



New data in the enantioselective hydrogenation of ethyl pyruvate on Pt-cinchona chiral catalyst using continuous-flow fixed-bed reactor system: The origin of rate enhancement

György Szöllösi^b, Szabolcs Cserényi^a, Katalin Balázsik^b, Ferenc Fülöp^{b,c}, Mihály Bartók^{a,b,*}

^a Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary

^b Stereochemistry Research Group of the Hungarian Academy of Sciences, Dóm tér 8, H-6720 Szeged, Hungary

^c Institute of Pharmaceutical Chemistry, University of Szeged, Eötvös u 6, H-6720 Szeged, Hungary

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ABSTRACT

The origin of rate enhancement in the enantioselective heterogeneous catalytic hydrogenation of ethyl pyruvate on Pt modified with the parent cinchonas, as compared to the unmodified Pt, was studied in a solvent mixture toluene/AcOH 9/1. Hydrogenation experiments were carried out in a continuous-flow fixed-bed reactor and in several cases for comparison in batch reactors over E4759 catalyst. Our results obtained using a novel procedure, namely racemic hydrogenation followed by three changes of the chiral modifier (on the same catalyst) supported an intrinsic “ligand acceleration” character of the rate enhancement in ethyl pyruvate hydrogenation.

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1. Introduction

Heterogeneous catalytic syntheses performed in continuous-flow fixed-bed (CFBR) reactor systems are of outstanding significance in the context of industrial applicability [1–3]. The same holds for the selectivity [2,4–6] and especially the enantioselectivity of organic reactions [7–13]. Since the subject of the manuscript is the enantioselective hydrogenation of the activated ketone ethyl pyruvate (EP) (Orito reaction [14,15], Scheme 1), below follows a short summary of the antecedents of the studies in this field. The summary also gives an outline of future tasks.

Reviews published in the field (see e.g. the reports published since 2006 [16–19]) continuously evaluate the results obtained in the heterogeneous catalytic hydrogenation of activated ketones, a reaction that can now be performed in enantioselectivities over 90% [20–27]. Recent publications mostly discuss the interpretation of the reaction mechanism.

Several publications have also been published on studying the Orito reaction in CFBR systems, demonstrating the importance of this research; to our best knowledge, the first of these was published in 1991 [28]. The majority of these reports discuss the hydrogenation of EP [29–40], but there are also

some that address the enantioselective hydrogenation of other α -ketoesters [33,36,39,41–43], 1,2-diketones [44,45] and ketopan-tolactone [29,39] on Pt and that of pyrones [46] and unsaturated carboxylic acids on Pd [47].

The recently published report entitled “Molecular insight into the dynamics of chiral modification of Pt/alumina” [40] presents important new results on the origin of the so-called “ligand acceleration” (LA), proposed by Garland and Blaser [48], associated with the controversial phenomenon of rate enhancement (RE). According to the conclusions of Baiker and co-workers [40,49]: “The study supports the contention that the origin of “ligand acceleration” is not the suppression of catalyst deactivation by addition of the chiral modifier, because under appropriate conditions, catalyst deactivation is negligible in pyruvate hydrogenation” and Margitfalvi et al. [50]: “The results indicate also that the overall increase is a kinetic phenomenon and cannot be attributed to the suppression of the poisoning effect of CO or oligomers formed from ethyl pyruvate”. These conclusions contradict those drawn by Jenkins et al. [51] and Toukoniitty and Murzin [52]. The present manuscript reports new results performed in CFBR, which may contribute with further information to the interpretation of the origin of RE in EP hydrogenation.

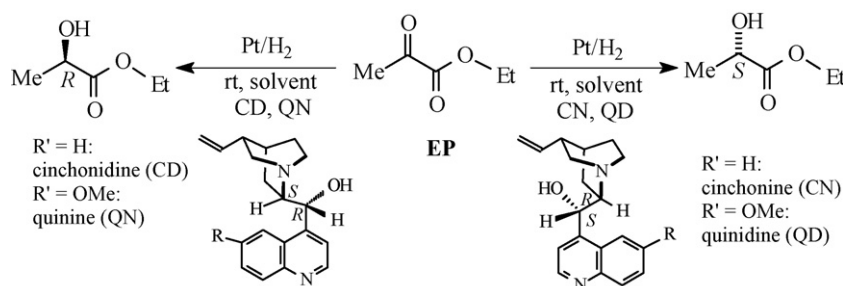
2. Experimental

2.1. Materials

EP, cinchona alkaloids (cinchonidine (CD), cinchonine (CN), quinine (QN), quinidine (QD)) and the solvents were from Aldrich or

* Corresponding author at: Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary. Tel.: +36 62 544 200.

