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Enantioselective Hydrogenation on Cinchona-Modified Metal Catalysts: Mechanistic Implications of Acid Additive

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The enantioselective hydrogenation of 4-hydroxy-6-methyl-2-pyrone in the presence of acetic acid and trifluoroacetic acid has been studied on cinchonidine-modified Pd/TiO_2. Catalytic experiments and theoretical calculations indicate the formation of a cinchonidine–trifluoroacetic acid cyclic ion pair. We propose that this is the actual modifier, which interacts with 4-hydroxy-6-methyl-2-pyrone in the enantiodifferentiating step. The new mechanistic model is assumed to be valid also for other reactions over cinchona-modified Pt or Pd, in the presence of trifluoroacetic acid.

Key Words: **enantioselective; asymmetric; hydrogenation; 4-hydroxy-6-methyl-2-pyrone; cinchonidine; palladium; trifluoroacetic acid.**

INTRODUCTION

Cinchona-modified, supported Pt and Pd are among the most efficient heterogeneous catalysts in enantioselective hydrogenation reactions (1–4). A common feature of these reactions is the special role of acids as reactants, solvents, or additives. In the Pd-catalyzed hydrogenation of C=C bonds the highest enantioselectivities have been achieved using those reactants which possess an acidic function, such as α,β-unsaturated carboxylic acids (5, 6) and a hydroxypyrone (7). In the hydrogenation of a neutral compound isophorone dihydrovinpocetin is a better modifier of Pd than is cinchonidine (CD), but the highest enantiomeric excess (ee) was achieved in the presence of AcOH (8, 9). The good enantioselectivities achieved using acidic reactants (α,β-unsaturated carboxylic acids) have been attributed to the formation of 1 : 1 and 1 : 2 complexes, in which the interaction of the acidic function of the reactant with the quinuclidine N atom of CD plays a crucial role (5, 6).

For the hydrogenation of activated ketones cinchona-modified Pt is commonly applied in AcOH, a medium in which the ee is remarkably higher than in other solvents of comparable polarity (10). Besides, small amounts of an acid cosolvent, in particular trifluoroacetic acid (TFA), improves the enantioselectivity (11, 12). Possible explanations for the positive effect of acids are the protonation of the quinuclidine N atom of CD and the dominance of the "open-(3)" conformation of the protonated alkaloid (13, 14).

Here we report an unexpected effect of TFA in the hydrogenation of 4-hydroxy-6-methyl-2-pyrone (**1** in Scheme 1) over CD-modified Pd, the observation of which led us to propose a new reaction mechanism.

EXPERIMENTAL

CD and AcOH were used as received; TFA and acetonitrile were distilled before use. 4-Hydroxy-6-methyl-2-pyrone (**1**; Fluka, 98%) was purified by column chromatography (silica gel, dry hexane/ethyl acetate (1 : 1)), followed by recrystallization from ethyl acetate. It has to be emphasized that even traces of impurities in the reaction mixture can lead to significant variations in ee. Preparation of the 5 wt% Pd/TiO_2 catalyst (metal dispersion, $D = 0.18$, determined by H_2 chemisorption) has been described elsewhere (15).

The hydrogenation reactions were carried out in a magnetically stirred 100-ml glass reactor. In a standard procedure, 20 mg of Pd/TiO_2 was prereduced in 10 ml of solvent with H_2 for 5 min, at 1 bar and room temperature. Then 5 mg of CD and 100 mg of **1** were added, and the reaction started. We showed earlier (7, 16) that hydrogenation of **1** is accompanied by the saturation of the quinoline rings of CD, leading to a successive drop in ee. To avoid this complication, here we used a rather large excess of CD, affording almost constant ee at conversions below 10% under the reaction conditions used.

