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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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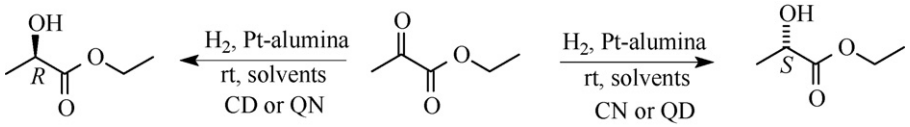
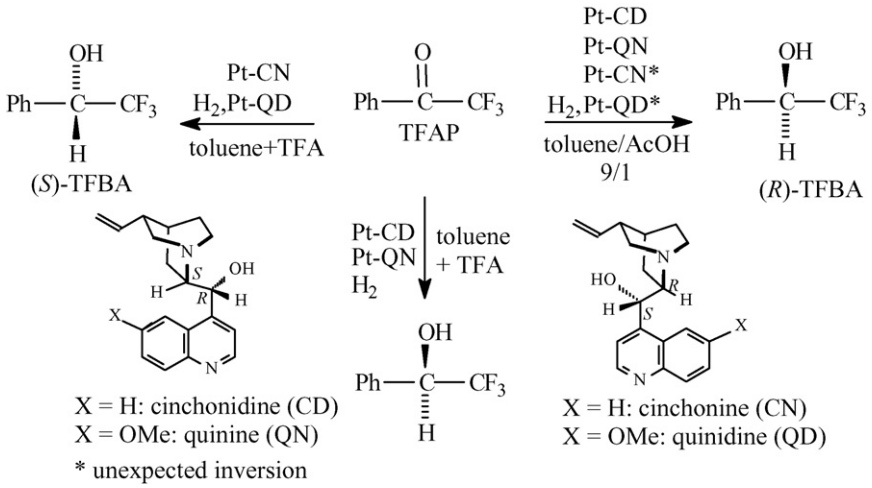


Scheme 1. The Orito reaction.



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

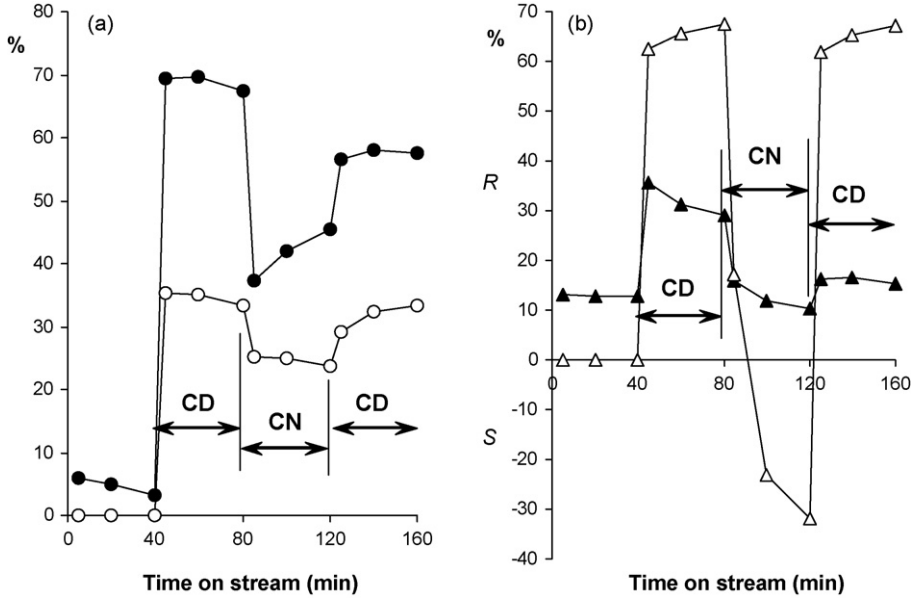


Fig. 1. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of CD followed by CN and again CD (conditions: 100 mg catalyst, [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).

