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Ruthenium-supported catalysts for the stereoselective hydrogenation of paracetamol to 4-*trans*-acetamidocyclohexanol: effect of support, metal precursor, and solvent

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Abstract

The influence of the support, the metal precursor, and the solvent on the selective hydrogenation of paracetamol (4-acetamidophenol) was studied over supported ruthenium catalysts. The catalysts supported on the oxidic supports Al_2O_3 and SiO_2 gave the best results in terms of activity, selectivity for the acetamidocyclohexanols (99%), and stereoselectivity for the *trans* isomer (53 and 46%, respectively). Carbon-supported catalysts produced larger amounts of secondary compounds, mainly N-cyclohexylacetamide, which was derived from the hydrogenolysis reaction of the OH group. The use of a chloride precursor resulted in the enhancement of the formation of N-cyclohexylacetamide and partially hydrogenated products; the stereoselectivity also increased. Moreover, because of the acidity caused by residual Cl, condensation led to oligomers of paracetamol. In spite of the decrease in the selectivity for cyclohexanol derivatives when the more polar solvent ethanol was used instead of isopropanol or tetrahydrofuran the stereoselectivity for the *trans* isomer increased from 30 to 38%.

The results confirm that the factors studied affect the mode of adsorption of the molecule of paracetamol on the catalyst in different ways. These effects determine the product distribution and the selectivity of the reaction.

Keywords: Stereoselective hydrogenation; *Cis* and *trans* isomers; 4-Aminocyclohexanol; Ruthenium-supported catalysts

1. Introduction

The hydrogenation of disubstituted aromatics, particularly of substituted phenols to the corresponding substituted cyclohexanones and cyclohexanols, has attracted the interest of the industry and researchers. The reason for this is that these compounds are used as key intermediates for the manufacture of fine chemicals for the fragrance and detergent industries. Moreover, the stereochemistry of the reactions is important since generally only one of the isomers of the *cis* and *trans* mixture has the desired properties. Several reports have dealt with the role of the nature of the metal phase in the hydrogenation reaction and its stereoselectivity [1–8]. Group VIII metals are generally used, but different behaviors are observed. Whereas Pd gives mainly the cyclohexanone derivatives, rhodium and platinum are very selective for the *cis* isomer. Nickel is more stereoselective for the *trans* isomer but generates higher amounts of hydrogenolytic cleavage products. However, exhaustive studies of the range of parameters that can influence the reaction (support, reaction conditions, promoters, or additives), as have been carried out for the hydrogenation of benzene or phenol [9–11], are scarce.

Among the substituted cyclohexanols, the synthesis of 4-*trans*-aminocyclohexanol is of great importance. This compound is an intermediate in the multistep synthesis of Ambroxol [12–14], N-(2-amino-3,5-dibromobenzyl)-*trans*-4-aminocyclohexanol, which is a bronchosecretolitic agent

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for the prevention and treatment of diseases of the respiratory tract and bronchial tubes [15,16]. Although several procedures have been tested for obtaining *trans*-4-aminocyclohexanol (i.e., hydrogenation of *p*-nitrophenol or *p*-aminophenol), the main route is the catalytic hydrogenation of 4-acetamidophenol (paracetamol) [17–19] to yield a *cis*/*trans* mixture of 4-acetamidocyclohexanol, which is subsequently hydrolyzed to *cis*/*trans*-4-aminocyclohexanol; the isomers are finally separated by fractional crystallization. Considering the complete process and that the product is used in pharmacology, the aim is to achieve the maximum yields of the *trans* isomer in the initial hydrogenation reaction to reduce the amounts of products of no interest. Apart from the economic and environmental benefits, this would simplify the workup and purification of the reaction product.

The purpose of this study was to investigate the factors that can affect the hydrogenation of paracetamol in the liquid phase over ruthenium catalysts. The effects of the support (metal oxides or carbon materials) and the ruthenium metal precursor and the role of the reaction solvent were investigated.

2. Experimental and methods

2.1. Catalyst preparation

The supports were silica (Aerosil Degussa, $S_{\text{BET}} = 180$ $m^2\,g^{-1}$); alumina (Puralox Condea, $S_{\text{BET}} = 192$ $m^2\,g^{-1}$); a molecular sieve of carbon, S ($S_{\text{BET}} = 970$ $m^2\,g^{-1}$); and an activated carbon (ICASA, Spain, $S_{\text{BET}} = 961$ $m^2\,g^{-1}$). The S carbon was synthesized by carbonization of the copolymer Saran (90% vinyliden chloride–10% vinyl chloride; Aldrich) under inert conditions (N_2; 100 $cc\,min^{-1}$) at 1273 K [20].

