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Quaternary ammonium derivatives of cinchonidine as new chiral modifiers for platinum

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Abstract

The mechanistic models developed for the enantioselective hydrogenation of ethyl pyruvate are based on the fundamental observation that transformation of the basic quinuclidine N atom of cinchonidine to quaternary cinchonidinium salts results in the complete loss of enantioselectivity. Astonishingly, the *N*-methyl, *N*-benzyl, and *N*,*O*-dimethyl derivatives of cinchonidine are effective chiral modifiers of Pt in the hydrogenation of a cyclic α-ketoester, ketopantolactone. All three alkaloid derivatives gave (*S*)-pantolactone in excess, the configuration that is the opposite of that provided by cinchonidine, *O*-methyl cinchonidine, and cinchonidinium hydrochloride. Under mild conditions at 3 bar, Pt/Al_2O_3 modified by *N*,*O*-dimethyl-cinchonidinium chloride afforded 44.5% ee, which is comparable to the performance of cinchonidine (51.5% ee). A mechanistic model is proposed that is based on an electrostatic interaction between the cinchonidinium cation and the free electrons of the keto group of the reactant. The observations highlight the importance of the structural rigidity of the reactant in the enantioselection and the frequently reported substrate specificity of chirally modified Pt. Under certain conditions (dichloromethane, *N*,*O*-dimethyl-cinchonidinium chloride as modifier), doubling of the ee with conversion was observed. The reason for this phenomenon could not be clarified, but it may be due to some restructuring of the nanoparticle surfaces on the atomic scale.

Keywords: *N*-methyl-cinchonidinium chloride; *N*,*O*-dimethyl-cinchonidinium chloride; Asymmetric hydrogenation; Heterogeneous catalysis; Pt/Al_2O_3; Ketopantolactone

1. Introduction

Various strategies have been applied in the development of heterogeneous chiral catalysts, among which modification of an achiral metal surface by a strongly adsorbing chiral molecule (commonly referred to as a modifier) is the simplest and most promising approach in practical catalysis [1–8]. Supported Pt modified by cinchonidine (CD) was discovered by Orito's group in the late 1970s [9], but it is still the most effective catalyst system for the enantioselective hydrogenation of various activated ketones [10–19]. The application range has been extended to several derivatives and analogues of cinchona alkaloids as chiral modifiers [20–23] and to other chiral amines and amino alcohols [24–28].

It has been shown that blocking of the N lone pair of the quinuclidine moiety by alkylation eliminates the enantiodifferentiating ability of CD in the hydrogenation of α-ketoesters, whereas methylation of the OH function barely affects the enantioselectivity [29]. Interestingly, 2% ee was achieved with the *N*-benzyl derivative of CD in pyruvate hydrogenation [30], but a racemic mixture was obtained in another laboratory [29]. It is now commonly accepted that the basic quinuclidine N atom of CD is crucial in the interaction with the activated ketone reactant; the real nature of this interaction is heavily debated, however (for a recent review see Ref. [31]). In the case of ketopantolactone hydrogenation, in situ spectroscopic evidence supports the model assuming the quinuclidine–ketone interaction via an N–H–O type H-bond [32].

The behavior of *N*-substituted and *N*,*O*-disubstituted CD was investigated in mechanistic studies in the hydro-

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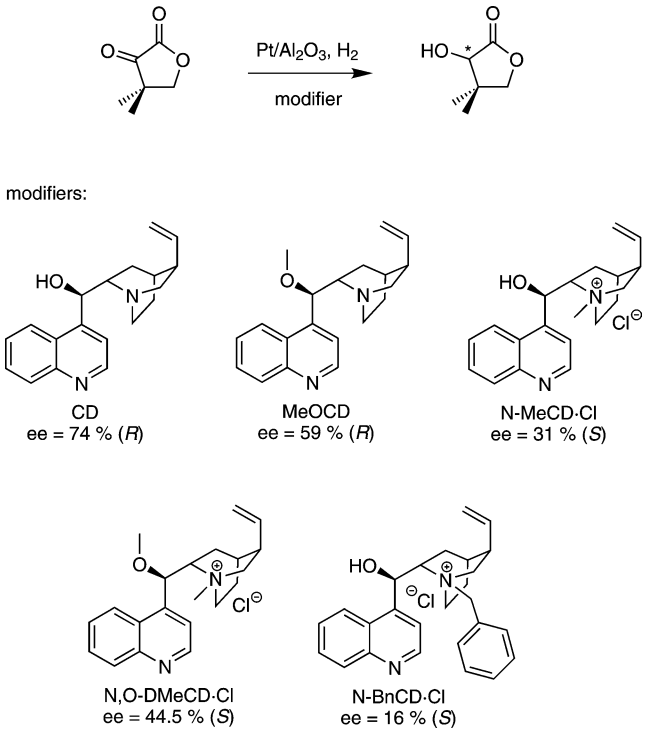

Scheme 1. Hydrogenation of ketopantolactone to (*R*)- or (*S*)-pantolactone over Pt/Al_2O_3 modified by cinchonidine derivatives and the highest ees achieved in this study.

genation of unsaturated carboxylic acids over Pd [33,34], but the *N*,*O*-dimethyl derivative of CD has never been tested as modifier for supported Pt or Pd.