E-mail address: bartok@chem.u-szeged.hu (M. Bartók).



Scheme 1. The Orito reaction (EP: ethyl pyruvate).

Fluka, and used as received. In several cases freshly distilled EP was used. The catalyst, Engelhard 5% Pt/Al₂O₃ (E4759) was pretreated in a fixed-bed reactor by flushing with 30 mL min⁻¹ He at 300–673 K for 30 min then hold in 30 mL min⁻¹ H₂ at 673 K for 100 min. After cooling to room temperature in H₂, the catalyst was flushed with He for 30 min and was stored under air until use. We note that initially we relied on the conclusion of Blaser and co-workers [53]: “The catalysts were prerduced for 2 h at 673 K under H₂. They could be stored for 2 weeks under air with no significant loss in selectivity or activity”. Since it was found that, following the high-temperature pretreatment, the catalyst surface is altered upon standing [26,54], later we reduced the storage time of the catalyst.

2.2. Hydrogenations in flow system and in batch reactor

Continuous hydrogenations were carried out in an H-Cube high-pressure continuous-flow system purchased from Thales Nanotechnology Inc. [55]. The experimental set-up has been described in previous publications [39,47]. In the tubular catalyst cartridge of 2 mm inner diameter and 30 mm length the given amount of catalyst was placed and was filled with additional alumina. The catalyst was rinsed for 0.5 h with 1 mL min⁻¹ flow of toluene/AcOH (9/1) solvent mixture followed by 0.5 h pretreatment with H₂ in the same solvent. The reactant and the modifier were dissolved in the solvent and this solution was delivered to the hydrogenation system using an HPLC pump (Knauer WellChrom HPLC-pump K-120), mixed with H₂ under the desired pressure and passed through the catalyst bed providing an ascendant flow of the reaction components. The catalyst cartridge holder was externally cooled to 283 ± 2 K. The modifier was changed by replacing the solutions delivered to the pump. Samples of 1 mL were taken at regular time intervals from the product flow and analyzed [47]. Standard conditions were: 80 mg E4759 catalyst, solvent: toluene/AcOH 9/1, liquid flow 1 mL min⁻¹, modifier concentration 0.044 mM, substrate concentration 45 mM, 80 bar H₂ pressure, 283 ± 2 K.

Hydrogenations in batch reactor were performed as in ref. [54]. Standard conditions were: 25 mg E4759, 5 mL solvent (AcOH or toluene), 1 bar H₂ pressure, 297 ± 2 K, 800–900 rpm, 1 mmol EP (unless otherwise noted).

2.3. Product analysis

The products were identified by mass spectrometric (HP 6890N GC-HP 5973 MSD, HP-1MS, 60 m capillary column) analysis. Conversions and enantiomeric excesses, ee% = ([R] - [S]) × 100 / ([R] + [S]), were determined by gas chromatography (HP 6890N GC-FID, 30 m long Cyclodex-B chiral capillary column). The reproducibility was ±2%. Turnover frequencies (TOF, h⁻¹) were calculated as described in a recent publication [40]. Transformation of the cinchona alkaloids was checked by ESI-MS measurements (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) operated under positive ion and auto MS-MS mode as described

earlier [56–58]. Note: It is well-known that the reproducibility of the results of the enantioselective heterogeneous catalytic hydrogenations demands special attention, as beside other factors the catalyst surface state also has significant influence on the data obtained. Thus, the acceptance of the data as reproducible needs numerous parallel experiments. During our study we had to realize that what is called reproducible results obtained “under identical conditions” are difficult to obtain even with freshly pretreated catalysts.

