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Origin of the rate enhancement and enantiodifferentiation in the heterogeneous enantioselective hydrogenation of 2,2,2-trifluoroacetophenone over Pt/alumina studied in continuous-flow fixed-bed reactor system

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ABSTRACT

A study on the origin of rate enhancement and enantiodifferentiation in the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone (TFAP) over a Pt/alumina catalyst modified by cinchona alkaloids in toluene/acetic acid (AcOH) solvent mixture with and without trifluoroacetic acid (TFA) using continuous-flow fixed-bed reactor system is presented. The experimental data of the racemic – cinchona 1–cinchona 2–cinchona 1 hydrogenation series confirm the intrinsic nature of rate enhancement, namely the so-called "ligand acceleration" phenomenon. Hydrogenation in the presence of 0.1% (v/v) TFA follows the general rule of the Orito reaction, according to which the products formed in excess are (*R*)-alcohols on Pt-cinchonidine and Pt-quinine and (*S*)-alcohols on Pt-cinchonine and Pt-quinidine chiral catalysts. In toluene/AcOH mixture without TFA, unexpected inversion took place on the Pt-cinchonine and Pt-quinidine catalysts since the (*R*)-product formed in excess instead of the (*S*)-product. The observed unexpected inversion can be interpreted on the basis of the nucleophilic intermediate complex. Based on these observations we propose that in the hydrogenation of TFAP the reaction route involves the equilibrium of electrophilic and nucleophilic intermediate complexes, which was found to be dependent on the acid strength and concentration.

1. Introduction

Among the most studied heterogeneous catalytic enantioselective hydrogenations are the hydrogenations of ketones and β-keto esters over tartaric acid modified Ni and the hydrogenations of activated ketones over cinchona alkaloid modified Pt (the so-called Orito reaction). The most significant results obtained in these reactions have been reviewed several times [1–8]. As a result of extensive studies, nowadays, in both enantioselective hydrogenations over 90% enantiomeric excess (ee) may be attained [3]. The main objective of recent studies on the Orito reaction (Scheme 1) has been to expand its field of utilization, to elucidate the reaction mechanism and to interpret the origin of enantiodifferentiation and rate enhancement in this context.

The results described here represent the continuation of our previous work [9] in which a study on the origin of rate enhancement in the enantioselective heterogeneous catalytic hydrogenation of activated ketones under the Orito reaction conditions using continuous-flow fixed-bed reactor over Pt catalyst modified with parent cinchona alkaloids was presented. To avoid repetition, we simply refer to Section 1 of our latest report [9], where the significance of this research, its status and future research objectives were discussed in detail. Here we only outline recent results on the Orito reaction to demonstrate the present state of the art of this area.

The recent research has mainly been focused on a better understanding of the reaction mechanism. New information has been presented on the relationship between modifier structure (their adsorption modes), the substrates and enantiodifferentiation [10–15] and between the rates of enantioselective and racemic hydrogenation [16–19]. Addressing the structure of the intermediate responsible for chiral induction has greatly contributed to the clarification of the mechanism of enantioselective hydrogenation and the origin of chiral induction [12,14,20–23]. Recognition and further investigation of the unexpected inversions of enantioselectivity (reversal of the sense of the ee as compared with the generally accepted one) in certain conditions also gave new

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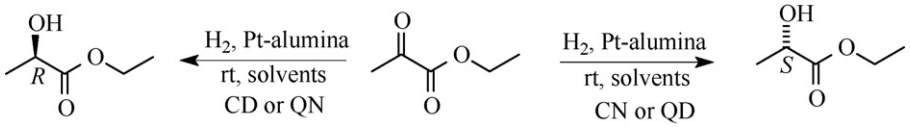
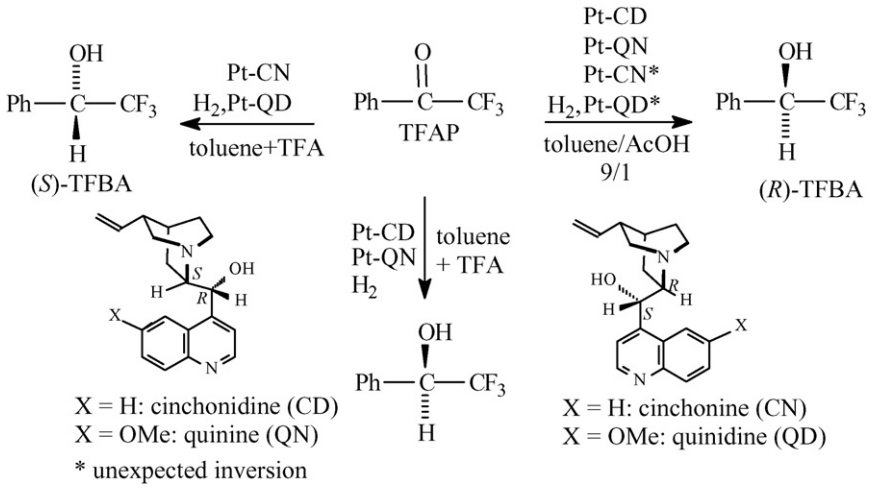


