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Methylethers of cinchona alkaloids in Pt-catalyzed hydrogenation of ethyl pyruvate and ketopantolactone: Effect of stereochemical factors on the enantioselectivity

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Abstract

We studied the enantioselective hydrogenation of ethyl pyruvate (EP) and ketopantolactone (KPL) under mild experimental conditions (hydrogen pressure 1 bar, room temperature) on Pt-alumina catalyst modified with *O*-methyl derivatives of parent cinchona alkaloids (MeOCD, MeOCN, MeOQN, MeOQD) in two solvents with highly different polarities (AcOH, toluene). The best ee's were achieved (91–96%) using MeOCD and MeOQN modifiers in AcOH. Hydrogenation, especially in the presence of the chiral modifiers MeOCN and MeOQD in toluene proceeded with exceptionally low enantioselectivities (35–46% for EP and 2–4% for KPL) as compared to the already well-known Pt-MeOCD catalyst (ee%: 71–74 for EP, 38–48 for KPL). Results of the hydrogenations of the modifiers and studies on the hydrogenation of substrates using modifier mixtures suggested that the low ee are attributable to stereochemical reasons. Namely, it seems justified to suppose that the low ee observed is dependent on the various tilted adsorbed structures of the substrate and modifier 1:1 intermediate complex responsible for enantiodifferentiation.

Keywords: Cinchona alkaloid derivatives; Enantioselective hydrogenations; Ethyl pyruvate; Ketopantolactone; Pt-alumina; Nonlinear phenomenon

1. Introduction

From heterogeneous catalytical hydrogenations [1] the enantioselective hydrogenation of prochiral ketones and C=C containing compounds with cinchona-alkaloid modified platinum and palladium (Orito reaction [2]) and by tartaric acid modified nickel [3] are the most studied asymmetric heterogeneous catalytic reactions. The state of research of Orito reaction (Scheme 1) has been the subject of numerous reviews [4–15]. In the majority of the studies methyl pyruvate (MP) or ethyl pyruvate (EP) was chosen as model compound for the optimization of reaction conditions (type and concentration of catalysts and modifiers; solvents, temperature, hydrogen pressure, substrate/modifier ratio, modifier/Pt ratio, etc.) in order to attain high enantioselectivities (enantiomeric excess (ee): 96–98%) [16–19]. Regarding the applicability of cinchona alkaloids and their derivatives as chiral modifiers in the hydrogenation of activated ketones, the results of studies published before 2000 are summarized by Blaser et al. [20].

A publication reporting a series of heterogeneous catalytic enantioselective hydrogenation experiments (at a hydrogen pressure of 50 bar) on activated ketones, in which the chiral modifiers and substrates were systematically varied, was published only in 2003 [21]. Based on these results, the following important conclusions were drawn for the derivatives of the parent cinchonas (CD, CN, QN, QD) and their C9-OMe derivatives (Fig. 1): (i) relatively small changes of the substrate and/or modifier structures strongly affected the ee; (ii) no "best" modifier exists for all substrates; (iii) the solvent strongly affected the structure-selectivity trend; (iv) higher ee's were obtained for the CD–QN series ((*R*)-products formed in excess) than for the CN–QD series ((*S*)-products formed in excess); (v) MeO-group on the quinoline moiety generally had a negative effect on ee; (vi) C9-OMe modifiers often resulted higher ee's in acetic acid (AcOH) but not in toluene (T) [21].

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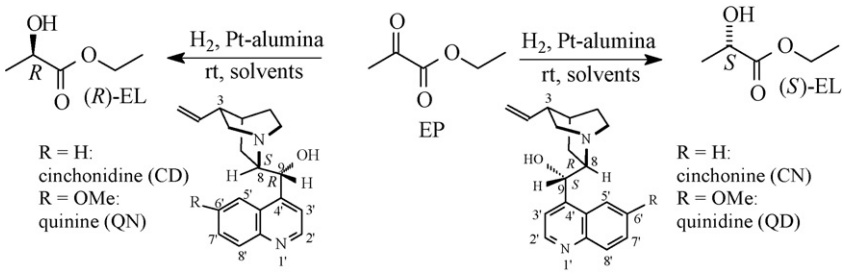


Scheme 1.

