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Heterogeneous Enantioselective Hydrogenation in a Continuous-flow Fixed-bed Reactor System: Hydrogenation of Activated Ketones and Their Binary Mixtures on Pt–Alumina–Cinchona Alkaloid Catalysts

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Abstract Under the experimental conditions of the Orito reaction the individual hydrogenation and the competitive hydrogenations of three binary mixtures of methyl benzoylformate (MBF), pyruvic aldehyde dimethyl acetal (PA) and 2,2-diethoxyacetophenone (DAP) on platinum–alumina catalysts modified by cinchonidine, cinchonine, quinine and quinidine (Pt–CD, Pt–CN, Pt–QN, Pt–QD) were studied for the first time using continuous-flow fixed-bed reactor system. Conversions of chiral (C_c) and racemic (C_r) hydrogenations of all three compounds and enantioselectivities (ee) were determined under the same experimental conditions (under 4 MPa H_2 pressure, at room temperature using toluene/AcOH 9/1 as solvent).The order of the rates of the enantioselective hydrogenations of the three substrates studied is MBF > PA > DAP, and the order of their ee values is MBF ~ PA > DAP. The hydrogenation rate and the effect of rate on ee depend on the structure of the cinchona used: hydrogenation of MBF and PA may produce ee values over 90 %, however, the ee values were conspicuously low in the presence of Pt–QN and especially of Pt–QD catalysts. In the chiral hydrogenation of DAP considering racemic hydrogenation rate decrease ($C_c/C_r < 1$) takes place instead of rate enhancement over all four catalysts. The new experimental data supported the so far known fundamental rules of the Orito reaction based on batch studies.

Keywords Cinchona alkaloid · Competitive hydrogenations · Enantioselective · Methyl benzoylformate · Pyruvaldehyde dimethyl acetal · 2,2-Diethoxyacetophenone · Pt–alumina · Continuous-flow reactor

1 Introduction

The heterogeneous enantioselective hydrogenation of prochiral ketones is one of the most important methods for the synthesis of chiral secondary alcohols [1–7]. Besides the widespread application of batch reactors the continuous-flow fixed-bed reactor system (CFBR) has also been utilized in the chiral hydrogenation of activated ketones [8–12], mainly to study the mechanism of the Orito reaction [13–17] and in lesser extent to the practical realization of the reactions [18, 19].

Competitive hydrogenation of ketone mixtures over metal catalysts is a widely used method in studies on the mechanism of their surface transformations [20, 21]. Research on competitive hydrogenations has yielded new information on the effect of the electronic and 3D structure of the substrates on adsorption and on surface reactions [22]. In the competitive chiral hydrogenation (C_c = conversion of chiral hydrogenation) over cinchonidine (Pt–CD) chiral catalyst of (diethoxyacetophenone) DAP + PA (pyruvic aldehyde dimethyl acetal) binary mixture the PA is hydrogenated faster than DAP, whereas in racemic hydrogenation

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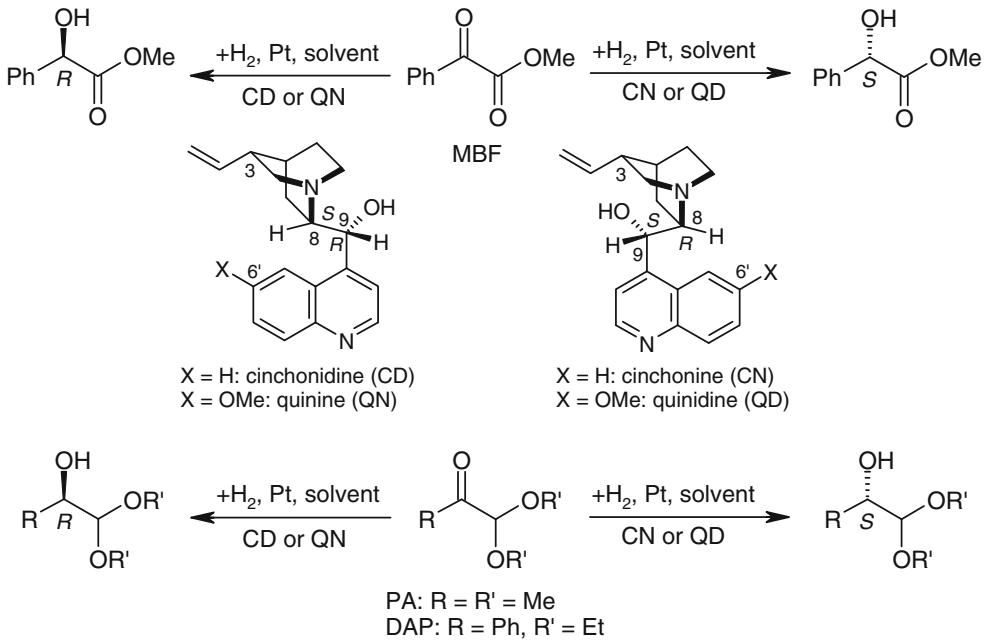