Scheme 1. The Orito reaction.



Scheme 2. Enantioselective hydrogenation of TFAP in continuous-flow system (* = unexpected sense of the ee).

insights in the reaction mechanisms of these complex hydrogenations [8,12,14,24].

A demonstrative example for the latter is shown in Scheme 2. According to these experimental data, the stereochemistry of the enantioselective hydrogenation of TFAP is significantly different from that of ethyl pyruvate (EtPy), since TFAP hydrogenation follows the "general rule" only in the presence of strong acids. Under these conditions, hydrogenation over Pt-CD or Pt-QN catalysts yields the (*R*)-product in excess, whereas over Pt-CN or Pt-QD produces the (*S*)-product in excess. In non-polar solvents or in the presence of weak acids (e.g. acetic acid), however, the product formed in excess in the presence of either of the four parent cinchonas is the (*R*)-alcohol. Our new measurements with 2,2,2-trifluoroacetophenone (TFAP), described in this report opened the possibility of drawing generalized conclusions about the origin of the rate enhancement and allowed novel suggestions to be made regarding the mechanism of the Orito reaction.

2. Experimental

2.1. Materials

Cinchona alkaloids – cinchonidine (CD), cinchonine (CN), quinine (QN) and quinidine (QD), trifluoroacetic acid (TFA), reagents

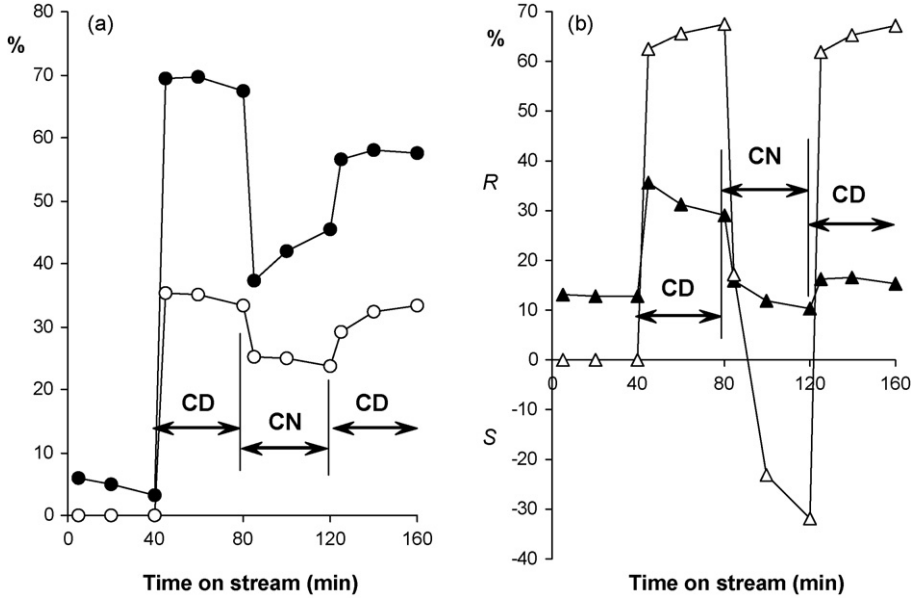


Fig. 1. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of CD followed by CN and again CD (conditions: 100 mg catalyst, [modifier]: 1 mM, liquid flow: 1 mL min^{-1}, [TFAP]: 45 mM; (a): toluene/AcOH 9/1, 283 K, pH_2: 1 MPa; (b): toluene/AcOH 9/1 + 0.1% (v/v) TFA, 293 K, pH_2: 4 MPa).