformer of cinchonidine in the liquid phase. A possible involvement of additional factors was proposed and discussed. The non-linear dependence of the ee on the dielectric constant was included in a kinetic model to describe quantitatively the variation of the ee in different solvents.

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## 1. Introduction

In the production of fine chemicals over heterogeneous catalysts, the choice of the solvent has a crucial impact; a bad selection of the solvent leads to a complete loss of selectivity and/or activity, thus destroying the possible utilization of a potentially efficient process in practice. Therefore, the choice of a solvent and the understanding of solvent effects

is of central importance and thus requires a careful investigation.

Solvent effects have been widely studied and the phenomena known as solvent effects cover a very broad topic [1,2]. The effects arising from the use of different solvents are observed as variations in activity, selectivity and stereoselectivity. However, the factors responsible for these variations can be several, e.g. solubilities of liquid and gaseous reactants and their adsorption on the catalyst surface, competitive adsorption of solvent molecules, interaction of solvent with the reactant(s) either in the liquid phase or on the catalyst surface as well as catalyst deactivation

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caused by the solvent [3]. Furthermore, complex organic molecules commonly coexist in various conformations and the apparent population of different conformers can vary as a function of solvent dielectric constant and thus affect the selectivity [1]. Therefore, the phenomena understood under the label of solvent effects are a combination of very different physical and chemical phenomena and thus it is difficult to understand them completely.

A mechanistically very interesting case of heterogeneous catalysis is asymmetric hydrogenation over chiral modified catalysts. These kinds of reactions are of interest for pharmaceutical industry, where more efficient catalytic methods have a potential in increasing the production capacity of optically pure compounds. The mechanism of enantiodifferentiation over heterogeneous catalyst has been extensively studied by using cinchonidine-modified Pt catalysts and  $\alpha$ -ketoesters as reactants. The effects of different parameters including the solvent effect have been thoroughly assessed and excellent reviews have been written [4–6]. Hydro-

genation of  $\alpha$ -ketoesters over Pt catalysts modified by cinchona alkaloids are one of the few examples, where the selectivities obtained over heterogeneous catalysts exceed those obtained over homogeneous ones [7]. In this mechanistically complex reaction, the selection of the solvent plays a central role in steering the enantioselectivity. The selectivity varies significantly in different solvents: enantiomeric excesses (ee) exceeding 95% is obtainable in a right solvent and under optimized conditions, while a bad choice of the solvent leads to a significant decline in both enantioselectivity and activity [8,9].

Generally, high enantioselectivities can be obtained in solvents with dielectric constant between 2–10 [8]. Consequently, acetic acid [9] and toluene are known to be among the best solvents. It was recently proposed that the dependence of the enantioselectivity with the dielectric constant correlate with the population of the Open(3) conformer of the modifier in liquid [10]. This offers a plausible explanation for the dependence of the enantioselectivity on the dielectric constant. The

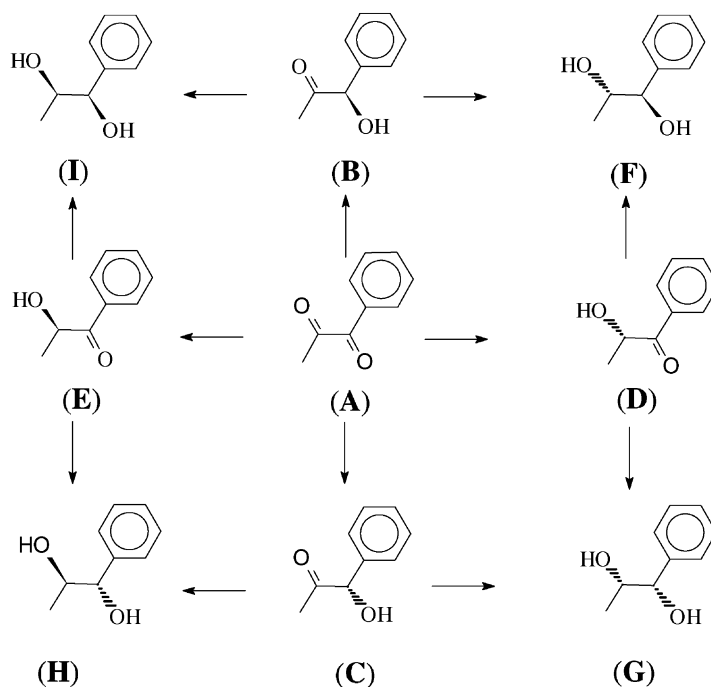


Fig. 1. Reaction scheme of 1-phenyl-1,2-propanedione hydrogenation. A: 1-phenyl-1,2-propanedione; B: (*R*)-1-hydroxy-1-phenylpropanone; C: (*S*)-1-hydroxy-1-phenylpropanone; D: (*S*)-2-hydroxy-1-phenylpropanone; E: (*R*)-2-hydroxy-1-phenylpropanone; F: (1*R*,2*S*)-1-phenyl-1,2-propanediol; G: (1*S*,2*S*)-1-phenyl-1,2-propanediol; H: (1*S*,2*R*)-1-phenyl-1,2-propanediol; I: (1*R*,2*R*)-1-phenyl-1,2-propanediol.

dependence of the Open(3) conformer population on the dielectric constant of the medium is non-linear, resembling the shape of the Onsager function [11].

Hydrogenation of asymmetric diketones produces hydroxyketones and diols, which consist of two pairs of enantiomers and four diastereomers, respectively. These compounds are biologically active and can be used as intermediates for pharmaceuticals. In this work, hydrogenation of asymmetric 1-phenyl-1,2-propanedione (**A**) over cinchonidine modified Pt catalyst was chosen as a model system [12]. The most prominent hydrogenation product is (*R*)-1-hydroxy-1-phenyl-2-propanone (**B**), also recognized by the trivial name of L(-)-phenylacetylcarbinol. This molecule acts as a key intermediate in the synthesis of many pharmaceuticals, e.g. L-ephedrine [13]. The complete reaction scheme is displayed in Fig. 1.

The general features of 1-phenyl-1,2-propanedione hydrogenation over cinchonidine modified Pt catalysts have been reported recently [12,14–16], including preliminary kinetic modeling [16]. Up to this moment, however, the solvent effects have not been studied in detail and the modeling of solvent effects has not been described previously. This very evident gap needs to be bridged and therefore, a more careful investigation and modeling of solvent effects is necessary. In this work, the solvent effects were studied experimentally and quantum chemical calculations were used to get a deeper theoretical insight about the reaction mechanism. An extension of the previously developed kinetic model [16] was included in order incorporate solvent effects. The effective modifier concentration plays a central role in the kinetic modeling.