The Ru-supported catalysts (2 wt% metal loading) on alumina (RuA), silica (RuSi), and activated carbon (RuC) were prepared by the incipient wetness technique with aqueous $Ru(NO)(NO_3)_3$ solutions. Another catalyst, RuClC, was prepared with an $RuCl_3 \cdot xH_2O$ ethanolic solution on activated carbon. The catalyst supported on S (RuS) was prepared by impregnation of the support (outgassed at 423 K for 1 h) with a methanolic solution of the $Ru(NO)(NO_3)_3$ precursor and subjected to a freeze-thaw cycle. After impregnation, all of the catalysts were dried overnight at 383 K. Furthermore, the catalysts supported on oxides were calcined in air at 723 K for 3 h.

2.2. Catalyst characterization

Temperature-programmed reduction (TPR) measurements were carried out in a quartz microreactor over 200 to 300 mg of prepared sample under a continuous flow at 25 $cc\,min^{-1}$ of a H_2/He gas mixture (10% H_2). The temperature was increased from room temperature to 873 K at 8 $K\,min^{-1}$. H_2 consumption was measured by on-line gas chromatography (Varian 3400) with a thermal conductivity detector (TCD).

The metal dispersion of the catalysts was determined from H_2 chemisorption measurements at 298 K in a volumetric system, described elsewhere [21]. The samples were subjected to in situ reduction pretreatment in H_2 at 673 K. Mean particle sizes were determined under the assumptions of $M{:}H_2 = 2{:}1$ stoichiometry and spherical metal particles ($\bar{d}$ (nm) $= 1.32/D$) [22].

The heat of CO adsorption at 330 K was measured in a differential heat-flow microcalorimeter (Tian–Calvet type C80 from Setaram). The adsorption vessels were connected to a Pyrex volumetric apparatus equipped with greaseless stopcocks that permitted the introduction of small pulses of CO [23]. The samples were activated in flowing H_2 at 673 K for 2 h and, after outgassing at this temperature for 16 h, were cooled to the adsorption temperature. Successive doses of CO were then transferred to the sample. The equilibrium pressure was measured by means of a Baratron pressure transducer MKS instrument. The calorimetric and volumetric data were stored and analyzed with a microcomputer.