3. Results and discussion

It was found already in the early experiments that (i) the CFBR method allows the achievement of high ee values [28] and (ii) continuous feeding of the modifier in ppm concentration is essential and may provide an interesting opportunity for process intensification [29–31]. It was established on the basis of solvent effect studies [29–36] that, in the case of EP, AcOH is the best solvent for avoiding various side reactions causing deactivation of the catalyst [37,40]. Transient measurements using CFBR yielded new information regarding the dynamics of the Orito reaction [33,34,36,37,40], especially in studies on the competition of chiral modifiers [40], where hydrogenation rates under racemic and chiral conditions were compared [33,34,40]. The main conclusions of these studies are the following [37,40]: (i) the order of adsorption strength on Pt is CD > CN > QD; (ii) catalyst deactivation during EP hydrogenation can be avoided by appropriate experimental conditions; (iii) the origin of RE is not the suppression of catalyst deactivation by the chiral modifier.

The question arose whether the contradictory claims regarding the origin of LA (refs. [40,48–50] as opposed to refs. [51,52]) may be due to differences in experimental conditions, the chiral modifier, multiple exchanges of the latter in the course of time on stream, or the purity of EP. In order to answer these questions, we performed hydrogenation of EP on Pt catalyst modified by each of the four parent cinchonas.

3.1. Transient EP hydrogenation measurements using CFBR system

These studies were carried out using pretreated E4759 5% Pt/Al₂O₃ catalyst. From the pretreatment methods (high temperature [54,59], ultrasound [60,61]) for activation of the catalyst we have used the former method. According to the external and internal mass transport measurements it was established that under the given standard experimental conditions, good mass transport was ensured in the system under a H₂ pressure of 80 bar. In the case of CD feeding the conversion was over 90%. Experiments using catalyst E4759 or its crushed form also indicated good mass transfer, which plays a determinant role especially in enantioselective liquid-phase heterogeneous catalytic hydrogenations [62,63].

The experimental results outlined in Fig. 1 demonstrate that using the standard conditions under 80 bar H₂ pressure both

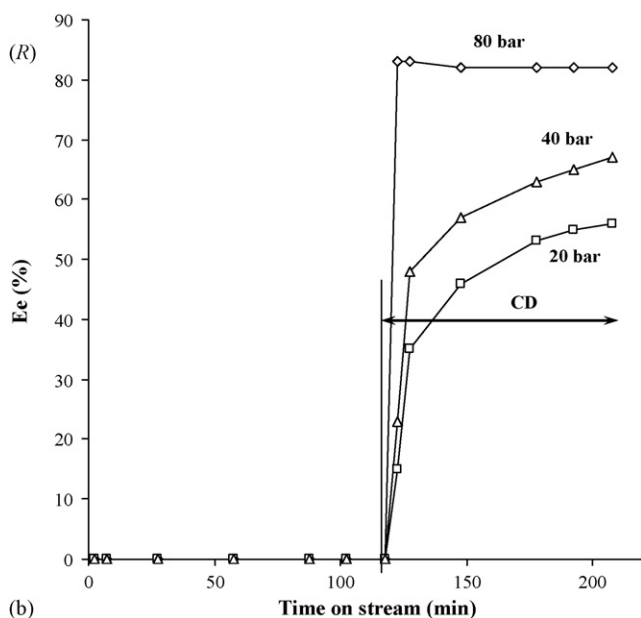
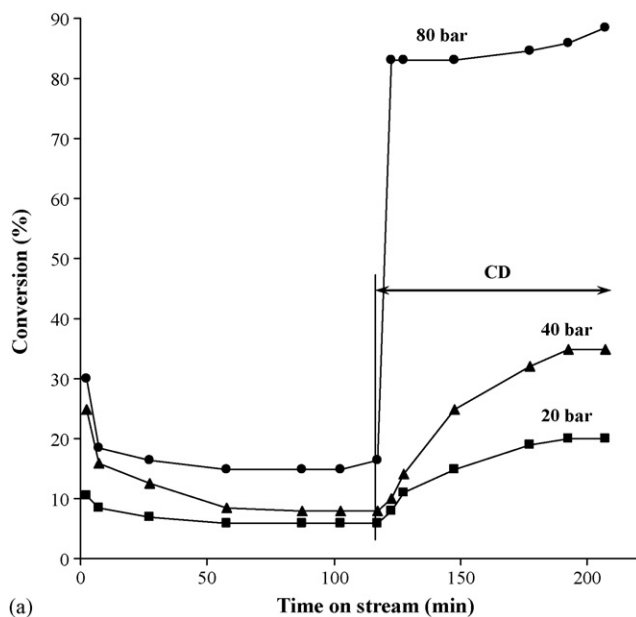