The conversion of **1** and chemoselectivity to **2** (see Scheme 1) were determined using a HP 6890 gas chromatograph with a HP-5 column. The ee was determined using a Chirasil-DEX CB column after methylation of **2**. Derivatization was carried out in 3 ml of methanol with 0.1–0.01 mmol of hydrogenation product and 10 mg of

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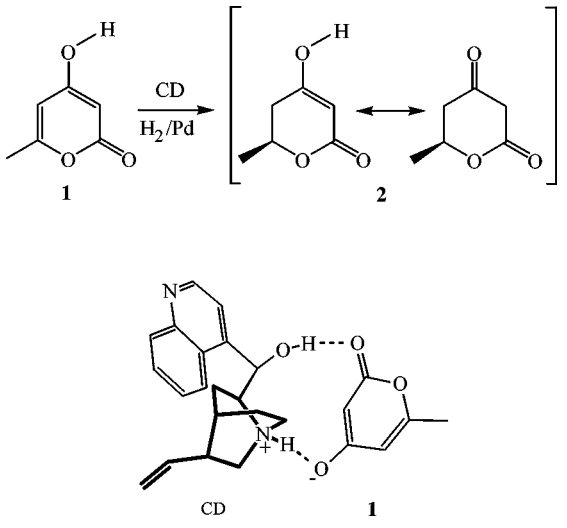

SCHEME 1. Hydrogenation of 4-hydroxy-6-methyl-2-pyrone (**1**) over cinchonidine (CD)-modified Pd and the proposed interaction of CD and **1** (topside view on the Pd surface).

trimethylorthoformate, in the presence of an acidic ion exchange resin (Diaion RCP1 60H).

GAUSSIAN98 was used for the quantum chemical calculations (17). The B3LYP (18) density functional hybrid method was applied together with a 6-31G* basis set. CD was assumed to be in its open-(3) conformation, which is the most stable conformation when the alkaloid is protonated at the quinuclidine N (13).

RESULTS

*Enantioselective Hydrogenation of **1** in the Presence of Acids*

The successful enantioselective hydrogenation of the hydroxypyrone **1** in acetonitrile has been rationalized assuming a complex formation, shown in Scheme 1 (15). The protonated quinuclidine N of CD ($pK_a = 10.0$ (19)) is bound to the deprotonated OH group of **1** ($pK_a = 4.7$ (20)), and a second H-bonding interaction involves the OH group of CD and the carbonyl group of **1**. Addition of a strong base or acid should therefore hinder the reactant–modifier interaction and diminish the ee. Indeed, the ee dropped to zero in the presence of an equivalent amount of 1, 8-diazabicyclo [5,4,0]undec-7-ene (DBU; $pK_a = 23.9$) relative to **1** (15).

In contrast, addition of even a large excess of TFA did not hinder enantiodifferentiation in acetonitrile but lowered the ee considerably (Fig. 1). The minor improvement by 0.5–1 equivalent of TFA is attributed to the neutralization of ethylamines produced from acetonitrile in a slow, competing hydrogenation reaction (15). The basicity of ethylamines ($pK_a \approx 10$) is similar to that of the quinuclidine N of CD; thus ethylamines can compete with the modifier for interacting with **1**. Note that interactions of TFA with the solvent acetonitrile is negligible, as the basicity of quinuclidine N of CD is about 20 orders of magnitude higher than that of acetonitrile (21). Solvents of lower basicity than acetonitrile (e.g., toluene) do not dissolve the reactant sufficiently (15).

The ee was much lower in AcOH and not altered by TFA. A feasible explanation for the poor ee in AcOH is that AcOH disturbs the H-bond interactions shown in Scheme 1 and Fig. 2c′. We proved by NMR analysis that addition of at least 24 equivalents of acetic acid or 14 equivalents of **1** completely protonates the quinuclidine N atom of CD (15). In contrast, addition of only one equivalent of TFA is sufficient to protonate the quinuclidine N and higher amounts of acid result in the protonation of the quinoline N atom (complete protonation at TFA/CD = 15 mol/mol). Accordingly, the low ee of 25% achieved in acetic acid without any coacid (TFA) is likely due to competitive protonation of CD by acetic acid and **1** (i.e., a significant disturbance in the mechanism suggested for reactions in the best solvent, acetonitrile) (Scheme 1).