2.3. Catalytic hydrogenation

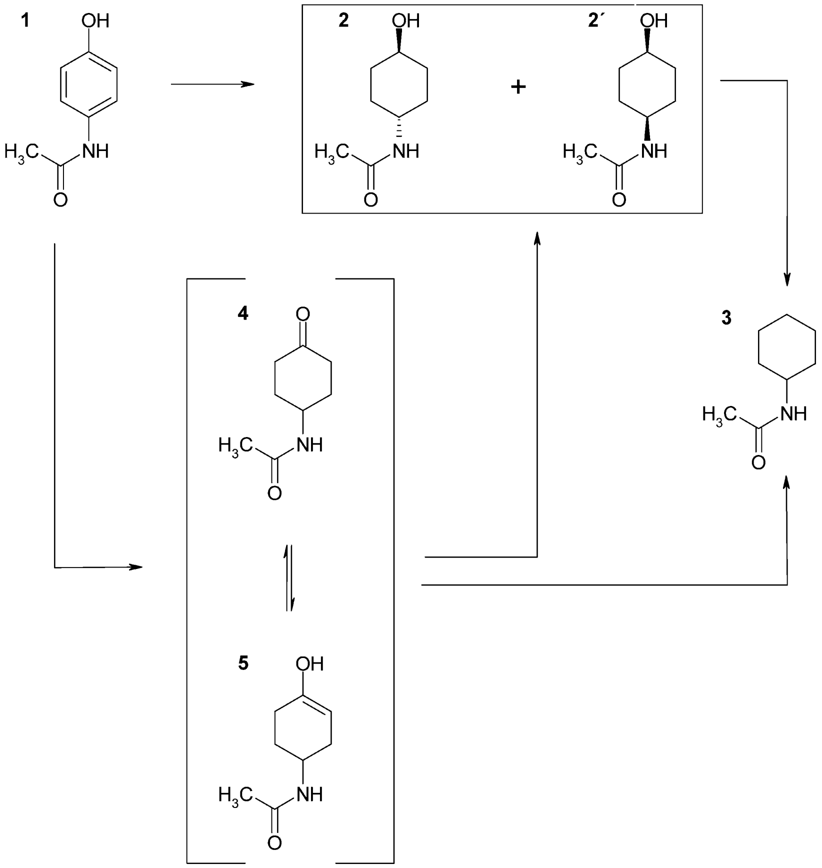
The hydrogenation reaction was carried out under high pressure in an autoclave fitted with a magnetically coupled stirring head, inlet/outlet ports, and a pressure gauge. After being reduced in flowing hydrogen at 673 for 2 h, the catalyst (500 mg) was transferred to the reactor flask, which contained a solution of paracetamol (98% 4-acetamidofenol; Research Chemical, Ltd.) in ethanol (ca. 25 $\mu mol\,ml^{-1}$). The autoclave was closed, purged in He, and heated to the reaction temperature (393 K). Then the autoclave was pressurized to 50 bar with H_2 and the reaction started. Samples were taken periodically and analyzed with a gas chromatograph (Varian 3800) equipped with a flame ionization detector (FID) and a capillary column (MFE-624, 25 m × 0.25 mm × 0.25 μm; initial temperature, 155 °C, 5 min; final temperature 200 °C, 6 min; rate 10 $°C\,min^{-1}$). Preliminary runs carried out at different rates of stirring, levels of loading, and catalyst grain size revealed the absence of external and internal mass transfer limitations.

Considering the possible reaction pathways (Scheme 1), we calculated the selectivities for alcohols (**2** and **2′**) (S_H), N-cyclohexylacetamide (**3**) (S_N), and other products (**4**) (S_O). The stereoselectivity between the two alcohol isomers (**2** and **2′**) was defined as $S_T = C_{trans} \times 100/(C_{cis} + C_{trans})$.

3. Results and discussion

3.1. Catalyst characterization

Fig. 1 displays the TPR profiles of H_2 consumption for the Ru-supported catalysts. RuA and RuSi catalysts showed



Scheme 1. Reaction pathways in the hydrogenation of paracetamol (**1**: paracetamol, **2**: *trans*-4-acetamidocyclohexanol, **2′**: *cis*-4-acetamidocyclohexanol, **3**: N-cyclohexylacetamide, **4**: 4-acetamidocyclohexanone, and **5**: 4-acetamidocyclohexenol).

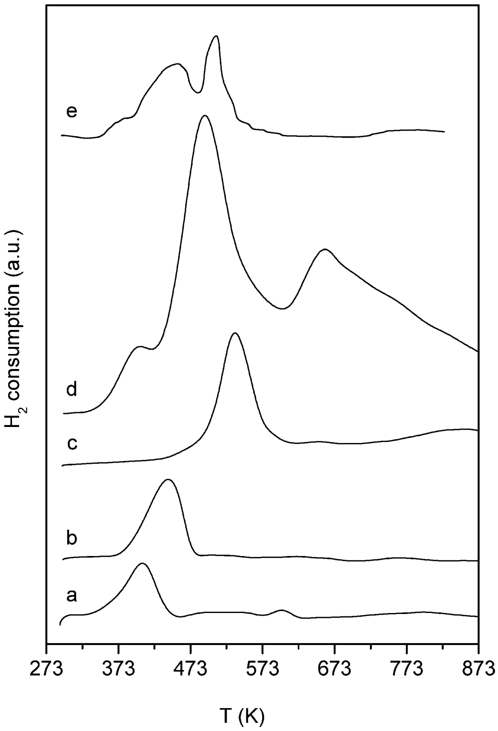


Fig. 1. Temperature-programmed reduction profiles for catalysts (a) RuA, (b) RuSi, (c) RuS, (d) RuC, and (e) RuClC.