Fig. 1. EP hydrogenation in CFBR: effect of hydrogen pressure on the conversion (a) and ee (b) using unmodified catalyst followed by modification with CD (standard conditions: 80 mg catalyst, [CD]: 0.044 mM, toluene/AcOH: 9/1, liquid flow 1 mL min^{-1} , temperature $283 \pm 2 \text{ K}$, [EP]: 45 mM, EP as received).

the conversion and the ee reaches its maximum, therefore our experiments were usually performed under a H_2 pressure of 80 bar. Although it is possible that in the CFBR system at the beginning of the reactor three phases are present, acting as a trickle bed reactor, in steady state conditions this did not affect the most important conclusions drawn in the present study. This is well illustrated by the same tendencies obtained under both 80 and 40 bar H_2 pressures.

Some characteristic results of the experiments conducted with the above objectives are shown in Figs. 2 and 3. The changes in the conversion and in the sense of chirality by replacing CD with QD after racemic hydrogenation are shown in Fig. 2a and b. The change of CD to QD caused a shift in the ee from about 60% (R)-Lt to about 20–30% (S)-Lt. The ee is not changed by increasing the amount of catalyst, whereas conversion is naturally increased. The relatively low ee values and the continuous decrease in the conver-

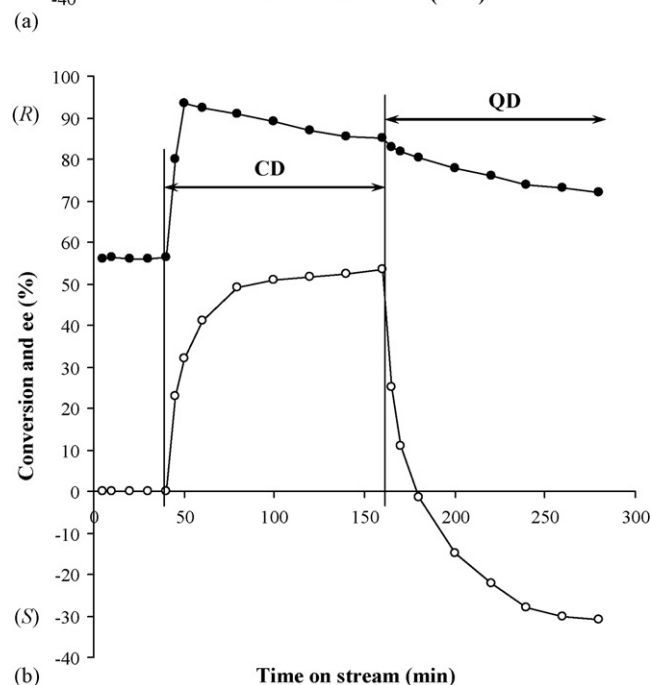
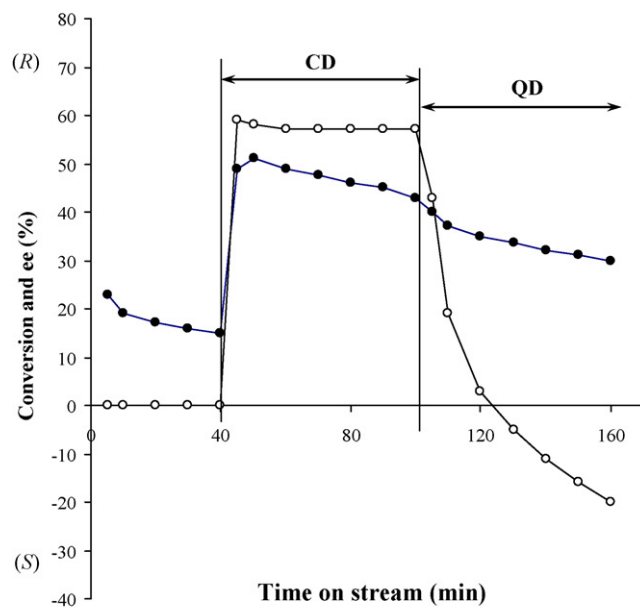


Fig. 2. Transient behaviour in EP hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (○) by addition of CD after racemic hydrogenation followed by change to QD over 30 mg (a) and 80 mg (b) catalyst (standard conditions such as in Fig. 1, EP as received).

sion suggest catalyst deactivation by (i) the oligomers formed in the course of racemic hydrogenation, (ii) decomposition reactions and (iii) contaminants of EP used “as received”. In the case of CD and QD the difference in the conversions due to RE is not significant. The larger conversion of enantioselective hydrogenation as compared to racemic hydrogenation points to the importance of the purifying effect of the chiral modifiers and/or to the role of the LA concept. These experimental results, however, do not allow differentiation between the two phenomena.