Here we report an unexpected finding, the remarkable enantiodifferentiating ability of *N*-methyl-, *N*-benzyl-, and *N*,*O*-dimethyl-cinchonidinium chlorides as chiral modifiers in the hydrogenation of ketopantolactone over Pt/Al_2O_3 (Scheme 1). In contrast to CD and MeOCD, which afford (*R*)-pantolactone with good ee [35,36], all *N*-alkylated CD derivatives give (*S*)-pantolactone in excess.

2. Experimental

2.1. Materials and synthesis of CD derivatives

Ketopantolactone (Hoffmann-La Roche), cinchonidine (Fluka), cinchonidinium hydrochloride (Sigma), *N*-benzyl-cinchonidinium chloride (Fluka), and acetic acid (HOAc, Fluka) were used as received. Toluene (J.T. Baker) and dichloromethane (CH_2Cl_2; J.T. Baker) were dried and stored over activated molecular sieves.

MeOCD [37] and N-MeCD·Cl [34] were prepared according to known recipes. N,O-DMeCD·Cl was prepared from MeOCD (2.0 g, 6.5 mmol) that was suspended in 11 ml dry MeOH. MeI (1.5 equivalent; 9.8 mmol, 0.61 ml) was purified by extraction with aqueous Na_2SO_3 solution until it turned colorless, washed with aqueous Na_2CO_3 solution, dried with $MgSO_4$, freshly distilled before use, and then added slowly under N_2. The reaction mixture was protected from light and stirred overnight. The solvent was evaporated under reduced pressure and low temperature. The residue was dissolved in 5 ml MeOH, AgCl (2.5 equivalent, 16.3 mmol, 2.34 g) was added, and the reaction mixture was stirred overnight. After dilution with MeOH the white precipitate was filtered off. The filtrate was concentrated under reduced pressure and evaporated to dryness at low temperature after the addition of a sufficient amount of toluene. The crude product was slowly crystallized from EtOH:ethyl acetate = 1:4–5 without heating (Yield: 1.57 g pale yellow powder (67.2%); m.p.: 225–226 °C (decomposition); $[\alpha]_D^{20} = -150.3$ ($c = 1$, $CHCl_3$); UV (MeOH, nm) 204, 227, 287 (br); HRMS (HiResESI) found $[M–Cl]^+ = 323.211$ (calculated 323.212); ^{1}H-NMR (δ, $CDCl_3$, 500 MHz) 8.97 (d, 1H, aromat., $J = 4.4$ Hz), 8.49 (d, 1H, aromat., $J = 8.4$ Hz), 8.16 (dd, 1H, aromat., $J = 8.4$, $J = 0.9$ Hz), 7.90–7.86 (m, 1H, aromat.), 7.81–7.78 (m, 1H, aromat.), 7.55 (br.d, 1H, aromat., $J = 3.7$ Hz), 5.88 (d, 1H, H(9), $J_{8,9} = 2.2$ Hz), 5.59 (ddd, 1H, H(10), $J_{10,11a} = 17.2$, $J_{10,11b} = 10.5$, $J_{3,10} = 6.5$ Hz), 5.27 (dd, 1H, H(11a), $J_{10,11a} = 17.2$, $J_{gem} = 1.2$ Hz), 4.98 (dd, 1H, H(11b), $J_{10,11b} = 10.5$, $J_{gem} = 1.2$ Hz), 4.65 (dd, 1H, H(2a), $J = 12.7$, $J = 10.7$ Hz), 4.29–4.23 (m, 1H, H(6a)), 4.16–4.12 (m, 2H, H(2b), H(6b), 4.05 (s, 3H, N^+CH_3), 3.93 (br.t, 1H, H(8)), 3.50 (s, 3H, OCH_3), 2.90 (br.m, 1H, H(3)), 2.14–2.01 (m, 4H, H(4), H(5a + b), H(7a)), 1.38–1.32 (br.m, 1H, H(7b)); ^{13}C-NMR (δ, $CDCl_3$, 500 MHz) 149.69 (aromat.), 148.64 (aromat.), 139.99 (aromat.), 136.84 (C(10)), 130.41 (aromat.), 130.11 (aromat.), 128.78 (aromat.), 125.31 (aromat.), 123.37 (aromat.), 118.95 (aromat.), 117.81 (C(11)), 76.19 (br, C(9)), 66.58 (C(8)), 64.69 (C(2)), 57.23 (OCH_3), 55.45 (C(6)), 49.25 (N^+CH_3), 37.99 (C(3)), 26.68 (C(4)), 25.48 (C(5)), 21.59 (C(7))).