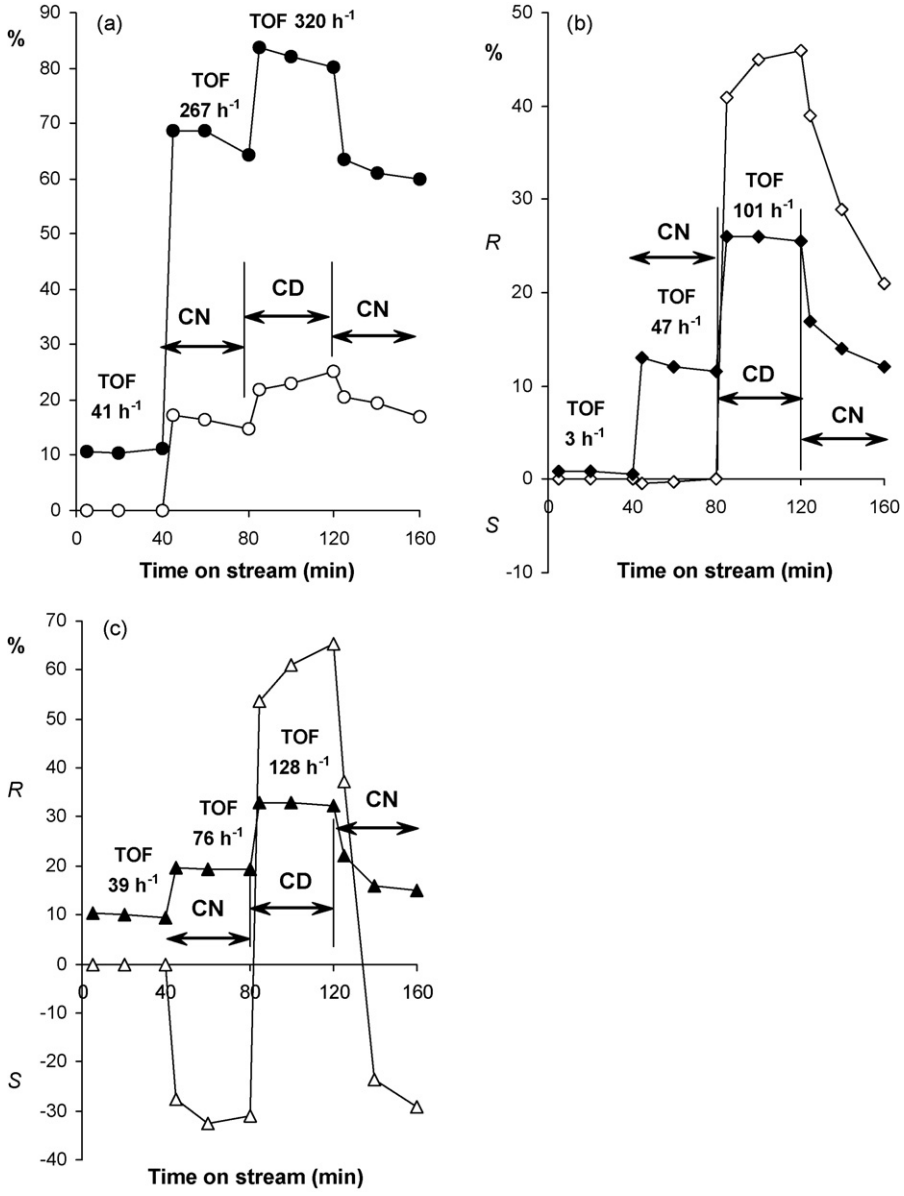


Fig. 2. Transient behaviour in TFAP hydrogenation using continuous system in toluene/AcOH 9/1 (a), toluene/AcOH 1/1 (b) and in the presence of TFA (c): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of CN followed by CD and again CN (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 1/1, 283 K, H_2: 1 MPa; (c): toluene/AcOH 9/1 + 0.1% (v/v) TFA, 293 K, pH_2: 4 MPa).

and solvents were purchased from Aldrich or Fluka, and used as received. TFAP (≥99%, Fluka) was distilled in vacuum using a Vigreaux-column. Engelhard 5% Pt/Al_2O_3 (E4759) was pre-treated in a fixed-bed reactor by flushing with 30 mL min^{-1} He at 300–673 K for 30 min then kept in 30 mL min^{-1} H_2 at 673 K for 100 min. After cooling to room temperature in H_2, the catalyst was flushed with He for 30 min and was stored under air until use [25]. The properties of E4759 catalyst are known from previous studies: Pt-content, 5% (w/w); Pt dispersion (after pre-treatment), 25%; mean Pt particle size, 4.4 nm.

2.2. Hydrogenations in flow system

Continuous hydrogenations were carried in H-Cube high-pressure continuous-flow system. The experimental set-up has been described in detail in our previous publication [9]. Standard conditions were: 100 mg E4759 catalyst, solvent: toluene/AcOH 9/1, liquid flow 1 mL min^{-1}, modifier concentration: 1 mM, TFAP concentration 45 mM, (a): 283 K and 1 MPa hydrogen pressure in the absence of TFA; (b): 293 K and 4 MPa hydrogen pressure in the presence of 0.1% (v/v) TFA.

2.3. Product analysis

These products were identified by mass spectrometric analysis (HP 6890 N GC-HP 5973 MSD, HP-1MS, 60 m capillary column). Conversions and enantiomeric excesses, $ee\% = |[R] - [S]| \times 100/([R] + [S])$, were determined by gas chromatography (HP 6890 N GC-FID, 30 m long Cyclodex-B chiral capillary column: 343 K 5 min, 5 K min^{-1} to 388 K, 388 K 18 min, head pressure 22 psi He). Retention times (min): TFAP 7.0, (*S*)-α-trifluoromethylbenzyl alcohol (TFBA) 25.0, (*R*)-TFBA 25.9. The reproducibility of the results was found to be ±1%. 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 [26].