Fig. 3 shows the replacement of CN by QN followed by QD at 40 bar H_2 pressure. In this case not only the expected inversion of enantioselectivity took place, but the changes in the conversions were also higher than in Fig. 2a and b. Since EP was used “as received”, again lower ee values were attained. Under 40 bar, as

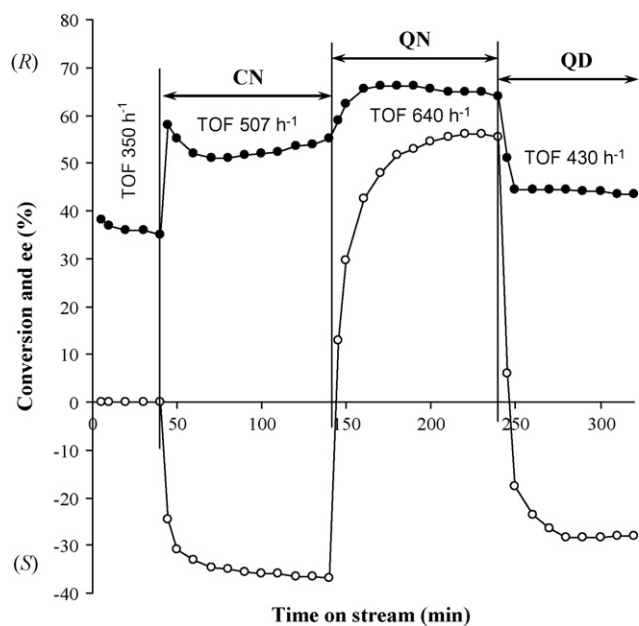
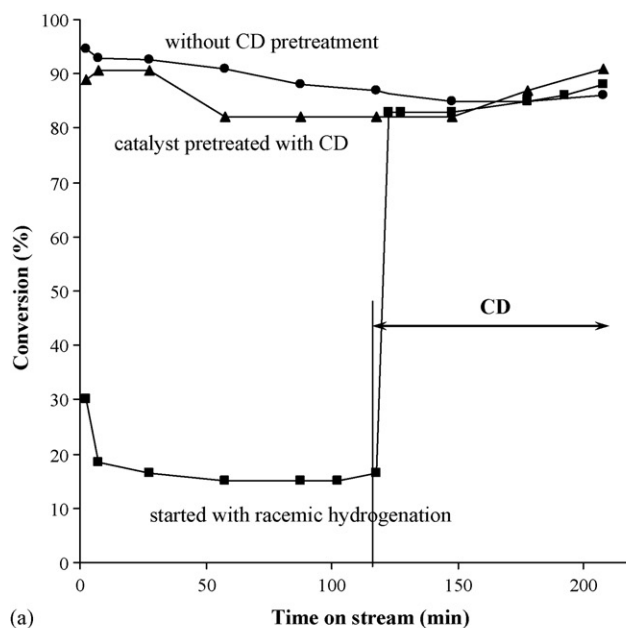


Fig. 3. Transient behaviour in EP hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (○) by addition of CN after racemic hydrogenation followed by changes of the modifier to QN and QD, respectively (standard conditions such as in Fig. 1, except over 40 mg catalyst, 293 ± 2 K, 40 bar H_2 , EP as received).

