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RESEARCH NOTE

Enantioselective Hydrogenation on Chirally Modified Platinum: New Insight into the Adsorption Mode of the Modifier

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A new modifier, 2-phenyl-9-deoxy-10,11-dihydrocinchonidine, has been synthesized for the enantioselective hydrogenation of ketopantolactone and α-ketoesters over chirally modified Pt/alumina. The results indicate flat adsorption of cinchonidine with the quinoline ring oriented parallel to the surface and, furthermore, give some insight into the conformation of the modifier within the transition state complex. Comparison of the structures and catalytic behaviors of 9-deoxycinchonidine and the new modifier allows to exclude the previously proposed perpendicular or tilted adsorption of the quinoline ring via the N atom.

Key Words: **cinchonidine; 9-deoxycinchonidine; 2-phenyl-9-deoxy-10,11-dihydrocinchonidine; ketopantolactone; ethyl pyruvate; platinum; enantioselective hydrogenation; adsorption state.**

INTRODUCTION

Asymmetric synthesis is a rapidly growing field in chemistry (1). Among the various strategies for the synthesis of optically pure compounds, asymmetric catalysis offers the advantage that small amounts of a chiral catalyst can produce large quantities of the desired chiral product. Heterogeneous enantioselective catalysis is of special interest for industrial application because of its advantages over homogeneous reactions in separation and reuse of the catalyst. There are, however, only a few heterogeneous enantioselective catalytic systems that have been investigated in some detail. One of those is the enantioselective hydrogenation of activated carbonyl compounds over cinchonidine-modified platinum (2–5).

Systematic variation of the modifier structure proved to be an efficient tool to shed light on the reaction mechanism. On the basis of such studies it has been proposed that cinchonidine (CD) interacts with the carbonyl O atom of the reactant through the quinuclidine N, since N-alkylation results in a complete loss of enantiodifferentiation, whereas substitution of the OH group leads only to a moderate decrease in enantioselectivity (4). An important issue for the development of a realistic mechanistic model is the adsorption mode of the modifier. Based on H/D exchange experiments (5) it has been proposed that the quinoline moiety of CD acts as the anchoring part; however, the exact adsorption state of the modifier is largely unknown and requires further attention. Previous experimental findings and molecular modeling are compatible with an adsorption state where the quinoline π system binds to the Pt, i.e., with the quinoline ring oriented parallel to the surface (flat adsorption) (3, 6, 7). Another conceivable adsorption mode is via the quinoline N with the aromatic ring perpendicular with respect to the Pt surface (8). It has also been proposed that the enantiodifferentiation in ethyl pyruvate hydrogenation is due to the shielding effect of CD adsorbed via the quinoline N atom in a tilted position over Pt (9). For pyridine adsorption on Pt(111), for example, it has been concluded from electron energy loss spectroscopy that an α-pyridyl species is formed that is bound to the Pt surface via the N and an α-C atom (10).

Direct investigation of the adsorption mode of the modifier over Pt is not (yet) possible. Any indirect evidence for the adsorption geometry is therefore of crucial importance for a better understanding of the reaction mechanism. Here we report on the synthesis, identification, and efficiency of a new derivative of CD, 2-phenyl-9-deoxy-10,11-dihydrocinchonidine (PDHCD) (see Scheme 1), which offers new insight into the adsorption mode of cinchona alkaloid modifiers during the enantioselective hydrogenation of activated carbonyl compounds. To our knowledge, this is the first report on a cinchonidine derivative arylated at the quinoline ring.

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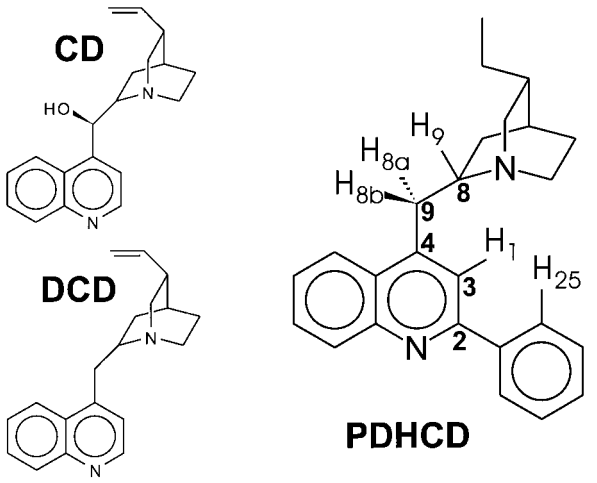

SCHEME 1. Cinchonidine (CD), 9-deoxycinchonidine (DCD), and 2-phenyl-9-deoxy-10,11-dihydrocinchonidine (PDHCD).

