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Cinchona methyl ethers as modifiers in the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd catalyst

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ABSTRACT

The enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd/Al_2O_3 modified by $(R)C^8$—$(S)C^9$ cinchona ethers resulted in the inversion of the sense of the enantioselectivity. To find the explanation of the phenomenon, the interaction of acids bearing different substituents with cinchona alkaloids was studied in solution by NMR spectroscopy and experiments using mixtures of modifiers were carried out. The prominent non-linear behaviour obtained revealed the altered adsorption of the cinchona methyl ethers when compared with the parent alkaloids. The investigations indicated that the interaction of the ether derivatives with the unsaturated acids is more flexible and the presence of the methyl group reshapes the chiral surface sites. The combination of these effects complemented by the bulkiness of the diaryl substituted acrylic acids may lead to the inversion of the docking preference of the substrates in the altered chiral pocket of the adsorbed modifier and consequently results in decrease in the enantioselectivity or even in the inversion of its sense. Novel evidence on the ligand-accelerated mechanism in the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over cinchona alkaloid-modified Pd in the presence of benzylamine was also presented.

1. Introduction

The asymmetric catalytic hydrogenation of the prochiral unsaturated acids is a widely used method for the preparation of optically pure chiral carboxylic acids used as intermediates in the fine chemical industry [1,2]. Extended efforts were devoted to develop heterogeneous catalytic systems for replacing the soluble metal complex catalysts used for these purposes [3]. The adsorption of chiral compounds so-called modifiers on the surface of metals provided efficient heterogeneous asymmetric catalytic systems such as the tartaric acid-modified Raney-Ni or the supported Pt and Pd catalysts modified by cinchona alkaloids [4–6]. Pd catalysts modified by cinchonidine (CD) were found efficient in the enantioselective hydrogenation of prochiral unsaturated carboxylic acids.

The early report on the enantioselective hydrogenation of *α,β*-unsaturated carboxylic acids over CD-modified Pd [7] was followed by efforts to increase the optical purity of the products either by optimization of the catalytic system or by extension of the scope on structurally different acids [8–20]. The studies of several research groups converged to similar conclusions concerning the effect of the substrate structure, *i.e.* moderate enantiomeric excess (ee) can be obtained in the hydrogenation of α,β-dialkyl substituted acids [8,19], while in the reaction of β-aryl substituted acids good optical purities could be reached, especially with aryl group in the α position, too [13,18,20]. Parallel with these investigations, studies aimed the elucidation of the nature of the modifier–unsaturated acid interactions to reveal the structures of the surface intermediate complex responsible for enantiodifferentiation were also conducted. However, *in situ* methodologies necessary to reveal the real interactions established on the surface in this complex three-phase system are not yet available. Thus, valuable information was gained from the effects of the alterations in the structure of the modifier [21,22] or the substrate [11,13,20], the non-linear behaviour obtained by using modifier mixtures [21,23] combined with the results of spectroscopic and computational methods [22,24,25].

These investigations resulted in several similarities and differences in the interpretation of the enantiodifferentiation occurring in the hydrogenations of acids bearing aliphatic or aromatic substituents. The protonation of the quinuclidine moiety of the modifier by the acids was demonstrated with both acid types by the loss of the enantioselectivity in the hydrogenation of the methyl esters of the acids or over N-methyl cinchonidinium salt-modified catalyst [21,22,24] and even by the effect of the acidity of the substrate tuned by substituting the β-phenyl group

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[13,17,18,20]. The involvement of the C^9—OH group of the cinchona alkaloid in the interaction with the aliphatic acids was demonstrated by using cinchonidine methyl ether (CDM) and FT-IR, ATR-IR, NMR spectroscopy combined with theoretical calculations [22,24,25]. These results also indicated that the most stable complexes are formed by the participation of two or three aliphatic acid molecules interacting with CD [25]. In contrast, the hydrogenation of (*E*)-2,3-diphenylpropenoic acid (**1**) was assumed to occur through a 1:1 CD–acid complex, and the interaction of C^9—OH group with the carboxylic group was assumed based on the result obtained by using dihydro-CDM [21]. While the differences in the stoichiometry of the complexes of the two acid types may be rationalized by the solvent effect, the interpretation did not explain the formation in the presence of dihydro-CDM of the opposite enantiomer in small excess when compared with CD.