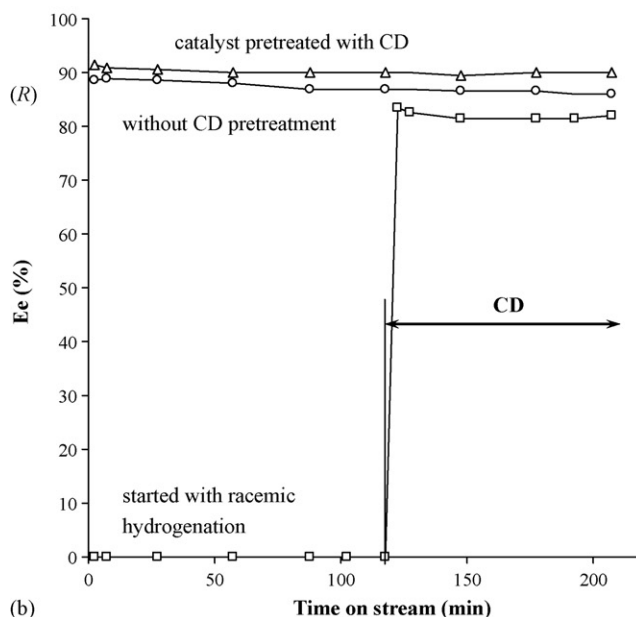
compared to 80 bar, changes in conversions with the various chiral modifiers were easier to record. As expected, RE is observed on modified catalyst as compared to the unmodified Pt. Hydrogenation was the fastest on the Pt-QN chiral catalyst and the slowest on the Pt-QD catalyst. The TOF values calculated from the data series presented in Fig. 3 showed well that as effect of CN the TOF increased by about 25% compared with the racemic hydrogenation, which further changed by about 20 and 30% on subsequent QN and QD feeding. In our opinion in the first TOF increase both the so-called purifying effect of the cinchona alkaloid and the LA played role, while the subsequent changes in the TOF may be ascribed to LA. To sum up the above, the order of the conversions is: conv. over Pt-QN > conv. over Pt-CN > conv. over Pt-QD. The divergence is due not only to differences in experimental methods and conditions, but, presumably, also due to the nature of the complexes formed by EP and the chiral modifier adsorbed on the surface of the catalyst.

The most important conclusion of the measurement series presented in Fig. 3 is, in our opinion, that it justifies the assumption of the intrinsic/kinetic character of RE. RE elicited by the effect of subsequently added QN and QD are indicative of a kinetic phenomenon, because the suppression of catalyst deactivation by cinchona alkaloids cannot be so different for the individual cinchonas: i.e. it cannot show a regularity of this kind.

These observations as well as the high ee values attained in the CFBR system made it necessary to carry out experiments using purified EP under similar conditions in the H-Cube system (Figs. 4 and 5). Fig. 4a and b shows the conversions and the ee values, respectively, obtained in the hydrogenations of freshly distilled EP on Pt catalysts without and with previous CD pretreatment as well as on the Pt catalyst used previously in racemic hydrogenation. Fig. 4a and b reveal that (i) it is possible to attain about 90% ee when purified EP is used; (ii) pretreatment with CD increases the ee only by a few percents; (iii) the rate of enantioselective hydrogenation following racemic hydrogenation did not change significantly as compared to the enantioselective hydrogenation, whereas (iv) ee decreased to about 80%, providing proof for a change in the morphology of the catalyst surface, caused by the previous racemic hydrogenation.



(a)



(b)

Fig. 4. EP hydrogenation in CFBR: effect of the catalyst pretreatment on conversion (a) and enantioselectivity (b) (standard conditions, see Fig. 1, freshly distilled EP).

In the case of freshly distilled EP, Fig. 5 shows the change in conversion and the sense of enantioselection obtained by replacing QN with CN followed again by QN after hydrogenation using an unmodified catalyst. The shape of the curves shown in Fig. 5 and the TOF data are similar to those presented in Fig. 3; the only difference is that the enantioselectivity increased from about 60% (R) to nearly about 80% (R) when QN was used as modifier. In regard to the intrinsic character of RE, a conclusion similar to that drawn from Fig. 3 can be arrived at: i.e. the change in conversion taking place upon the QN-CN and CN-QN changes in the feed may not solely be the consequence of the purifying effect of the cinchona. Thus, in our opinion the measurement presented in Fig. 5 convincingly demonstrates that – in addition to the suppression effect of the cinchonas – LA is also present in RE. These novel experimental observations are coherent with the conclusions reached by studying the dependence of the adsorption strength of the cinchona

