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On the role of modifier structure in the palladium-catalyzed enantioselective hydrogenation of furan-2-carboxylic acid

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Abstract

Enantioselective hydrogenation of the aromatic ring of furancarboxylic acids is an important new application of cinchona-modified palladium as there is no synthetically useful method yet available for this transformation. Here we report a mechanistic investigation of the hydrogenation of furan-2-carboxylic acid. The 5 wt.% Pd/Al_2O_3 catalyst was chirally modified by cinchonidine (CD) derivatives, (*R*)-1-(1-naphthyl)ethylamine derivatives, and (*R*)-1-(1-naphthyl)-ethanol. Variation of the structure of the modifiers revealed that the major requirement an efficient chiral modifier has to fulfill is the presence of a basic N and an OH function. The relative position of the two functional groups and the acidity (proton donor ability) of the OH group are not critical as indicated by the similar efficiency of 1,2- and 1,3-amino alcohols and amino phenols. The enantioselection is attributed to the formation of a cyclic, 2:1 acid:modifier complex that adsorbs close to parallel to the Pd surface via π-bonding of the aromatic rings of substrate and modifier. The model can interpret also the effect of a strong acid additive. The poor performance of amine type modifiers is attributed to the formation of too flexible, acyclic structures.

Keywords: Hydrogenation; Palladium-catalyzed; Furan-2-carboxylic acid

1. Introduction

Hydrogenation of aromatic and heteroaromatic compounds is an important synthetic transformation. Only a few reports have appeared yet on the successful application of soluble chiral complexes for the enantioselective hydrogenation of heteroaromatic compounds, including 2-methylquinoxaline [1], indoles [2], and quinolines [3]. When considering heterogeneous enantioselective catalysis, most of the reactions are characterized by poor *ee*s [4–8].

There is no synthetically useful method yet for the enantioselective hydrogenation of furan derivatives. Only 2% *ee* was obtained in the saturation of the furan ring of some functionalized 2-furanones over the Raney Ni-tartaric acid catalyst system [9]. A homogeneous Rh diphosphine catalyst afforded 24% *ee* to tetrahydrofuran-2-carboxylic acid at very low conversion of furan-2-carboxylic acid [10]. Recently we have reported that cinchonidine (CD)-modified Pd/Al_2O_3 has a greater potential: facile hydrogenation of furan-2-carboxylic acid gave high yields and over 30% *ee* to the (*S*)-enantiomer of tetrahydrofuran-2-carboxylic acid [11]. In the hydrogenation of benzofuran-2-carboxylic acid the *ee* was even higher (up to 53%) but competing hydrogenation of the quinoline ring of CD was considerable during the slow transformation of the bulky substrate. Note that chirally modified, supported Pd is presently the best heterogeneous catalyst for the hydrogenation of C=C bonds of functionalized olefins (*ee* up to 72%) [12–21] and the pseudo-aromatic 2-pyrones (*ee* up to 94%) [22].

The aim of the present work was to improve our understanding of the reaction mechanism and thus facilitate the development of more effective catalysts for the synthesis of chiral tetrahydrofuran carboxylic acids. Hydrogenation of furan-2-carboxylic acid over Pd/Al_2O_3 was used as a test reaction (Scheme 1). Two classes of chiral modifiers have been applied: CD derivatives and 1-(1-naphthyl)ethylamine derivatives. Systematic variation of the modifier structure gave useful hints to the probable nature of substrate – modifier interaction on the Pd surface.