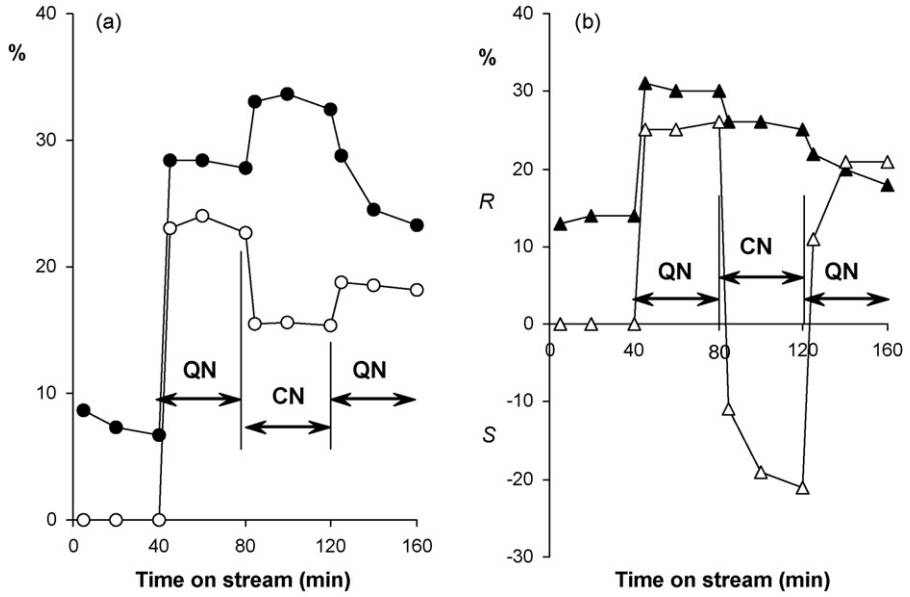


Fig. 3. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of QN followed by CN and again QN (conditions: 100 mg catalyst, [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).

3. Results

3.1. Introduction

Refs. [27–29] describe detailed experiments on the hydrogenation of TFAP over Pt-CD chiral catalyst using a batch reactor system. In the present study we examined the enantioselective hydrogenation of TFAP in continuous-flow system using the transient method, under experimental conditions similar to those employed in Refs. [9,30] using Pt-CD, Pt-CN, Pt-QN and Pt-QD catalysts. The essence of the transient method is the serial replacement of the cinchona alkaloids serving as chiral modifiers in continuous-flow hydrogenation with others that produce the opposite enantiomer [17]. Continuous sampling allows the determination of changes in ee and conversion. Measurement series were started over unmodified catalyst. After certain time, racemic hydrogenation was followed by the addition of the first cinchona, and continued by replacement with a second and later again with the first one. In the case of CD feeding the conversion was over 90%. Experiments using various amounts of catalyst or its crushed form indicated lack of mass transfer limitation, which may play a determinant role in liquid-phase heterogeneous catalytic hydrogenations [31].

3.2. TFAP hydrogenation in 9/1 toluene/AcOH solvent mixture with and without TFA in a continuous-flow system

These continuous-flow experiments were performed under similar conditions as used in the hydrogenation of other activated

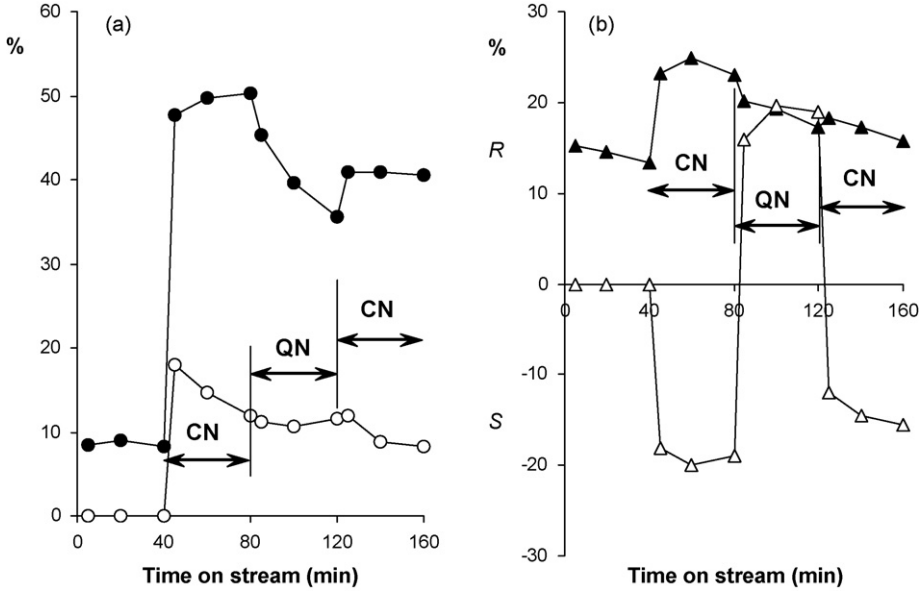


Fig. 4. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of CN followed by QN and again CN (conditions: 100 mg catalyst, [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).