## 2. Experimental

### 2.1. Hydrogenation experiments

A pressurized micro reactor (Sotalem 100 cm<sup>3</sup>) with a liquid volume of 50 cm<sup>3</sup> was used in the hydrogenation experiments. The reaction temperature and the hydrogen pressure were 25 °C and 10 bar, respectively. The stirring rate was 2000 rpm. The catalyst (Johnson Matthey 94, 74 mg) was reduced at 400 °C before the reaction. The reactant ( $c_A = 50 \times 10^{-3} \text{ mol dm}^{-3}$ ), 1-phenyl-1,2-propanedione (Aldrich, 99%) and (-)-cinchonidine (Aldrich, 96%)

( $c_M = 0.7 \times 10^{-3} \text{ mol dm}^{-3}$ ) were injected into the reactor and the reaction was commenced (in situ catalyst modification). Two approaches were employed: (i) several solvents, toluene (J.T. Baker, 99.5%), ethyl acetate (LAB-SCAN, 99.8%), methyl acetate (Acros, 99%), tetrahydrofuran (LAB-SCAN, 99.8%), 1-pentanol (Fluka, 98%), 2-propanol (LAB-SCAN, 99.7%), ethanol (Primalco, 99.5%), methanol (J.T. Baker, 99.8%) with dielectric coefficients ( $\epsilon$ ) varying between 2 and 33, were tested, and for more elaborated studies, two inert solvents were selected (ethyl acetate and 2-propanol), their mixtures were prepared and tested. The chemicals were used as received without further purification. Samples from the reactor were withdrawn and analyzed with a gas chromatograph equipped with a chiral column and a flame ionization detector (FID); the details of the analytical procedure have been reported previously [12].

The catalyst characterization has been previously reported [17]. The main results are as listed here: the metal dispersion 22%, the BET specific surface area 131 m<sup>2</sup> g<sub>cat</sub><sup>-1</sup> and the pore volume 0.93 cm<sup>3</sup> g<sub>cat</sub><sup>-1</sup>.

### 2.2. Hydrogen solubility measurements

The solubility of hydrogen in different solvents at 25 °C and 10 bar pressure was measured with a gas chromatograph (Varian 1400) equipped with a thermal conductivity detector (TCD), two sampling loops and a packed column (Chromosorb 102, length of 3.5 m, 80/100 mesh). The construction of the injection system allowed the carrier gas to flow through the one sampling loop, while the reactor content was circulated in the other one. By switching the injection valve, the loop contents from the reactor entered the GC. The column and detector temperatures were 110 and 250 °C, respectively. Nitrogen was used as a carrier gas (16 cm<sup>3</sup> min<sup>-1</sup>). The solvents were flushed with hydrogen prior to the measurements to degas the solvent. Hydrogen pressure was applied and the temperature was adjusted to the desired level. An HPLC-pump was utilized to circulate the reactor contents (the solvent containing dissolved hydrogen) through the sampling loop of the GC and back into the reactor. A liquid trap was mounted before the GC column, because it was found necessary to remove the main bulk of the liquid to prevent column damages. An H<sub>2</sub>/N<sub>2</sub> gas mixture (996 ppm H<sub>2</sub> in N<sub>2</sub>, AGA) was used for

Table 1  
Dielectric coefficients ( $\epsilon$ ) of the solvents used in the calibration of Dipolmeter DM01

Solvent	$\epsilon$ (at 25 °C)
Ethyl acetate	6.02
Tetrahydrofuran	7.43
1-Octanol	9.90
1-Pentanol	13.9
Cyclohexanol	15
Acetophenone	17.4
2-Propanol	18.3
1-Propanol	20.1
Acetone	20.7
Ethanol	24.3

calibration of the quantitative analysis. A single solubility value was calculated as an average of at least five independent measurements. Due to the low dione and catalyst modifier concentrations used in the catalytic experiments, the hydrogen solubility was measured in pure solvents, but it could be attributed to reaction mixtures.

### 2.3. Measurement of the dielectric coefficient of the solvent mixtures

The dielectric coefficient ( $\epsilon$ ) of the medium (also known as relative permittivity), was measured with Dipolmeter DM01. The apparatus was calibrated with solvents having known dielectric coefficients (Table 1). After the calibration, the dielectric constants of following solutions were measured at 25 °C: (a) the 0.05 mol dm<sup>-3</sup> reactant solutions in ethyl acetate and 2-propanol, (b) ethyl acetate and 2-propanol mixtures with the mole fractions of ethyl acetate 0.25, 0.50 and 0.75 and (c) tetrahydrofuran at 25 °C.

### 2.4. Quantum chemical calculations

The structure of 1-phenyl-1,2-propanedione was first optimized by the Hartree–Fock (HF) approximation with the 6-31 + G\*\* [18–21] basis set. In order to investigate the solvent effect on the reactant geometry, the Mulliken atomic charges and dipole moment calculations using the polarized continuum model (PCM) [22] were carried out applying the HF approximation and the density functional theory (DFT) with 6-31 + G\*\* basis set. The solvents

considered in the calculations were toluene, ethanol and methanol having dielectric constants of 2.4, 24.3 and 32.6, respectively. In the DFT calculations, the B3LYP [23] functional was used where Becke's three parameter hybrid functional (B3) [24] is applied for the exchange part and Lee–Yang–Parr (LYP) functional [25] for the correlation part. Gaussian 98 [26] software was used in the calculations.

## 3. Results

The complete reaction scheme of 1-phenyl-1,2-propanedione (**A**) hydrogenation in the presence of cinchonidine is displayed in Fig. 1. When referring to dielectric constants in the text, the dielectric constants of pure solvents were used excluding the effect of small amounts of reactant and modifier. To verify this assumption, the dielectric constant of the reactant solution (0.05 mol dm<sup>-3</sup>) in ethyl acetate and 2-propanol were measured and the difference in the dielectric constants of the medium with respect to the pure solvent were within the experimental error (Table 2). Therefore, due to the low concentrations of the reactant and modifier used, the approximation of employing the dielectric constants of pure solvent is justified. In the sequel, the qualitative hydrogenation kinetics in various solvents is described in terms of reaction rates, the regio- and enantioselectivity as well as the diastereoselectivity, after which the aspects of solvent effects are discussed, and finally, a quantitative model is developed.

### 3.1. Reaction rate

The reaction rate varied in different solvents, the highest reaction rate was observed in 2-propanol and very low reaction rates in 1-pentanol and tetrahydrofuran (THF), while relatively high rates were obtained in the other solvents studied. As can be seen from Table 2, the initial hydrogenation rate did not correlate with the measured hydrogen solubilities. The measured hydrogen solubility decreased with an increasing solvent dielectric constant. No correlation between the activity and the dielectric constant was observed. In THF, the reaction practically seized after the first hydrogenation step to hydroxyketones, and did not proceed further to diols. The low reaction rate in 1-pentanol was an

Table 2

Dielectric coefficient of the solvents ( $\epsilon$ ), measures hydrogen solubility given as mole fraction ( $x_{\text{H}_2}$ ) at 10 bar  $\text{H}_2$  in different solvents, initial reaction rate and regioselectivity (rs) at 80% conversion of reactant in the hydrogenation of 1-phenyl-1,2-propanedione (**A**)

Solvent	$\epsilon$ (at 25 °C)	$x_{\text{H}_2}$ ( $10^{-4}$ )	Initial reaction rate ( $10^{-3} \text{ mol dm}^{-3} \text{ min}^{-1} \text{ g}_{\text{cat}}^{-1}$ )	rs
Toluene	2.38	3.2		7.8
Ethyl acetate	6.02	3.5	39	6.7
0.05 M <b>A</b> in ethyl acetate	6.18 <sup>a</sup>		39	
Methyl acetate	6.68	3.0	42	7.1
Ethyl acetate ( $x = 0.75$ )–2-propanol ( $x = 0.25$ ) mixture	7.3 <sup>a</sup>	–	49	6.9
Tetrahydrofuran	7.4 <sup>a</sup>	2.9	23	8.5
Ethyl acetate ( $x = 0.50$ )–2-propanol ( $x = 0.50$ ) mixture	9.25 <sup>a</sup>	–	53	7.1
Ethyl acetate ( $x = 0.25$ )–2-propanol ( $x = 0.75$ ) mixture	12.2 <sup>a</sup>	–	54	6.3
1-Pentanol	13.9	2.7	23	7.8
2-Propanol	18.3	2.7	62	5.8
0.05 M <b>A</b> in 2-propanol	18.8 <sup>a</sup>		62	
Ethanol	24.3	2.1	38	8.5
Methanol	32.6	–	36	5.3

<sup>a</sup> Measured values.

exception with respect to the other alcohols screened. The activity in the binary solvent mixtures is described later (Section 3.6).