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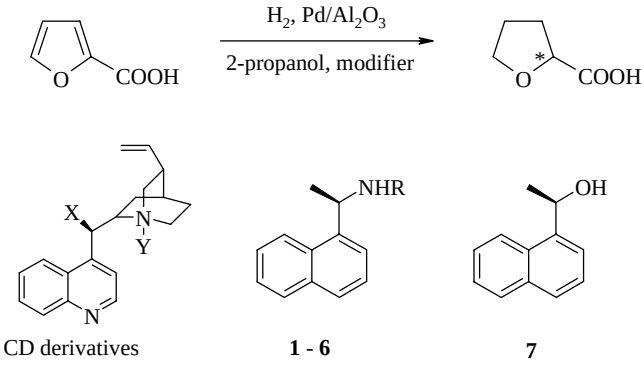


Scheme 1. Enantioselective hydrogenation of furan-2-carboxylic acid on Pd/Al_2O_3 and the structure of chiral modifiers. Derivatives of cinchonidine and (*R*)-(+)-1-(1-naphtyl)ethylamine are specified in Tables 1 and 2, respectively.

2. Experimental

2.1. Materials

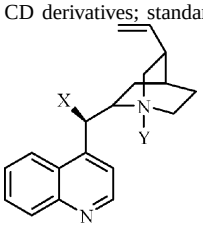
Furan-2-carboxylic acid (Fluka, 98%) was purified by sublimation followed by recrystallization from hexane. Cinchonidine derivatives used as chiral modifiers are summarized in Table 1. *N*-Methyl cinchonidinium chloride (NMeCD·Cl) was synthesized according to a method described in literature [23]. *O*-Methylcinchonidine (MeOCD, Ubichem Research), cinchonidine (CD, Fluka, 98% alkaloid), cinchonidinium hydrochloride (CD·HCl, Sigma), (*R*)-(+)-1-(1-naphthyl)ethylamine (**6**, Lancaster 99%), and (*R*)-(+)-1-(1-naphthyl)-ethanol (**7**, Aldrich, 99%) were used as received. Modifiers 1–5 (Table 2) were synthesized by reductive alkylation or acylation of **6**. Details of the method will be published elsewhere [24].

2.2. Catalytic hydrogenation

A 100 mL autoclave equipped with a 50 mL glass liner and a PTFE cover, and a magnetic stirrer (500 rpm) were used for hydrogenations. Total pressure and H_2 uptake were controlled by a computerized constant volume constant pressure equipment (Büchi BPC 9901). Under standard conditions the catalyst pretreatment and the hydrogenation reactions were carried out at room temperature and 30 bar. At first, 40 mg 5 wt.% Pd/Al_2O_3 catalyst (Engelhard 40692, Pd dispersion: 0.21 as determined by TEM) was prereduced with hydrogen for 5 min at 30 bar in 10 mL 2-propanol. Then 0.45 mmol furan-2-carboxylic acid and the modifier were added and the reaction started. No mass transport limitation was observed in the rather slow hydrogenation of the furan ring.

Conversion and enantioselectivity were determined after derivatization by an HP 6890 gas chromatograph, using a Chirasil-DEX CB (Chrompack 7502, 25 m × 0.25 mm × 250 nm) capillary column. Conditions: split injection (250 °C, 20:1), He carrier gas (42 cm s^{-1}), FID detector (275 °C), 80–180 °C column temperature. Derivatization was carried out by heating ca. 5 mg carboxylic acid and 0.1 mL of a 1 M solution of trimethylchlorosilane in MeOH for 2 h. After evaporation of the solvent the residue was dissolved in 1 mL ethyl acetate. The estimated standard deviation of the determination of *ee* is ±0.5% (±1% at close to zero *ee*).

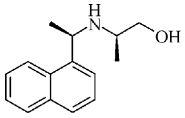
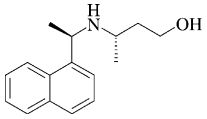
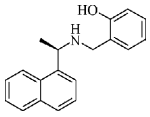
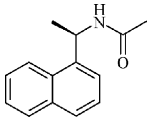
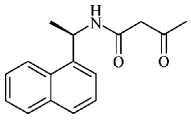
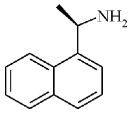
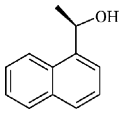
Table 1
Hydrogenation of furan-2-carboxylic acid over Pd/Al_2O_3 modified with CD derivatives; standard conditions



Modifier	X	Y	Modifier (μmol)	Conversion (%)	Time (h)	*ee* (%)
CD	OH	–	34	27[a]	2	33 (*S*)
MeOCD	OCH_3	–	34	25	1	4 (*S*)
CD·HCl	OH	HCl	52	10	6	24 (*S*)
NMeCD·Cl	OH	CH_3·Cl	52	8	6	4 (*R*)

[a] 20 mL 2-propanol, instead of 10 mL.