A valuable method for obtaining *in situ* information on the surface reaction was found to be the application of modifier mixtures or sequentially added modifiers. The non-linear behaviour obtained in the hydrogenation of activated ketones over Pt [26–31] or of 2-pyrone derivatives over Pd [32,33] indicated differences in the adsorption strength and geometry of the modifiers during the reactions. The striking non-linear behaviour observed in the enantioselective hydrogenation of **1** using mixtures of CD with dihydro-CDM was interpreted as a confirmation of the H-bonding between the alkaloid C^9—OH and the acid [21]. Very recently, mixtures of CD and CN were also applied in the reaction of the same acid; the lack of deviation from the linearity demonstrated that the lower ee obtained with CN when compared with CD is not due to the different adsorption properties of the two alkaloids [23].

In our present study, we sought to obtain further details on the interaction of (*E*)-2,3-diphenylpropenoic acid derivatives with the modifier by investigating the hydrogenations of six (*E*)-2,3-diphenylpropenoic acids (unsubstituted, OCH_3 and/or F substituted) over Pd catalyst modified by the four parent cinchona alkaloids, *i.e*. CD, cinchonine (CN), quinine (QN) and quinidine (QD), their C^9—OCH_3 ethers (CDM, CNM, QNM, QDM) and β-isocinchonine (β-ICN). The interpretation of the results was aided by the NMR spectroscopic investigation of the interaction of cinchona alkaloids with the acids in solution and by experiments using mixtures of the chiral modifiers.

2. Experimental

2.1. Materials

The catalyst used in this study was commercial 5% Pd/Al_2O_3 (Engelhard, 40692), which was pretreated in H_2 flow at 523 K as described before [17,18]. The parent cinchona alkaloids were commercial products (CD, CN, QN, QD all Fluka, ⩾98%). The cinchona methyl ethers and β-ICN were prepared by previously described methods [34,35]. Benzylamine (BA, Fluka, ⩾99.5%), N,N-dimethylformamide (DMF, Scharlau, Multisolvent grade) and H_2 gas (Linde AG, 99.999%) were used as received. (*E*)-2,3-Diphenylpropenoic acid (**1**, Aldrich, ⩾97%) was purified by crystallization in acetone–water. The preparation by the Perkin condensation, purification and characterization of the OCH_3 and/or F substituted (*E*)-2,3-diphenylpropenoic acid derivatives has been described previously [17,18].

2.2. Hydrogenation procedure and product analysis

The hydrogenations were carried out in batch reactors under atmospheric H_2 pressure and room temperature (unless otherwise noted) in a glass hydrogenation apparatus using magnetic agitation (1000 rpm). The H_2 uptake was followed by a gas burette, and the consumption between 15% and 25% of the total uptake was used for calculating the initial rates (R_i, mmol h^{-1} g^{-1}). In a typical run, 0.025 g catalyst and 3 cm^3 DMF containing 2.5 vol.% dist. H_2O were introduced into the reactor, the apparatus was flushed with H_2 and the catalyst was pretreated for 0.5 h by stirring the slurry. After pretreatment, 0.025 mmol modifier ([modifier] = 5 mM), 0.5 mmol acid ([acid] = 0.1 M), 0.5 mmol BA (when used; [BA] = 0.1 M) and another 2 cm^3 solvent were added, the system was flushed with H_2 and the reaction started by stirring the mixture. After the specified time (6–8 h), 5 cm^3 CH_3OH was added, and the catalyst was filtered and washed with another 5 cm^3 CH_3OH. The resulting compounds were identified by GC–MS analysis (Agilent Techn. 6890N GC – 5973 MSD, 60 m HP-1MS capillary column) and by ^1H and ^{13}C NMR spectroscopy (Bruker Avance DRX 400 spectrometer in d_6-DMSO, see Supporting information).