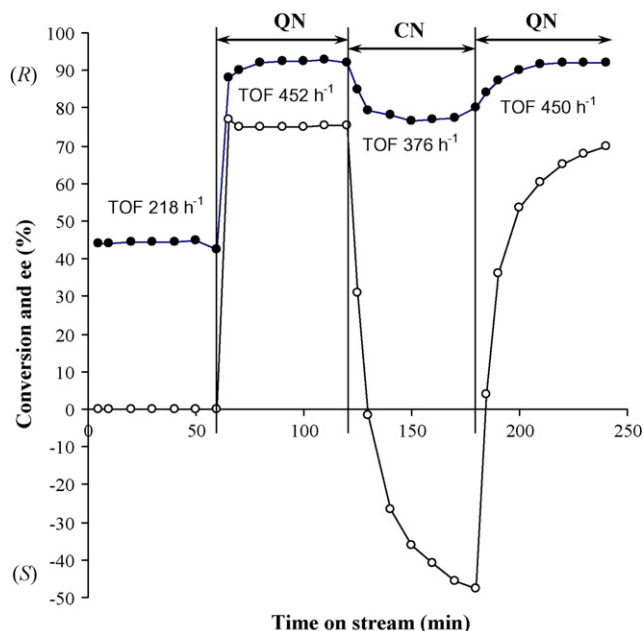


Fig. 5. Transient behaviour in EP hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (○) after racemic hydrogenation by addition of QN followed by CN and again QN (standard conditions such as in Fig. 1, except, 293 ± 2 K, 40 bar H_2 , freshly distilled EP).

alkaloids on the nonlinear phenomenon observed in this catalytic system [64–69], which also bear an intrinsic character. A study on the interconnection between the adsorption strength of the cinchonas, the nonlinear behaviour and the substrate structure in the Orito reaction was reported in ref. [70].

The investigations described above support the intrinsic character of RE observed by Baiker et al. in the enantioselective hydrogenation of EP [40,49] and also the interpretation proposed by Garland and Blaser [48] that the origin of LA is a kinetic phenomenon.

3.2. EP hydrogenation in batch reactor

The hydrogenations in a batch reactor were performed as in ref. [54]. In the interpretation of RE observed in the enantioselective hydrogenation of EP, Toukoniitty and Murzin [52] emphasized the role of cinchona alkaloids to inhibit catalyst deactivation. The authors arrived at this conclusion based, among others, on their study on the kinetics of the hydrogenation at low EP concentrations (<0.1 M) over a CD-modified Pt catalyst in toluene. Blaser et al. also included in their detailed kinetic analysis the effect of EP concentration on the hydrogenation rate [71]. They found that the courses of the rate vs. EP concentration curves were markedly different between hydrogenations over modified and unmodified Pt catalysts. However, in the later study no data was collected for hydrogenations at substrate concentrations below 0.1 M. Based on the interesting results reported in ref. [52], we carried out a few experiments (Figs. 6 and 7) in a batch reactor under conditions similar to those employed in ref. [52].

As shown in Fig. 6, the experimental results are similar to those reported by Toukoniitty and Murzin, according to which racemic hydrogenation proved to be faster than chiral hydrogenation (ee 63% (*R*) enantiomer) under conditions significantly different from those of the Orito reaction. Results of this type may naturally be derived from macroscopic rate determinations; however, that cannot exclude the intrinsic-kinetic character of RE, especially when the potential effect of the irreversible adsorption of the chiral modifier on the enantioselectivity is considered [72–75].