Scheme 1 The Orito reaction of MBF, PA and DAP

(C_r = conversion of racemic hydrogenation) the DAP is hydrogenated faster than PA [23]. In view of this unexpected experimental observation, it seemed expedient to study the competitive hydrogenation of binary activated ketone mixtures in the CFBR system not only over Pt–CD, but using cinchonine (Pt–CN), quinine (Pt–QN) and quinidine (Pt–QD) chiral catalyst, too.

The objective of the present research was to study the hydrogenation of 3 binary mixtures of the activated ketones shown in Scheme 1, i.e. (methyl benzoylformate) MBF + PA, MBF + DAP and PA + DAP, under the experimental conditions of the Orito reaction. Comparison of the experiments on Pt–alumina catalyst modified by parent cinchona alkaloids was the main goal. The present studies on the hydrogenation of these binary mixtures confirmed the unexpected experimental observation obtained using the batch method [24].

2 Experimental

2.1 Materials

Cinchona alkaloids (CD, CN, QN, QD), activated ketones studied (MBF, PA, DAP) and solvents were purchased from Aldrich or Fluka. MBF, PA and DAP were distilled under vacuum using a Vigreux-column. Engelhard 5 % Pt/Al_2O_3 (E4759) was pretreated in a fixed-bed reactor by flushing with 30 mL min^{-1} He at 300–673 K for 30 min and 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 before use [25, 26]. The properties of E4759 catalyst: Pt-content, 5 % (w/w); Pt dispersion (after pretreatment), 25 %; mean Pt particle size, 4.4 nm.

2.2 Hydrogenations in Flow System (CFBR)

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 [14]. The same catalyst was used per measurement cycle (of 160 min) washing the catalyst for 1 h between substrate exchanges (S1, S2, S1 + S2, S1). A typical series of measurement began with pre-hydrogenation of the catalyst (60 min), continued with chiral hydrogenation of individual substrates and followed by chiral hydrogenation of binary mixture. The measurement series were ended by hydrogenation of the first substrate. The purpose of the latter was to monitor the deactivation of the catalyst in the course of the measurement cycle.

Standard conditions were: 50 mg E4759 catalyst, 293 K, 4 MPa hydrogen pressure, solvent: toluene/AcOH 9/1, liquid flow 1 mL min^{-1}, modifier concentration: 0.44 mM, substrate concentration 11 mM. In our earlier experiments we verified that our measurements proceed in a kinetic regime [14], which is also confirmed by the high ee values, since it is well-known that mass transfer limitations can dramatically decrease ee values [4]. Conversions (C) and enantiomeric excesses, ee % = $|[R]-[S]| \times 100/([R]+[S])$, were determined by gas chromatography (HP 6890 N GC-FID, 30 m Cyclodex-B chiral capillary column). The reproducibility of the results was ±2 %.