2.2. Catalytic hydrogenation

A 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was used for the hydrogenation experiments after prereduction at 673 K for 1 h in flowing hydrogen. After it was cooled to room temperature in flowing hydrogen and flushed with nitrogen, the catalyst was transferred to the reaction vessel containing the proper amount of solvent. The Pt dispersion was 0.33 after heat treatment, as calculated from the average particle size determined by STEM. The reactions were carried out in a stainless-steel autoclave equipped with a glass liner and a PTFE cover, with mechanical mixing.

Under standard reaction conditions 20 mg catalyst was added to 5 ml solvent (10 ml in the experiments at 1 bar) containing 6.8 μmol modifier and 236 mg ketopantolactone; the slurry was briefly shaken, and the reaction started at room temperature. In the experiments at 1 bar ketopantolactone was dissolved in 3 ml solvent and injected after the glass vessel had been purged with H_2. When premixing or ultrasonic treatment was applied, the catalyst was put into the solvent containing only the modifier, and this slurry was

Table 1
Solvent effect in the hydrogenation of ketopantolactone to (*S*)-pantolactone on Pt/Al_2O_3 modified by quaternary ammonium derivatives of CD. The highest ees achieved after a limited optimization (pressure between 3 and 55 bar, amount of catalyst) are presented. Standard conditions, no premixing or ultrasonication, conversions in the range 96–100%

Solvent	E_T^N	N-MeCD·Cl			N,O-DMeCD·Cl			N-BnCD·Cl		
		p (bar)	Cat. (mg)	ee (%)	*p* (bar)	Cat. (mg)	ee (%)	*p* (bar)	Cat. (mg)	ee (%)
$PhCH_3$	0.099	10	10	31	3	20	28	30	20	15.5
CH_2Cl_2	0.309	3	20	30	1	20	41[a]	–	–	–
*i*PrOH	0.546	–	–	–	10	10	18	–	–	–
HOAc	0.648	1	20	13	1	20	22	30	20	16

[a] Slow reaction (21 h) due to high vapor pressure of the solvent.

stirred for 2.25 h under H_2, or exposed to ultrasound for 15 min under H_2 or air, before ketopantolactone was added and hydrogenation was started. A conventional ultrasonic bath (35 kHz, 150 W) was used to study the effect of the ultrasonic treatment on the catalyst performance. The conversion was usually complete within 2–2.25 h. The products were analyzed by gas chromatography with a Chirasil-DEX CB capillary column (ChromPack).

2.3. Other methods

NMR spectra were recorded on a Bruker Avance 500 spectrometer with TMS as an internal reference. Signal assignment was assisted by correlation spectroscopy (COSY).

Scanning transmission electron microscopic investigations were performed on a Tecnai F30 microscope (FEI, Eindhoven; field emission cathode, operated at 300 kV). The catalyst was dispersed in ethanol and deposited on a perforated carbon foil supported on a copper grid. For particle size calculations, several hundred particles were measured to obtain a reliable statistical value.

3. Results and discussion

In many respects, the characteristics of Pt/Al_2O_3 modified by CD and its quaternary ammonium derivatives are remarkably different. In the following, the performance of three N-functionalized derivatives of CD (Scheme 1) is compared with that of CD, CD·HCl, and MeOCD in the hydrogenation of ketopantolactone.

Table 2
Effect of pressure on the enantioselectivity in dichloromethane; standard conditions, full conversion

Modifier	ee at					Major product
	1 bar	1.5 bar	3 bar	10 bar	30 bar	
CD	47.5	49	51.5	65	74	(*R*)
N-MeCD·Cl	25[a]	28.5	30	29.5	27	(*S*)
N,O-DMeCD·Cl	41[a]	38	30.5	28	23	(*S*)

[a] Reaction was run overnight (21 h) to achieve full conversion.

3.1. Effect of solvent and pressure

Preliminary experiments revealed that the two most important reaction parameters are the chemical nature of the solvent and the (hydrogen) pressure. Their influence on the enantioselectivity is illustrated by some examples in Tables 1–3. The N-functionalized modifiers yielded (*S*)-pantolactone in excess, whereas CD, CD·HCl, and MeOCD afforded (*R*)-pantolactone in all solvents tested [23,38]. The enantioselectivity decreased with increasing solvent polarity characterized by the empirical solvent parameter E_T^N. CD was most effective at high pressure, in agreement with earlier observations in toluene (70–100 bar [38]), whereas close to

Table 3
Initial rate (TOF) of ketopantolactone hydrogenation on Pt/Al_2O_3 modified by CD and some of its derivatives in different solvents. Standard conditions, 1 bar, no premixing or ultrasonication, ee determined at full conversion after 2 h

