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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: $X\,(\%) = 100 \times ([S] + [R])/[\mathrm{acid}]_i$; ee (%) = $100 \times |[S] - [R]|/([S] + [R])$; where $[\mathrm{acid}]_i$ 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: $ee^{calc}\ (\%) = (x_1 \times R_{i1} \times ee_1 + x_2 \times R_{i2} \times ee_2)/(x_1 \times R_{i1} + x_2 \times R_{i2})$; 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}) = $x_1 \times R_{i1} + x_2 \times R_{i2}$.

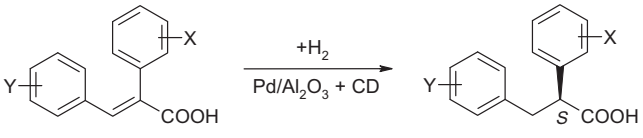
2.3. ^1H and ^{13}C NMR investigations

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 ($\Delta\delta$, 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: $\Delta\delta(H^x \text{ or } C^x) = \delta(H^x \text{ or } C^x)_{\text{Cinchona alkaloid}} - \delta(H^x \text{ or } C^x)_{\text{Cinchona alkaloid + acid}}$.

3. Results

3.1. Effect of the modifier structure

The hydrogenation of **1** and its substituted derivatives over CD-modified Pd catalyst results in the excess formation of the corresponding (*S*)-2,3-diphenylpropionic acids (see Scheme 1). The ees obtained in the hydrogenation of the carboxylic acids selected for this study (Fig. 1) in the absence and presence of BA are presented in Table 1. The reaction conditions were selected based on our previous studies using CD as modifier [17,18], and for the sake of comparison, all the reactions were carried out under identical conditions, although these conditions may not be the optimal for all the examined cinchona alkaloid–acid pairs, similarly with the hydrogenation of activated ketones [34].



Scheme 1. Enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd catalyst modified by CD.

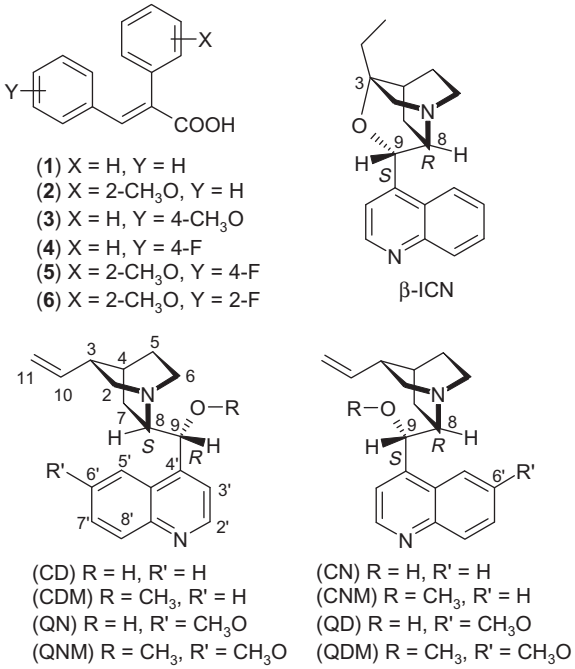


Fig. 1. Structure of the examined substituted 2,3-diphenylpropenoic acids and cinchona alkaloid derivatives.

Using CN instead of CD resulted in the formation of the *R* saturated acids in excess as expected based on the opposite configuration of the C^8 and C^9 chiral centres of CN when compared to CD and having in mind the accepted assumption that these chiral atoms form the stereogenic centre responsible for enantiodifferentiation [5,16,21]. The ees obtained on CN-modified catalyst were always lower when compared with CD-modified Pd, similarly with the recent report on the hydrogenation of **1** [23] or other unsaturated acids [16], though in the hydrogenation of 2-pyrone derivatives [32] or some N containing unsaturated acids [36,37] opposite tendencies were also observed. The presence of BA in the reaction mixture increased the ee and the R_i over CN-modified Pd, too. The cinchona alkaloids bearing OCH_3 substituent in the $C^{6'}$ position were found much less efficient in inducing enantioselection, though in the hydrogenation of **5** even with QN up to 65% ee was obtained. In the hydrogenations using the four parent cinchona alkaloids, the acid structure had similar effect on the ee, *i.e.* the ee decreased in the order: **5** > **3** > **4** > **2** > **1** > **6**.

Based on the suggested CD-acid intermediate [21], one would expect the formation of close-to-racemic products over Pd modified by the cinchona methyl ethers. However, the report on the hydrogenation of **1** using dihydro-CDM already prognosticated a peculiar behaviour in the presence of such modifiers. When CDM was used in the absence of BA, the results obtained were more or less in line with the expected low ees. However, in the presence of BA even with this modifier, moderate ees were obtained (**3**, **4** and **5** up to 42%, 38% and 54% ee, respectively). Completely different behaviour was observed in the hydrogenations over CNM-modified catalyst. Moderate ees were obtained with each substrate, moreover, in the hydrogenation of **6**, the ee exceeded even the value obtained in the presence of CD. Moreover, inversion of the sense of the ee was obtained in the hydrogenation of each acid when compared with the parent CN. The highest ees over CNM-modified catalyst were obtained in the hydrogenation of acids **2** and **3**, (52% and 55%) in contrast with the parent cinchonas. The ee and R_i decreased in the presence of BA (except **1**), though this additive usually has opposite effect [9,18].