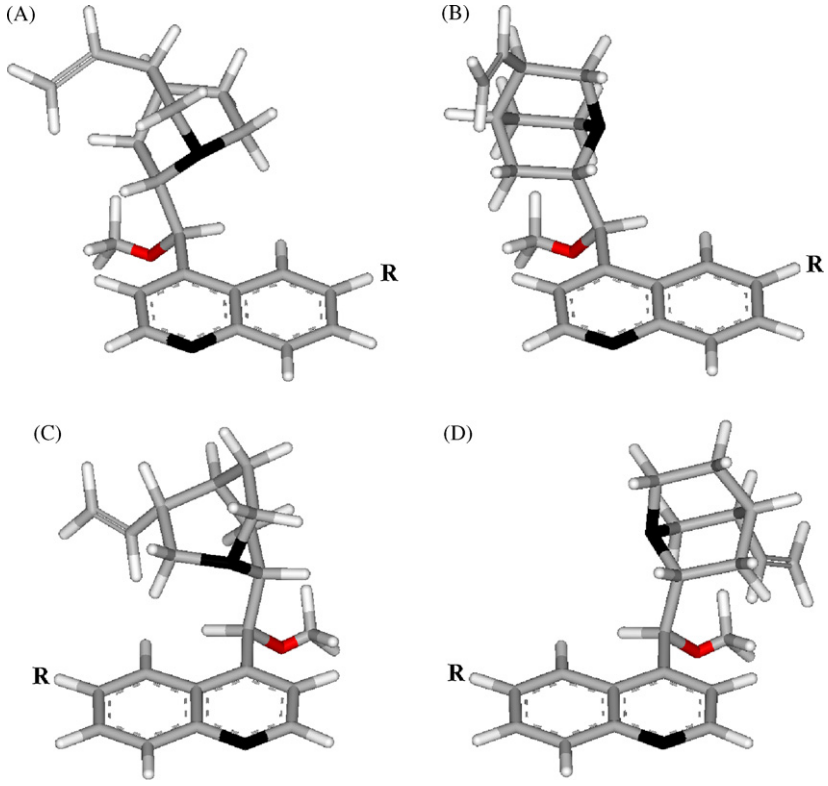
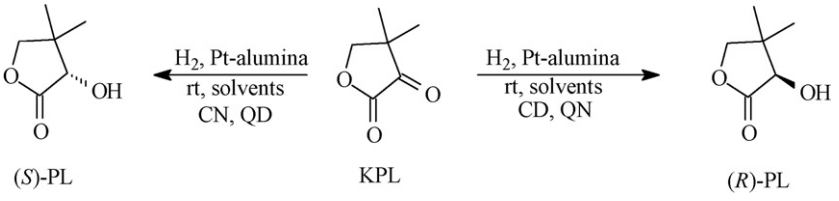


Fig. 1. Structure of closed 2 and open 3 conformations of C9-OMe-ethers of parent cinchona alkaloids: **A** MeOCD closed 2 (R = H), MeOQN closed 2 (R = MeO); **B** MeOCD open 3 (R = H), MeOQN open 3 (R = MeO); **C** MeOCN closed 2 (R = H), MeOQD closed 2 (R = MeO); **D** MeOCN open 3 (R = H), MeOQD open 3 (R = MeO).

Incomplete knowledge available at the time on the mechanism of the Orito reaction and, more specifically, on the structure of the intermediate complex (IC) responsible for enantioselection did not allow interpretation of the above relationships. The objective of the present manuscript is studying the relationships mentioned above (i) under milder experimental conditions (at a hydrogen pressure of 1 bar); (ii) using substrates and chiral modifiers not studied before; (iii) aiming at the qualitative interpretation of the correlation between substrates, modifiers and ee's based on further measurements on modifier mixtures and on the hydrogenation of C9-OMe cinchonas; and (iv) in the light of the latest results published in the pertinent literature. Our results will be described in two manuscripts. The present manuscript discusses our studies on the substrates EP (Scheme 1) and ketopantolactone (KPL) (Scheme 2), whereas the second manuscript, now in preparation, will present the



Scheme 2.

results of the hydrogenation of methyl benzoylformate and pyruvaldehyde dimethyl acetal.

2. Experimental

2.1. Materials

EP, KPL, parent cinchona alkaloids (CD, CN, QN, QD) and solvents were from Aldrich or Fluka, and used as received. EP were distilled in vacuum using Vigreaux-column. C9-OMe cinchonas were synthetized according to Ref. [21]. Based on the data in the literature [10,12,13,15], from several catalysts the one most often used is Engelhard 4759 (E4759). E4759 was pretreated before use in a fixed bed reactor by flushing with 30 mL min^{-1} helium at 300–673 K for 30 min and 30 mL min^{-1} hydrogen at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min and was stored under air before use [22].

2.2. Hydrogenations

Hydrogenations were performed in an atmospheric batch glass reactor with volume of 10 mL at room temperature (rt). The catalytic system including catalyst and solvent was purged three times with hydrogen. The catalyst was stirred and prehydrogenated for 30 min. The calculated amount of modifier (or modifier mixtures) solution was injected and after 0.5–1 min the substrate was added and stirred in the presence of hydrogen for the required reaction time. Standard conditions were: 12.5 mg E4759, 2.5 mL solvent, 1 bar hydrogen pressure, 294–297 K, 900–1000 rpm, 0.5 mmol of substrate. The product identification and the enantiomeric excess $[ee\% = ([R] - [S]) \times 100/([R] + [S])]$ were monitored by gas chromatography (HP 6890 N GC-FID (21.65 psi He), 30 m long Cyclodex-B capillary column. Retention times (min): EP 343 K: 6.6 of (*R*)-EL, 7.3 of (*S*)-EL; KPL 398 K: 10.6 of (*S*)-PL, 11.2 of (*R*)-PL. The reproductibility was ±2%. Hydrogenation of C9-OMe-cinchonas were examined using the above conditions. The products formed were analysed by ESI-MS.

2.3. Measurements using mixtures of modifiers

Hydrogenation with mixtures of modifiers and transient behavior measurement was carried out in T and AcOH as described above for a single modifier with the exception that hydrogenation was continued after the addition of the second modifier to the reaction mixture containing the first modifier. The procedure was as follows: hydrogenation was performed at a modifier concentration of 0.05 mmol/L until 10–20% conversion was achieved; at this point stirring was stopped and after 1 min a sample was taken. The second modifier was added next and hydrogenation and sampling were continued. ee was measured as described above.