Modifier	Toluene		HOAc		CH_2Cl_2		Major product
	TOF[a] (h^{-1})	ee (%)	TOF[a] (h^{-1})	ee (%)	TOF [a] (h^{-1})	ee (%)	
no	2170	–	1080	–	990	–[b]	–
CD	3210	41.5	3120	43.5	1160	47.5	(*R*)
CD·HCl	2550	40.5	610	12	930	52 [c]	(*R*)
MeOCD	4180	30	2790	39	1470	38.5	(*R*)
N-MeCD·Cl	1620	19	880	12.5	250	25[b]	(*S*)
N,O-DMeCD·Cl	1290	21	770	22	270	41[b]	(*S*)

[a] The molar amount of ketopantolactone converted per hour divided by the molar amount of surface Pt atoms; calculation is based on the conversion achieved in 15 min.
[b] Reaction was run overnight (up to 23 h).
[c] full conversion after 4 h.

ambient conditions were advantageous for the *N*-methylated derivatives. In the latter case the detrimental effect of high pressure was particularly strong in the most polar (and protic) solvent acetic acid (not shown). The probable explanation is that saturation of the quinoline ring of the modifiers, the transformation of which weakens the adsorption on Pt, is faster in acidic medium and in the absence of the basic quinuclidine N atom.

3.2. Modifier stability

To confirm that under mild conditions and in the absence of acid the modifier has sufficient stability, the best modifier, N,O-DMeCD·Cl, was hydrogenated in dichloromethane, and the products were analyzed by NMR. The vinyl group attached to the quinuclidine fragment was completely hydrogenated, but this transformation barely affects the performance of cinchona alkaloids as modifiers [10,39,40]. In addition, the quinoline ring was partially hydrogenated (ca. 30%). These results are similar to those reported for CD [40,41]. Significant cleavage of the C–O or C–N bonds was not observed. In conclusion, under low-pressure conditions the major part of N,O-DMeCD·Cl was still present as the 10,11-dihydro derivative in the reaction mixture after 2 h of hydrogenation. Note also that cleavage of the C–N bond and regeneration of the basic quinuclidine N should result in a decrease, or even the inversion, of enantioselectivity, but this phenomenon was never observed.

It is expected that deprotection of *N*-benzylcinchonidinium chloride (C–N bond hydrogenolysis) is more favored than that of the methyl derivatives, and this modifier was not used for further detailed studies.

3.3. Rate acceleration or deceleration?

The hydrogenation rates characterized by the initial TOF are shown in Table 3. Three solvents were selected for this study: toluene and acetic acid, which are the solvents most used for CD, and dichloromethane, which is the best solvent for the N-functionalized CD derivatives. The initial TOF was calculated from the conversion achieved in 15 min, and the final ee at full conversion was determined after the catalyst was filtered off and washed carefully to avoid any distortion by the stereospecific crystallization of pantolactone [35]. Variation of the reaction rate (conversion) in dichloromethane with the modifier structure is shown in Fig. 1a, and the solvent effect on the conversion with N,O-DMeCD·Cl as modifier is presented in Fig. 2a. Although the solvent had a strong influence on the reaction rate, the characteristics of the modifiers can be simply summarized as follows:

(i) The modifiers that possess free N-lone pair electrons (CD and MeOCD) induce significant rate enhancement compared with the nonmodified reaction. Rate acceleration by the addition of CD is typical for α-ketoester hydrogenation

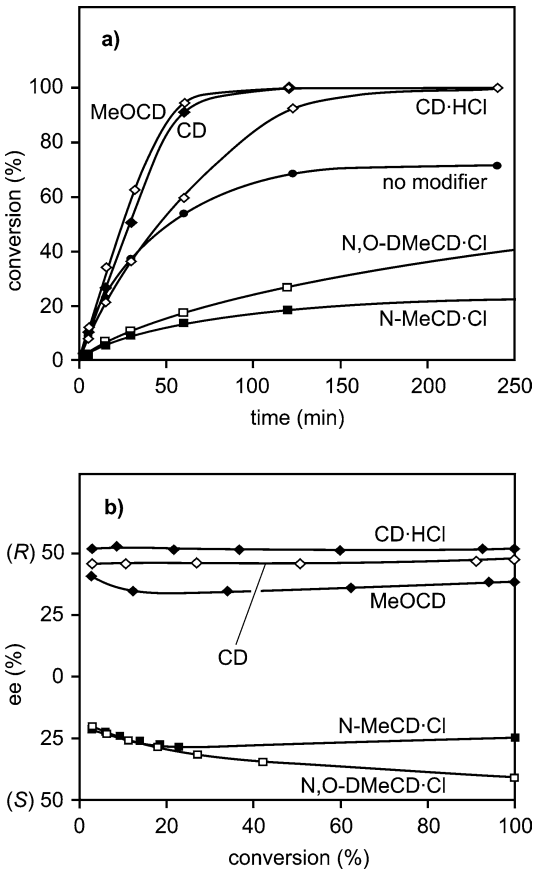

Fig. 1. Variation of conversion (top, (a)) and enantioselectivity (bottom, (b)) during hydrogenation of ketopantolactone over Pt/Al_2O_3 modified by CD and its derivatives. Standard conditions, dichloromethane, 1 bar.