The $C^{6'}$—OCH_3 substituted methyl ethers (QNM and QDM) gave lower ees than CDM and CNM, as expected based on the results obtained with the four parent cinchona alkaloids. Although the hydrogenation of **1** and **2** resulted in racemic products over QNM-modified catalyst, the other acids led to small excess of the *R* enantiomers in the absence of BA, opposite to QN. Over catalyst modified by QDM, the inversion of the sense of the ee observed by

Table 1
Effect of alterations in the modifier structure on the ee and R_i in the hydrogenation of (*E*)-2,3-diphenylpropenoic acids **1**–**6**.[a,b]

Modifier	1	2	3	4	5	6
CD	70*S*/73*S* (8/12)[b]	76*S*/85*S* (6/8)	83*S*/89*S* (5/11)	73*S*/85*S* (10/15)	86*S*/93*S* (3/7)	20*S*/29*S* (5/7)
CN	34*R*/37*R* (13/16)	29*R*/45*R* (4/7)	47*R*/56*R* (6/7)	38*R*/53*R* (8/9)	55*R*/74*R* (4/6)	9*R*/11*R* (4/5)
QN	11*S*/6*S* (11/20)	15*S*/5*S* (4/8)	40*S*/17*S* (6/6)	27*S*/16*S* (7/8)	65*S*/36*S* (3/5)	11*S*/4*S* (4/10)
QD	3*S*/2*R* (12/20)	3*S*/1*R* (5/9)	11*R*/14*R* (5/6)	6*R*/8*R* (7/9)	21*R*/30*R* (4/7)	2*R*/4*R* (4/4)
CDM	3*S*/22*S* (10/12)	7*R*/10*S* (8/7)	16*S*/42*S* (7/7)	6*S*/38*S* (8/10)	25*S*/54*S* (6/5)	4*R*/3*S* (4/4)
CNM	47*S*/34*S* (9/10)	52*S*/41*S* (5/3)	55*S*/37*S* (6/5)	42*S*/22*S* (7/6)	44*S*/34*S* (7/7)	29*S*/15*S* (5/5)
QNM	0/1*S* (22/33)	0/0 (6/11)	16*R*/2*S* (7/8)	13*R*/2*S* (8/10)	9*R*/2*S* (5/4)	–
QDM	12*S*/2*S* (17/32)	12*S*/2*S* (5/8)	27*S*/1*S* (6/7)	20*S*/1*R* (7/12)	30*S*/0 (4/4)	–
β-ICN	–	22*S*/16*S* (4/5)	–	–	3*S*/1*R* (5/4)	–

[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol.% H_2O, 0.025 mmol modifier ([modifier] = 5 mM), 0.5 mmol substrate (for the structure of the acids see Fig. 1), 0.1 MPa H_2, 295 K, ee determined at X = 95–100%.

[b] ee (%) and absolute configuration of the product obtained in the absence/presence of 0.5 mmol BA, in brackets the R_i (mmol h^{-1} g^{-1}) in the absence/presence of BA determined from the H_2 uptake curves.

using CNM was also detected, though the ees were lower (up to 30%) and further decreased in the presence of BA. Replacing the methyl ethers with the rigid, cyclic ether derivative β-ICN in the reaction of **2** and **5,** the ee decreased when compared with CNM, however, inversion of the sense of the enantioselectivity was also observed.

The interpretation of these results should take into account both the alterations in the interaction of the cinchona alkaloids with the acids and the metal surface. Methods for investigating simultaneously these interactions under the conditions of the hydrogenations are not yet available. However, useful hints may be obtained by examining the alkaloid–acid complex in solution and treating the results carefully due to the essential effect of the metal surface and adsorbed hydrogen on the structure of the intermediate.

3.2. NMR spectroscopic investigation of the modifier–acid–BA interaction

In the present study, the cinchona–acid interaction in liquid phase was examined by NMR spectroscopy. The interaction of selected modifiers with the acids **1**, **2**, **3** and **5** was investigated in d_7-DMF + 2.5 vol.% D_2O solvent. The signals in ^1H and ^{13}C NMR spectra were assigned using published data [16,38–40]. Variations in the chemical shift ($\Delta\delta$) of the H and C signals were used to indicate the relative strength of the cinchona–acid interactions. Alterations may also result due to the conformational mobility of the alkaloids by rotation around the $C^{4'}$—C^9 and C^9—C^8 axis [38,39,41], which occur when the cinchona is protonated on the quinuclidine N [38,42].

The $\Delta\delta$ obtained in the ^1H NMR spectra of CD, in the presence of **1**, **2**, **3** and **5** and CDM and CNM in the presence of **5** showed the formation of the acid salts as expected (see Fig. 2a and Supporting information: Table SI-1). However, in the spectra of CD, the H^9 signal was shifted the most, which is attributed to the involvement of the C^9—OH of CD in H-bonding, as was previously assumed [21]. Similarly, in the ^{13}C NMR spectra besides the signals of the quinuclidine C atoms, the C^9 and $C^{4'}$ signals were also shifted (see Fig. 2b and Table SI-2), supporting the involvement of the C^9—OH in the interaction. In the spectra of the methyl ethers, the smaller $\Delta\delta$ of the H^9 and C^9 signals (Fig. 2) when compared with CD showed that the acid does not or interacts much weaker with the C^9—OCH_3 group than with the C^9—OH.

The $\Delta\delta$ values in the spectra of CD were dependent on the structure of the acids (Figs. 2 and 3). As the acidity of **1** is higher than of **3** (pK_a(**1**) 7.00; pK_a(**3**) 7.23 [43]), the stronger shift of the H^9 signal in presence of the former is attributed to the looser contact between the N^+—H and the carboxylate group, resulting in a stronger H-bonding to the C^9—OH. The shift of this signal was found to be much smaller in the presence of the acids *ortho*-OCH_3 substituted on the α-phenyl ring (**2** and **5**). Accordingly, this substituent increases the N^+—H···O—C=O interaction strength when compared with **3** and decreases the strength of the C^9—O—H···O=C—O bond. Addition of BA to the samples decreased the $\Delta\delta$ values, however, remained still shifted when compared with the spectra of the modifiers (Figs. 3 and 4 and Fig. SI-2).