2.4. ESI-ion-trap-MS measurements

The ESI-MSD-ion-trap (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion and auto MS-MS mode using following parameters: ESI: capillary (needle) voltage = 3.5 kV, capillary exit voltage = 136 V, drying gas (N_2) = 9 L min^{-1}, drying gas temperature = 623 K, nebulizer gas = 40 psi; ion-trap: scan range = 80–350 *m/z*, maximum accumulation time = 300 ms, fragmentation amplitude = 1.5 V, fragmentation time = 40 ms. Solvent: MeCN/0.1% AcOH; flow rate: 0.5 mL min^{-1}; concentration of sample: 0.1 μmol L^{-1}; injected volume 1.5 μL.

Table 1
Experimental data on enantioselective hydrogenation of EP on Pt-alumina catalyst modified by C9-OMe-cinchona alkaloids (standard conditions, tw = this work, [21] = experimental data under 50 bar of H_2 pressure and 3.3 mmol L^{-1} modifier concentration)

Entry	Modifier (mmol L^{-1})	Solvent	Time (min)	Conversion (%)	Ee (%)	
					tw	[21]
1	CD 0.01	AcOH	13	98	91 *R*	
2	CD 1	AcOH	14	98	92 *R*	88 *R*
3	CD 0.01	T	12	100	64 *R*	
4	CD 1	T	12	100	74 *R*	69 *R*
5	MeOCD 0.01	AcOH	10	100	94 *R*	91 *R*
6	MeOCD 1	T	15	100	72 *R* [23]	71 *R*
7	CN 0.01	AcOH	30	93	82 *S*	
8	CN 1	AcOH	20	100	85 *S*	84 *S*
9	CN 0.01	T	12	100	65 *S*	
10	CN 1	T	12	96	64 *S*	65 *S*
11	MeOCN 0.01	AcOH	30	48	62 *S*	
12	MeOCN 1	AcOH	25	90	80 *S*	85 *S*
13	MeOCN 10	AcOH	40	100	78 *S*	
14	MeOCN 0.01	T	15	98	30 *S*	
15	MeOCN 1	T	11	99	46 *S*	31 *S*
16	MeOCN 10	T	20	100	23 *S*	
17	QN 1	AcOH	8	100	92 *R*	93 *R*
18	QN 1	T	7	99	85 *R*	75 *R*
19	MeOQN 1	AcOH	11	100	93 *R*	94 *R*
20	MeOQN 1	T	15	100	65 *R*	58 *R*
21	QD 1	AcOH	10	98	81 *S*	86 *S*
22	QD 1	T	15	100	63 *S*	53 *S*
23	MeOQD 1	AcOH	40	100	82 *S*	90 *S*
24	MeOQD 1	T	30	97	35 *S*	53 *S*

3. Results and discussion

3.1. Results of enantioselective hydrogenations

The results of enantioselective hydrogenations on Pt-MeO-cinchona alkaloid chiral catalysts in two solvents (AcOH, T) allowing the highest ee [4,5] are summarized in Tables 1 and 2. For comparison, Tables 1 and 2 also contain the data obtained using the parent cinchona alkaloids as chiral modifiers under identical experimental conditions. In addition, Table 1 contains ee% values obtained at a hydrogen pressure of 50 bar by Studer and co-workers [21] and Table 2 lists the ee% values realized by Baiker et al. for the hydrogenation of KPL [24–26].

The experimental data in Table 1 lead to following main conclusions: (i) just like for the parent cinchonas, in the case of MeO-cinchonas the ee is higher in AcOH than in T; (ii) although smaller or larger differences exist, the ee values are, on the whole, very similar to the ee values measured at a hydrogen pressure of 50 bar [21]; (iii) hydrogenation is somewhat faster in T as com-

Table 2
Experimental data on enantioselective hydrogenation of KPL on Pt-alumina catalyst modified by C9-OMe-cinchona alkaloids (standard conditions, tw = this work

Entry	Modifier (mmol L^{-1})	Solvent	Time (min)	Conversion (%)	Ee (%)	
					tw	Refs.
1	CD 0.1	AcOH	8	100	52 *R*	57 *R* [49]
2	CD 0.1	T	6	100	54 *R*	51 *R* [25]
3	MeOCD 0.01	AcOH	14	100	44 *R*	
4	MeOCD 1	AcOH	6	100	50 *R*	
5	MeOCD 0.01	T	4	100	38 *R*	
6	MeOCD 1	T	5	100	42 *R*	48 *R* [25]
7	MeOCD 0.05	Cyclohexane	13	100	60 *R*	
8	CN 0.1	AcOH	8	100	42 *S*	75 *S* [26]
9	CN 0.1	T	6	100	57 *S*	
10	MeOCN 0.01	AcOH	20	99	28 *S*	
11	MeOCN 1	AcOH	6	100	23 *S*	
12	MeOCN 0.01	T	5	100	10 *S*	
13	MeOCN 1	T	5	100	2 *S*	
14	MeOCN 0.05	Cyclohexane	15	100	27 *S*	
15	QN 1	AcOH	7	100	54 *R*	
16	QN 1	T	8	99	55 *R*	
17	MeOQN 1	AcOH	12	100	63 *R*	
18	MeOQN 1	T	7	100	27 *R*	
19	QD 1	AcOH	6	100	57 *S*	
20	QD 0.1	T	5	100	40 *S*	
21	MeOQD 1	AcOH	20	97	39 *S*	
22	MeOQD 1	T	12	97	4 *S*	

pared to AcOH; (iv) again quite similarly to parent cinchonas, in the case of MeO-derivatives ee is higher in the case of MeOCD and MeOQN than it is in the case of the MeOCN–MeOQD pair (in the case of the latter pair (*S*)-EL is formed in excess, whereas the presence of the former leads to the formation of (*R*)-EL in excess); (v) the most remarkable results are the low ee values attained when using the chiral catalysts Pt-MeOCN and Pt-MeOQD, especially in T; (vi) the presence of the OMe group (QN, QD and derivatives) on the quinoline skeleton does not favor a high ee, especially in the QD-series; interestingly Baiker and coworkers found that at atmospheric pressure even QD is more effective than CD [27]. Further studies are needed for verification of this phenomenon.