[42,43], although the early observations have been questioned recently [44,45].

(ii) All ionic modifiers that have Cl^- as a counter-ion decrease the initial rate; the only exception is CD·HCl in toluene. The considerable decrease in the reaction rate relative to the unmodified reaction (by up to a factor of 4) is probably due to the intrinsically slower carbonyl reduction in the presence of these modifiers, although some catalyst poisoning by the Cl^- ion may also contribute. Note that according to the classical observations in metal-catalyzed hydrogenation reactions [46], CD (considered a quinoline derivative) is expected to strongly retard the reaction because of site blocking.

3.4. Conversion-dependent enantioselectivity

Variation of the enantioselectivity with conversion has been investigated for all reactions presented in Table 3; some typical examples are depicted in Figs. 1 and 2. In dichloromethane the enantioselectivity changed with conversion when Pt was modified by any of the methylated alkaloids but remained constant in the presence of CD or CD·HCl (Fig. 1b). We have to emphasize again that de-*N*-methylation of the new modifiers can be excluded as an explanation, because this side reaction would yield the hy-

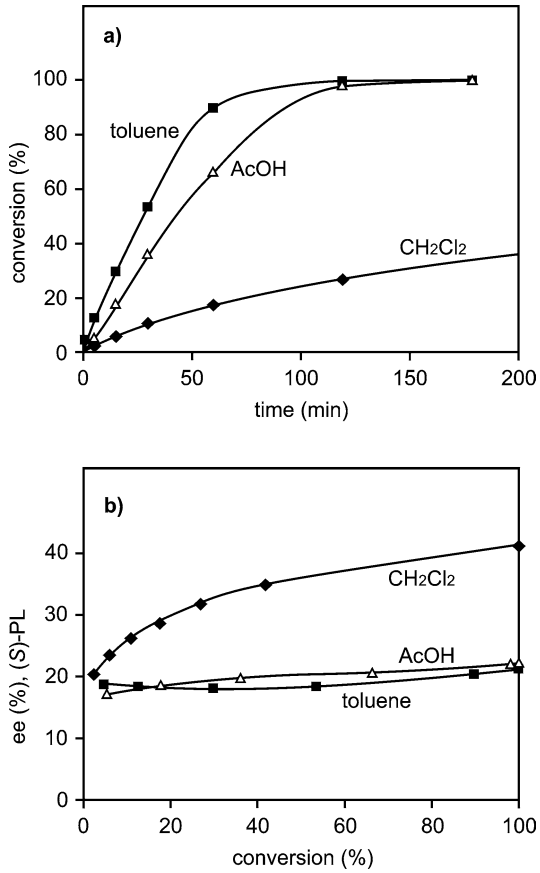

Fig. 2. Variation of conversion (top, (a)) and enantioselectivity (bottom, (b)) during hydrogenation of ketopantolactone in three different solvents using N,O-DMeCD·Cl as modifier. Standard conditions, 1 bar.

drochloride of CD and MeOCD, which afford (*R*)-pantolactone in excess.

The biggest change in ee with conversion was observed with N,O-DMeCD·Cl, but this behavior strongly depended on the solvent (Fig. 2). The reaction was the fastest in toluene, and in this solvent the enantioselectivity was almost constant. The rate was somewhat lower in acetic acid, and the ee increased moderately with conversion. In other words, both fast reactions afforded low ee. In dichloromethane at a total pressure of 1 bar (corresponding to a hydrogen partial pressure of 0.43 bar [47]), the reaction was very slow and had to be run overnight to achieve full conversion. During this long time the ee doubled. This selectivity enhancement is even more striking when we consider that the ee is an integral value; the final value of the differential ee at high conversion is expected to be bigger. It seems that the selectivity enhancement with conversion in dichloromethane is connected with the long reaction time in this solvent.

A less striking transient behavior was observed with N-MeCD·Cl (not shown). The ee increased slightly in all solvents, and the effect was the smallest in acetic acid. Moreover, this reaction was extremely slow in dichloromethane.

Considering the possible role of the Cl^- counter-ion, it is important that in the presence of CD·HCl the ee was almost constant during reaction in all solvents; with CD the ee increased slightly in acetic acid but remained practically constant up to full conversion in toluene and dichloromethane. Both reactions were very fast, however, compared with that carried out in the presence of N,O-DMeCD·Cl in dichloromethane.