unique peaks at 405 and 440 K, respectively. The temperature of reduction corresponds to the reduction of RuO_2 formed after the calcination of the catalysts; unsupported bulk RuO_2 is reduced in a single peak at 490 K [24]. On the other hand, the RuC and RuClC catalysts showed several regions of hydrogen consumption: below 423 K, between 423 and 573 K, and above 623 K. The first and second regions are ascribed to the decomposition of the residual metal precursor salt, nitrate or chloride, and the reduction of Ru(III) to Ru^0. Reduction of unsupported $RuCl_3$ occurs at temperatures around 433 K [24]. The maxima of the H_2 consumption were observed at 510 K for RuC and at 440 and 508 K for RuClC. The detection of two peaks for the latter catalyst indicates that two different species are present, one of which is probably ruthenium oxidized by atmospheric air exposure. The band in the third region was found only for the RuC catalysts. Evolution of CH_4 and CO, parallel to H_2 consumption, indicates partial gasification of the support around the metal particles [23–26] and decomposition and hydrogenation of the surface oxygen groups [27–30]. These oxygen groups are generated on the carbon surface during impregnation with the oxidizing solution of the metal precursor $RuNO(NO_3)_3$. The RuS sample showed a peak centered at 540 K (Fig. 1c), indicating that the reduction of the metal is hindered compared with that of the RuC catalyst. The ab-

Table 1
Catalytic results of ruthenium-supported catalysts on the hydrogenation of paracetamol at 393 K

Catalyst	d_H (nm)	Activity (μmol g_M^{-1} s^{-1})	TOF (s^{-1})	Selectivity[a] (%)			Stereoselectivity, S_T (%)
				S_H	S_N	S_O	
RuA	19	183	0.26	99	1	0	53
RuSi	33	56	0.14	99	1	0	46
RuS	26[b]	10	0.02	94	4	2	46
RuC	2.6	45	0.01	80	17	3	38
		325[d]	0.06	89	10	1	33
		91[e]	0.02	92	6	2	30
RuClC	29[c]	7	0.01	64	24	13	42

[a] Selectivity to *cis*/*trans*-acetamidocyclohexanol (S_H), N-cyclohexylacetamide (S_N), other products (S_O), and stereoselectivity to *trans*-acetamidocyclohexanol (S_T).

[b] 2–5 nm (determined by XRD and TEM).

[c] Reduction at 723 K and 7.8 nm determined by CO chemisorption.

[d] Solvent IPA.

[e] Solvent THF.

sence of a band at higher temperatures indicates a decrease in surface gasification and surface oxidation, probably as a consequence of the differences in the preparation method, as indicated in Section 2. The higher temperature of reduction for the two carbon-supported catalysts prepared with the nitrate precursor, RuC and RuS, compared with the catalysts supported on oxides may be due to the presence of oxide-like Ru species, formed after drying in air and during the precursor decomposition, which interact with the oxidized surface and consequently are more difficult to reduce.

The results of the H_2 chemisorption experiments, carried out on the ruthenium catalysts, are shown in Table 1. The catalysts supported on the oxides, RuA and RuSi, showed low dispersion, probably because of calcination, which favors the sintering and migration of the RuO_2 species. The chemisorption measurements indicated that 26-nm particles are present on the RuS catalyst. On the other hand, ruthenium is homogeneously dispersed on the RuC catalyst, with particles ranging from 2 to 3 nm. The particle size of RuClC increased to 29 nm. This seems to be a consequence of the metal precursor used for catalyst preparation. The presence of some poisoning chloride species may explain the low hydrogen adsorption capacity of this sample. Moreover, the discrepancy between the particle sizes as determined by H_2 and CO chemisorption on this catalyst (7.8 nm) [31] support this assumption.

The particle sizes obtained with H_2 chemisorption are consistent with that determined by XRD and TEM for all of the samples except the RuS catalyst [32]. Both techniques gave a smaller mean particle size (2–5 nm) for this sample.

3.2. Catalyst reactivity in the hydrogenation of paracetamol

3.2.1. Effect of support

According to the mechanisms proposed for the hydrogenation of phenol and alkyl-substituted phenols [3,33,34], the hydrogenation reaction of paracetamol can follow the reaction pathways shown in Scheme 1. The main products obtained under the experimental conditions are a mixture of *cis*- and *trans*-4-acetamidocyclohexanol, N-cyclohexylacetamide, and partial hydrogenation products (such as 4-acetamidocyclohexanone). The typical evolution of the reaction composition with reaction time is displayed in Fig. 2. Table 1 gives the catalytic results of the hydrogenation of paracetamol obtained with the Ru catalysts after reduction at 673 K. The TOF values were calculated from the dispersion determined by H_2 chemisorption. The data show that the initial catalytic activity (μmol g_{Ru}^{-1} s^{-1}) follows the trend RuA > RuSi > RuC > RuS (Table 1). Moreover, if we take into account that the metal particle size for the RuS catalyst, as determined by H_2 chemisorption, is overestimated [32], the general trend indicates that the activity per surface metal site increases with the metal size. These results agree well with previous findings reported for Ru catalysts supported on graphite [35].