The results of the enantioselective hydrogenation of KPL (Table 2) call attention to the following: (i) under conditions identical with those of EP hydrogenation, KPL is hydrogenated in lower enantioselectivity and at a higher rate than EP in the presence of either chiral modifier, which is probably due to its rigid structure; (ii) similarly to EP, KPL hydrogenation is faster in T than in AcOH; (iii) the most unexpected result is the low enantioselectivity observed in the presence of the chiral modifiers MeOCN and MeOQD, especially in T; (iv) the ee values on Pt-MeOCD catalyst in cyclohexane (60%) and on Pt-MeOQN catalyst in AcOH (63%) are outstandingly high.

The unexpected new experimental observations regarding Pt-MeOCN and Pt-MeOQD chiral catalysts that, to our knowledge, have never been studied before (namely, that ee in the hydrogenation of both substrates decrease considerably, and differentially in both solvents), raise several new questions. In order to find the answers to these questions, let us review the results of studies on the conformation of MeO-cinchonas, the role of solvents, and the stability and the strength of adsorption of MeO-cinchonas under the conditions of the hydrogenations.

3.2. The conformation of C9-O-methyl cinchonas

In the chiral induction in the Orito reaction, the most researchers assumed the determinant role of the open-3 conformation (see reviews [10–15]). This could later be experimentally confirmed by rigid isocinchona alkaloids [28]. These cinchona alkaloids, due to inhibition of rotation along the C8–C9 bond can exist only in open-3 conformation.

In a combined NMR, molecular mechanics and X-ray approach Sharpless and co-workers have already came to the conclusion that "when the alkaloids are protonated, they all form the open conformation 3, irrespective of both their starting conformation and solvent" [29]. This conclusion has been corroborated by further studies [30,31]. There are NMR studies on the conformations of MeOQD [29] and MeOCN [32] too. Although C9-substituted cinchonas containing bulky groups are not included in the subject of this manuscript, it is necessary to call attention to some very instructive studies on the conformation of 9-phenoxy-CD and its putative role in the Orito reaction [33,34].

Based on the above, it is justified to suppose even without further experimental evidence that both the parent cinchona alkaloids and their methyl ethers are present in the open-3 conformation in the liquid phase in the experiments described in Tables 1 and 2 and, presumably, also in the IC responsible for enantioselection.

Table 3
Relative abundances of the ESI-MS spectra of products formed by hydrogenation of MeO-cinchonas on Pt-alumina catalyst (12.5 mg E4759, [MeO-cinchonas]: 1 mmol L^{-1}, 2.5 mL solvent, 298 K, 1 bar H_2 pressure, 0.5 mmol EP)

Modifier	Solvent	Time (min)	*m/z* values (relative peak intensity %)							
			299	311	313	315	341	343	345	
MeOCD	T	15	0	100	0	2	–	–	–	2
MeOCD	AcOH	15	2	100	41	56	–	–	–	99
MeOCN	T	15	0	100	0	4	–	–	–	4
MeOCN	AcOH	15	0	100	13	53	–	–	–	66
MeOQN	T	18	4	0	0	6	100	8	0	18
MeOQN	AcOH	20	2	0	1	2	100	7	1	14
MeOQD	T	16	2	0	0	8	100	6	0	16
MeOQD	AcOH	16	0	0	0	9	100	16	2	27

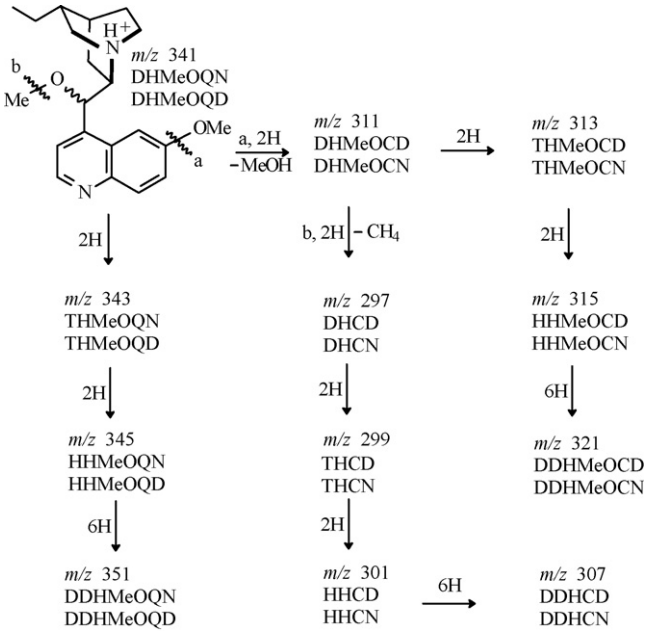
Table 4
Relative abundances of the ESI-MS spectra of products formed by hydrogenation of parent alkaloids on Pt-alumina catalyst (12.5 mg E4759, [alkaloids]: 1 mmol L^{-1}, 2.5 mL solvent, 298 K, 1 bar H_2 pressure, 0.5 mmol EP; time of hydrogenation: 10 min)