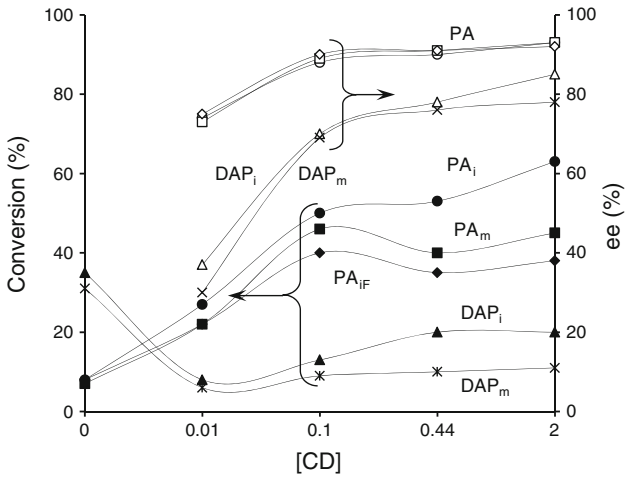

Fig. 1 Enantioselective hydrogenation of PA, DAP and their binary mixture: effect of the modifier concentration on the conversion *(closed symbols)* and on ee *(open symbols)*; (subscript *i* individual, *m* mixture, *iF* final individual hydrogenation, see Sect. 2.2)

3 Results and Discussion

Hydrogenation of activated ketones over Pt–CD catalysts under the conditions of the Orito reaction in a batch reactor has been discussed in numerous reviews [4–7]. The majority of the reports were studies of ethyl pyruvate, a smaller fraction investigates MBF, whereas only very few publications report experiments on PA [23, 27–29] and DAP [23, 27]. However, no experimental observations on the competitive hydrogenation of these substrates and their binary mixtures have been reported yet in the CFBR using Pt–QN, Pt–CN and Pt–QD chiral catalysts.

3.1 Enantioselective Hydrogenation of PA, DAP and Their Binary Mixture: Dependence of Conversion and ee on Modifier Concentration

In our previous work we studied in CFBR the competitive hydrogenation of binary mixtures of activated ketones over CD-modified (0.44 mM) Pt catalyst [23]. Our further aim was to elucidate the effect of the chiral modifier concentration on conversion and enantioselectivity. The experimental data obtained with PA and DAP are shown in Fig. 1.

In batch reactor strong increase with maximum or saturation-type dependence for both rate and enantioselectivity were observed as a function of modifier concentration for hydrogenation of ethyl pyruvate and ethyl benzoylformate. It was plausible to assume that CD is adsorbed stronger than either solvent or the substrate [30]. Studies of this type have been carried out with PA [29]; however, no results have been published using DAP, not even for batch measurements.

The data in Fig. 1 allow the following conclusions to be drawn:

Table 1 Conversion of hydrogenations of individual substrates (C_{Si}) and of competitive hydrogenations of binary mixtures (C_{Sm}) and enantiomeric excesses (ee, %) obtained over chiral catalyst (Pt–M) using the CFBR system

		Individual hydrogenation				Hydrogenation of binary mixtures			
		Conversion (%)		ee (%)		Conversion (%)		ee (%)	
S1 + S2	M	C_{S1i}	C_{S2i}	ee_{S1i}	ee_{S2i}	C_{S1m}	C_{S2m}	ee_{S1m}	ee_{S2m}
MBF + PA	–	80	8	–	–	68	4	–	–
MBF + PA	CD	95	53	89 (*R*)	90 (*R*)	88	38	87 (*R*)	90 (*R*)
MBF + PA	QN	94	37	54 (*R*)	86 (*R*)	93	32	62 (*R*)	85 (*R*)
MBF + PA	CN	83	30	63 (*S*)	64 (*S*)	78	18	62 (*S*)	73 (*S*)
MBF + PA	QD	73	17	23 (*S*)	52 (*S*)	66	8	25 (*S*)	53 (*S*)
MBF + DAP	–	87	30	–	–	80	17	–	–
MBF + DAP	CD	95	20	92 (*R*)	77 (*R*)	90	12	92 (*R*)	77 (*R*)
MBF + DAP	QN	93	5	61 (*R*)	8 (*R*)	86	3	63 (*R*)	8 (*R*)
MBF + DAP	CN	96	9	66 (*S*)	49 (*S*)	94	7	67 (*S*)	48 (*S*)
MBF + DAP	QD	67	4	18 (*S*)	8 (*S*)	63	3	19 (*S*)	5 (*S*)
PA + DAP	–	8	35	–	–	7	31	–	–
PA + DAP	CD	54	14	90 (*R*)	76 (*R*)	40	10	91 (*R*)	76 (*R*)
PA + DAP	QN	28	4	82 (*R*)	7 (*R*)	18	3	82 (*R*)	3 (*R*)
PA + DAP	CN	37	6	68 (*S*)	40 (*S*)	23	4	72 (*S*)	40 (*S*)
PA + DAP	QD	17	4	52 (*S*)	6 (*S*)	9	3	44 (*S*)	6 (*S*)