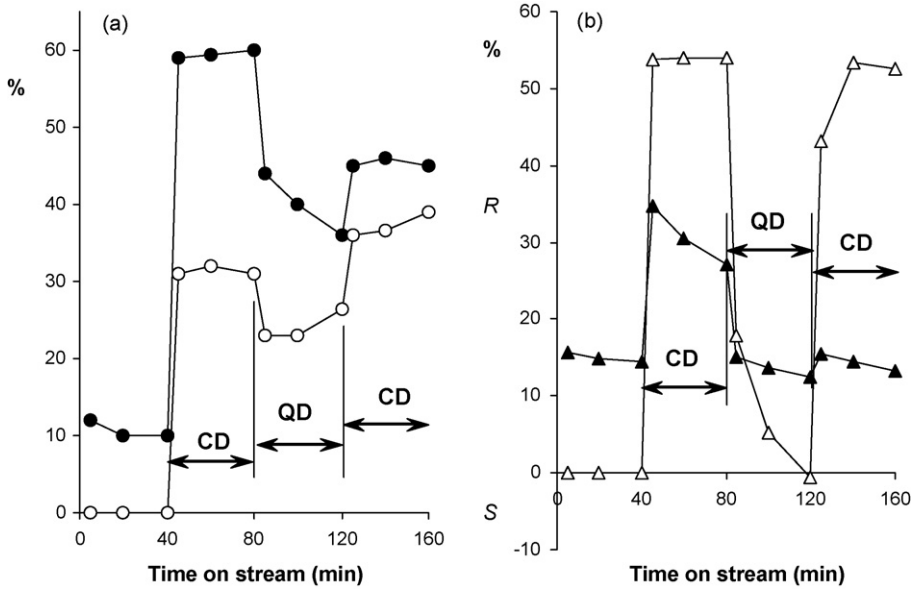


Fig. 5. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of CD followed by QD and again CD (conditions: 100 mg catalyst, [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).

ketones, in a toluene/AcOH (9/1) solvent mixture (with one exception when toluene/AcOH 1/1 was used) [9,30] with and without 0.1% (v/v) TFA content. Although AcOH is not a favourable component in TFAP hydrogenation [29,30], due to its effect to increase the solubility of cinchonas it is a generally used solvent constituent in continuous-flow studies, where higher modifier concentrations are required. The hydrogenation conditions were selected on the basis of the preliminary experiments. Namely, measurements in the presence of the parent cinchona alkaloids were performed at 283 K and a H_2 pressure of 1 MPa in the solvent mixture without TFA. The hydrogenations were significantly decelerated by TFA, and the results did not improve by raising the temperature either. The finally selected experimental parameters based on these experiments were the following: 293 K, 4 MPa, 0.1% (v/v) TFA toluene/AcOH 9/1 solvent mixture. Characteristic experimental data are presented in Figs. 1–7.

The changes in the conversion and the sense of chirality by replacing CD with CN and again with CD and using the opposite order, that is change of CN to CD and again to CN are shown in Figs. 1 and 2. The changes in conversion due to feeding of various modifiers are easily detected: starting from 8 to 13% conversions in racemic hydrogenation, the addition of CD increases the conversion to ~90% (i.e. a significant rate enhancement is observed). The conversion of enantioselective hydrogenation is somewhat reduced by CN and is again increased by CD feeding (Fig. 1a). Similar changes in conversions can also be observed in the racemic – CN–CD–CN measurement series (Fig. 2a and b).