Modifier	Solvent	*m/z* values (relative peak intensity %)					
		297	301	307	327	329	
CD	T	100	0	0	0	0	0
CD	AcOH	100	33	13	0	0	46
CN	T	100	0	0	0	0	0
CN	AcOH	100	10	2	0	0	12
QN	T	0	0	0	100	0	0
QN	AcOH	0	3	0	100	31	34
QD	T	0	0	0	100	0	0
QD	AcOH	0	4	0	100	91	95

3.3. Catalytic hydrogenation of C9-OMe-cinchonas on Pt-alumina

In the course of studies on the Orito reaction it was recognized at an early stage that, in addition to the rapid hydrogenation of CD to DHCD at the time of the hydrogenation of the substrate, the quinoline skeleton might also be hydrogenated [35]. As a result of detailed studies, this phenomenon became applicable in research on the adsorption of cinchona alkaloids [22,25,36–46]; on the other hand, these studies led to the following important conclusions: (i) the main direction of CN hydrogenation differs from that of CD, which can be correlated with their modes of adsorption; (ii) the hydrogenation of CD is faster than that of MeOCD; (iii) it was verified that, due to its high sensitivity, the ESI-MS technique is suitable for rapid testing of the progress of hydrogenation.

Hydrogenation of MeO-cinchonas using ESI-MS, MS2 methods has been examined under the conditions of the enantioselective hydrogenation of EP. The results of the experiments, as well as the hydrogenation results of the parent cinchonas added for comparison are shown in Tables 3 and 4 and allow the following direct conclusions to be drawn: (i) under the conditions of hydrogenation the stability of cinchonas and their MeO-derivatives is higher in T than in AcOH; (ii) the stability of parent cinchonas is generally higher than that of the MeO-derivatives (with the exception of QN and QD hydrogenation in AcOH); (iii) the order of the hydrogenation rates of MeO-cinchonas in T is MeOQN ∼ MeOQD > MeOCD ∼ MeOCN, whereas in AcOH the order is reversed: MeOCD > MeOCN > MeOQD > MeOQN; (iv) the main directions of H_2-uptake are hydrogenolysis of C6′–O and the O–Me bonds on C9, and successive hydrogenation of the quinoline skeletons of the resulting compounds, that may theoretically lead to the formation of the tetrahydro-



Scheme 3.

(TH), hexahydro- (HH) and dodecahydro- (DDH) cinchona derivatives sketched in Scheme 3; under relatively mild experimental conditions (rt, 1 bar of H_2 pressure, short reaction time) TH- and HH-derivatives were formed, except for CD; (v) in presonicated conditions in AcOH it is interesting to note that, using DHMeOCD as a modifier, the hydrogenation of the N-containing aromatic ring occurred to a smaller extent than in CD; benzenoid ring saturation, however, is completely missing [41].

Comparison of the experimental data in Tables 3 and 4 with the ee values (Table 1) gives no unequivocal proof for the expected correlation, namely an inverse correlation between the hydrogenation rate of the modifier and ee. However, in either T or AcOH the low ee values observed in the case of MeOCN and MeOQD cannot be interpreted in this way.

There is no consensus in the special literature for the reason of the lower ee values in T than in AcOH. Interpretation of the data on the hydrogenation of MeO-cinchonas described above is even now based on mere assumptions. Our former data on the hydrogenation of CD, CN and their derivatives [22,23,36,46] and examination of the hydrogenation of MeO-cinchonas under identical conditions in T and AcOH, however, can give a hint regarding the type of adsorption these compounds undergo. Adsorption of MeO-cinchonas is presumably tilted towards the surface at different degrees, which is promoted by the C9-OMe, C6′-OMe and the ethyl (CN, QD, MeOCN, MeOQD) groups close to the surface.

The complex interaction of factors such as the adsorption, the conformation and the solubility of the cinchona alkaloid, the solvation of the complex formed, etc. may all contribute to the generation of a phenomenon, namely the rate and direction of the hydrogenation of the modifier. Further studies are needed for the identification of the determinant factor in the hydrogenation of MeO-cinchonas (it may also be necessary to study the hydrogenation of modifiers over longer reaction times and as a function of modifier concentration).

3.4. Results of modifier mixtures

The so-called nonlinear phenomenon (NLP) recognized in homogeneous catalytic reactions [47] also proved to be operative in heterogeneous catalytic enantioselective hydrogenations and was applicable to studying the relative adsorption strengths of chiral modifiers [25,27,43,44,48–52]. We also found it practicable to use this approach for studying the behavior of C9-OMe-cinchonas in the enantioselective hydrogenation of EP and KPL in T and in AcOH. In case of parent cinchona alkaloids it was established earlier that under identical experimental conditions the most probable order of adsorption strength in both solvents is CD > CN ~ QN > QD [44]. The adsorption strength of CN and QN depends somewhat on solvent, which may be due to the different solvation of the two alkaloids.

In order to determine the relative adsorption strengths of chiral modifiers, several measurements were carried out in modifier mixtures of various compositions (Figs. 2 and 5), but in the majority of cases the transient method was used (Figs. 3, 4, 6 and 7).