Reaction conditions: 50 mg Pt/Al_2O_3 (E4759) catalyst, 293 K, 4 MPa H_2 pressure, solvent: toluene/AcOH 9/1, liquid flow 1 mL min^{-1}, modifier (M) concentration: 0.44 mM, substrate concentration: 11 mM; subscript *i* hydrogenation of the individual substrate, *m* hydrogenation of the substrate in binary mixture

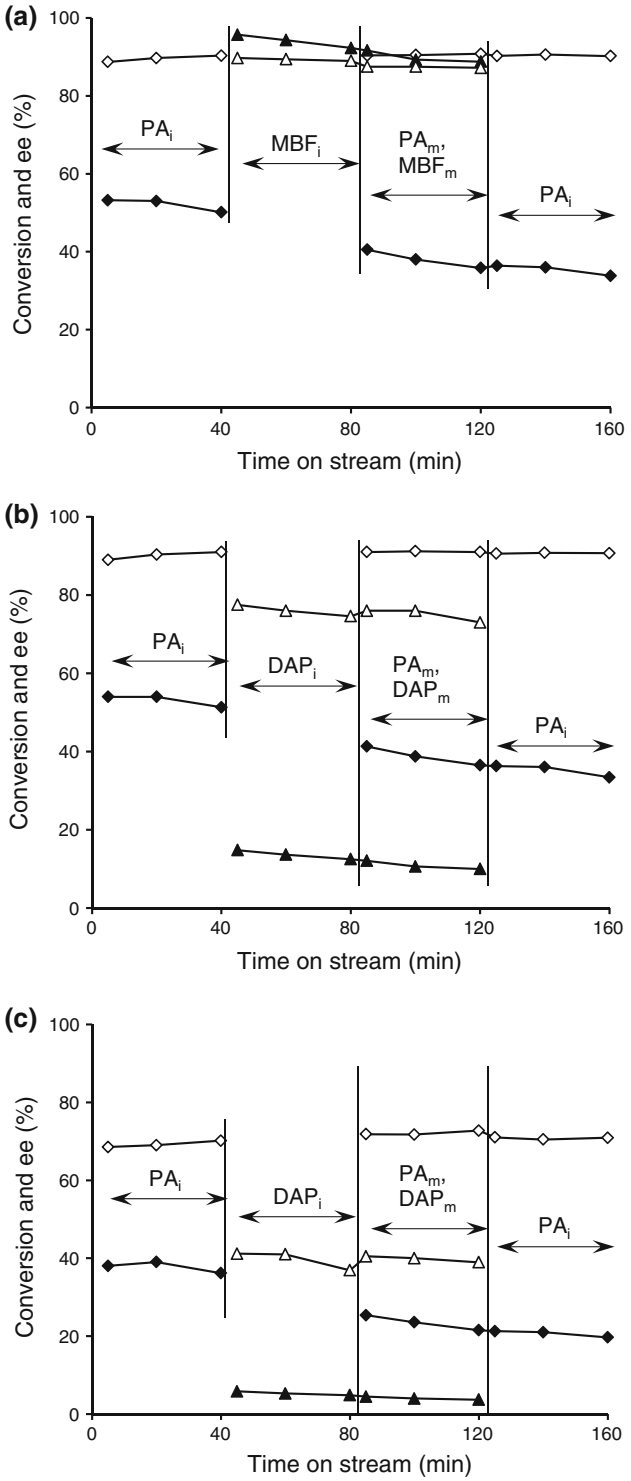

Fig. 2 Conversions (*closed symbols*) and ees (*open symbols*) as a function of time on stream obtained in the enantioselective hydrogenation of **a** PA and MBF; **b** PA and DAP over Pt–CD catalyst and **c** PA and DAP over Pt–CN catalyst (under standard conditions, subscript *i* individual hydrogenation, *m* hydrogenation of the two activated ketone mixture)

(i) Continuous deactivation of the catalyst is observed with the advancement of measurement time, as verified by the comparison of the first and last measurements of the series. (ii) In hydrogenations of both substrates (PA and DAP) $C_i > C_m$ and $ee_i > ee_m$, which can be explained by the higher concentration and/or faster conversion of the surface complex responsible for chiral induction. (iii) Conversion as well as ee increase continuously with modifier concentration in the case of both the individual substrates and their mixtures (with the exception of racemic hydrogenations of DAP). (iv) Just like the chiral hydrogenation of the majority of activated ketones, that of PA also proceeds according to the "ligand acceleration" (LA) mechanism [19]; in the chiral hydrogenation of DAP, however, a rate decrease ("ligand deceleration") was observed instead of rate enhancement.