Internal and external mass transfer limitations were found to have a negligible effect on the enantio- and regioselectivity in the hydrogenation of **A** [27]. The reaction order with respect to hydrogen has been found to be close to zero in detailed kinetic experiments [28] carried out in ethyl acetate. Therefore, it is understandable that the differences in the hydrogen solubility have a minor effect on the reaction rate and selectivity as well. For this reaction, other effects originating from the utilization of different solvents play a much more decisive role than the concentration of dissolved hydrogen.

### 3.2. Enantioselectivity

The main effort was focused on the understanding of the variation of the enantioselectivity in different solvents. Enantiomeric excess of (*R*)-1-hydroxy-1-phenylpropanone (**B**) over (*S*)-1-hydroxy-1-phenylpropanone (**C**) defined as  $ee = ([\mathbf{B}] - [\mathbf{C}]) / ([\mathbf{B}] + [\mathbf{C}])$ , varied significantly in different solvents, the ee being almost zero in methanol and exceeding 65% in toluene. Fig. 2 shows a highly non-linear dependence of the ee on the dielectric constant of the solvent. The ee as well as the enantioselectivity,  $es = \{r_{\mathbf{B}}/r_{\mathbf{C}}\}$ , decreased with increasing solvent dielectric constant.

A decrease of ee with an increasing solvent dielectric constant has been reported, e.g. in ethyl pyruvate [8] and ketopantolactone [29] hydrogenation over cinchonidine-modified Pt catalysts.

The ee was relatively constant with increasing conversion of dione in ethyl acetate, methyl acetate and alcohols, i.e. methanol, ethanol, 1-pentanol and 2-propanol. In tetrahydrofuran, the ee decreased with increasing conversion of dione.

At very high conversion levels (>90%) of 1-phenyl-1,2-propanedione, the kinetic resolution between (*R*)- and (*S*)-1-hydroxy-1-phenylpropanones increases the ee. An analogous kinetic resolution has been observed in the hydrogenation of 2,3-butanedione [30,31].

### 3.3. Quantum chemical calculations

Numbering of the atoms and definition of the torsion angles are presented in Fig. 3. All the relevant torsion angles, bond distances and Mulliken atomic charges in equilibrium are reported in Tables 3–5. Calculated dipole moments in different media are reported in Table 6.

#### 3.3.1. HF/PCM calculations

In the previous study [32], it has been shown that C=O bond in position 1 is slightly weaker than the one in position 2. This is a plausible explanation for regioselectivity in the hydrogenation of 1-phenyl-1,

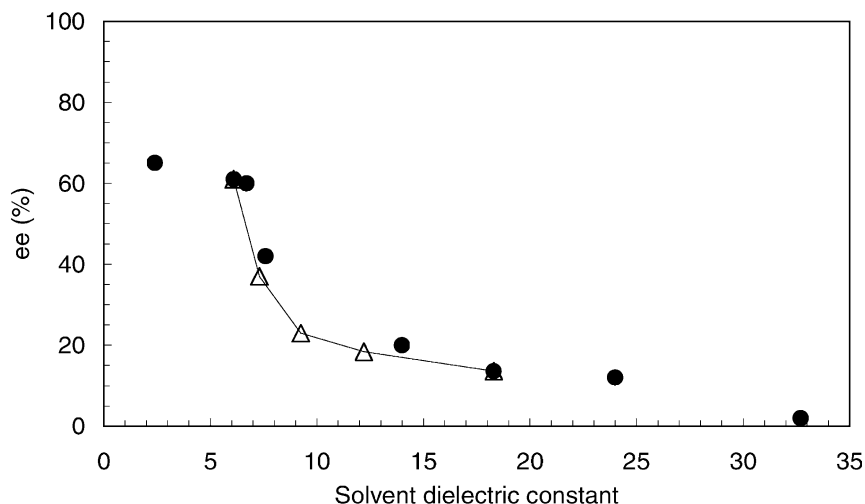


Fig. 2. Dependence of enantiomeric excess on solvent dielectric constant. Symbols: (●), neat solvents; (△), binary mixtures of ethyl acetate and 2-propanol.

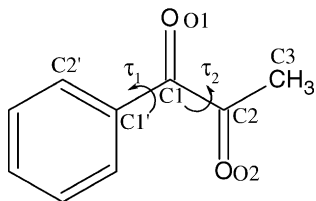


Fig. 3. Planar structure of 1-phenyl-1,2-propanedione. Selectively numbered atoms and definition of torsion angles  $\tau_1$  and  $\tau_2$  ( $\tau_1 = \text{C2}'\text{-C1}'\text{-C1-O1}$ ,  $\tau_2 = \text{O1-C1-C2-O2}$ ).

2-propanedione. In the HF optimized structure of 1-phenyl-1,2-propanedione in vacuum ( $\epsilon = 1$ ), the torsion angle  $\tau_1$  is almost  $0^\circ$  indicating that the carbonyl group in position 1 is coplanar with the phenyl ring. The torsion angle  $\tau_2$  has a value  $136.6^\circ$  indicating the *s-trans* conformation with nonplanar carbonyl

groups. There were no remarkable changes in the geometry or in the Mulliken atomic charges as the effect of solvent was included. In toluene, the geometry and the Mulliken atomic charges are almost the same as in the HF optimized structure in vacuum. This was expected, because dielectric constant of toluene ( $\epsilon = 2.4$ ) is close to 1. The dipole moment in toluene (2.80 D) was also close to the value in vacuum (2.48 D). A polar medium shows a more pronounced solvent effect than toluene. In ethanol and methanol, the torsion angle  $\tau_1$  increased slightly to  $-9^\circ$  and the torsion angle  $\tau_2$  decreased to  $126^\circ$  giving a less pronounced *s-trans* character to the molecule. Hence, the dipole moment increased by 1 D, which was expected in the more polar medium. The dipole moments of *s-trans* and *s-cis* conformers ( $\tau_2$  constrained to 0 and  $180^\circ$ ) were, 0.99 and 5.85 D, respectively. The bond length

Table 3

Mulliken atomic charges of 1-phenyl-1,2-propanedione in different media calculated by using HF/PCM and B3LYP/PCM methods

Atom	HF optimized				B3LYP optimized			
	Vacuum	Toluene	Ethanol	Methanol	Vacuum	Toluene	Ethanol	Methanol
C1'	0.67	0.64	0.46	0.47	0.04	0.82	0.61	0.62
C1	-0.18	-0.15	-0.07	-0.07	0.34	-0.24	-0.13	-0.15
C2	0.53	0.53	0.59	0.60	0.37	0.59	0.55	0.57
C3	-0.47	-0.47	-0.52	-0.52	-0.38	-0.56	-0.58	-0.58
O1	-0.44	-0.46	-0.50	-0.50	-0.46	-0.41	-0.46	-0.46
O2	-0.44	-0.46	-0.51	-0.51	-0.42	-0.40	-0.44	-0.45