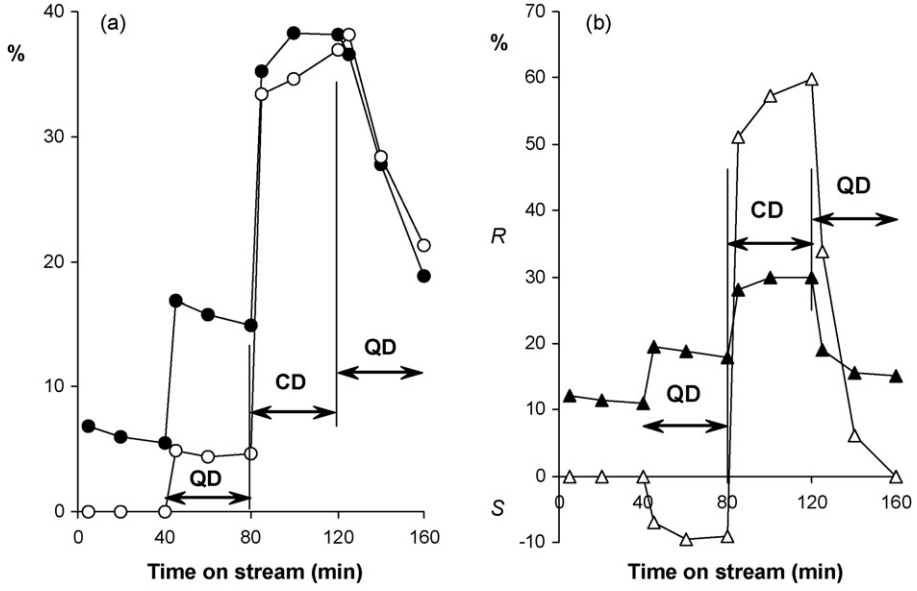


Fig. 6. Transient behaviour in TFAP hydrogenation using continuous system in the absence (a) and in the presence of TFA (b): changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of QD followed by CD and again QD (conditions: 100 mg catalyst, [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).

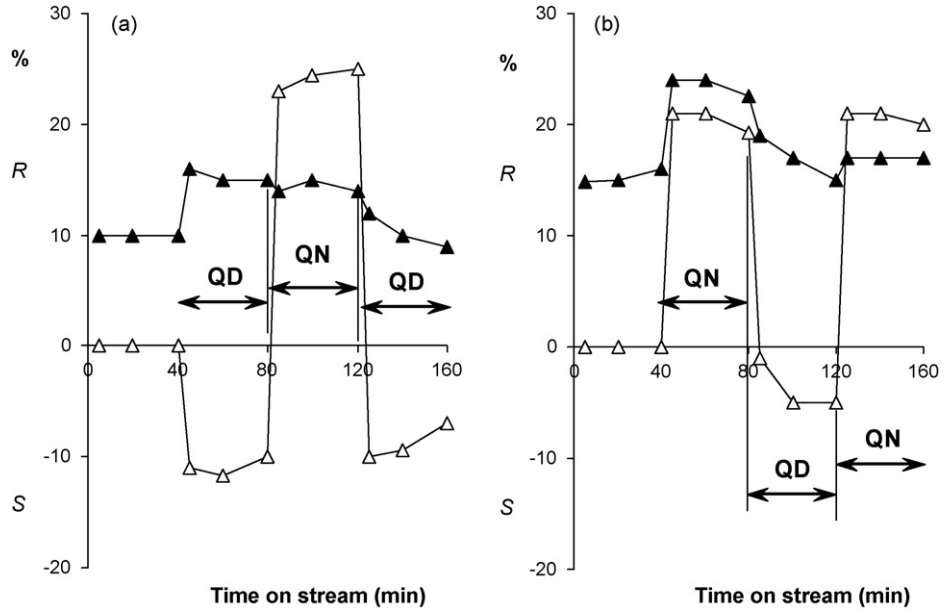


Fig. 7. Transient behaviour in TFAP hydrogenation using continuous system in the presence of TFA: changes in conversion (closed symbols) and enantioselectivity (open symbols) by addition – after racemic hydrogenation – of QD followed by QN and again QD (a), and in opposite order (b) (conditions: 100 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).

The most prominent observation is that the increase in the AcOH amount in the solvent mixture or the use of a much stronger acid (TFA) results in significant decrease in conversions (and the TOF values, see Fig. 2). Thus, when TFA is used the reaction conditions had to be changed (both the H_2 pressure and the reaction temperature were increased) in order to attain satisfactory conversions (see Figs. 1a and 2a vs Figs. 1b, and 2b and c). Meanwhile the ee showed opposite tendency: significantly higher ee values are obtained using CD as modifier by increasing the AcOH content of the solvent mixture or by the use of TFA. In solvent containing TFA, the ee changed from 66% (*R*)-product in the presence of CD to ~30% (*S*)-product when CN was fed and then shifted again to 68% (*R*)-product after feeding CD for the second time. Interestingly, in the hydrogenations in toluene/AcOH 9/1 solvent mixture without TFA, no change of the sense of the ee occurred (Figs. 1a and 2a). Moreover, in 1/1 toluene/AcOH mixture over Pt-CN catalyst only very low ee (close to racemic product) was obtained in favour of the (*S*)-enantiomer (see Fig. 2b). These observations in our opinion pointed to a change in the reaction mechanism, when the acid content of the solvent or the strength of the added acid was increased.