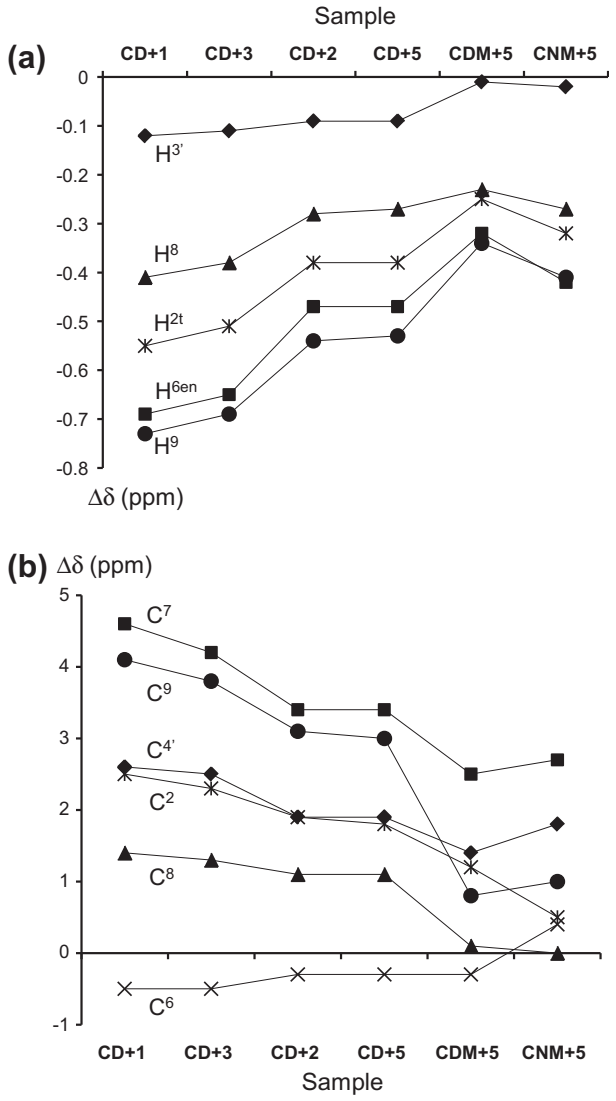


Fig. 2. Chemical shift changes, $\Delta\delta$ (ppm), in the ^1H NMR (**a**) and ^{13}C NMR (**b**) spectra of cinchona alkaloids in the presence of (*E*)-2,3-diphenylpropenoic acids (for atom numbering see Fig. SI-1; the lines between the data points are just to guide the eye).

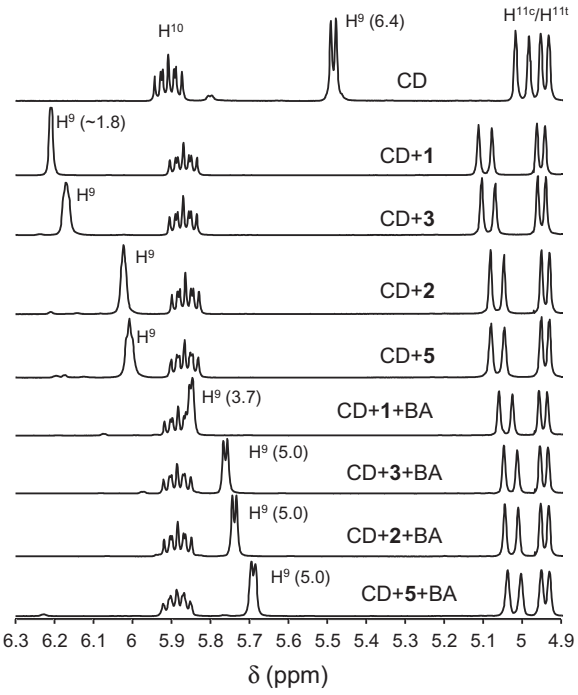


Fig. 3. ^1H NMR traces of CD, CD + acid and CD + acid + BA solutions (see Section 2.3; $^3J(H^8—H^9)$ values (Hz) are given in brackets).

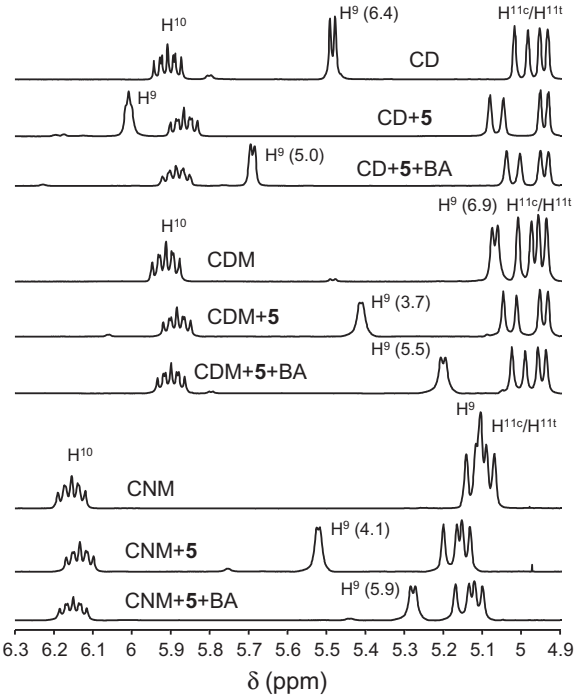


Fig. 4. ^{1}H NMR traces of cinchona derivatives in the absence and presence of **5** and BA (see Section 2.3; $^3J(H^8—H^9)$ values (Hz) are given in brackets).