Table 2
Conversions and enantioselectivities (to (*S*)-product) in the hydrogenation of furan-2-carboxylic acid over Pd/Al_2O_3 modified with different modifiers; standard conditions, 34 μmol modifier

	Modifier	Time (h)	Conversion (%)	*ee* (%)
1		4	23	32
2		4	21	27
3		4	19	26
4		3	15	0
5		3	19	0
6		2	13	6
7		3	37	0

3. Results and discussion

3.1. Stability of the modifiers under reaction conditions

In preliminary experiments it was found that the chiral modifiers of Pd were not stable during the relatively slow hydrogenation of furan-2-carboxylic acid. 1-(1-Naphthyl)ethylamine derivatives 1-5 (Table 2) suffered hydrogenolysis of the C–N bond as shown in Scheme 2 on the example of **1**. The products were identified by ^{13}C-NMR and GC–MS. Degradation of the modifiers was slower when the hydrogen pressure was lowered from 30 to 5 bar but 1-ethylnaphthalene was detectable in solution already after 4 h. For comparison, some derivatives of 1-(1-naphthyl)ethylamine have been used successfully as chiral modifiers of Pt in the hydrogenation of ethyl pyruvate [25,26]. The major differences between the two applications are that pyruvate hydrogenation is a very fast reaction compared to saturation of the furan ring, and Pt is less active in C–N bond cleavage than Pd [27].

We have shown earlier [11] that also the transformation of CD is significant during the slow hydrogenation of furancarboxylic acids. NMR analysis revealed that the major product shown in Scheme 2 is formed by hydrogenation of the C=C bond and partial saturation of the quinoline ring of CD. Partial loss of the aromatic character of the quinoline ring leads to a weaker adsorption of the π-bonded modifier on Pd [28]. Until there is sufficient amount of modifier in solution, the intact CD molecules will replace the partially hydrogenated ones and the gradual loss of *ee* can be avoided.

In order to minimize distortion of the results by transformation of the modifiers, relatively high modifier/substrate and modifier/Pd ratios were applied in the following experiments, and the enantioselectivities were compared at moderate conversions.

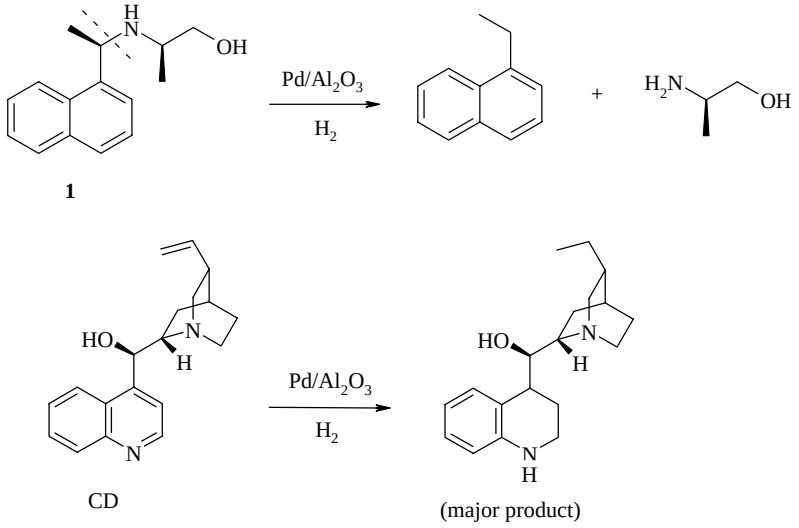
3.2. Enantioselective hydrogenation with CD derivatives