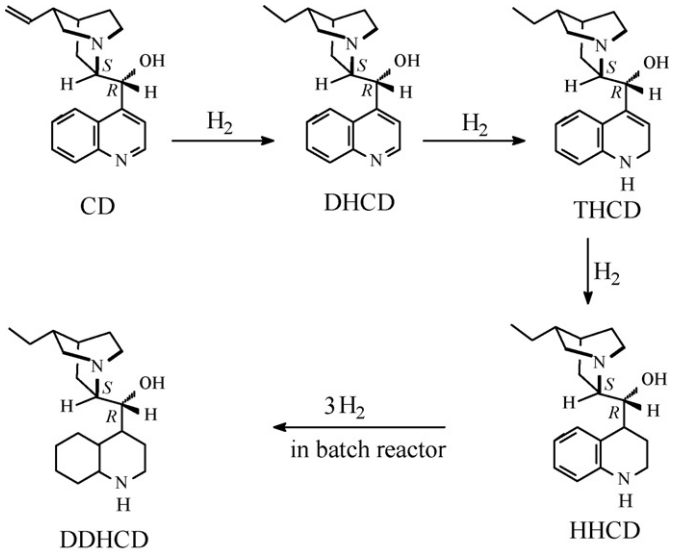
The TOF values calculated from the data series presented in Fig. 2a–c showed an ~6–7 fold increase as effect of CN in toluene/AcOH 9/1 as compared with the initial racemic hydrogenation, while in the presence of TFA only a twofold increase was detected over Pt-CN as compared with the unmodified catalyst. The TOF increased on subsequent CD feeding. In our opinion in the first TOF enhancement both the so-called purifying effect of the cinchona alkaloid and the ligand acceleration [6] played a role, while the subsequent changes in the TOF may be ascribed to ligand acceleration, namely the measurement series presented above justifies the assumption of the intrinsic character of rate enhancement. In our opinion the suppression of catalyst deactivation by cinchona alkaloids cannot be so different for the individual cinchonas as showed the results presented in Figs. 1a and 2a; moreover this cannot show a regularity as observed by the several changes of the modifiers. Since, according to earlier results, the reaction rate is proportional to the adsorption strength of cinchonas [32,33], these measurements also confirm the adsorption strength order: CD > CN.

The results obtained in other measurements series, such as the racemic – QN–CN–QN; racemic – CN–QN–CN; racemic – QD–CD–QD; racemic – CD–QD–CD (Figs. 3–6); racemic – QN–QD–QN; racemic – QD–QN–QD (Fig. 7) may be interpreted in a similar way. The results of the experiments carried out in the CN–QN and QN–CN systems (Figs. 3 and 4) call the attention

Table 1
Relative abundances of the ESI-MS spectra of products formed by hydrogenation of CD on Pt/alumina catalyst[a].

	m/z values (relative peak intensity, %)[b,c]							
Time on stream (min)	[DHCD + H]$^+$ (297)		[THCD + H]$^+$ (299)		[HHCD + H]$^+$ (301)		[DDHCD + H]$^+$ (307)	
5	31	100	100	5	69	8	0	0
10	26	100	100	15	68	23	0	7
20	10	100	100	17	85	30	0	15
40	15	100	100	20	73	60	0	22
60	20	92	100	43	75	100	0	38
65	11		100		67		0	
90	2		100		88		0	
120	2		85		100		0	
150	1		88		100		0	
t185	0		83		100		0	

[a] Conditions: 20 mg E4759, 4 MPa H_2 pressure, for other conditions, see Section 2, solvent toluene/AcOH 9/1.
[b] The 60 min stream of CD in solvent was followed by CD + TFAP stream in the same solvent.
[c] 2nd column: batch experiment (100 mg E4759, 0.1 MPa H_2) [25].

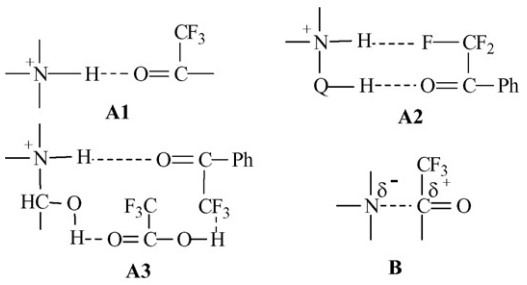


Scheme 3. Transformation of CD during hydrogenation.

on the differences in the reaction mechanism in the two solvent systems. According to the experiences gained from the enantioselective hydrogenations of other activated ketones over Pt-CN and Pt-QN catalysts, it is still ambiguous the observed difference in the activity of the two catalysts [9]. However, as seen from the data presented in Figs. 3a and 4a, the Pt-CN catalyst was found to be more active as compared with Pt-QN. Over Pt-QN in the presence of TFA the conversion of the first enantioselective hydrogenation was significantly higher than that of the second one, which may be explained by the deactivation of the catalyst during time on stream. However, it was also clearly visible, that CN displaced QN easier from the Pt surface than vice versa. The well-known significantly higher adsorption strength of CD as compared to QD is clearly illustrated by Figs. 5 and 6, as well as the weaker adsorption strength of QN and QD among the parent cinchonas (Fig. 7).