Theoretical Calculations

For the reactions carried out in acetonitrile in the presence of the strongly acidic TFA (Fig. 1) we propose a different mechanism, in which the anion plays a crucial role. We assume it is not the cinchona–alkaloid but the alkaloid–TFA ion pair that is the actual chiral modifier of Pd, which interacts with **1** in the enantiodifferentiating step.

The feasibility of this assumption is supported by theoretical calculations. Interaction of CD with TFA leads to

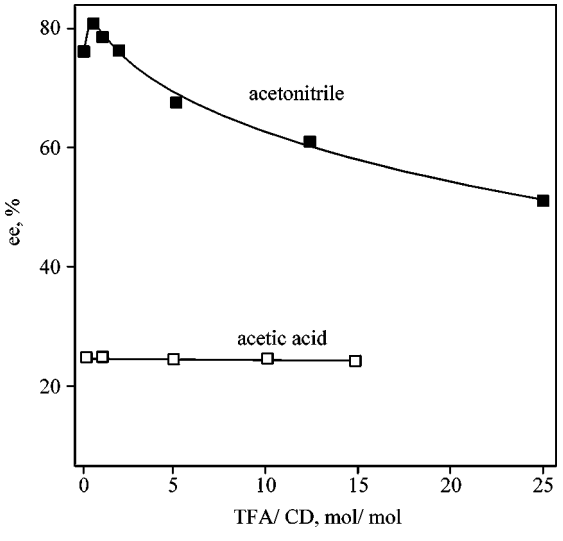

FIG. 1. Effect of TFA on enantioselectivity in the hydrogenation of **1** in acetonitrile and AcOH. Conditions: 100 mg of **1**, 20 mg of 5 wt% Pd/TiO_2, 5 mg of CD, 10 ml of solvent, 30°C, 1 bar, 1 h (3 h in acetonitrile). Conversion was 3–7%. Chemoselectivity to **2** was better than 90%.

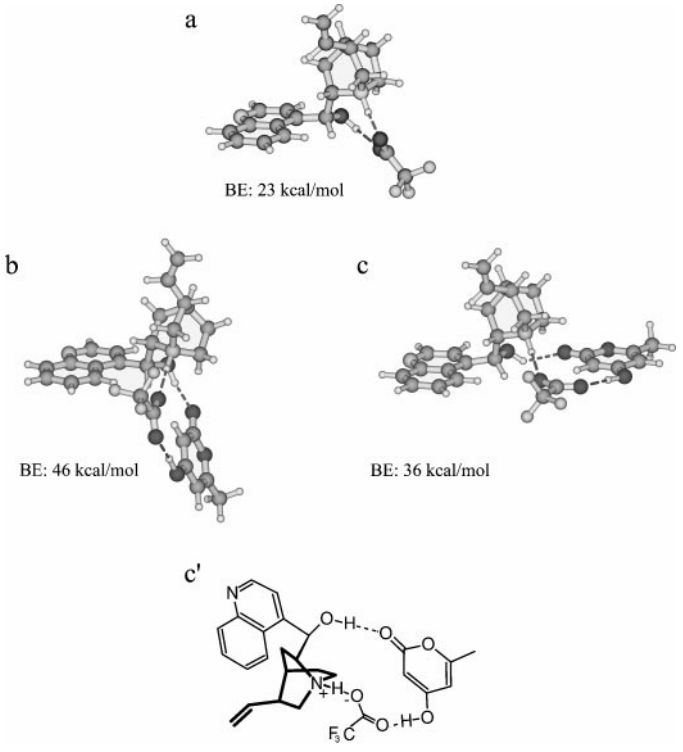

FIG. 2. Structures of possible CD–TFA–**1** complexes, calculated at the ab initio level.

the formation of a cyclic ion pair characterized by a considerable binding energy of 23 kcal/mol (Fig. 2a). The reactant **1**, which has both hydrogen bond donor (OH) and acceptor groups (C=O), can easily bind to the CD–TFA ion pair, as illustrated by the calculated structure in Fig. 2b. The C=O group of TFA serves as the hydrogen bond acceptor for the OH group of **1**, whereas the OH group of CD binds to the C=O group of **1**. The two hydrogen bonds fix the reactant in a position which leads to the formation of the (*S*) enantiomer as the major product on hydrogen addition from "below" (i.e., from the metal surface), in agreement with the experimental observations.