EXPERIMENTAL

Cinchonidine (Fluka, purum) was used as received. Synthesis of 9-deoxycinchonidine (DCD) as a reference material was based on a previously reported method (11). PDHCD was prepared by reacting 9-*O*-methyl-cinchonidine with phenyl lithium followed by hydrogenation of the vinyl group. 9-*O*-methyl-cinchonidine was prepared according to a former procedure (4). In the next step arylation of the quinoline ring was accompanied by hydrogenolysis of the 9-methoxy group. Hydrogenation of the vinyl group was used to facilitate purification of the product. After each step the product was purified by recrystallization and column or flash chromatographic separation.[3] NOESY and COSY spectra were used to identify the product PDHCD.[4]

The catalytic hydrogenation of ketopantolactone (dihydro-4,4-dimethyl-2,3-furandione) and ethyl pyruvate was carried out in a magnetically stirred stainless-steel 100-ml autoclave equipped with a glass liner and a PTFE cover. Sixty milligrams of 5 wt% Pt/Al_2O_3 (Engelhard 4759) catalyst was pretreated in a H_2 stream at 400°C prior to the reaction (12). Six millimoles of substrate dissolved in 20 ml toluene was used for the reaction. The enantiomeric excess (ee) and conversion were determined with a HP 5890A gas chromatograph (WCOT cyclodextrin-β-2,3,6-M-19 column, Chrompack).

RESULTS

Enantioselectivities obtained at high conversions are summarized in Table 1. Though the reaction conditions were not optimized, the results demonstrate that (i) the efficiencies of PDHCD and DCD are comparable (compare entries 4–6 with entry 8) and (ii) both modifiers are less efficient than CD itself (compare entry 1 with 2 and entry 7 with 6 and 8). Note that more than 90% ee has been recently achieved in both reactions over CD-modified Pt (13–15), but the 57% ee in the presence of DCD is higher than the formerly reported value (4). Enantioselectivities provided by CD and 10,11-dihydrocinchonidine (HCD) are almost identical (4), likely due to the rapid hydrogenation of the vinyl group of CD under high-pressure conditions.

Figure 1 shows the structure of PDHCD as calculated by complete optimization of all the 159 internal degrees of freedom at the *ab initio* Hartree Fock level using a standard 4-31G* basis set. The conformation of PDHCD shown in Fig. 1 is analogous to the "Open(3)" conformation of CD which has been demonstrated to be the most stable in apolar solvents (16). Due to repulsive interaction between H_1 and H_{25} the phenyl ring is tilted by 29.3° with respect to the quinoline plane (see side view in Fig. 1). A second conformer (not shown) with nearly equal energy was found with a similar tilt but in opposite direction, i.e., with H_{25} below the quinuclidine plane, instead of above as shown in Fig. 1. Assuming a flat adsorption of PDHCD parallel

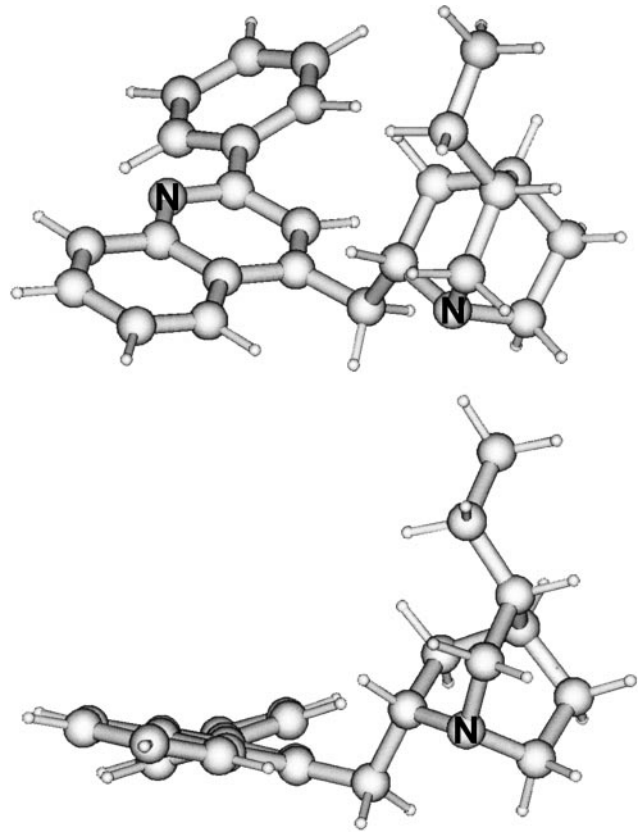

FIG. 1. Structure of PDHCD [Open(3) conformer] optimized at the ab initio Hartree Fock level using a 4-31G* basis set.