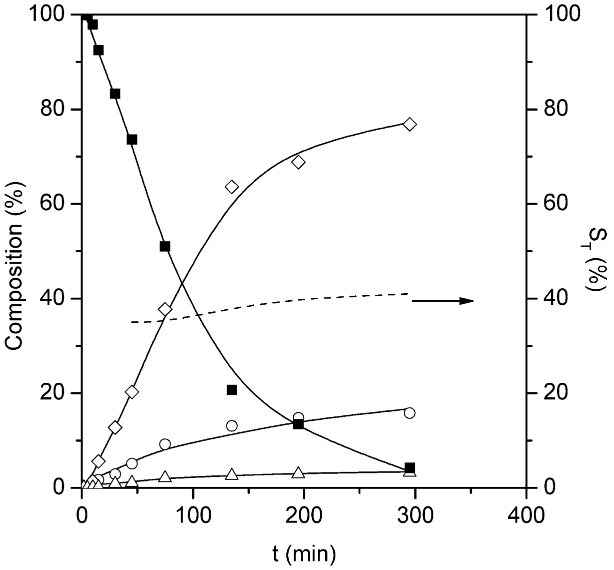


Fig. 2. Evolution of stereoselectivity to *trans*, S_T, (---), and of composition with time in reaction, (■) paracetamol, (□) *cis*/*trans*-acetamidocyclohexanol, (○) N-cyclohexylacetamide, (△) other products. Catalyst, RuC; temperature, 393 K; $P(H_2) = 50$ bar; solvent, ethanol.

As far as the selectivity is concerned, the catalysts supported on alumina and silica resulted mainly in hydrogenated products, with selectivities higher than 99% for the *cis* and *trans* alcohols. For the catalysts supported on carbon materials, the selectivity for the hydrogenated products decreased in favor of N-cyclohexylacetamide and products due to partial hydrogenation, which appeared mostly at the beginning of the reaction. The highest stereoselectivity for the *trans* isomer was obtained for the RuA catalyst, with values around 53%. Whereas high values were also obtained with the RuSi and the RuS catalysts, a stereoselectivity of only 38% was reached with the RuC sample.

In general, it is postulated that the bonding of an aromatic to the metal occurs via π-bonds involving electron transfer from the ring to the unoccupied d metal orbitals [36]. Paracetamol is a molecule with a flat structure and has weak acidic properties; the presence of OH and acetamide substituents in the aromatic ring has positive resonance effects and would enhance the adsorption of the aromatic ring by stabilizing the π-complex. On the catalysts supported on carbon, this adsorption through the aromatic ring would be stronger because of the smaller size of the ruthenium particles, leading to lower activity (Table 1) and to reaction beyond the complete hydrogenation of the ring to produce the cyclohexyl derivative. However, in addition to aromatic ring interactions, the paracetamol molecule can adsorb via the hydroxyl group. Assuming a scenario similar to that postulated for phenol and alkyl-phenols [33,37], the results obtained may be a consequence of the existence of two adsorbed species on the catalyst surface: with the ring orientated in a coplanar or a nonplanar fashion with respect to the surface. On the RuA and RuSi catalysts, the presence of incompletely reduced Ru species ($Ru^{\delta+}$), stabilized by interaction with the support, should favor the coplanar adsorption of the molecule, leading to complete hydrogenation. Simultaneously, 4-acetamidocyclohexanol may be formed after the stepwise addition of hydrogen to species adsorbed in the nonplanar mode. However, the influence of the acid–base properties of the support on the product distribution, as postulated for the hydrogenation of phenol and alkyl-phenols, cannot be ruled out.