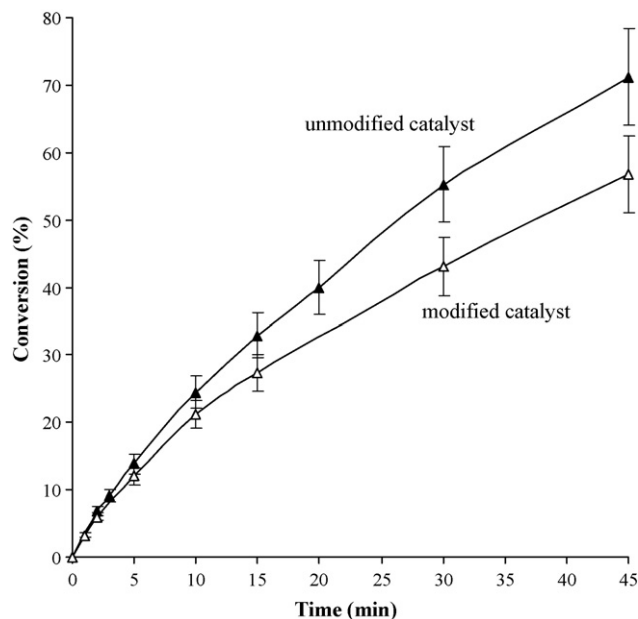


Fig. 6. Enantioselective hydrogenation of EP in batch reactor (conditions: 4 mg E4759, 5 mL toluene, 1 bar H_2 , 273 K, [CD]: 0.1 mM, 0.06 mL freshly distilled EP; the curves are average data, the reproducibility is shown by the error bars).

Fig. 7 provides an opportunity to compare the results of racemic hydrogenation (on unmodified catalyst, **um**) and chiral hydrogenation (on modified catalyst, **m**) carried out in the two most frequently used solvents in the enantioselective hydrogenation of EP (AcOH, toluene) under identical experimental conditions. Although similar studies on this subject have already been reported in a review published in 1997 [59], the conclusions below have never been drawn. It was known that the use of AcOH allows the achievement of higher ee values and that hydrogenation is faster in toluene. Fig. 7, however, also allows the following conclusions to be drawn: (i) the ratio of the rates of chiral and racemic hydrogenation is significantly higher

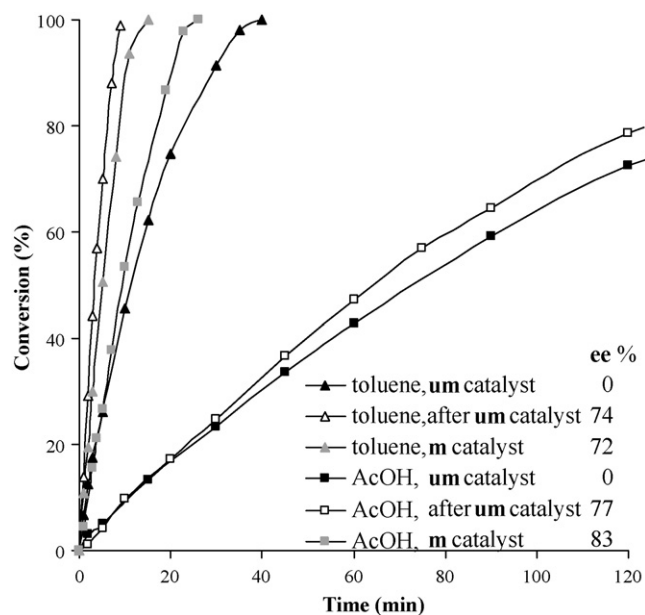


Fig. 7. Enantioselective hydrogenation of EP in batch reactor (conditions: 25 mg E4759, 5 mL solvent (AcOH or toluene), 1 bar hydrogen pressure, 297 ± 2 K, 800–900 rpm, 1 mmol EP, [CD]: 0.8 mM over modified catalyst (**m**) and 0 mM over unmodified catalyst (**um**), enantioselective hydrogenation after racemic hydrogenation (after **um**), freshly distilled EP).

in AcOH than in toluene; (ii) the same holds for the ratio of the rates of chiral hydrogenation and the rates of the chiral hydrogenations that follow racemic hydrogenations; (iii) the experimental results obtained in the two solvents may indicate the operation of different reaction mechanisms, as we have already discussed in some of our earlier reports [10,11,26,76,77]. We assume that these experimental facts also point to the kinetic character of RE. Based on the convincing arguments [49] and his own theoretical calculations, recently, Murzin also seems to agree with these conclusions [78].

4. Conclusion

The experimental results reported in the present manuscript also suggest that RE occurring in the enantioselective hydrogenation of EP is attributable to the so-called ligand acceleration mechanism proposed by Garland and Blaser [48], in accordance with earlier experimental data [40,49,50] and their interpretation. This conclusion, however, does not exclude the suppression of catalyst deactivation by the addition of cinchona alkaloids as chiral modifiers. Our transient measurements in progress that use ketopantolactone, methyl benzoylformate, pyruvaldehyde dimethyl acetal and 2,2,2-trifluoroacetophenone in a continuous-flow fixed-bed reactor will hopefully provide further experimental evidence for the deeper understanding of this complex heterogeneous catalytic process.

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