Combination of these results with the conclusions of the measurements shown in Figs. 1 and 2 yielded the adsorption strength order: CD > CN > QN > QD, which is identical with the order established for the hydrogenation of other activated ketones under similar conditions [9]; however, is not identical with the order found during the hydrogenation of EtPy [30,34]. The difference is presumably due to the different properties of the complexes formed by the cinchona alkaloids adsorbed on the catalyst surface and the substrates to be hydrogenated [35,36].

Based on these data, the following conclusions can be drawn in the enantioselective hydrogenation of TFAP using continuous-flow system: (i) the most noteworthy experimental result is the unexpected inversion on catalysts Pt-CN and Pt-QD in toluene/AcOH 9/1 solvent mixture without TFA, resulting in the formation of the (*R*)-product in excess instead of the expected (*S*)-product (Figs. 1a–6a); (ii) increasing the AcOH content of the solvent mixture to 50 vol% results in very low excess of (*S*)-alcohol over Pt-CN, thus, gives the expected product in excess based on the general empirical rule of the Orito reaction (Fig. 2b); (iii) enantioselective hydrogenation of TFAP in the presence of TFA follows the general empirical rule of the Orito reaction, namely that the products formed in excess are (*R*)-alcohols on Pt-CD and Pt-QN catalysts and (*S*)-alcohols on Pt-CN and Pt-QD catalysts [3–6]; (iv) the rate enhancement observed on a subsequent asymmetric hydrogenation as compared with the initial racemic hydrogenation (on the same catalyst) strongly supported the ligand acceleration phenomenon [6] for TFAP as well.



Scheme 4. Proposed intermediate complexes in the enantioselective hydrogenation of TFAP.

3.3. ESI-MS measurements of CD hydrogenation

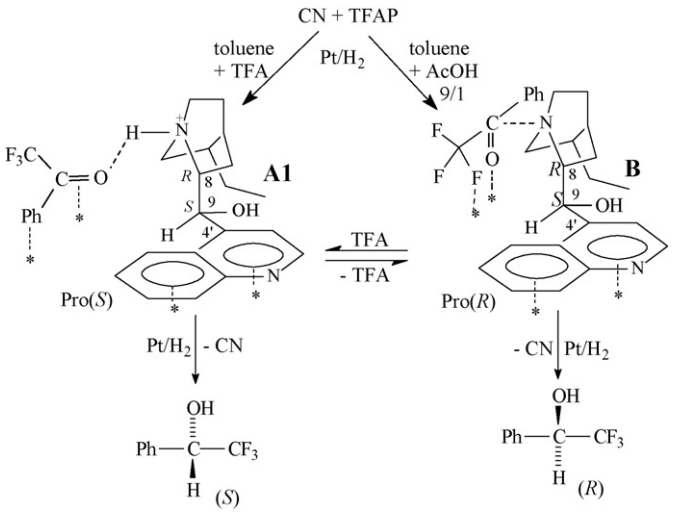
Since reports on the hydrogenation of CD under the conditions of the Orito reaction in a continuous-flow system have not been published, preliminary measurements were carried out to observe the transformation of the modifier in these conditions. The results are shown in Table 1.

There was a significant difference in the product distribution of CD hydrogenation between the batch reactor method [3,25] and the continuous-flow system (see Scheme 3). As a consequence of the short contact time in the continuous-flow system, CD hydrogenation ceased after the formation of HHCD in spite of the high H_2 pressure applied (4 MPa), which means that fast hydrogenation of the vinyl group is followed by hydrogenation of the pyridine skeleton associated with the formation of THCD and HHCD, while the benzene ring remains unaltered. When the amount of catalyst added was doubled (40 mg) in TFAP hydrogenation, the ratio in the intensities of *m*/*z* 301/299 increased to 10. Thus, after a 60 min pretreatment of the catalyst with CD the compounds detected in the solution are mainly THCD and HHCD. One may presume that mostly DHCD, the compound with higher adsorption strength, is present on the catalyst surface and participates in enantiodifferentiation.