[3] Details of the synthesis are available on request.
[4] Spectra are available on request.

TABLE 1

Catalytic Results for the Enantioselective Hydrogenation of Ketopantolactone and Ethyl Pyruvate over Modified Pt/Alumina

Entry	Modifier	Modifier concentration (μmol/liter)	Substrate	T (°C)	P (bar)	Conversion (%)	ee (%)
1	CD[a]	10	Ketopantolactone	18	50	100	83
2	PDHCD	10	Ketopantolactone	18	50	100	67
3	CD	10	Ethyl pyruvate	18	50	99	83
4	PDHCD	10	Ethyl pyruvate	18	50	99	37
5	PDHCD	25	Ethyl pyruvate	18	50	98	53
6	PDHCD	125	Ethyl pyruvate	18	50	98	48
7	CD	136	Ethyl pyruvate	22	70	100	79
8	DCD	136	Ethyl pyruvate	22	70	100	57

[a] CD, cinchonidine; DCD, 9-deoxycinchonidine; PDHCD, 2-phenyl-9-deoxy-10,11-dihydrocinchonidine.

to the Pt surface, the interaction of the quinoline π system with the Pt surface is less favorable than for DCD due to this tilted arrangement. On the other hand, the resulting weakening of the quinoline–Pt interaction is compensated by the presence of an additional aromatic ring which can also interact with the Pt surface. Figure 1 demonstrates that although the presence of the phenyl ring leads to a slight tilt of the quinoline moiety with respect to the Pt surface, the flat adsorption mode is still possible for PDHCD. The adsorption strength can be expected to be similar for PDHCD and DCD.

DISCUSSION

The adsorption of PDHCD via the quinuclidine N with the aromatic rings oriented perpendicular to the Pt surface is strongly inhibited by the additional phenyl ring, as shown in Fig. 1. For CD and DCD this interaction mode is much less hindered. We also note that while for CD and DCD the H in α-position to the quinoline N can be abstracted in analogy to pyridyl formation on Pt(111) (10), this is not possible for PDHCD since there is no H in α-position to N and C–C bond dissociation is very unlikely under the conditions applied. On the other hand, the ee achieved in the enantioselective hydrogenation of EP is similar when using PDHCD and DCD as chiral modifier, and lower by 16–30% than in the case of CD, suggesting that the adsorption state is similar for the three modifiers. Since the perpendicular adsorption for PDHCD is very unlikely for the reason outlined above, the catalytic results presented in Table 1 suggest flat adsorption of the modifiers. This suggestion is also corroborated by the fact that replacement of the quinoline anchoring moiety by naphthyl has no significant effect on enantiodifferentiation (17).

Moreover, the fact that PDHCD shows catalytic behavior similar to that of DCD indicates that the region around C_2 is not directly involved in the modifier–reactant interaction responsible for enantiodiscrimination. There is substantial evidence that in the enantiodifferentiating transition complex the quinuclidine N interacts with the carbonyl O atom of the reactant (3, 4, 18–21). A more subtle issue is the question which conformer of cinchonidine is involved in the enantiodifferentiating step. It has been demonstrated using NMR and *ab initio* calculations that in apolar solvents, which are favorable for ketopantolactone and ethyl pyruvate hydrogenation, the conformer Open(3) is the most stable followed by Closed(1) (16). The abundance of conformer Open(3) in solution has been shown to exhibit the same solvent dependence as ee for the enantioselective hydrogenation of ketopantolactone over CD-modified Pt, which seems to indicate that conformer Open(3) plays a crucial role (16). The present study is in full accord with this suggestion. From Fig. 1 it can be seen that in conformer Open(3) the quinuclidine N is far away from C_2 and that the N lone pair points away from C_2. Hence, substitution of the hydrogen at position C_2 by a phenyl group when going from DCD to PDHCD is expected to have only minor influence on the modifier–reactant interaction and enantiodifferentiation. On the other hand, for the second most stable conformer Closed(1) of CD in apolar solvents the quinuclidine N is much closer to C_2 and the N lone pair points in the direction of C_2 (16). The carbonyl reactant is thus expected in close vicinity to C_2. This is illustrated in Fig. 2 where a possible arrangement of ethyl pyruvate and the Closed(1) conformer of PDHCD is shown. The transition state complex is influenced due to the repulsion between the phenyl ring of PDHCD and ethyl pyruvate (arrow in Fig. 2) and a big effect on ee can be anticipated when replacing DCD by PDHCD if conformer Closed(1) is involved in enantiodifferentiation. The absence of a large effect thus seems to indicate that conformer Closed(1) is not important for the enantiodifferentiation.