The values of $^3J(H^8—H^9)$ coupling constant may be used for the approximation of the equilibrium population of the cinchona conformers [38,39]. In our solvent mixture, the 6.4 Hz value (Fig. 3) corresponds to a relatively low population (~40%) of open(3) conformer [38], and closed conformers, which are irrelevant from the point of view of the hydrogenation over the metal surface, are in excess. Addition of **1** to the CD solution decreased significantly the $^3J(H^8—H^9)$ to 1.8 Hz, which is close to that calculated for the open(3) conformer [38]. The shape of the H^9 signal in the presence of the substituted acids used in our study indicated the split of this signal to superimposed doublets with low $^3J(H^8—H^9)$. Based on the $^3J(H^8—H^9)$ values (Fig. 4) in our solvent mixture, CDM was found to be in ~33% (6.9 Hz) as the open(3) conformer, which increased in the presence of **5** to 75% (3.7 Hz), For CNM, a similar value of ~70% (4.1 Hz) was found. The H^9 signals appeared as doublets in contrast to the superimposed double doublets found in the spectra of CD.

By addition of BA to the samples containing CD, the $^3J(H^8—H^9)$ increased indicating that the additive may be attached to the CD–acid complex and alters the population of the different conformers. The increase in the coupling constant was also detected in the samples containing CDM and CNM, thus the interaction of BA with the cinchona–acid complex occurs even if the C^9—OH is protected by the methyl group.

3.3. Hydrogenations using modifier mixtures

The relative adsorption strength of the four parent cinchona alkaloids and their methyl ethers during the hydrogenation of **1**, **2**, **4** and **5** was investigated by using 1/1 modifier mixtures both in the absence and presence of BA (see Tables 2 and 3). The experimentally obtained ee values were compared with those calculated presuming a linear behaviour (for R_i see Supporting information Tables SI-3 and SI-4).

The deviations from the linear behaviour obtained by the use of the mixture of CD and CN were much smaller as expected based on the lower ee obtained with CN when compared with CD. Similarly, a mixture of QN and QD in the hydrogenation of **5** resulted only in small deviations from the linear behaviour. Prominent non-linear behaviour was obtained using mixtures of the $C^{6'}$-substituted QN or QD with CN or CD. The ee obtained with these mixtures were close to those attained by using the latter modifiers alone. Interestingly, in some reactions, the 1/1 mixtures led to slightly higher ee than the sole CD or CN, *i.e.* CD + QD, CN + QN (see Table 3). The use of the methyl ethers (CDM or CNM) in mixture with CD or CN also resulted in marked deviation from the linear behaviour, the latter modifiers dominating the chiral induction. Using QD + methyl ether (CDM or CNM) mixtures, the enantiodifferentiation was dominated by the methyl ethers and the ees deviated from the calculated values. Moreover, in the hydrogenations using QD + CNM, the ees were higher than with CNM alone.

As in some reactions higher ees were obtained than with the sole "dominating" modifier, we investigated the effect of the CD amount to ascertain that the results are not caused by variations in the modifier concentration. The effect of the CD concentration ([CD]) on the ee and R_i in the hydrogenation of **5** is presented in

Table 2
Enantioselectivities obtained in the hydrogenation of (*E*)-2,3-diphenylpropenoic acid derivatives **1**, **2** and **4** in presence of 1/1 modifier mixtures.

Modifier mixture	Additive	(*E*)-2,3-diphenylpropenoic acid derivatives		
		1 ee[a] (ee[calc])	**2** ee (ee[calc])	**4** ee (ee[calc])
CD + CN	–	19*S* (5*S*)	22*S* (32*S*)	19*S* (25*S*)
CD + CN	BA	22*S* (11*S*)	25*S* (26*S*)	36*S* (33*S*)
CD + QD[b]	–	67*S* (29*S*)	68*S* (40*S*)	73*S* (41*S*)
CD + QD	BA	68*S* (27*S*)	67*S* (39*S*)	82*S* (49*S*)
CN + QN	–	31*R* (14*R*)	30*R* (7*R*)	35*R* (7*R*)
CN + QN	BA	37*R* (13*R*)	38*R* (18*R*)	33*R* (21*R*)
CN + CDM	–	23*R* (18*R*)	20*R* (14*R*)	24*R* (15*R*)
CN + CDM	BA	32*R* (11*R*)	30*R* (16*R*)	39*R* (6*R*)
CN + CNM	–	20*R* (1*R*)	15*R* (14*S*)	28*R* (0)
CN + CNM	BA	45*R* (9*R*)	31*R* (18*R*)	47*R* (25*R*)

Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol.% H_2O, 0.025 mmol 1/1 mixture of modifier ([modifier] = 5 mM), 0.5 mmol substrate (see Fig. 1), 0.1 MPa H_2, 295 K, ee determined at X = 90–100%.

[a] ee – enantiomeric excess obtained experimentally and the configuration of the excess enantiomer, ee[calc] – theoretical ee corresponding to the linear behaviour (see Section 2).

[b] The "dominating" modifier in determining the enantioselectivity with bold characters.

Table 3
Enantioselectivities obtained in the hydrogenation of **5** using 1/1 modifier mixtures.

Modifier mixture	Without additive ee[a] (ee[calc])	Using BA additive ee (ee[calc])
CD + CN[b]	31*S* (2*S*)	33*S* (10*S*)
CD + QD	89*S* (27*S*)	94*S* (27*S*)
CD + QN	87*S* (75*S*)	93*S* (68*S*)
CD + CNM	72*S* (56*S*)	89*S* (63*S*)
CN + QN	47*R* (3*R*)	75*R* (26*R*)
CN + QD	53*R* (40*R*)	74*R* (50*R*)
CN + CDM	22*R* (10*R*)	56*R* (15*R*)
CN + CNM	43*R* (6*S*)	71*R* (18*R*)
QD + QN	19*S* (21*S*)	4*S* (4*R*)
QD + **CDM**	10*S* (7*S*)	42*S* (6*S*)
QD + **CNM**	46*S* (22*S*)	35*S* (1*S*)

Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol.% H_2O, 0.025 mmol 1/1 mixture of modifier ([modifier] = 5 mM), 0.5 mmol substrate (see Fig. 1), 0.1 MPa H_2, 295 K, ee determined at X = 90–100%.