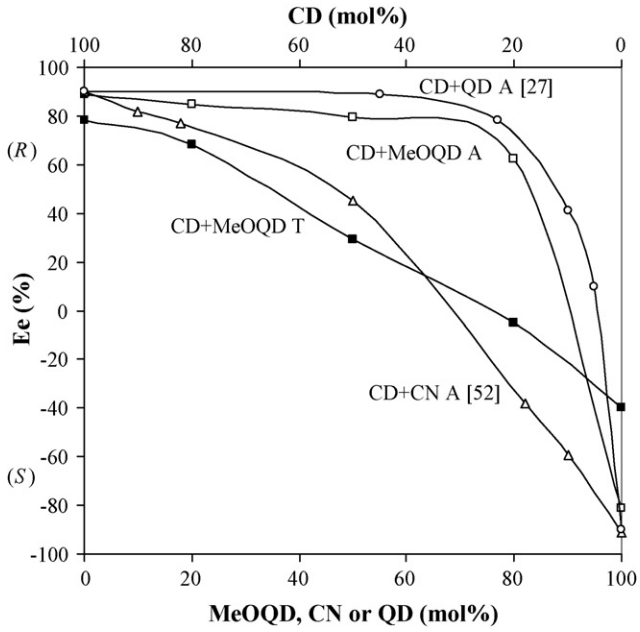


Fig. 2. Hydrogenation of EP over Pt-alumina modified by cinchona alkaloids mixtures (standard conditions: [modifiers] = 0.1 mmol L^{-1}, T = toluene, A = AcOH).

3.4.1. NLP in EP hydrogenation (Figs. 2–4)

In the case of EP hydrogenation, based on experiments using modifier mixtures (Fig. 2) the most probable order of adsorption strengths in AcOH is CD > CN > QD ~ MeOQD, because CD desorbs QD and MeOQD at similar rates, whereas desorption of CN is much slower. It is interesting, however, that MeOCD is displaced by CD on the Pt surface considerably slower. Based on the analysis/evaluation of the results in

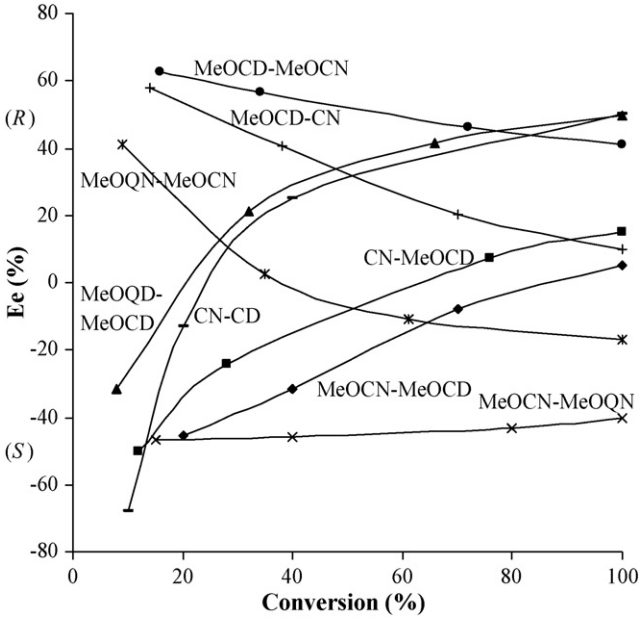


Fig. 3. Transient behavior in the enantioselective hydrogenation of EP in toluene: effect of modifier mixtures (standard conditions, [modifiers] = 0.05 mmol L^{-1}, first abbreviation—modifier used first, second abbreviation—modifier added afterwards).

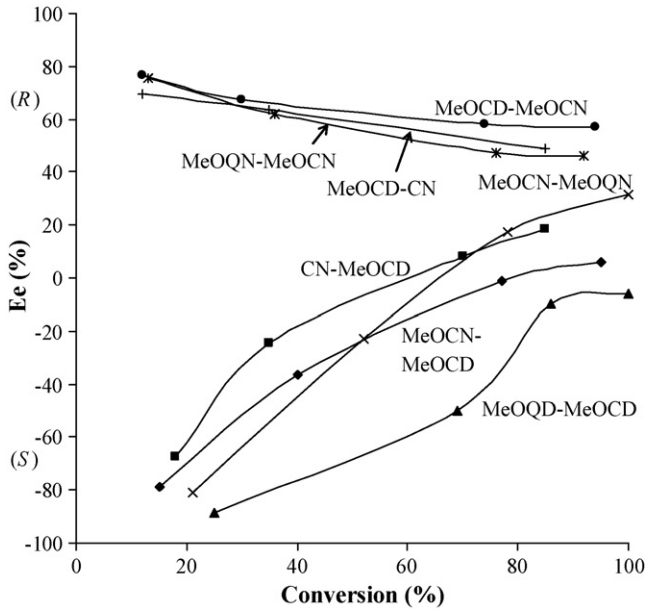


Fig. 4. Transient behavior in the enantioselective hydrogenation of EP in AcOH: effect of modifier mixtures (standard conditions, [modifiers] = 0.05 mmol L^{-1}).