Table 4

Selected bond distances (in pm) of 1-phenyl-1,2-propanedione in different media calculated by using HF/PCM and B3LYP/PCM methods

Bond	HF optimized (in pm)				B3LYP optimized (in pm)			
	Vacuum	Toluene	Ethanol	Methanol	Vacuum	Toluene	Ethanol	Methanol
C1'–C1	149	149	148	148	149	148	148	147
C1–C2	154	154	153	154	155	155	154	154
C2–C3	150	150	150	150	151	150	150	150
C1–O1	120	120	120	120	122	123	123	123
C2–O2	119	119	119	120	122	122	122	122

Table 5

Torsion angles  $\tau_1$  and  $\tau_2$  ( $^\circ$ ) of 1-phenyl-1,2-propanedione in different media calculated by using HF/PCM and B3LYP/PCM methods

	HF optimized ( $^\circ$ )				B3LYP optimized ( $^\circ$ )			
	Vacuum	Toluene	Ethanol	Methanol	Vacuum	Toluene	Ethanol	Methanol
$\tau_1$	–2.9	–4.4	–9.3	–9.2	–2.4	–2.2	–6.2	–5.5
$\tau_2$	136.6	136.5	126.4	126.4	154.0	136.9	124.1	120.1

Table 6

Dipole moments of 1-phenyl-1,2-propanedione in different media calculated by using the HF and B3LYP methods

Method	Dipole moment/Debye			
	Vacuum	Toluene	Ethanol	Methanol
HF	2.48	2.80	3.86	3.87
B3LYP	1.66	2.86	4.71	5.00

between the phenyl ring and carbon C1 decreased by 1 pm. In methanol, the length of the double bond C2–O2 increased to 120 pm having equal length with the other C=O double bond C1–O1. There were also changes in the Mulliken atomic charges. With an increasing dielectric constant, the carbons C1', C3 and both oxygen atoms gain, while the carbonyl carbons C1 and C2 lose electrons, although the change was not significant. It was largest in carbon C1' (–0.2).

### 3.3.2. B3LYP/PCM

The B3LYP optimized structure in vacuum has a larger  $\tau_2$  torsion angle (154 $^\circ$ ) and a large divergence in Mulliken atomic charges for carbons atoms C1' and C1 compared to the HF optimized structure. In toluene, however, the structure was very similar to the one optimized in toluene by using HF/PCM, except for the small differences in the Mulliken atomic charges. In all solvents, the bond distances and torsion angles are

almost the same as the corresponding values in the HF optimized structure, although both torsion angles were slightly smaller. The dipole moments were larger than in the HF optimized structure and the largest variation can be seen in the Mulliken atomic charges. This can be partly explained by the smaller torsion angle  $\tau_2$  giving a less *s-trans* character to the molecule. Furthermore, the C=O bonds were 3 pm longer than in the HF optimized structures. The B3LYP optimized C=O distances were close to the values calculated earlier with the Møller–Plesset perturbation theory of second-order [32].

### 3.4. Regioselectivity

The regioselectivity (rs) is defined as the ratio between the concentrations of 1-hydroxy-1-phenylpropanone (**1-OH**) and 2-hydroxy-1-phenylpropanone (**2-OH**) and can be expressed as follows:

$$rs = \frac{[\mathbf{B}] + [\mathbf{C}]}{[\mathbf{D}] + [\mathbf{E}]}$$

The rs was relatively constant until about 90% conversion levels of the reactant, after which rs gradually increased due to the kinetic resolution of regioisomers **1-OH** and **2-OH**. The rs did not exhibit any strong dependence on the dielectric constant. However, a slight non-linear decrease in the regioselectivity as a function

of the dielectric constant was observable (Table 2), excluding the high regioselectivities in THF, 1-pentanol and ethanol. The *rs* in toluene ( $\epsilon = 2.4$ ) was about eight, but decreased to about five in methanol ( $\epsilon = 33$ ). The *rs*'s reported in Table 2 were calculated at 80% conversion of the reactant, this point is representative of the constant *rs*-value observed from 10 to 90% conversion of the reactant. In the beginning of the reaction (at lower than 10% conversion), the experimentally recorded *rs*-values were unreliable due to the small amounts of **2-OH**.

### 3.5. Diastereoselectivity

The final hydrogenation products consist of four diastereomers (**F**, **G**, **H**, **I**, Fig. 1). Interestingly, as enantioselectivity, also the product distribution among diols varied in different solvents. The main product in non-polar solvents was (*R,S*)-1-phenyl-1,2-propanediol, **F**, (yield of **F** = 55%), whereas (*1S,2R*)-1-phenyl-1,2-propanediol, **H**, (yield of **F** = 25%) was the main diol in polar solvents. The yield of (*1S,2S*) and (*1R,2R*)-1-phenyl-1,2-propanediols (**G** and **I** in Fig. 1) remained low in all of the investigated solvents (yield<sub>*1R,2R+1S,2S*</sub> < 25%).

### 3.6. Binary mixtures of ethyl acetate and 2-propanol

The dielectric constant range from 6.2 to 18.3 was investigated by using binary solvent mixtures of ethyl acetate ( $\epsilon = 6.2$ ) and 2-propanol ( $\epsilon = 18.3$ ). The dielectric constants of the prepared ethyl acetate—2-propanol mixtures were measured (Table 2) and the solutions were used in the hydrogenation. The dependence of the *ee* on the dielectric constant is illustrated in Fig. 2. The *ee* decreased with increasing dielectric constant, without any major deviations from the general trend observed for different solvents (Fig. 2). The hydrogenation rates in solvent mixtures varied between the boundary values observed in pure ethyl acetate and 2-propanol. This was not the case when 1-pentanol ( $\epsilon = 14$ ) and THF ( $\epsilon = 7.6$ ) were used as solvents, in which the reaction rate was considerable lower (Table 2). However, the *ee*'s obtained in THF and 1-pentanol followed the general trend displayed in Fig. 2. In other words, despite the significant differences in the hydrogenation rates the *ee* still obeyed the same trend.

The data illustrate the advantage of using solvent mixtures instead of different solvents, while verifying the solvent effects. The dependences on the dielectric constant are clearly visible and no unexpected differences in activity appear, arising from the non-inertness of the solvents. However, there exist some complications in this approach, which should be considered. The selection of the components in a binary solvent mixture should be done with care (at least inert solvents are needed with no mutual reactions). Physical parameters (e.g. dielectric constant) characterizing the binary mixtures should be measured, because these kind of data are not readily available in literature under desired conditions. A linear approximation of the dielectric constant as a function of the mole fractions might be insufficient. For instance, in the present case, a non-linear dependence on the mole fraction of ethyl acetate in 2-propanol was observed (Table 2).

## 4. Discussion

In enantioselective hydrogenation, the solvent effects comprise an interplay between catalyst surface, reactant, products, catalyst modifier and the solvent. The following treatment highlights features relevant to the topic; for a more detailed treatment of solvent effects, excellent literature is available [1–3,33].

### 4.1. Solvent interactions with catalyst surface-catalytic activity

Solvent interactions with the catalyst surface can be of adsorptive type and/or of reactive type (solvent decomposition or hydrogenation) and can be significant due to the large liquid-phase concentration of the solvent. In cases the adsorption strengths of the solvent and reactants are similar the solvent competes with the reactant on the available surface and consequently, occupies a majority of the surface due to its significantly higher liquid-phase concentration and inhibits the reaction. The interaction of THF with Pt surface is known to be very high due to the oxygen lone pair orbital bonding [34,35], and competition of solvent and reactant might explain the low initial activity and inhibition of the further reaction to diols when THF was used as a solvent. The exceptionally



high hydrogenation rate in 2-propanol can be due to the hydrogen donating properties [35]. The low hydrogenation rate in 1-pentanol was somewhat an exception; other alcohols tested gave relatively high reaction rates. The exceptionally low reaction rates in THF and 1-pentanol were due to the deactivation induced by the solvent and solvent impurities.