Under standard conditions, hydrogenation of furan-2-carboxylic acid on CD-modified Pd/Al_2O_3 afforded over 30% *ee* to (*S*)-tetrahydrofuran-2-carboxylic acid (Table 1). When the OH function of CD was protected by methylation (MeOCD), the reaction rate doubled but the *ee* dropped to 4%. Methylation of the basic quinuclidine N atom of CD (NMeCD·Cl) resulted in a low *ee* to the opposite enantiomer. The reference reaction with CD·HCl showed that protonation of the quinuclidine N atom reduced only moderately the *ee* compared to the reaction with CD. The reaction rates of the two reactions with CD·HCl and NMeCD·Cl were similarly low.

These experiments demonstrate that both the OH and the basic quinuclidine N functions of CD have a crucial role in enantioselection. Similar conclusions have been drawn earlier from the hydrogenation of (*E*)-α-phenylcinnamic acid [29] and *trans*-2-methyl-2-butenoic acid (tiglic acid) [30] over supported Pd catalysts modified by *O*- or *N*-methylated cinchonidine. The importance of acid–base type interactions between substrate and modifier is supported also by an earlier observation [11] that hydrogenation of furan-2-carboxylic acid methyl ester gives racemic mixture of tetrahydro-furancarboxylic acids.

3.3. Test of naphthylethylamine derivatives as new modifiers

Next, (*R*)-(+)-1-(1-naphthyl)ethylamine (**6**) and some of its simple derivatives were used as chiral modifiers of Pd (Table 2). The efficiency of the amino alcohol and amino phenol type modifiers **1**–**3** was astonishingly similar to that of CD: the enantioselectivities to the (*S*)-product varied in a narrow range 26–33%. Most importantly, the relative position of the N and OH functions barely influenced the *ee*.



Scheme 2. Major products formed during hydrogenation of **1** and CD under standard conditions but in the absence of substrate (35 μmol modifier).

Modifier **1** (and also CD) is a 1,2-amino alcohol, while in modifiers **2** and **3** the two functions are in 1,3 position. Besides, the acidity of the OH groups (primary alcohol in **2** and phenolic OH in **3**) did not play an important role either.

The enantioselectivity dropped to zero when applying amides without an OH function (**4**, **5**), or when the modifier molecule contained only an OH function (**7**). A single amine functional group in **6** gave a low *ee* but the efficiency of this modifier is not comparable to that of aminoalcohols and aminophenols (CD and **1**–**3**). These results underline the above conclusion that in the hydrogenation of furancarboxylic acids on Pd a necessary requirement for an effective chiral modifier is the presence of a basic amino and an OH group.

3.4. Mechanistic considerations

Various mechanistic models have been proposed for a similar reaction, the hydrogenation of α,β-unsaturated carboxylic acids over cinchona-modified Pd [30–32]. According to the model of Nitta and Shibata [31], the deprotonated carboxyl group in (*E*)-α-phenylcinnamic acid interacts with the protonated quinuclidine N of CD. A second H-bonding involving the OH function of CD stabilizes the structure of the cyclic 1:1 complex. For aliphatic α,β-unsaturated carboxylic acids we suggested a 2:1 type cyclic complex in which an acid dimer (in *trans* position) interacts with cinchonidine [30]. The model was supported by ab initio calculations and IR studies [33,34] though no direct evidence to this stoichiometry could be found. Using these models as analogies, the probable interaction complexes between CD and furan-2-carboxylic acid are depicted in Fig. 1 A and B. A recent ATR-IR study of CD adsorption on Pd revealed that the alkaloid adsorbs via the π-bonded quinoline ring being close to parallel to the Pd surface [35]. Adopting this adsorption geometry, the interacting complexes shown in Fig. 1 may be considered as top views over the Pd surface, and uptake of two hydrogen atoms from below (from the Pd surface) affords the major enantiomer.