A chiral modifier concentration of 0.44 mM was chosen for further measurements in spite of the fact that, according to the experimental data shown in Fig. 1, the 2 mM concentration was somewhat more favorable. The reason for our choice was to make possible the comparison of the new experimental data with the previous CFBR measurements performed at a cinchona concentration of 0.44 mM.

3.2 Enantioselective Hydrogenation of Individual Substrates and Their Binary Mixtures

Results of the measurements are presented in Table 1, and typical measurement series are shown as examples in Fig. 2. Fig. 2a presents a hydrogenation associated with an outstandingly high ee (MBF, PA, Pt–CD catalyst), whereas Fig. 2b, c shows chiral hydrogenations of the rarely studied substrates PA and DAP over Pt–CD and Pt–CN catalysts. According to Fig. 2, catalyst activity is somewhat diminished with the progress of reaction time. Deactivation is mainly the consequence of the substrates side reactions (decomposition accompanied by carbonaceous deposition and CO formation) [4, 31, 32]. Due to the character of the measurement, steady state cannot be reached within the hydrogenation time of 160 min. Some of the conversion data (C_{Si}) in Table 1 indicate inconsistent reproducibility: it is well-known that catalyst systems treated with chiral modifiers are somewhat more sensitive than unmodified hydrogenation catalysts. The reason for this is, among others, that depending on the initial state of the catalyst, the chiral modifier brings about dynamic and continuous changes in the structure of the active sites [28, 33–40]. This effect of the modifier also depends on its irreversible adsorption under the different conditions of the reactions [34, 41, 42].

Table 2 Data calculated from Table 1

S1 + S2	M	C_{S1i}/C_{S2i}	C_{S1m}/C_{S2m}	$C_{S1i/m}$	$C_{S2i/m}$	$ee_{S1i/m}$	$ee_{S2i/m}$	C_c/C_r	
								$S1_i$	$S2_i$
MBF + PA	CD	1.8	2.3	1.1	1.7	1.0	1.0	1.2	6.6
MBF + PA	QN	2.5	2.9	1.0	1.2	0.9	1.0	1.2	4.6
MBF + PA	CN	2.8	4.3	1.1	1.7	1.0	0.9	1.0	3.8
MBF + PA	QD	4.2	8.3	1.1	2.1	0.9	1.0	0.9	2.1
MBF + DAP	CD	4.8	7.5	1.1	1.7	1.0	1.0	1.1	0.6
MBF + DAP	QN	18	29	1.1	1.7	1.0	1.0	1.1	0.1
MBF + DAP	CN	11	13	1.0	1.3	1.0	1.0	1.1	0.3
MBF + DAP	QD	17	21	1.1	1.3	1.0	1.6	0.8	0.1
PA + DAP	CD	4	4	1.4	1.4	1.0	1.0	6.8	0.4
PA + DAP	QN	7	6	1.6	1.3	1.0	2.0	3.5	0.1
PA + DAP	CN	6	5.8	1.6	1.5	0.9	1.0	4.6	0.1
PA + DAP	QD	4	3	1.9	1.3	1.2	1.0	2.1	0.1

For abbreviations see Table 1; C_c/C_r = ratio of conversions of chiral and racemic hydrogenation