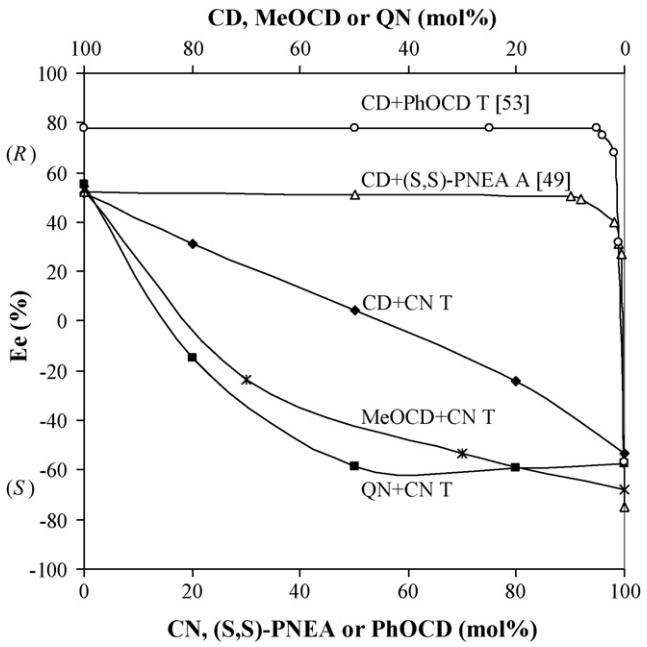


Fig. 5. Hydrogenation of KPL over Pt-alumina modified by chiral modifier mixtures (standard conditions: 273 K, [modifiers] = 0.1 mmol L^{-1}, toluene, PNEA = pantoyl naphtylethylamine).

Fig. 4 as well as the data in Ref. [43] and Fig. 3, the order of the adsorption strengths of the modifiers is the following: CD > MeOCD > QN > CN > MeOQN > MeOCN > QD ~ MeOQD. Partial results: MeOCD > MeOQD, MeOQN > MeOCN, MeOCD > MeOCN, MeOCD > CN.

The results of transient measurements in T (Fig. 3) are not sufficient for the determination of the order of adsorption strengths for the eight modifiers. The order for parent cinchonas is CD > QN ~ CN > QD and that for MeO-cinchonas is MeOCD > MeOCN > MeOQN > MeOQD. Partial results: CN > MeOCN, MeOCN > MeOQN, MeOCD ~ CN, MeOCD > MeOQD. It is especially interesting that MeOCN > MeOQN, which is reversed in AcOH. In T the displacement of MeOQN by CD is slower than in AcOH (Fig. 2). Solubility of modifiers may be the decisive factor here.

Some comments on these results: MeOCD has a stronger effect on the desorption of CN in AcOH than in T, in other words CN only has a slight effect on the desorption of MeOCD in T; in the case of MeOCN–MeOCD this difference is smaller; MeOCD has a stronger effect on the desorption of MeOCN than the other way round in both solvents.

3.4.2. NLP in KPL hydrogenation (Figs. 5–7)

Baiker et al. studied the nonlinear behavior of modifier mixtures CD + PhOCD (in T) and CD + (*S*,*S*)-PNEA [25,53] (in AcOH) (Fig. 5), furthermore competition between CD and its C9-ethers using the transient method (in THF) [25] in the enantioselective hydrogenation of KPL. Based on these experiments the following order of adsorption strengths was proposed: CD > MeOCD > EtOCD > PhOCD ~ TMSOCD.

The experimental data in Figs. 5–7, which – to our knowledge – have not been published before, may add the following conclusions to those enumerated above for EP. In the case of KPL, the order of adsorption strengths in T proposed on the basis of Fig. 5 is CD ~ CN > QN ~ MeOCD. Measurements using the transient method (Figs. 6 and 7) suggest that there is no significant difference between the adsorption strengths of CD and CN and CN > MeOCD in either solvent. Namely, (i) the second modifier added at 1× concentration is not capable of desorbing the first modifier applied in 10× concentration; (ii) the second modifier added at 10× concentration desorbs the first modifier added at 1× concentration to a similar extent, this effect in T is greater; (iii) the above conclusion is also supported by tran-

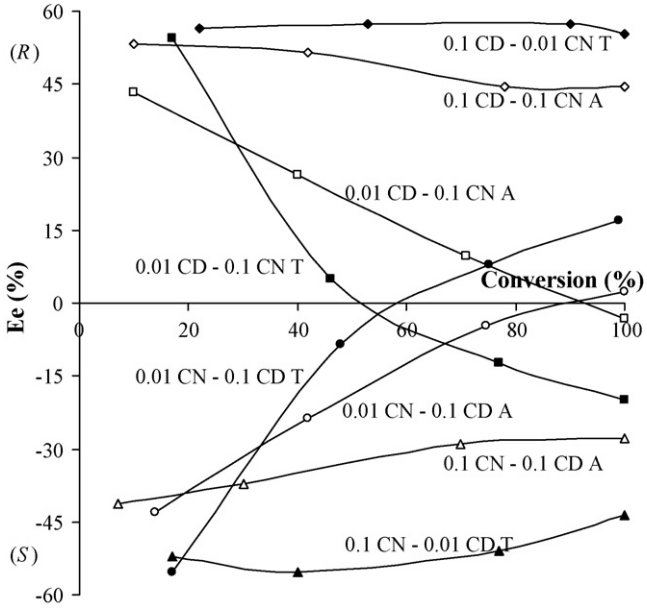


Fig. 6. Transient behavior in the enantioselective hydrogenation of KPL in toluene: effect of concentration of modifier mixtures (standard conditions, 273 K).