#### 4.2. Solvation of modifier

The effect of *solvation* in catalytic hydrogenation have been reported previously [3,36], the rule of thumb being that polar organic compounds (reactant and modifier) remain more strongly solvated in polar media and thus the non-polar components can adsorb more facile on the catalyst surface, i.e. solvation directly affects adsorption equilibria. The situation is vice versa in non-polar media.

Adsorption studies of cinchonidine on Pt/Al<sub>2</sub>O<sub>3</sub> [37] in different solvents have revealed that more cinchonidine was adsorbed from toluene on the catalyst than from methanol. Based on this observations, it is probable that the solvent dependence of enantioselectivity is affected by the differences in the solvation of the modifier. However, in the present case, rather high modifier concentrations were used and therefore, the effect of modifier solvation can be considered to be minor.

#### 4.3. Effect of modifier conformation

The conformational behavior of cinchona alkaloids has been studied in detail [10,38,39]. Cinchonidine exhibits a rich conformational behavior: at room temperature six different conformers have been recognized consisting of two “Closed” conformers and four “Open” conformers [10]. This complex liquid-phase equilibrium varies as a function of the solvent dielectric constant. The Open(3) and Closed(1) conformers are displayed in Fig. 4. Many authors conclude that the “Open form” (Open(3) conformer) of the modifier is involved in the enantio-differentiating step [5,40]. Experimental support on the involvement of open form of the modifier has been provided by the high enantiomeric excesses obtained by using rigid cinchona modifiers, which have a fixed Open(3) conformation [41]. In non-polar solvents, the Open(3) conformer of cinchonidine is the most stable one and

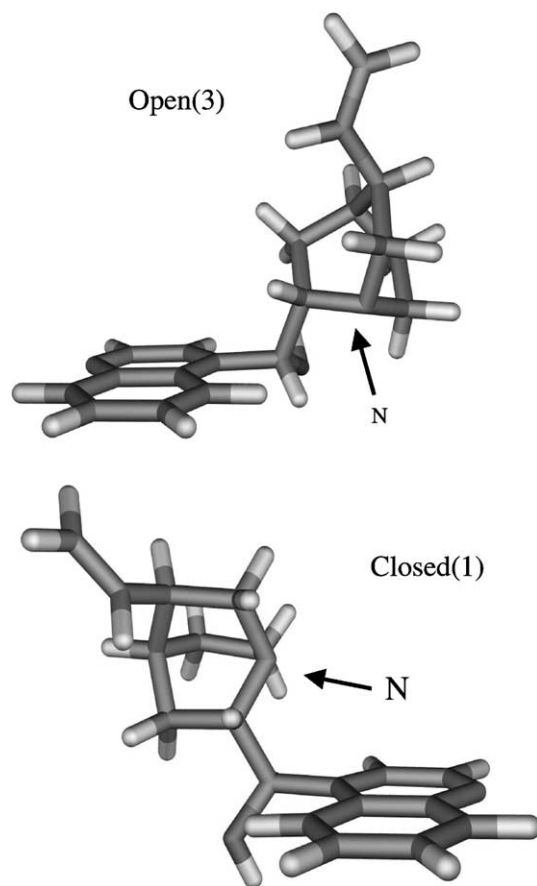


Fig. 4. Open(3) and Closed(1) conformers of cinchonidine. The arrow is pointing to the quinolinicidine N atom.

the stability decreases with an increasing dielectric constant [10].

The dielectric constant dependence of enantioselectivity using different reactants over cinchonidine-modified Pt/alumina catalysts is displayed in Fig. 5. As can be seen, in the case of ethyl pyruvate, a linear dependence dominates, whereas, for ketopantolactone and 1-phenyl-1,2-propanedione an exponential decline of the dependence is visible. Fig. 5 also describes the modeled dependence of Open(3) conformer and experimental data determined by NMR [10].

Some interesting effects can be observed. Firstly, the population of the Open(3) conformer decreases from about 70% to about 30% attaining a constant value at higher dielectric constant. Secondly, the ee values impair significantly in the case of ketopantolactone and

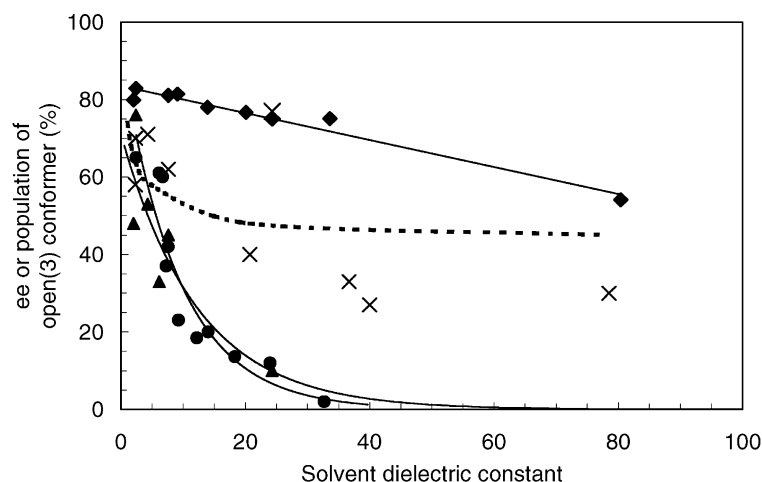


Fig. 5. Experimentally observed enantiomeric excesses (ee) and population of Open(3) conformer of cinchonidine as a function of solvent dielectric constant. Symbols: (◆), ee in ethyl pyruvate hydrogenation [8]; (●), ee in 1-phenyl-1,2-propanedione hydrogenation; (▲), ee in ketopantolactone hydrogenation [10], (×), experimentally determined (NMR [10]) population of Open(3) conformer and (---) modelled population (B3LYP 6–31 + G\*\* [10]).

1-phenyl-1,2-propanedione and the enantioselectivity is practically lost at  $\epsilon = 30$ , whereas, for ethyl pyruvate the decline in ee is much less. This raises a question that is it the population of Open(3) conformer, which is solely responsible for the observed dependencies or should some other factors be considered.

When comparing the case of ketopantolactone and 1-phenyl-1,2-propanedione with the case of ethyl pyruvate, the loss of ee in the former and the less than 20% decline of ee in the latter case explained by the analogous loss of slightly over 50% of the Open(3) conformer (from 70 to 30%) in the liquid phase seem to be a bit contradictory. In all of the results presented in Fig. 5, the effect of the Open(3) conformer should be almost the same due to the similar type of catalyst and modifier used and yet no clear correlation is visible. Therefore, in the light of Fig. 5 and the previous statements, it is difficult to imagine that the decline in ee could be exclusively attributed to the Open(3) conformer appearance on the solvent dielectric constant.

#### 4.4. Role of reactant conformation

The effect of reactant conformation in  $\alpha$ -ketoesters, including ethyl pyruvate (EP) and ketopantolactone

(KPL) hydrogenation over analogous systems has been reviewed [42], but no clear involvement of a particular conformer of reactant on the enantio-differentiating step could be revealed.