Table 4
Change of enantioselectivity (ee %) caused by ultrasonication of the catalyst slurry before ketopantolactone hydrogenation. The results of the "silent" reactions are shown in Table 2. Reactions were carried out under standard conditions in dichloromethane; ee was determined at full conversion

Modifier	Sonication under H_2; reaction at 1.5 bar	Sonication under air; reaction at 3 bar	Major product
CD	50%	51.5%	(*R*)
N-MeCD·Cl	31%	30%	(*S*)
N,O-DMeCD·Cl	33%	25.5%	(*S*)

Table 5
Effect of stirring of the catalyst slurry under hydrogen for 2.25 h, in the presence or absence of N,O-DMeCD·Cl, before hydrogenation of ketopantolactone. Ketopantolactone hydrogenation was carried out under standard conditions in dichloromethane; ee was determined at full conversion, (*S*)-pantolactone was formed in excess

Entry	Pre-stirring	Modifier present during pre-stirring	Pressure (bar)		ee (%)
			during pre-stirring	during reaction	
1	–	–	–	1.5	38
2	+	+	1.5	1.5	39
3	–	–	–	3	30.5
4	+	+	3	3	40
5	+	+	10	3	44.5
6	+	–	10	3	29
7	+	+	30	3	42

3.5. The role of catalyst pretreatment

Since the early work of Orito's group it has been known for cinchona-modified Pt that pretreatment of the catalyst before use may have a large influence on the enantioselection [9]. Here we applied a combination of different methods. In all cases the catalyst powder was prereduced in flowing hydrogen at 400 °C. Additional ultrasonic treatment of the prereduced catalyst was carried out under hydrogen or air in dichloromethane, in the presence of modifier. A comparison of the results in Table 4 with those of the "silent" reactions in Table 2 reveals that ultrasonication had no significant positive effect on the ee. In the case of N,O-DMeCD·Cl ultrasonication led to a reduction of ee, independently of the presence of hydrogen or air. Therefore, ultrasonication was not applied further. Note that this method has been applied successfully in the hydrogenation of ethyl pyruvate [48,49], 1-phenyl-1,2-propanedione [50], and isophorone [51,52], and the positive effect of sonication was attributed to some catalyst restructuring.

In the present study, stirring of the catalyst slurry under hydrogen before addition of the reactant proved to be a more useful pretreatment method [53,54]. The slurry containing the prehydrogenated catalyst and the proper amount of N,O-DMeCD·Cl in dichloromethane was stirred for 2.25 h before ketopantolactone was added and the hydrogenation started. Because N,O-DMeCD·Cl was most effective at low hydrogen pressure, hydrogenation of ketopantolactone was always conducted at low pressure, whereas catalyst prestirring was examined under higher hydrogen pressure as well (Table 5). The best ee of 44.5% (14% improvement compared with the reference reaction; see entries 3 and 5) was achieved after the catalyst slurry was prestirred at 10 bar before ketopantolactone hydrogenation at 3 bar. It is also clear from a comparison of entries 3 and 6 that prestirring the slurry is ineffective in the absence of modifier. When MeOCD was used as modifier under the same conditions (prestirring at 10 bar, hydrogenation at 3 bar), (*R*)-pantolactone was formed with 59% ee.

3.6. Catalyst restructuring

Variation of the enantioselectivity during catalyst pretreatment in the liquid phase and during the hydrogenation reaction has been the topic of increasing interest in chiral heterogeneous catalysis. The changes in enantioselectivity have been attributed to several factors; evidence from physicochemical methods has been found for side reactions of the activated ketone reactant on the Pt surface [55] and restructuring of the metal particles [56,57].

When N,O-DMeCD·Cl was used in dichloromethane, doubling of the enantioselectivity during reaction (Figs. 1b and 2b) and the remarkable selectivity enhancement by a factor of almost 1.5 due to prestirring of the catalyst slurry before ketopantolactone hydrogenation (Table 5) are strong indications of some restructuring of the catalyst or transformation of the modifier. NMR analysis indicated that under low-pressure conditions N,O-DMeCD·Cl was sufficiently stable, and no chemical transformation could be detected that would lead to a better performance. The other possibility, restructuring of the Pt particles, was examined next by transmission electron microscopy. The Pt particle size distribution in the 5 wt% Pt/Al_2O_3 catalyst before and after ketopantolactone hydrogenation and the role of prestirring of the catalyst slurry are shown in Fig. 3. Unexpectedly, the changes were minor and the average particle size of Pt varied in the narrow range of 3.57 ± 0.10 nm. Although there is some change visible in the particle size distribution, the variation in the average is statistically irrelevant.

Recently we found that the enantioselectivity of CD-modified Pt/Al_2O_3 more than tripled in the hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone after pretreatment of the catalyst slurry under nitrogen [57]. The selectivity enhancement was coupled with changes in the Pt particle size due to erosion and accelerated by the presence of quinoline or CD as "ligands" of Pt and by the absence of hydrogen.