[a] ee – enantiomeric excess obtained experimentally and the configuration of the excess enantiomer, ee[calc] – theoretical ee corresponding to the linear behaviour (see Section 2).

[b] The "dominating" modifier in determining the enantioselectivity with bold characters.

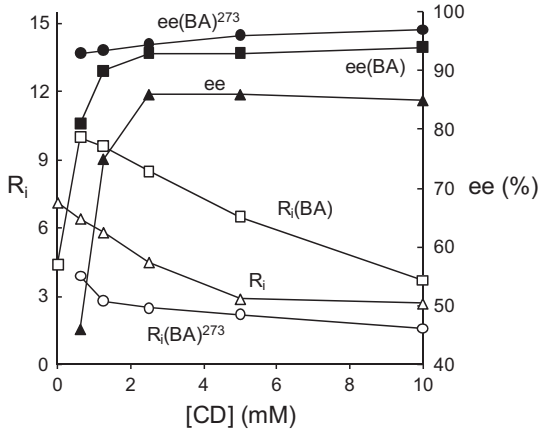


Fig. 5. Effect of [CD] on the ee (closed symbols) and R_i (mmol h^{-1} g^{-1}, open symbols) in the hydrogenation of **5** in the absence (▲, △) and in the presence of BA (■, □ at 295 K; ♦, ◇ at 273 K). For reaction conditions see Table 1 and Section 2.

Fig. 5. A continuous increase in the ee was obtained by increasing the [CD] up to 2.5 mM, followed by constant or very slow increase by further increase in the [CD]. Accordingly, with cinchona mixtures, the increase in the ee over the value obtained with CD should be due to the presence of the second alkaloid. Surprising was the low R_i attained during the racemic hydrogenation in the presence of BA. Although the increase in the [CD] led to decrease in the R_i, in the presence of BA, the racemic hydrogenation proceeded at much lower rate than at low [CD].

The non-linear behaviour in the hydrogenation of **5** was studied in detail using the modifiers pairs: CD + QD, CN + QN and CN + CNM, respectively. The ee and R_i values *vs* the modifier composition were plotted in Figs. 6–8. Using CD + QD, prominent alterations from the linear behaviour was observed (Fig. 6). CD dominated the enantioselection, similarly with the hydrogenation of 4-methoxy-6-methyl-2-pyrone [32]. The R_i values deviated substantially from the values corresponding to the linear behaviour in the absence of BA at low CD/QD ratio, approaching those obtained in the presence of BA (see Fig. 6b). Similar behaviour showed the CN + QN pair, with CN dominating the enantioselection (Fig. 7). The found R_i values were close to the values reached with CN alone, except in the absence of BA at low CN amounts. Pronounced non-linear behaviour was also obtained with the CN + CNM mixtures, CN determining the enantioselection (Fig. 8). The R_i reached the value corresponding to pure CN even at low CN amounts (up to x_{CN} = 0.25) and remained constant to this value on further increase in the x_{CN}.

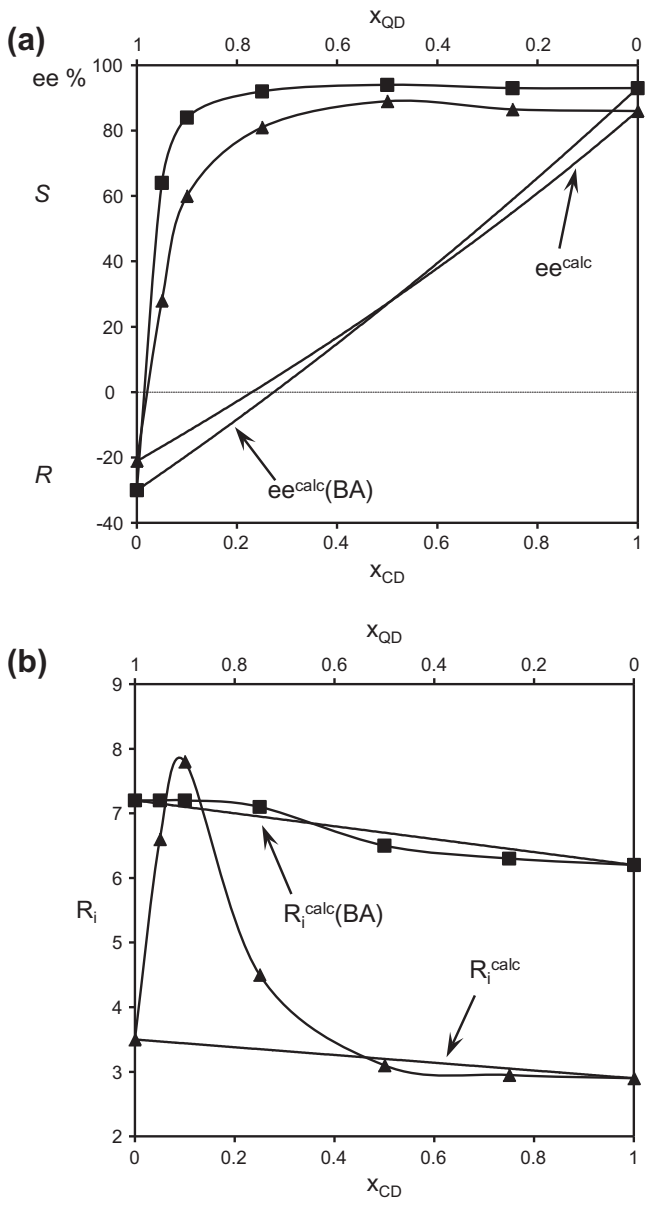


Fig. 6. Effect of CD + QD mixture composition on the ee (%) (**a**) and R_i (mmol h^{-1} g^{-1}) (**b**) obtained in the hydrogenation of **5** in the absence (▲) and in the presence (■) of BA. For reaction conditions see Table 3, [modifier] = 5 mM; ee^{calc} and R_i^{calc} – calculated ee and R_i curves corresponding to the linear behaviour (see Section 2).