The effect of conformation of 1-phenyl-1,2-propanedione was studied by means of quantum chemical calculations. Both methods, HF and B3LYP, were giving similar results in different media (Tables 3–6). The effect of a polar solvent gave only a slight decrease in the torsion angle  $\tau_2$  and thus, the dipole moment of the molecule increased in polar media. In general, the effect of the solvent on the reactant conformation can be considered relatively minor. This was the case also with ethyl phenylglyoxylate (EPG), where the potential energy surface over  $\tau_2$  has a similar shape [42].

When comparing the solvent dielectric constant dependence of ee in 1-phenyl-1,2-propanedione (A), EP [8], methyl pyruvate [43], KPL [29], EPG [43], 2,3-butanedione [44], some interesting differences can be seen (the structures are illustrated in Fig. 6). It became clear that KPL, A and EPG [32,42] exhibit pronounced solvent dependencies, whereas, the others have less pronounced solvent dependence (i.e. decline in ee with increasing solvent dielectric constant). Therefore, some reactant specific factors should be involved in the explanation of solvent effects.

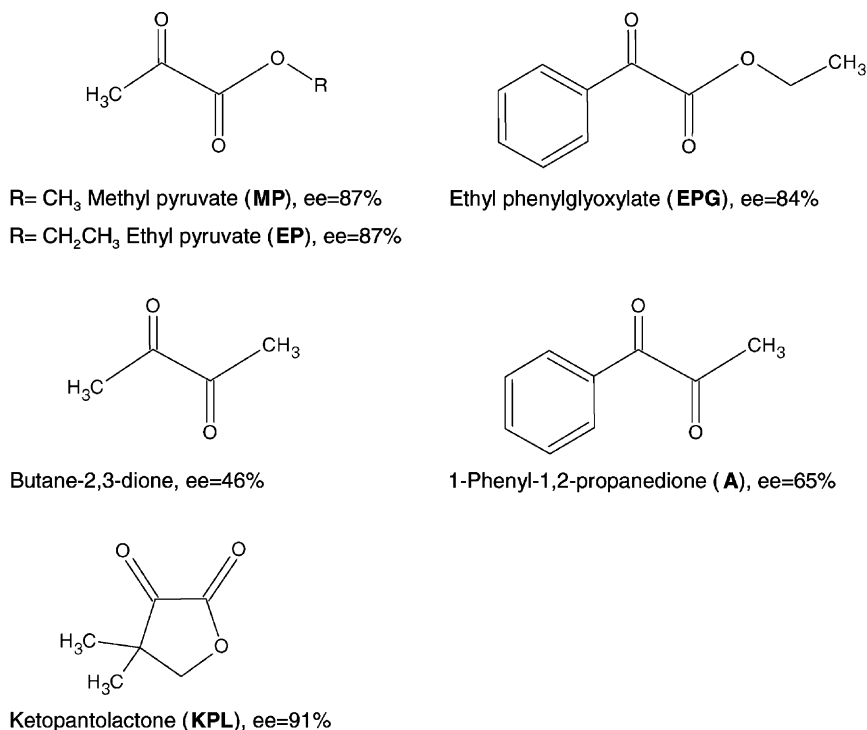


Fig. 6. Different substrates and maximum enantiomeric excesses obtained in hydrogenation over cinchonidine modified Pt/alumina catalysts. For conditions see [29,31,43,46,47] and this work).

#### 4.5. Reaction between reactant and alcoholic solvents

In general, in alcoholic solvents the ee remained rather low (Fig. 2). The reasons for this are not yet clear, however, formation of acetals from the reactant and alcoholic solvents can be a contributing factor. Formation of hemiketals was shown [49] to be important when there is a strong electron-withdrawing group in  $\alpha$  position to the keto-carbonyl group, i.e. in hydrogenation of  $\alpha,\alpha,\alpha$ -trifluoromethylketone. In the latter case, there is a strong tendency of the ketone to undergo enolization, reaction which is much less profound for other ketones. For instance in ethyl pyruvate hydrogenation, the acetals (hemiketals) were reported to have minor role [48,49]. It is thus reasonable to assume that hydrogenation of 1-phenyl-1,2-propanedione via the hemiketal formation route is not significant.

Another complication with alcoholic solvents is that they are prone to hydrogen bonding and these

interactions might disturb the hydrogen bonding between the quinuclidine nitrogen and the carbonyl group ( $\text{N} \cdots \text{H} \cdots \text{C}=\text{O}$ ) of the reactant. In the transition state complex between the reactant and the modifier hydrogen bond interaction is in central role, as proposed by mechanistic models for ethyl pyruvate hydrogenation [6]. It could well be that the alcoholic solvent inhibits these specific hydrogen bonding interactions and thus leads to low enantioselectivity.

#### 4.6. Effect of solvent polarity on diastereoselectivity

The product distribution of diols has been studied in ethyl acetate both in batch and continuous reactors and the excess formation of *RS*-diol (**F**) has been observed in the presence of cinchonidine. In the absence of the modifier, a racemic mixture of *SR*-diol (**H**) and *RS*-diol (**F**) was obtained [32]. The excess formation of **F** exhibited analogous behavior with respect to the enantiomeric excess of **B** as a function of the modifier concentration. In the continuous fixed bed reactor

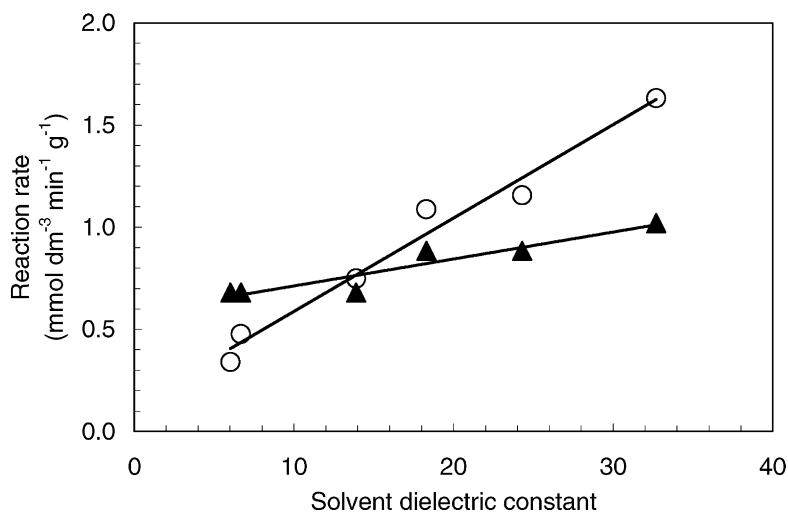


Fig. 7. Disappearance rate of **B** (▲) and **C** (○) in the second hydrogenation step to diols as a function of solvent dielectric constant.

[32], the development of the ee and the excess of **F** were interrelated, too. Therefore, it can be assumed that similar enantio-differentiating interactions are responsible for both effects in ethyl acetate. As the ee declined with increasing solvent dielectric constant one would expect the excess of **F** to diminish and approach a racemic (50% *RS*: 50% *SR*) diol mixture. However, this was not the case because an excess of *RS*-diol (**F**) was formed in polar media.

