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Conformational rigidity: a necessary prerequisite of chiral modifiers used in heterogeneous enantioselective catalysis?

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Abstract

In the hydrogenation of ketopantolactone, the (*R*,*R*) and (*R*,*S*) diastereomers of a new chiral modifier, pantoyl-naphthylethylamine, afforded 74 and 40% *ee*, respectively, to (*R*)-pantolactone. On the basis of NOE studies and theoretical calculations, the different properties of the diastereomers and in particular the effect of acid on the modifier structure are deduced from differences in conformational rigidity and steric constraint. In case of the (*R*,*R*)-diastereomer, a loose, extended structure in apolar solvent changes to a compact conformation via an additional intramolecular hydrogen bond, resulting in a more defined “chiral pocket” available for the reactant on the Pt surface.

Keywords: Acid effect; Asymmetric heterogeneous catalysis; Pt/Al_2O_3; Ketopantolactone; Hydrogenation; Ab initio calculation; NOE; Modifier conformation

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1. Introduction

Cinchona alkaloids are the most versatile chiral modifiers in heterogeneous enantioselective catalysis [1–5]. It was determined early, based on the efficiency of some cinchonidine derivatives in pyruvate ester hydrogenation, that there are three important features of cinchona alkaloids [6]:

(i) An extended aromatic ring that anchors (adsorbs) the modifier to the metal surface;
(ii) A basic quinuclidine N atom for interaction with the ketone reactant; and
(iii) Stereogenic centers that induce enantiodifferentiation during hydrogen uptake.

With this knowledge, cinchona analogues [7–9], epicinchona alkaloids [10–13] and other alkaloids [14,15], various other chiral amines [16–18], amino alcohols [19–28], amino acids [29], amino acid derivatives [30,31], and a diol [32] have been synthesized and tested in the enantioselective heterogeneous hydrogenation of activated ketones, mostly ethyl pyruvate. As it is clear from the reviews covering the topic [2,3,22], none of the synthetic substances prepared so far can surpass the outstanding performance of cinchona alkaloids or their simple derivatives.

Here we discuss another fundamental characteristic of an effective chiral modifier: the conformational rigidity. This is a known concept in homogeneous catalysis that may be illustrated by examples where rotation of a functionalized side chain is hindered [33], rigid aromatic backbones or ring structures restrict conformational flexibility of the ligands [34], or the accessibility of the reacting group is greatly reduced by a bulky group or an aromatic system [35]. In contrast, the effect of conformational constraints in heterogeneous asymmetric catalysis has received less attention so far. An early example is the hydrogenation of C=C and C=O bonds over Pd modified by dihydro-vinpocetine [15,36]. The modifier was synthesized by hydrogenation of apovincaminic acid ethyl ester (vinpocetine), and the different efficiencies of the *cis* and *trans* epimers could be rationalized

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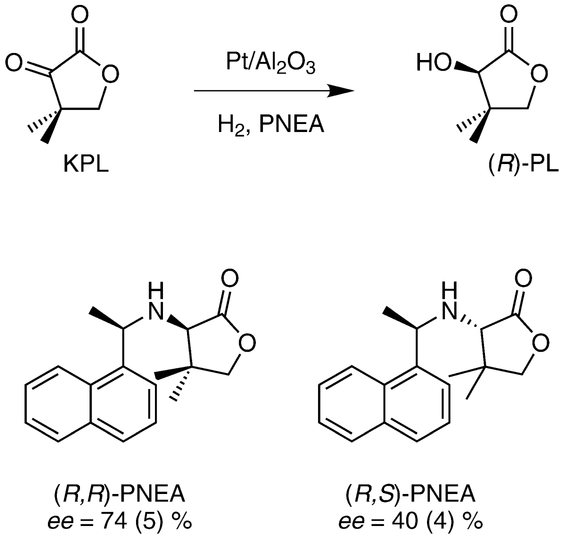

Scheme 1. Enantioselective hydrogenation of ketopantolactone to pantolactone over Pt/Al_2O_3 modified by the diastereomers of PNEA. The enantiomeric excesses (*ee*) were measured at full conversion in HOAc or toluene (in brackets) [43].

by their different conformations [37]. A comparison of cinchona and the conformationally rigid *iso*-cinchona alkaloids in which the rotation around the C(9)–C(8) bond is hindered provided interesting information concerning the probable conformation of cinchonidine during interaction with ethyl pyruvate [10–13]. Related areas are the diastereoselective hydrogenation of bulky reactants over metal catalysts [38–41] and the role of the structural rigidity of chiral molecules in adsorption on single-crystal metal surfaces [42].