4. Discussions

The present study on the hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd/Al_2O_3 modified by the four parent cinchona alkaloids and their methyl ethers showed inversion of the sense of the ee by using the (*R*)C^8—(*S*)C^9 cinchona ethers. Inversions of the sense of the ee were reported in asymmetric catalytic reactions inclusive in hydrogenations over modified metal catalysts [44]. Most of these occurred in the hydrogenation of activated ketones over Pt [28–30,35,44–51]. Inversion of the ee in the hydrogenation of prochiral olefins over Pd was seldom reported [21,36,52,53]. Our previous study demonstrated that the adsorption of the unsaturated acids in presence of CD is directed by the β-substituent [11]. According to the present study in the hydrogenation of diaryl substituted acids, the adsorption may also be inverted by methylation of the modifier, without changing the configuration of the stereogenic centre. As the cinchona alkaloid–diphenylpropenoic acid interaction is not yet fully understood, we attempted to explain this inversion based on investigating the alterations in the cinchona–acid interactions in solution and the competitive adsorption of the cinchona derivatives on the Pd combined with the effect of substitution of the acid on the phenyl rings.

Although the effect of the substituents of both the acid phenyl rings and the cinchona C^9—O on the alkaloid–acid interaction was studied by NMR spectroscopy in solution, we presume that the found effects on the modifier–acid bonding may also occur under the reaction conditions, complemented by the effect of the hydrogen saturated metal surface. The results demonstrated the binding of the acids to both the quinuclidine N and the C^9—OH of the alkaloid, as presumed previously [21]. Decrease in the acidity (by the β-phenyl-*para*-OCH_3) increased the strength of the N^+—H···O—C=O bond and weakened the C^9—OH···O=C—O bond,

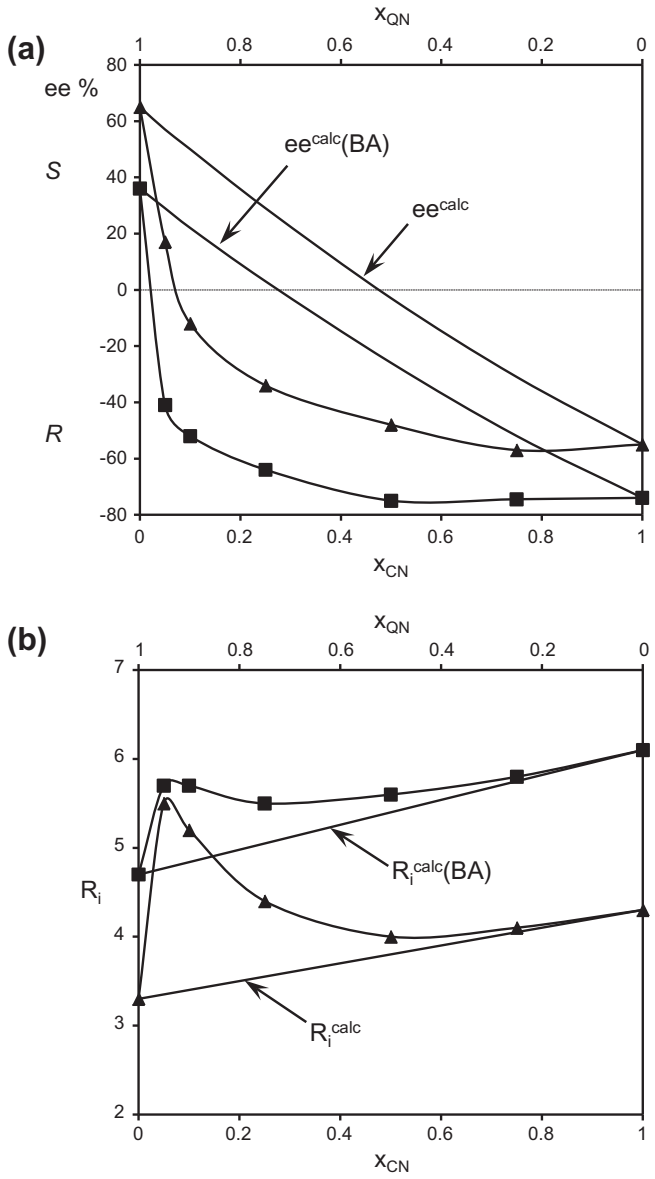


Fig. 7. Effect of CN + QN mixture composition on the ee (%) (**a**) and R_i (mmol h^{-1} g^{-1}) (**b**) obtained in the hydrogenation of **5** in the absence (▲) and in the presence (■) of BA. For reaction conditions see Table 3, [modifier] = 5 mM; ee^{calc} and R_i^{calc} – calculated ee and R_i curves corresponding to the linear behaviour (see Section 2).