Portions of these solutions were used for transforming the acids in methyl esters by reaction with CH_3OH using conc. H_2SO_4 and/or with CH_2N_2 ethereal solution. Conversions (*X*%) and enantioselectivities expressed as ee (%) were calculated from the gas chromatographic analysis of these samples (YL6100 GC equipped with FID and Cyclosil-B, 30 m × 0.25 mm, J & W Sci. Inc., chiral capillary column) by the formulae: $X\,(\%) = 100 \times ([S] + [R])/[\text{acid}]_i$; $\text{ee}\,(\%) = 100 \times |[S] - [R]|/([S] + [R])$; where $[\text{acid}]_i$ is the initial concentration of the unsaturated acid; [*S*] and [*R*] are the concentrations of the product enantiomers. The experiments were repeated giving results reproducible within ±1%. The absolute configurations of the excess enantiomers obtained in presence of CD were assigned in previous studies to be *S* [7,13,17,18] based on the rotation sign of the saturated products. Optical rotation measurements (Polamat A polarimeter, *l* 0.5 dm, *c* 1, methanol) showed that the use of CD results in the excess formation of the dextrorotatory (*S*) enantiomers, while with CN the levorotatory (*R*) enantiomers resulted in excess. The configuration of the excess enantiomers formed by using the other cinchona derivatives were assigned by chiral GC measurements using as reference the products obtained with CD and CN.

The hydrogenations in the presence of modifier mixtures and the product analysis were carried out similarly as with a single modifier except the corresponding mixture of modifier was added to the pretreated catalyst. The theoretical ee values (ee^{calc}) corresponding to the linear behaviour for a modifier mixture were calculated with the formulae: $\text{ee}^{\text{calc}}\,(\%) = (x_1 \times R_{i1} \times \text{ee}_1 + x_2 \times R_{i2} \times \text{ee}_2)/\,(x_1 \times R_{i1} + x_2 \times R_{i2})$; where x_1 and x_2 are the molar fractions of modifiers 1 and 2; R_{i1} and R_{i2} (mmol h^{-1} g^{-1}) are the initial rates and ee_1 and ee_2 (%) are the enantiomeric excesses obtained with the modifiers 1 and 2, respectively. The theoretical initial rates (R_i^{calc}) were calculated with the formulae: R_i^{calc} (mmol h^{-1} g^{-1}) $= x_1 \times R_{i1} + x_2 \times R_{i2}$.

2.3. ^1H and ^{13}C NMR investigations

The interaction of the substrates with the modifiers and BA in liquid phase was studied by ^1H and ^{13}C NMR spectroscopy. Spectra were recorded on a Bruker Avance DRX 500 NMR instrument operated at 500 MHz (^1H) or 125 MHz (^{13}C) using the solvent signals as reference. The 0.025 mmol cinchona alkaloid was dissolved in 0.5 mL d_7-DMF + 2.5 vol.% D_2O solvent mixture, and their ^1H and ^{13}C NMR spectra were recorded. To these samples, 0.1 mmol acid was added and the spectra were recorded followed by addition of 0.1 mmol BA and recording again the spectra. Changes in the chemical shift (Δδ, ppm) of the H or C atom signals were calculated by subtracting the chemical shift (δ, ppm) of the H or C atom signals in the mixtures from the δ of the corresponding atom signals in the spectra of the pure compounds using the formulae: $\Delta\delta(H^x \text{ or } C^x) = \delta(H^x \text{ or } C^x)_{\text{Cinchona alkaloid}} - \delta(H^x \text{ or } C^x)_{\text{Cinchona alkaloid + acid}}$.