The disappearance rates of **B** and **C** are illustrated in Fig. 7. It is clear that in non-polar media the *R*-enantiomer, **B**, reacts faster than the *S*-enantiomer, **C**, yielding an excess of **F** (*RS*-diol). In polar solvents, the situation is opposite and an excess of **H** (*SR*-diol) is formed. This is true, if the minor contributions (yield<sub>*RR+SS*</sub> < 25%) of the *SS*- and *RR*-diols (**G** and **I** in Fig. 1), which could not be separated, is excluded and also the effect of **2-OH** converted to diols (<5%). The origin of the observed change in the diol distribution cannot at present be rigorously studied due to the separation difficulties of diols in GC. However, it cannot be solely attributed to the effects, which are responsible for the loss of ee with an increasing solvent polarity, because in that case one would end up with a racemic diol mixtures. The excess formation of *SR*-diol (**H**) in polar solvents could be due to a specific interaction with the alcoholic solvents and the intermediate hydroxyketones as the polar solvents considered in this work were all alcohols. Further studies are

needed to elucidate the origin of the changes in diol distribution.

## 5. Modelling of solvent effects

### 5.1. Kinetic model for enantioselective hydrogenation of 1-phenyl-1,2-propandione

The general principle of a kinetic model used in this work was based on the previously developed model [16] for enantioselective hydrogenation of **A**, 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 modified sites result in the selective formation of the *R*-enantiomer (e.g. **B**) The reversible reactant and modifier adsorption is assumed to be rapid, whereas, the irreversible addition of dissociated hydrogen is rate determining according to the model. Generally, the rates on modified and unmodified sites can be written according to Eqs. (1)–(3),

$$r_j = r_{j,\text{mod}} + 0.5r_{j,\text{unmod}} \quad (1)$$

$$r_{j,\text{mod}} = k_{j,\text{mod}} f(p_{\text{H}_2}) \frac{K_{\text{A}_i\text{M}} K_{\text{MCA}_i} c_{\text{M}}}{D} \quad (2)$$

$$r_{j,\text{unmod}} = k_{j,\text{unmod}} f(p_{\text{H}_2}) \frac{K_{\text{A}_i} c_{\text{A}_i}}{D} \quad (3)$$

where  $K_i$  is the adsorption equilibrium constant of compound  $i$ ,  $f(p_{H_2})$  is a function which describes the hydrogen pressure dependence on the rate and  $D$  is the adsorption term  $D = 1 + K_{MC_M} + \sum K_{A_i} c_{A_i} + \sum K_{A_i M} K_{M C_{A_i} C_M} + K_{S C_S}$ . Noteworthy is that the enantioselectivity is exclusive caused by the modified reactions occurring on the modified sites. This implies in practice that a specific substrate-modifier complex is formed on the modified sites.

### 5.2. The solvent effect extension

The issue of how the solvent interaction should be included in the model can be tackled with the aid of transition state theory. Keeping in mind that the enantio-differentiating transition state includes both the reactant and the modifier, which can be treated as the dipole–dipole interaction. The Kirkwood treatment [45] for the case when the reactants are not charged leads to

$$\ln k_{\text{mod}} = \ln k_{\text{mod}}^o - k' \frac{(\mu^{\ominus})^2 - (\mu_A)^2 - (\mu_M)^2}{\varepsilon} \quad (4)$$

where  $\varepsilon$  is the dielectric constant and  $\mu$  denotes the dipole moments, and  $k'$  is a constant, which depends on temperature.

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

$$k_{\text{mod}} = k_{\text{mod}}^o e^{\alpha/\varepsilon} \quad (5)$$

where  $\alpha$  is a constant, which demonstrates how strongly the rate constant depends on the solvent polarity.

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

$$\begin{aligned} \frac{1}{\rho_B} \frac{dc_B}{dt} &= r_{B,\text{mod}} + r_{B,\text{unmod}} \\ &= k_{B,\text{mod}}^o f(p_{H_2}) \frac{K_{AM} K_{M C_A C_M}}{D} e^{\alpha/\varepsilon} \\ &\quad + k_{B,\text{unmod}} f(p_{H_2}) \frac{K_{A C_A}}{D} \end{aligned} \quad (6)$$

where  $\rho_B$  is the catalyst bulk density.

Analogously the generation rate of **C** is expressed by

$$\frac{1}{\rho_B} \frac{dc_C}{dt} = r_{C,\text{unmod}} = k_{C,\text{unmod}} f(p_{H_2}) \frac{K_{A C_A}}{D} \quad (7)$$

Similar expressions hold for the generation rates of **E** and **D**,

$$\begin{aligned} \frac{1}{\rho_B} \frac{dc_E}{dt} &= r_{E,\text{mod}} + r_{E,\text{unmod}} \\ &= k_{E,\text{mod}}^o f(p_{H_2}) \frac{K_{AM} K_{M C_A C_M}}{D} e^{\alpha/\varepsilon} \\ &\quad + k_{E,\text{unmod}} f(p_{H_2}) \frac{K_{A C_A}}{D} \end{aligned} \quad (8)$$

$$\frac{1}{\rho_B} \frac{dc_D}{dt} = r_{D,\text{unmod}} = k_{D,\text{unmod}} f(p_{H_2}) \frac{K_{A C_A}}{D} \quad (9)$$

Eqs. (6)–(9) provide a direct possibility to express the regioselectivity as a function of dielectric constant:

$$rs = \frac{[B] + [C]}{[D] + [E]} = \frac{1 + f_1 \exp(\alpha/\varepsilon)}{f_2 + f_3 \exp(\alpha/\varepsilon)} \quad (10)$$

where

$$\begin{aligned} f_1 &= \frac{k_{B,\text{mod}}^o K_{AM} K_{M C_M}}{k_{B,\text{unmod}} K_A + k_{C,\text{unmod}} K_A} \\ &= \frac{k_{B,\text{mod}}^o K_{AM} K_{M C_M}}{2k_{B,\text{unmod}} K_A} \end{aligned} \quad (11)$$

$$\begin{aligned} f_2 &= \frac{k_{E,\text{unmod}} K_A + k_{D,\text{unmod}} K_A}{k_{B,\text{unmod}} K_A + k_{C,\text{unmod}} K_A} \\ &= \frac{k_{E,\text{unmod}} K_A}{k_{B,\text{unmod}} K_A} \end{aligned} \quad (12)$$

$$\begin{aligned} f_3 &= \frac{k_{E,\text{mod}}^o K_{AM} K_{M C_M}}{k_{B,\text{unmod}} K_A + k_{C,\text{unmod}} K_A} \\ &= \frac{k_{E,\text{mod}}^o K_{AM} K_{M C_M}}{2k_{B,\text{unmod}} K_A} \end{aligned} \quad (13)$$

According to the model the rate constants  $k_{B,\text{unmod}} = k_{C,\text{unmod}}$  and  $k_{E,\text{unmod}} = k_{D,\text{unmod}}$  are equal, as the reaction on unmodified sites leads to a racemic mixture of products.

Similarly to the regioselectivity, the enantioselectivity in the formation of the major product can be

expressed as a function of  $\varepsilon$  by Eq. (14),

$$es = \frac{B}{C} = \frac{k_{B,mod}^o K_{AM} K_M C_M \exp(\alpha/\varepsilon) + k_{B,unmod} K_A}{k_{C,unmod} K_A} \quad (14)$$

$$= 1 + f_4 \exp\left(\frac{\alpha}{\varepsilon}\right)$$

where

$$f_4 = \frac{k_{B,mod}^o K_{AM} K_M C_M}{k_{C,unmod} K_A} \quad (15)$$

Eq. (14) was used to describe the dependence of enantioselectivity as a function of dielectric constant (Fig. 8). A very good description was obtained as shown in Fig. 8. The values of the parameters obtained by non-linear regression were  $f_4 = 0.0143$  and  $\alpha = 35.6$ . This value of  $\alpha$  was utilized in parameter estimation for regioselectivity (Eq. (10)). The number of parameters in the regression was reduced by specifying the value of parameter  $f_2$ , as in fact this parameter determines the regioselectivity in the absence of the modifier, which was found to be equal to 5.