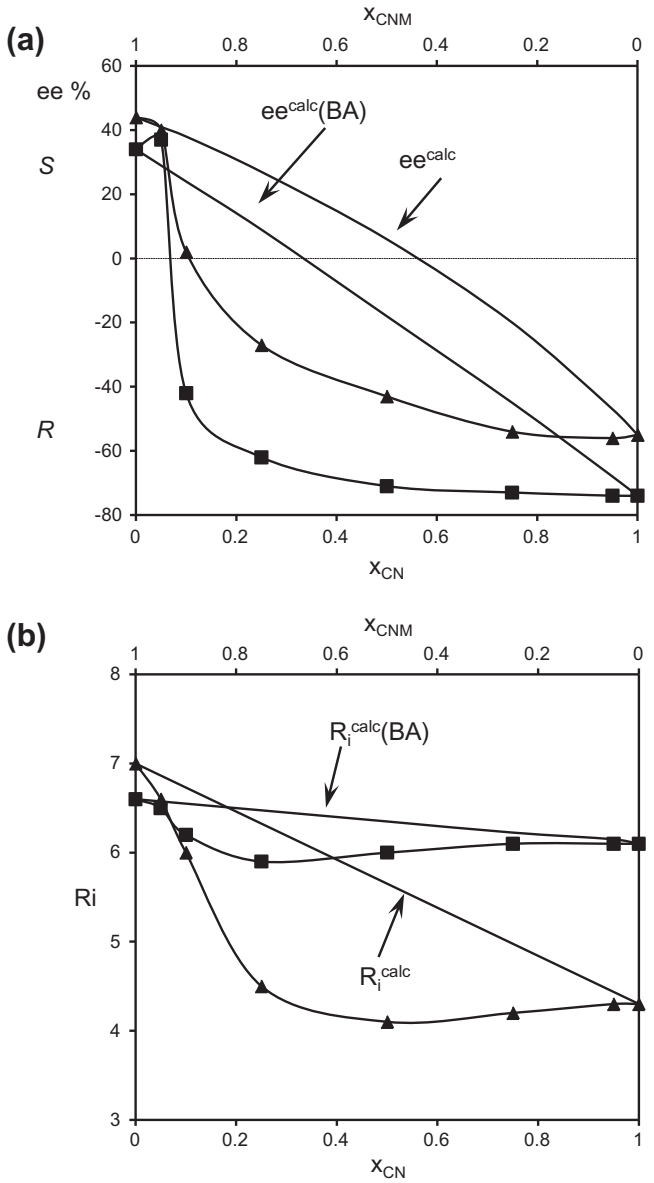


Fig. 8. Effect of CN + CNM mixture composition on the ee (%) (**a**) and R_i (mmol h^{-1} g^{-1}) (**b**) obtained in the hydrogenation of **5** in the absence (▲) and in the presence (■) of BA. For reaction conditions see Table 2, [modifier] = 5 mM; ee^{calc} and R_i^{calc} – calculated ee and R_i curves corresponding to the linear behaviour (see Section 2).

indicated by the $\Delta\delta$ of the H^9 signal. The α-phenyl-*ortho*-OCH_3 substituent (**2**, **5**) increases more the strength of the N^+—H···O—C=O bond and further decreases the C^9—OH···O=C—O interaction strength. Although it is not yet clarified by what means, the ee increasing effect of the α-phenyl-*ortho*-OCH_3 group is due to this change in the strengths of the two H-bonds.

Accordingly, the CD–acid interaction may be sketched similarly as previously supposed [21] (Fig. 9, Fig. S1), complemented with the mentioned equilibration in the strengths of the two H-bonds vital for obtaining high ee. In the presence of the cinchona methyl ethers, we assume the formation of structures **S2** and **S2′** (Fig. 9) which allow higher mobility to the acids. The decrease in the $^3J(H^8—H^9)$ by the acids showed transformation of the modifiers either to open(3) conformer or to other stable conformers, such as the so-called "bridged" conformers resulted in the presence of HCl or HF, having the $C^{4'}$—C^9—C^8—N torsional angle rotated with almost 360° (when compared with the open(3)) [42]. This may explain the acid structure-dependent split of the H^9 signal leading to superimposed doublets. In contrast, the H^9 doublet was not split in the spectra of the methyl ethers in the presence of **5**, suggesting that these conformers are not formed when the C^9—OH is protected.

In the presence of BA, the less shifted NMR signals may be due to the interaction of the CD–acid complex with the additive as suggested in Fig. 10 (**S3**–**S5**). However, the present experiments cannot differentiate between the structures; attempts to identify the real intermediate(s) are in progress. Similarly, using the cinchona methyl ethers in the presence of BA structures containing the additive may form (Fig. 10, Fig. S6), the illustrated flexible contact could explain the decrease in the ee in the presence of BA. The increase in the $^3J(H^8—H^9)$ in the presence of BA showed either a decrease in the population of the open(3) conformer or a transformation of the suggested "bridged" conformers by interaction with BA.

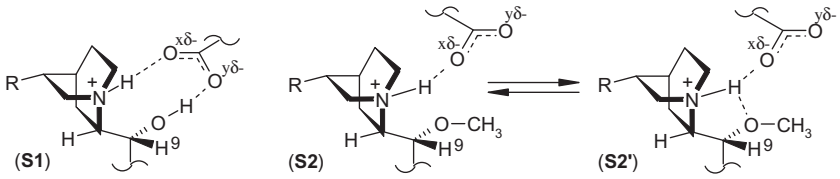


Fig. 9. Proposed structures of the modifier–acid complexes in liquid phase with the parent cinchona alkaloids (**S1**) and with their methyl ethers (**S2**, **S2′**).