Variation of the enantioselectivity in the presence of CD derivatives (Table 1) or 1-(1-naphthyl)ethylamine derivatives (Table 2) support the key feature of both models, namely the existence of two H-bonding interactions between the modifier and the substrate. More conclusive are the similar enantioselectivities provided by **1** or CD (1,2-amino alcohols), and **2** or **3** (1,3-amino alcohol and amino phenol). This important observation indicates that the size of the substrate-modifier complex is not critical, and thus supports the 2:1 type interaction (Fig. 1B). Ab initio calculations [30,33] revealed that a major difference between the two mechanistic models developed for the hydrogenation of α,β-unsaturated carboxylic acids is their rigidity. The 2:1 interaction complex is sterically flexible and can easily adopt the steric requirements of adsorption even on an extended flat Pd surface typical for low metal dispersion. In contrast, the 1:1 interaction is very rigid; the angle between the plane of the quinoline ring and that of the carboxylic acid is around 110°. Adsorption of this structure on Pd would require special surface sites such as steps or kinks; an adsorption geometry in which both aromatic rings are close to parallel to a flat metal surface (e.g. a terrace) is impossible without breaking the weaker O–H–O interaction. If the 1:1 type complex would be responsible for enantioselection, enlargement of the ring (by replacing a 1,2-amino alcohol by a 1,3-amino alcohol) should result in a considerable release in stress and an easier adsorption of the complex on Pd, and thus a significant change of the rate and enantioselectivity of the reaction.

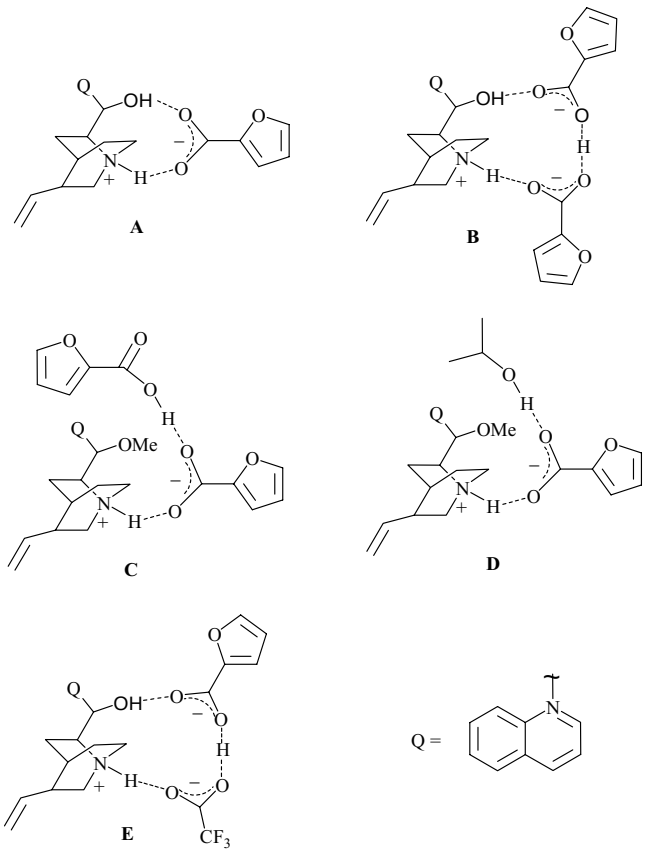


Fig. 1. Feasible interaction complexes between the chiral modifier and the substrate: (A) 1:1 type double interaction between CD and furan-2-carboxylic acid; (B) 1:2 type double interaction between CD and the dimer of furan-2-carboxylic acid; (C) 1:2 type single interaction between MeOCD and the dimer of furan-2-carboxylic acid; (D) 1:1 type single interaction between MeOCD and furan-2-carboxylic acid stabilized by a H-bonding solvent molecule; (E) 2:1 acid:CD type double interaction in the presence of the strong acid TFA.