The results of the calculations demonstrated, that the model was able to describe the trend of increasing regioselectivity with decreasing  $\varepsilon$  (Fig. 9), the exceptions being the high regioselectivities in 1-pentanol and THF, which were excluded from the calculations. The values of parameters were  $f_1 = 0.049$  and  $f_3 = 0.007$ .

The impact of solvent polarity on the hydrogenation rate can be evaluated from Eqs. (6)–(9). Neglecting the adsorption terms of products one arrives at a following expression:

$$t = \frac{1}{\rho_B \{f_5 c_H^* + f_6 c_H^* \exp(-f_3 \varepsilon)\}} \times \left[ \ln \frac{c_{0A}}{c_A} + f_7 (c_{0A} - c_A) \right] \quad (16)$$

where  $t$  is the reaction time, at which the reactant concentration is  $c_A$ , while  $c_{0A}$  corresponds to the beginning of the reaction ( $t = 0$ ). The  $f_5, f_6, f_7$  are parameters, which include rate constants. According to Eq. (16), the reaction rate decreases with increasing

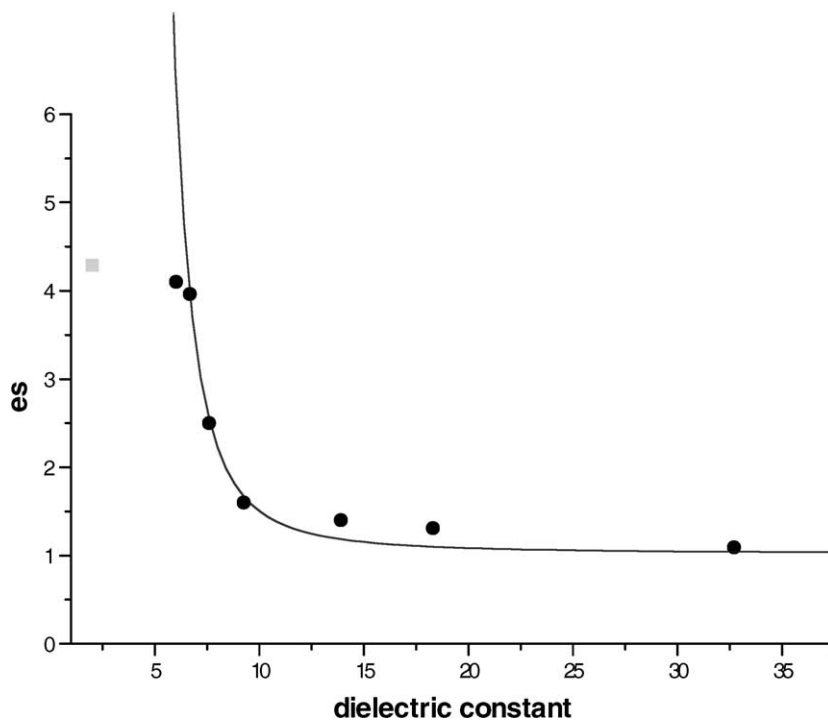


Fig. 8. Dependence of enantioselectivity on solvent dielectric constant. Points: experimental; line: calculated.

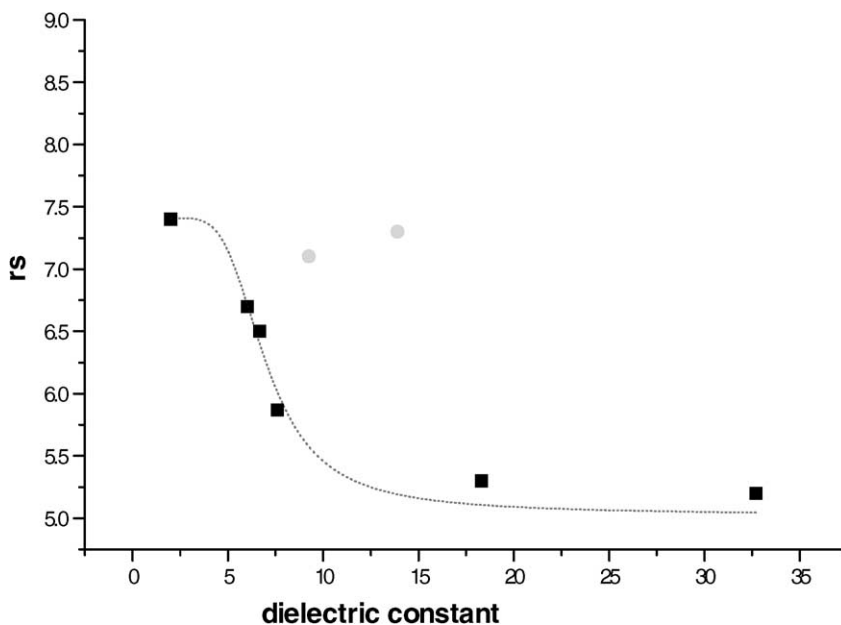


Fig. 9. Dependence of regioselectivity on solvent dielectric constant. Points: experimental; line: calculated.

solvent dielectric constant, if hydrogen solubility is taken as constant. The rates vary within boundary values as a function of  $\epsilon$ . The two exceptions were 2-propanol and 1-pentanol. The former had a very high reaction rate with respect to  $\epsilon$ , while for the latter one, the behavior was somewhat exceptional, the reaction rate was low and the catalyst deactivated.

## 6. Conclusions

Solvent effects in enantioselective hydrogenation of 1-phenyl-1,2-propanedione (**A**) were investigated in a batch reactor over a cinchonidine modified commercial 5 wt.% Pt/Al<sub>2</sub>O<sub>3</sub> (JM94) catalyst at 25 °C and 10 bar H<sub>2</sub>. The effect of different solvents, binary solvent mixtures and solvent dielectric constant on the regio- and enantioselectivity as well as on the overall hydrogenation reaction rate was studied. The hydrogenation rate did not correlate with the experimentally recorded hydrogen solubilities, which could be expected based on the zero-order dependence of the rate on hydrogen pressure. The highest reaction rate was observed in 2-propanol and the lowest in 1-pentanol. No correlation between the solvent dielectric constant

and hydrogenation rate could be found. The highest enantiomeric excesses (ee) of 65% was obtained in toluene as solvent. The ee decreased non-linearly with increasing solvent dielectric constant being close to nil in methanol.

The role of the reactant conformation in different solvents was evaluated using polarized continuum model applying the Hartree–Fock approximation and density functional theory. The results demonstrated that the solvent did not change significantly the reactant conformation and structure compared to the vacuum-optimized structure.

The solvent dielectric coefficient dependence of ee could not solely be attributed to the abundance of the Open(3) conformer of cinchonidine in liquid. Thus the incorporation of additional factors, characteristic to the structure of the reactant were proposed. The solvent effect was included in a previously proposed kinetic model in order to describe quantitatively the variation of enantioselectivity in different solvents. The dielectric constant dependence was taken into account 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 developed model was able to predict the behavior

of the system as a function of the solvent dielectric constant and a good description of both  $\epsilon_s$  and  $\epsilon_{rs}$  was obtained.

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