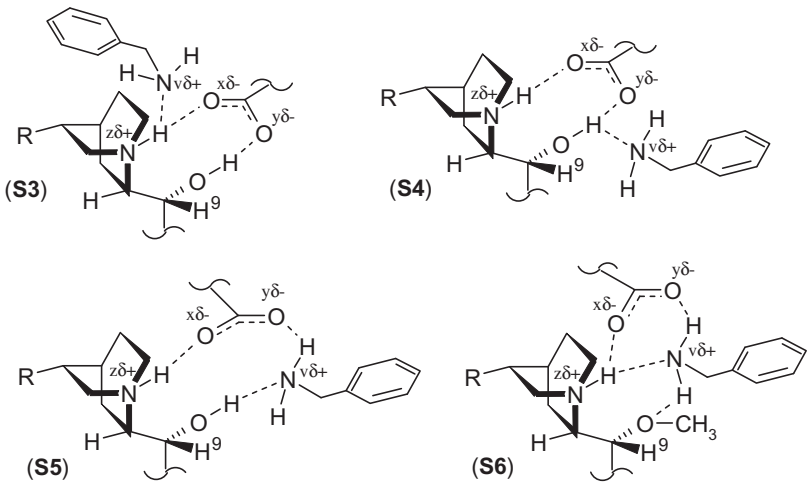


Fig. 10. Proposed structures of the modifier-acid complexes in liquid phase in the presence of BA with the parent cinchona alkaloids (**S3**–**S5**) and with their methyl ethers (**S6**).

The non-linear behaviour obtained using cinchona alkaloid pairs indicated large differences in the adsorption of the modifier-acid salts as effect of the presence of either $C^{6'}$—OCH_3 or the C^9—OCH_3 group. The adsorption strength order derived from the "domination" order was CD ≈ CN > CNM ≈ CDM > QN ≈ QD, resembling the one found in the hydrogenation of 4-methoxy-6-methyl-2-pyrone [33]. Accordingly, the lower ee obtained with CN or QD when compared with CD or QN cannot be attributed to the adsorption strength of the modifiers. Thus, this may be ascribed to the less efficient CN(QD)—acid interaction for inducing enantiodifferentiation, as recently suggested [23]. As the basic strength of CN is slightly higher than that of CD [54], the decrease in the N^+—H···O—C=O interaction strength in the CN–acid complex explains the lower ee. The studies with the cinchona alkaloid pairs over the full composition range showed that the adsorption strength of the cinchona-acid salt is influenced decisively by the $C^{6'}$—OMe substituent, by promoting the tilted adsorption of the quinoline moiety [27,33]. This weak adsorption leads to the low ees by using these modifiers, while in mixture with CD, these derivatives may take the place of the BA additive in increasing the R_i and the ee (see Figs. 5 and 6, *i.e.* at [CD] 1.25 mM ee 75% and 81%, respectively). The deviations from the linearity obtained with mixtures of CD or CN and cinchona methyl ethers are caused by both the weakened interaction strength of the acid with the methyl ethers and the alterations in the adsorption of the methyl ether–acid complexes on the surface. It is known that the parent cinchonas adsorb stronger on the Pd surface than their methyl ethers, as shown by the higher adsorption energy of CD when compared with CDM [50].

Accordingly, the origin of the inversion obtained by using the (*R*)C^8—(*S*)C^9 cinchona ethers may be traced back on the altered acid–cinchona methyl ether interaction, which should be coupled with an additional effect of the C^9—OCH_3 group on the surface leading to switch in the preferred arrangement of the acid. We suggest that this occurs due to reshaping of the chiral metal sites by the methyl substituent by its steric interference within the site, allowing the inversion of the docking preference of the acid, also due to the flexibility of the acid–modifier interaction and the steric hindrances exerted by the bulky substrates, in contrast with the aliphatic α,β-unsaturated carboxylic acids. This suggestion is supported by the opposite effect on the ee of the α- and β-phenyl-*ortho* substituents of the acid in the reshaped chiral site, when compared with the parent cinchonas. Thus, better ee was obtained in the hydrogenation of **6** in the presence of CNM than CD and lower ee resulted in the hydrogenation of **5** than in that of **3** or **1** over CNM-modified catalyst. As the interaction of the acids was proved to be less efficient with the (*R*)C^8—(*S*)C^9 cinchonas, the reshaping effect induced by the methyl substituent had stronger effect on the enantiodifferentiation by using these modifiers than their (*S*)C^8—(*R*)C^9 stereoisomers. Moreover, the differences in the hydrogenation of the anchoring quinoline moiety of the cinchonas belonging to the two series over metal catalyst [55], which under the present hydrogenation conditions we will study in the future, may also lead to the observed differences in the results obtained with CDM and CNM.

Finally, in the presence of BA, the much higher rate observed at low [CD] when compared with the racemic hydrogenation is a novel evidence on the ligand-accelerated catalytic hydrogenation of the acids over Pd, similarly with the enantioselective hydrogenation of activated ketones over cinchona-modified Pt [5,56]. The acceleration effect of the modifier was only very recently observed for the first time over Pd in the absence of BA [23].

5. Conclusions

Our study on the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd/Al_2O_3 modified by the four parent cinchona alkaloids, their methyl ethers and β-isocinchonine revealed the inversion of the sense of the enantioselectivity in presence of the (*R*)C^8—(*S*)C^9 cinchona ethers. In search for explanation, we studied the interaction of the acids with CD, CDM and CNM in liquid phase by NMR spectroscopy. The results demonstrated the

formation of bidentate complexes in which the carboxylate group is H-bonded to the C^9—OH group accompanied by a conformational change of the CD. The cinchona methyl ethers form flexible monodentate complexes without involvement of the C^9–OCH_3 group. It was assumed that the latter group influenced the shape of the surface chiral sites based on the non-linear effect obtained by using binary mixtures of the parent cinchona alkaloids with the methyl ethers. Accordingly, the bulkiness and rigidity of these unsaturated acids may lead to steric interference even with the methyl group within the chiral site, while the flexibility of the acid–modifier interaction, which is less efficient with (*R*)C^8—(*S*)C^9 cinchonas than with the (*S*)C^8—(*R*)C^9 stereoisomers, allows the inversion of the docking preference of the acid on the surface.

We stress out that the present study is the first in which significant inversion of the ee, detail study on the non-linear behaviour and novel evidence on the ligand-accelerated mechanism in the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over cinchona alkaloid-modified Pd are presented.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcat.2010.09.020.

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