Finally, the poor *ee* of 4 and 6% in the presence of MeOCD and **6**, respectively, may originate from a single interaction between the amine type modifier and the acidic substrate. Two feasible interactions are depicted in Fig. 1C and D: protonation of the amine modifier by the furan-2-carboxylic acid dimer, and the 1:1 type interaction between amine and the furan-2-carboxylic acid

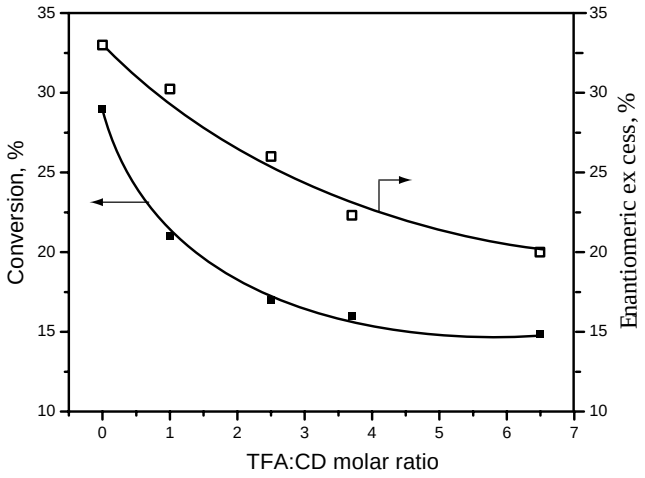


Fig. 2. Hydrogenation of furan-2-carboxylic acid in the presence of a strong acid (TFA); standard conditions, 68 μmol CD, 2 h.

monomer stabilized by interacting with a proton donor solvent molecule [36]. Obviously, these loose structures cannot provide significant *ee*.

3.5. Effect of a strong acid additive

It was shown in Table 1 that protonation of CD by HCl diminishes the *ee* but does not hinder the enantiodifferentiation. This observation is astonishing when considering the importance of the acid–base type interaction, the protonation of the quinuclidine N of CD ($pK_a = 10.0$ [37]) by the weak acid substrate ($pK_a = 4.03$ [38]) in the reaction mechanism (Fig. 1). To clarify this point, hydrogenation of furan-2-carboxylic acid was repeated in the presence of increasing amount of trifluoroacetic acid (TFA, $pK_a = 0.52$ [39]). The curves in Fig. 2 show that addition of TFA decreases both the reaction rate and the enantioselectivity to about one-half but does not prevent enantiodifferentiation.

A probable explanation for the effect of TFA is that not the cinchona alkaloid but the alkaloid-TFA ion pair [40] is the actual chiral modifier of Pd, which interacts with furan-2-carboxylic acid in the enantiodifferentiating step. The resulting cyclic structure (Fig. 1E) is similar to furan-2-carboxylic acid dimer-CD complex (Fig. 1B), in which one of the substrate molecules is replaced by a TFA molecule. An analogous three-membered complex was proposed for the enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone over CD-modified Pd, when addition of even large excess of TFA did not hinder enantiodifferentiation in acetonitrile but only lowered the *ee* [41].

4. Conclusions

The enantioselection achieved in the hydrogenation of furancarboxylic acids over supported Pd is attributed to acid–base interactions between substrate and chiral modifier, both adsorbed on the metal surface during hydrogen uptake. The presence of a basic N and an OH function in the modifier, and the carboxylic group in the substrate are inevitable. On the basis of analogies to former mechanistic models developed for the hydrogenation of α,β-unsaturated carboxylic acids, we propose that a cyclic acid dimer-CD interaction is responsible for the moderate *ee* achieved with the Pd–CD system [11]. The almost equal efficiency of 1,2- and 1,3-amino alcohol and amino phenol type modifiers support the stoichiometry of the enantio-differentiating complex that can well interpret also the effect of strong acid additives on the *ee*.

Acknowledgements

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