The coupling constants $^3JH_9H_{8a}$ (5.0 Hz) and $^3JH_9H_{8b}$ (9.3 Hz) allow us to estimate the population of conformer

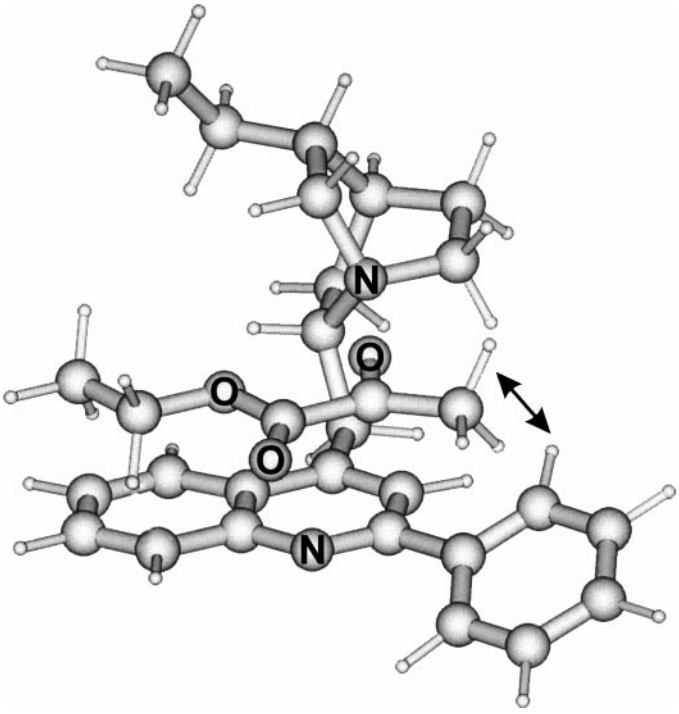

FIG. 2. Structure of PDHCD [Closed(1) conformer] illustrating the close proximity of the phenyl ring with ethyl pyruvate as its carbonyl group interacts with the quinuclidine N of PDHCD.

Open(3) and the closed conformers in $CDCl_3$ by applying a modified Karplus equation (22, 23). This analysis requires knowledge of the dihedral angles $H_{8a}(H_{8b})$–C_9–C_8–H_9 for the different conformers which have recently been calculated for CD using *ab initio* methods (16). The analysis gives a fraction of conformer Open(3) of about 69%. This ratio is in good agreement with the value derived independently from the volumes of the NOESY cross-peaks of H_5 with H_{8a} and H_{8b}, respectively, which are measures for the population of conformers Open(3) and Closed(1), respectively (16, 24). We have found similar coupling constants $^3JH_9H_{8a,b}$ (5.5 and 8.5 Hz) for DCD in $CDCl_3$, indicating that the relative stability of the conformers is similar for PDHCD and DCD. NMR experiments and *ab initio* calculations revealed that conformer Closed(1) is stabilized relative to Open(3) when going from CD to DCD (16, 24). The observed decrease in ee when replacing CD by DCD and PDHCD could be attributed to a stabilization of conformer Closed(1) relative to Open(3), in accordance with the above argumentation that Closed(1) plays no dominant role in the enantiodifferentiating step.

CONCLUSIONS

The enantiodiscriminating potential of the new CD derivative PDHCD provides strong support for the flat adsorption of the modifier parallel to the Pt surface and for the mechanistic model proposed earlier (3) for the reactant–modifier interaction over the Pt surface. The present findings substantiate the crucial role of conformer Open(3) of CD in the enantiodiscriminating diastereomeric complex formed during α-ketoester hydrogenation over cinchona-modified Pt.

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