We have found very recently [43] that in the hydrogenation of ketopantolactone (KPL) on Pt/Al_2O_3, numerous derivatives of (*R*)-1-(1-naphthyl)ethylamine (NEA) performed well as chiral modifiers only in acidic medium (Scheme 1). The considerably higher *ee* achieved in acidic medium (up to 79%) was attributed to the much stronger H-bond (N^+–H–O bond) formed between the protonated N atom and the keto O atom of KPL [44]. The best modifier was prepared by reductive alkylation of NEA with KPL. The efficiencies of the two diastereomers of pantoyl-naphthylethylamine, (1′*R*,2*R*)- and (1′*R*,2*S*)-PNEA, were equally poor in toluene, but in AcOH the difference in the enantioselectivities exceeded 30% (Scheme 1). A similar difference in *ee* was observed when Pt/alumina was modified by the two diastereomers synthesized by alkylation of NEA with ethyl pyruvate [43]. The aim of the present work is to show that the remarkably different behaviors of these diastereomers can be explained by differences in their conformational rigidities.

2. Experimental

Ketopantolactone (KPL) (Hoffmann–La Roche), (*R*)-1-(1-naphthyl)ethylamine (Acros), trifluoroacetic acid (TFA) (Fluka), and acetic acid (HOAc) (Fluka) were used as received. Toluene (Baker) was dried and stored over an activated molecular sieve. Synthesis of the two diastereomers of pantoyl-naphthylethylamine (PNEA) is described elsewhere [43].

A 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was used for the hydrogenation experiments after pre-reduction at 673 K for 1 h in flowing hydrogen [45]. 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 PTFE cover. Solvent (5 ml) containing 6.8 µmol modifier and 236 mg KPL were added to 5 mg catalyst. When TFA was also used, the pre-reduced catalyst was stirred in 10 ml solvent under H_2 at 30 bar for 10 min. Then TFA and the modifier were added, and the mixture was further stirred for 5 min under N_2 at 1 bar. Finally KPL was added and the reaction started at room temperature and 8 bar. The products were analyzed at full conversion with gas chromatography with a Chirasil-DEX CB capillary column (ChromPack). When TFA was added, the product mixture was evaporated to dryness and diluted with ethyl acetate before injection into the column.

NMR spectra were recorded on a Bruker Avance 500 spectrometer with TMS as an internal reference. Spectra were measured at 300 K. Signal assignment was sometimes assisted through correlation spectroscopy (COSY).

3. Results and discussion

3.1. Effect of acid

The considerable difference in enantioselectivities observed in the hydrogenation of KPL to (*R*)-pantolactone in toluene and acetic acid (Scheme 1) may be attributed to protonation of the chiral modifiers (*R*,*R*)- and (*R*,*S*)-PNEA or to a solvent effect. To clarify this point, we repeated the reaction in toluene in the presence of increasing amounts of TFA (Fig. 1). When 20 eq. of TFA ($pK_a = 0.2$) related to (*R*,*R*)-PNEA was applied, the *ee* was 74%, the same as in acetic acid ($pK_a = 4.7$). Clearly, this selectivity enhancement is due to protonation of the N atom; the considerable excess of TFA relative to the stoichiometric amount of modifier is necessary to compensate for adsorption on the basic sites of the alumina support.

In the following we investigated the structural changes occurring by protonation of the more effective modifier, (*R*,*R*)-PNEA. For the other diastereomer, (*R*,*S*)-PNEA, the interpretation, especially of the theoretical calculations, would be less reliable, because the *ee* of (*R*)-PL increased from 4 to only 40% when we changed from toluene to HOAc [43].