4. Discussion

There has recently evolved, with our participation, an extensive debate on hypotheses on the origin of rate enhancement. We set forth our detailed opinion in our recent report [9]. Our standpoint has since been confirmed by the results of other laboratories (for details see [8]). In view of the fact that similar studies have not been performed on the hydrogenation of TFAP, we deemed it necessary to carry out these experiments under conditions identical with those of studies on other activated ketones in order to see whether or not the opinion regarding the origin of rate enhancement can be generalized. In the EtPy hydrogenation on Pt-CD chiral catalyst it is generally accepted that the rate enhancement and enantiodifferentiation are closely connected effects and should be discussed together and that the intermediate complex responsible for enantioselection is the adsorbed 1:1 complex of the cinchona alkaloid (chiral modifier) and the substrate [3–8]. No consensus has been reached, however, concerning the structure of this intermediate. The question arises which of the intermediates proposed so far (Scheme 4) is the most suitable for the interpretation of the enantioselective hydrogenation of activated ketones containing an α-CF_3 group and for the explanation of the experimental observations made in the case of TFAP.

Hydrogenation results obtained under conditions of the Orito reaction, in the continuous system with TFAP in toluene/AcOH solvent mixtures with and without TFA in racemic – cinchona 1–cinchona 2–cinchona 1 measurement series confirm the intrinsic nature of rate enhancement. In our opinion such a regular dynamics of the changes in conversions as observed in the pre-



Scheme 5. The proposed reaction routes for the enantioselective hydrogenation of TFAP over CN-Pt catalyst in continuous-flow system.

sented measurements series is caused mainly by the different adsorption mode of the formed intermediate complexes [9,30]. Consequently, these new experimental data with TFAP not only suggest the validity of the ligand acceleration based interpretation of rate enhancement [6], but also confirm its general character in the hydrogenation of activated ketones. The two reaction routes summarized in Scheme 5 essentially point to the common origin of those processes of the Orito reaction that involve electrophilic and nucleophilic intermediate complexes.

As regards the enantioselective hydrogenation of TFAP on Pt-CN catalyst, Scheme 5 is based on the following data: (i) the N atom of quinuclidine is protonated by strong acids (such as TFA), which ensures the formation of the pro(*S*) complex **A1** [5,37] (recently the role of the hydrogen adsorbed on the surface in the protonation was suggested); (ii) formation of (*S*)-TFAB may also be interpreted by the two-point H-bonding model (**A2** pro(*S*) complex) [21,38] or by cyclic TFAP–CN–TFA ion pairs (**A3** pro(*S*) complex [5,38,39]) (Scheme 4); (iii) although, about 25 equivalents of AcOH are able to protonate the quinuclidine N atom of cinchonas to the same extent as one equivalent of TFA [37,40], in the hydrogenation of TFAP the ee values obtained in the presence of AcOH were not close to those obtained in the presence of TFA (Fig. 2); (iv) nucleophilic addition of amines to ketones is catalyzed by weak acids (e.g. AcOH), because these acids increase the polarity of the carbonyl group [41]; due to its electrophilic character, the CF_3 group also enhances the electrophilic strength of TFAP, which favours the formation of complex **B**; (v) direct evidence was found by NMR spectroscopic methods and theoretical calculations on the occurrence of the nucleophilic interaction [22,23] between ethereal derivatives of cinchonas and ketopantolactone; (vi) the adsorption mode of TFAP has a profound effect on the formation of surface TFAP–CN complexes: the formation of complex **B** is promoted by the end-on "η^1(O)" type adsorption of C=O.

When the scheme regarding the equilibrium is generalized, it cannot be excluded that both complexes may be present in the Orito reaction, depending on the H^+ concentration and the chemical properties of the substrate and the modifier. Their life-time may be determined by the rate of their transformation on the surface of the Pt, which may depend on the type and adsorption mode of the modifier and the substrate, the surface state of Pt and the type of solvent used, to mention just the most important ones (summarized in Refs. [3–7]).

5. Conclusion

Our new experimental results in continuous-flow fixed-bed reactor system allowed the following conclusions to be drawn: (i) since in the TFAP hydrogenation over Pt-CN catalyst there is no unexpected inversion in the presence of TFA, the observed unexpected inversion in toluene [42] and in toluene/AcOH (9/1) can be interpreted with a nucleophilic intermediate complex instead of the one containing the protonated quinuclidine moiety; (ii) proposal of reaction routes involving the equilibrium of the electrophilic and nucleophilic intermediates depending on the acid strength and the chemical nature of the substrate; this is also indicated by the results of the reactions carried out in batch reactor in the presence of CH_3SO_3H and the studies reported by Baiker and coworkers on the enantioselective hydrogenation of ring-substituted acetophenone derivatives [43]; (iii) hydrogenation of the chiral modifier CD proceeds no further than the formation of HHCD; (iv) this research also suggested that the origin of enantiodifferentiation and rate enhancement is the same, namely, both may be traced back – probably in different ways – to the role of the intermediate complexes of the hydrogenation, to its formation and transformation, which in turn depends on numerous factors. However, the full interpretation of these novel and unexpected observations needs further investigations.

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