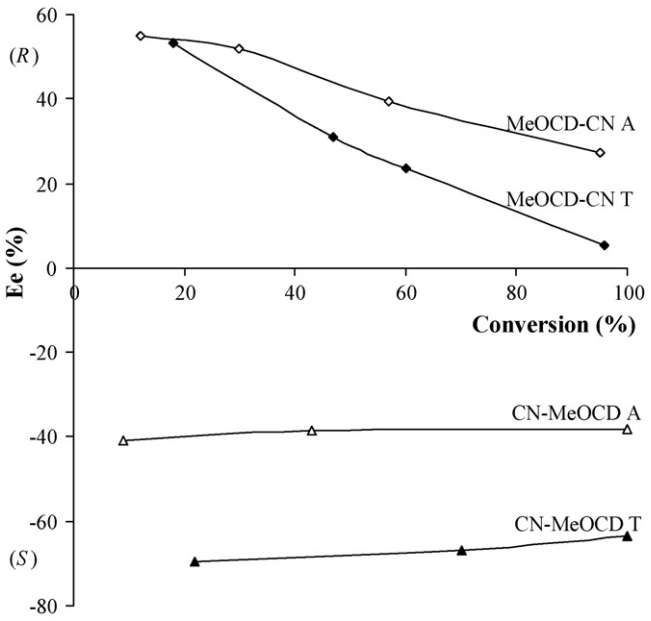


Fig. 7. Transient behavior in the enantioselective hydrogenation of KPL: effect of modifier mixtures and solvents (standard conditions, 273 K, [modifiers] = 0.05 mmol L^{-1}).

sient measurements using equal concentrations of CD–CN or CN–CD in AcOH (it must be noted that in the case of EP, in the CN–CD system CD affects the desorption of CN but the reverse is not true [44]); (iv) CN affects the desorption of MeOCD in both solvents, but in the reverse case there is no effect; (v) in contrast to the results obtained by Baiker et al. [25,43,48,49,54] and our laboratory, studies using *in situ* RAIRS [55] established a different order for the adsorption strengths of cinchona alkaloids. In our opinion this discrepancy is due to differences in the experimental conditions, which is well demonstrated by the differences between experimental results obtained in AcOH/T with EP/KPL as substrate, shown above.

4. Interpretation of the results and conclusion

In spite of the complex studies on the Orito reaction [9–15], a large number of unanswered questions have risen, one of the most important of which is the identity of the factors influencing the structure of the IC responsible for enantioselection. In order to contribute to the resolution of this problem, this manuscript presents a study of the effects on ee of the C9-OMe derivatives of parent cinchona alkaloids serving as chiral modifiers under identical experimental conditions. The enantioselective hydrogenation of EP and KPL was studied in AcOH and in T (and, occasionally, also in cyclohexane). The most unexpected result was the observation of very low ee values relative to other modifiers in the case of using the chiral modifiers MeOCN and MeOQD, especially in T (35–46% for EP and 2–4% for KPL). In order to interpret this result, the effects of the conformation, the hydrogenation and the adsorption strength of chiral modifiers on ee were studied.

As regards the conformation of MeO-cinchonas, data published earlier [29,32,56] suggest that under the given experimental conditions the most stable conformation in liquid phase is the open-3 conformation. The low ee observed in the case of MeOCN and MeOQD is of course not explained by their identical conformations (open-3). To our best knowledge, no experimental data are available on the conformation of adsorbed C9-OMe-cinchonas, which leaves the numerous observations on the adsorption of CD [10,11,57–59] and the recently published information on CN [59] to be considered. Conclusions drawn from these studies suggest that, depending on surface coverage, CD may be: strongly adsorbed parallel to the Pt-surface of the quinoline moiety via multicenter π-bonding and two weaker adsorbed CD species where the quinoline moiety is tilted toward the surface [57,58]. It must be noted that DFT calculations have also yielded other conformers on Pt [56,60–62]. CN showed similar adsorption modes, except that the parallel adsorbed CN molecules were significantly more mobile than CD molecules [59]. In our opinion this is the consequence of the tilted adsorption of CN [44].

There are two important factors to be considered with respect to the formation of the adsorbed IC. First, the adsorption of the quinoline moiety on the Pt surface can be modified not only by the C6′-OMe group, but by the C9-OMe and the CH_2 of the C3-ethyl group (formed after the rapid hydrogenation of vinyl group) (Fig. 1, **D**). Second, according the anchor points of the cinchona modifiers responsible for the substrate binding, the activated ketones are attached to the cinchonas mainly through the N-lone pair of the quinuclidine part, however, according to recent evidence the C5′-H region of the quinoline moiety may also play a role [32,63,64].

Based on the experimental data of MeO-cinchonas and on the data in the literature on the adsorbed conformation of cinchona alkaloids, it seems well-grounded to suppose that, in the course of adsorption, MeO-cinchonas adopt a position tilted to various extents on the platinum surface. Namely, the planar adsorption of the quinoline skeleton is hindered due to both MeO-groups (C6′-OMe, C9-OMe). C6′-OMe inhibits the formation of a hydrogen bond between the reactant and C5′-H. In the case of the CN and the QD series, rotation around the C8–C9 axis is also hindered due to the proximity to the surface of the ethyl group. Since all these inhibitory factors are present in the four MeO-cinchonas studied in different numbers and ways, adsorption may give rise to different tilted adsorption structures. We assume that the extent of tiltedness (i.e. the extent of divergence from flat adsorption) increases in the following order: MeOCD < MeOQN < MeOCN < MeOQD. Different extents of divergence from flat adsorption results in different spatial positions and orientations of the N-lone pair of quinuclidine. Experimental observations acquired with methyl benzoylformate and pyruvaldehyde dimethyl acetal going to be published in a second paper of this topic will enable us to give a more detailed analysis.

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