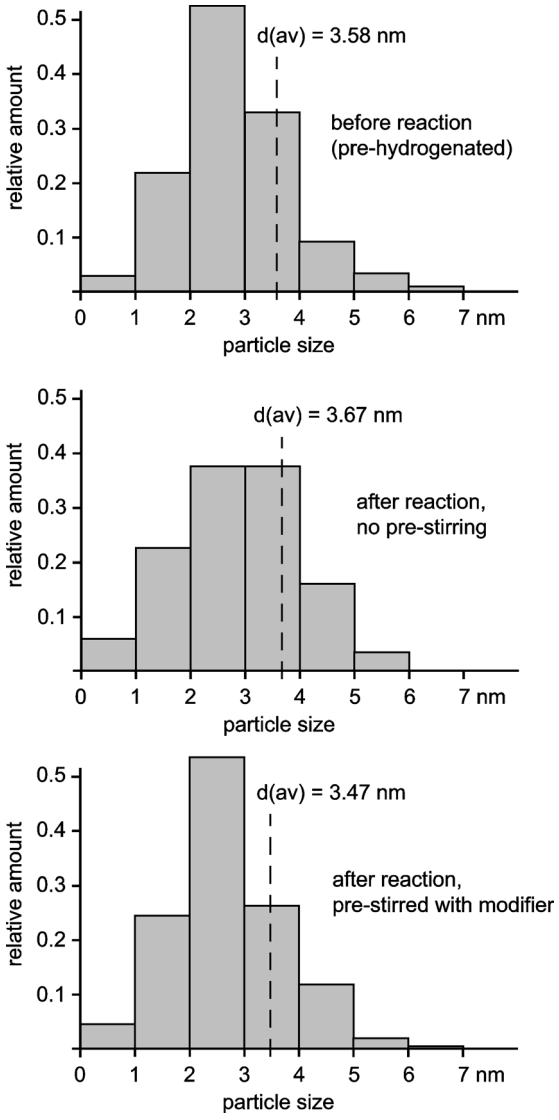

Fig. 3. Metal particle size distribution of Pt/Al_2O_3 of the pre-reduced catalyst before reaction, after the reaction (entry 3 in Table 5) and after the pre-stirred reaction (entry 5 in Table 5).

A comparison of those results with the present observation indicates that the hydrogen atmosphere applied here during prestirring of the catalyst slurry (Table 5) stabilizes the Pt particles against restructuring. Nevertheless, the missing change in the particle size does not exclude any restructuring of the surface of the nanoparticles on an atomic scale that may explain the improved enantioselectivity.

We can speculate that the dechlorination activity of Pt may not be negligible and that some HCl is formed from the solvent dichloromethane. This strong acid may interact with Pt to form surface metal chloride and thus deactivate the catalyst. However, we did not see any sign of catalyst deactivation, and application of CD·HCl instead of CD did not show any significant deviation from the behavior of the Pt–CD system. We carried out some experiments in the presence of 20 equivalents of the strong acid TFA, and no deactivation or any significant change in ee with conversion could

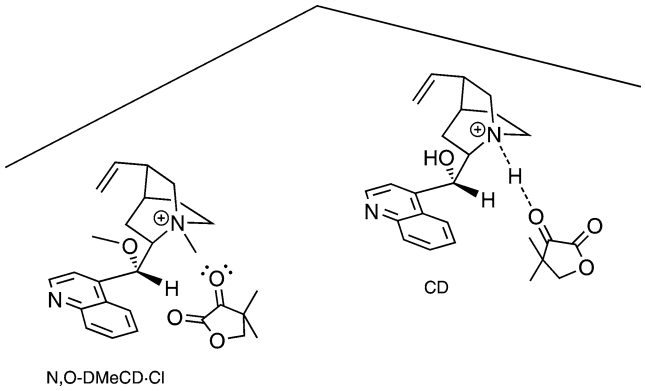

Fig. 4. Proposed models for the interaction of ketopantolactone with CD via hydrogen bonding (right) and the N,O-dimethylated CD derivatives via electrostatic attraction (left) on the metal surface. The anions are not shown.

be detected. A possible explanation is that the acid—if it is formed—is strongly bound to the basic sites of the alumina support.

3.7. Nature of the modifier–reactant interaction

Investigation of the influence of reaction conditions and catalyst pretreatment has revealed that in the hydrogenation of ketopantolactone, N,O-DMeCD·Cl affords 44.5% ee to (*S*)-pantolactone under mild conditions, in dichloromethane at 3 bar (Table 5). The enantioselectivity is comparable with that achieved with CD under similar conditions (51.5% to (*R*)-pantolactone), although CD gives at best 91.6% ee at 70 bar in toluene [35]. An intriguing question is, what is the nature of interaction between the quaternary ammonium compound N,O-DMeCD·Cl and ketopantolactone leading to enantioselection? As mentioned previously, this modifier gave racemic lactate in pyruvate hydrogenation [29], and we could not detect any ee in a control experiment.