The experimental data in Tables 1, 2 and Fig. 2 lead to several conclusions related to the hydrogenations of MBF, PA and DAP under the same experimental conditions. (i) The order of the rates of the enantioselective hydrogenations of the three substrates studied is MBF > PA > DAP not only over Pt–CD [23] but over Pt–QN, CN, QD catalysts too and the order of their ee values is MBF ~ PA > DAP. (ii) The order of the rates of the racemic hydrogenations due to strongly adsorbing phenyl group is MBF > DAP > PA [23]. (iii) The hydrogenation rate and the ee depend on the structure of the cinchona used: in accordance with measurements in batch reactor [24, 43] the most favorable modifier in the Orito reaction is CD. (iv) The order of conversions (C) and that of ee values in MBF hydrogenation are: C: CD ~ QN > CN > QD, ee: CD > CN > QN > QD; the orders for PA hydrogenation are: C: CD ~ QN > CN > QD, ee: CD > QN > CN > QD; the orders for DAP hydrogenation are: C: CD > CN > QN > QD, ee: CD > CN > QN ~ QD. These orders indicate that the optimal parameters of the hydrogenations of activated ketones with different structures are different. (v) As regards the magnitudes of conversions and ee values, in accordance with batch measurements [24] in the case of $C^{6'}$-OMe cinchonas (QN, QD) the values are generally lower than in the case of cinchonas lacking the $C^{6'}$-OMe group (CD, CN); this phenomenon that calls attention to the important role of two-point H-bonding interactions in the cinchona:substrate 1:1 complex [44–47]. (vi) In agreement with the rule recognized for ethyl pyruvate, the configuration of the resulting alcohols is *R* in the presence of CD and QN ($C^8(S)$, $C^9(R)$), and *S* in the presence of CN and QD ($C^8(R)$, $C^9(S)$) (see Scheme 1). (vii) As compared with previous investigations [23] experimental evidence was provided that not only over Pt–CD but over Pt–QN, CN, QD catalysts rate enhancement takes place too (the values of $C_c/C_r > 1$) in the chiral hydrogenation of the PA; however, a rate decrease is observed ($C_c/C_r < 1$) in the DAP hydrogenation, which points to differences in one or more steps of the mechanism of the hydrogenation of these compounds. From this point of view MBF has an intermediate behaviour.

Table 2 gives a comparison of the hydrogenation data of the individual substrates and their binary mixtures. These data allow some general conclusions to be drawn (the order of the data listed in Tables 1 and 2 was determined according to $C_{S1} > C_{S2}$): (i) in the case of hydrogenations proceeding at relatively high rates (MBF), $C_{S1m}/C_{S2m} > C_{S1i}/C_{S2i}$, independently of cinchonas, whereas in the case of relatively slower hydrogenations (PA + DAP) this ratio is nearly identical, which is in agreement with the higher adsorptivity and/or reactivity of the S1: cinchona 1:1 complex as compared to S2; the same is suggested by the $C_{S1i/m}$ and the $C_{S2i/m}$ ratios; (ii) attainable ee values are: ee_{high} (76–92 %) over Pt–CD catalyst in hydrogenations of all three substrates and over Pt–QN catalyst in the hydrogenation of PA; ee_{med} (40–70 %) over Pt–CN catalyst in hydrogenations of all three substrates and over Pt–QN catalyst in the hydrogenation of MBF; and, finally, ee_{low} (5–24 %) over Pt–QD catalyst in hydrogenations of all three substrates and especially DAP; (iii) there were no differences among the ratios of enantioselectivities.

4 Conclusions

Using CFBR method in the enantioselective hydrogenation attention is called to the following: the magnitude of conversions and enantioselectivities obtained under

identical experimental conditions depends on the structure of the cinchona alkaloid present and that of the substrate to be hydrogenated. The slow rate of the PA hydrogenation, which is significantly different from the MBF hydrogenation, together with the outstandingly high ee may indicate differences in some steps of the multistep reaction mechanism. The slow hydrogenation rate of PA and DAP may presumably be related to their adsorption mode and to the desorption of the product. This phenomenon—slow reaction rate and high ee—unusual in the Orito reaction calls for further studies (see in Ref. [30], Fig. 8). As regards the ee values, in the case of all three substrates outstandingly high, medium and low ee values were also obtained. The lowest ee values mainly occured with the use of Pt–QD catalyst. The highest ee values could be attained in the presence of Pt–CD catalyst.

These experimental observations showed identical tendencies as were obtained in batch reactors. However, the interpretation, of the differences between the results obtained in batch and in continuous flow reactors necessitates further studies and a more profound knowledge of reaction kinetics.

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