The complex shown in Fig. 2b was calculated by complete relaxation of all intra- and intermolecular degrees of freedom, resulting in a binding energy of 46 kcal/mol with respect to the separated neutral molecules. The quinoline part of the modifier ("anchoring moiety") is supposed to be oriented nearly parallel to the Pd surface. Similarly, the molecular plane of **1** should lay on the Pd surface during hydrogen uptake although it is not coplanar to the quinoline rings in this most stable complex. Their simultaneous adsorption on Pd would require special surface sites, such as steps and terraces, which are dominant only on highly dispersed metals. A more feasible explanation is depicted in Fig. 2c. The calculated three-membered complex is flexible enough to allow parallel adsorption even on an extended, flat Pd surface typical for low metal dispersion. The complex (Fig. 2c), with a binding energy of 36 kcal/mol, was optimized with the constraint that the quinoline part of CD and the molecular plane of **1** are coplanar. The binding energies of Figs. 2b and c should be compared to the binding energy of 23 kcal/mol calculated for Fig. 2a. Hence, interaction of **1** with the CD–TFA ion pair results in a calculated stabilization of 23 kcal/mol for Fig. 2b and 13 kcal/mol for Fig. 2c. Although, the calculations support our assumption that the CD–TFA ion pair and not the alkaloid alone should be viewed as the enantiodifferentiating unit, final confirmation requires *in situ* spectroscopic evidence which is presently targeted.

DISCUSSIONS

The model in Fig. 2c′ can clarify the unexpected observation that enantiodifferentiation in the hydrogenation of **1** does not cease by addition of a large excess of TFA. The successive decrease of ee from around 80 to 50% (Fig. 1) is attributed to the shift in the reaction mechanism. Another possible reason for the lower ee is the protonation of the quinoline rings of the alkaloid, which might change the adsorption geometry of the alkaloid on the Pd surface (22–24).

The feasibility of the model in Fig. 2c′ is corroborated by the similar complexes proposed for the enantioselective hydrogenation of α,β-unsaturated alkenoic acids over cinchona-modified Pd (25). In this three-membered complex the alkenoic acid dimer protonates the quinuclidine N of CD and the dimer is bound via the carbonyl group of the second acid molecule to the OH function of CD. A cyclic 2 : 1 acid : CD complex was found to be more stable than the corresponding cyclic 1 : 1 complex. Recently, the existence of such complexes was demonstrated by NMR and IR studies using AcOH as a model acid (26).

An intriguing question is what the role is of CD–AcOH complexes in the enantioselective hydrogenation of **1**, or in any other reaction where a cinchona alkaloid is the chiral modifier in AcOH solvent. Though a clear answer cannot be given yet, it has to be considered that AcOH is a much weaker H-bond donor and acceptor than is TFA, and involvement of any CD–AcOH complex as the actual modifier in the reaction mechanism requires unambiguous evidence.

During calculations of the CD–TFA and CD–TFA–**1** interactions (Fig. 2) no special assumptions were made concerning the chemical nature of the active metal surface. Hence, the suggested alkaloid-TFA cyclic ion pair (Fig. 2a) may also play a role in hydrogenations over cinchona-modified Pt and explain the positive effect of TFA (12).

It was shown in the enantioselective hydrogenation of ethyl pyruvate on Pt/alumina that replacing CD by its hydrochloride (CD · HCl) increases the ee considerably (27).

This change should be attributed only to protonation of the quinuclidine N of CD.

CONCLUSIONS

Catalytic experiments and theoretical calculations indicate that changes in the efficiency of CD by protonation with TFA cannot simply be interpreted as a transformation of the modifier from a nucleophile (quinuclidine N of CD) to an electrophile (protonated N of CD). Formation of a three-membered cyclic complex involving the alkaloid modifier, TFA, and the reactant might be a feasible explanation also for other hydrogenations over cinchona-modified Pd or Pt where addition of TFA has a significant influence on enantioselection.

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