The mechanistic model developed for CD-modified Pt in non-acidic medium is based on N–H–O-type hydrogen bonding [38]: in the enantiodifferentiating complex the basic quinuclidine N atom interacts with the half-hydrogenated state of ketopantolactone. This type of interaction has recently been verified by ATR-IR spectroscopy on a Pt/Al_2O_3 thin film [32]. An alternative model, supported by theoretical calculations [38], considers the interaction in acidic medium, assuming that the protonated quinuclidine N atom as a good H-bond donor interacts with the ketone adsorbed to the Pt surface (Fig. 4, right). An analogous N^+–H–O-type interaction was adopted also for 1-(1-naphthyl)ethylamine and its *N*-substituted derivatives, which were used as modifiers in acidic medium [28].

It emerges from the inversion of enantioselectivity induced by N-alkylation of CD that the above interactions are not feasible models for the cinchonidinium salts. Another possibility, interaction involving the methoxy O atom of the modifier, is unlikely because of its weak basicity.

We propose that the enantioselection is based on electrostatic interaction between the positively charged N atom of N,O-DMeCD·Cl and the free electrons of the carbonyl O atom (Fig. 4, left). In addition to this attractive interaction, another, repulsive interaction is assumed, that is critical for determining the configuration of the major product. The repulsive interaction may originate from steric hindrance by the quinoline or the quinuclidine moieties of the modifier; clarification of this point needs further (theoretical) study. We assume that the considerably different distance between the interacting atoms relative to the above-discussed N^+–H–O-type interaction (Fig. 4, right) leads to a different relative position of reactant and modifier, and thus to a different repulsive interaction and an inversion of enantioselectivity. Note the related observation, the inversion of enantioselectivity in the hydrogenation of ketopantolactone and other activated ketones induced by the replacement of CD with its bulky ether derivatives [23,37].

Considering the less efficient quaternary derivatives of CD, the lower ee achieved with N-BnCD·Cl (Scheme 1) may be attributed to the lower accessibility of the quaternary N atom due to shielding by the bulky benzyl substituent. An alternative explanation that can be applied to the other monomethylated derivative N-MeCD·Cl is connected with the presence of the unprotected OH group. This additional function may interact with one of the carbonyl groups of the reactant via an O–H–O-type H bond, and this competing interaction would diminish the ee.

Another interesting point that may be clarified by future theoretical calculations is the strikingly different stereochemical outcome of the hydrogenation of the two structurally related reactants, ethyl pyruvate and ketopantolactone. The absence of enantioselection in the former reaction is tentatively attributed to the flexible structure of the α-ketoester, in contrast to the rigid cyclic structure of the α-ketolactone.

In homogeneous catalysis there are important asymmetric reactions catalyzed by chiral quaternary ammonium salts derived from cinchona alkaloids [58]. These cinchona derivatives are used as efficient chiral phase transfer catalysts, although the basis of enantioselection is not fully understood. Corey et al. [59] proposed for the enantioselective enolate alkylation that the reactant–catalyst interaction is based on a close and sterically rigid contact between the reactant counter-ion and the N^+ atom of the CD derivative. Another related reaction is the hydrolysis of *p*-nitrophenyl acetate catalyzed by quaternary ammonium salts (surfactants). Quantum mechanical calculations with model compounds revealed an electrostatic interaction between the carbonyl O atom and the N^+ atom of the surfactant regarded as a general acid catalysis of the nucleophilic attack on the carbonyl compound [60]. These examples support the feasibility of our mechanistic model based on electrostatic interaction between the cinchonidinium cation and the free electrons of the keto O atom of ketopantolactone (Fig. 4, left).

4. Conclusions

The N-alkylated CD derivatives N-MeCD·Cl, N-BnCD·Cl, and N,O-DMeCD·Cl have been used as chiral modifiers in the enantioselective hydrogenation of KPL over Pt/Al_2O_3. In contrast to ethyl pyruvate as a reactant (where *N*-alkylated CD derivatives were ineffective as modifiers), (*S*)-pantolactone was obtained in all solvents tested, with up to 44.5% ee at full conversion in dichloromethane. N,O-DMeCD·Cl performed significantly better than N-MeCD·Cl and N-BnCD·Cl. The observed phenomenon of decreasing rate and increasing selectivity during hydrogenation was most pronounced in dichloromethane as a solvent and when N,O-DMeCD·Cl was used as a modifier. Catalyst prereduction in flowing hydrogen at 400 °C, followed by stirring of the catalyst slurry in the presence of modifier and hydrogen, proved to be the most beneficial pretreatment method. However, dramatic morphological changes in the catalyst did not occur during pretreatment, as indicated by STEM, and thus the nature of the transient behavior is not clear. The most probable explanation for the remarkable selectivity enhancement with reaction time (conversion) is some surface restructuring of the Pt particles, although this assumption needs verification.

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