The production of *trans* isomers is generally explained by isomerization processes or double bond migration of the partially hydrogenated cyclic alcohol and is associated with a rollover mechanism [36]. For alkyl-substituted phenols the stepwise addition leads to the alkylcyclohex-1-en-1-ol, which is not isolated and which is transformed to the alkylcyclohexanone by tautomerism. Whereas the hydrogenation of the alkylcyclohexanone leads to both *cis* and *trans* alkylcyclohexanols, the enol is hydrogenated to the *cis* isomer, increasing its concentration in the final mixture [3]. Thus, the selectivities for *cis* and *trans* isomers, obtained in the hydrogenation of paracetamol, may indicate that the catalyst influences the keto-enol equilibrium. On the RuC catalyst, this equilibrium may shift to the enol form, which is hydrogenated to the *cis* isomer, increasing its proportion in the mixture. On the other hand, the absence of 4-acetamidocyclohexanone shows that the intermediate is not desorbed and is further hydrogenated to the cyclohexanol derivatives, contrary to what is observed for Pd catalysts, where the main products are the cyclohexanone derivatives [3].

3.2.2. *Effect of metal precursor*

The effect of the metal precursor on the performance of the catalysts was studied on the carbon-supported sample. The initial activity (Table 1) for RuClC was lower than that for RuC, but the TOF value is of the same order, which does not correlate well with the general trend observed, that is, an increase in activity with the metal particle size. However, as indicated above, the mean particle size determined for RuClC by H_2 chemisorption is overestimated. Moreover, a strong deactivation with time was detected for the ex-chloride catalysts. Although a similar selectivity for N-cyclohexylacetamide was obtained, the amount of hydrogenated products decreased to 64% in favor of an increase in products of partial hydrogenation and side reactions, probably hydrogenation of the acetamide group and polymerization reactions. In an acidic solution, carbon oligomers of paracetamol are created by condensation according to the “head to tail” mechanism [38]. The observed stereoselectivities of the two catalysts differed slightly: 38% for the $RuNO(NO_3)_3$ and 42% for the $RuCl_3$ precursor.

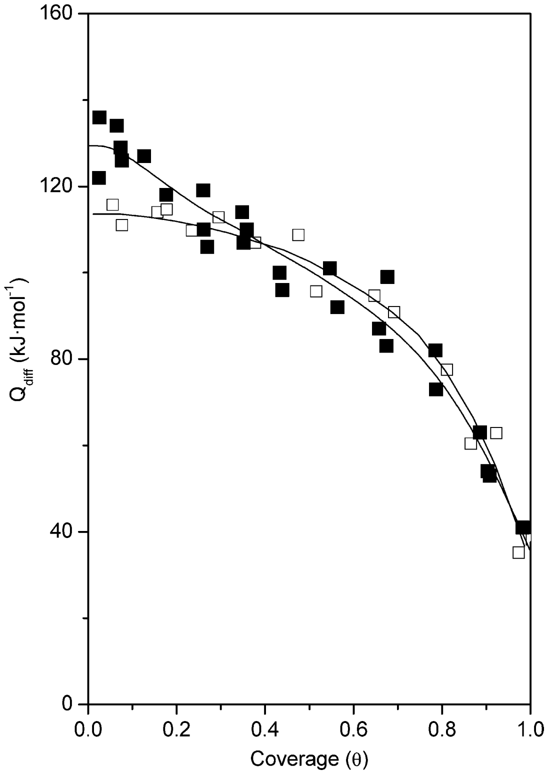


Fig. 3. Differential heat of CO adsorption at 330 K for (■) RuC and (□) RuClC.

The nature of the metal precursor can have an impact on the metal surface structure, affecting dispersion, particle shape, site blocking, or reconstruction [39,40]. In the present case, slightly lower metal particle sizes are obtained for the Cl-free catalysts, which agrees well with previous findings. It has been suggested that this is due to the speciation of the aqueous solutions used, as $RuCl_3$ solutions contain polymeric species, but it may also be due to sintering favored in the presence of chloride ions [41]. Moreover, the presence of residual chlorine on the catalyst after the calcination and/or reduction steps could favor electronic interactions between Cl and the metal particles or adsorbed species [31,42]. To study the possible influence of the electronic density of the metal atoms on the catalyst reactivity, microcalorimetric CO adsorption experiments were carried out. The profiles of differential heat of adsorption (Fig. 3) showed a heterogeneous distribution of active sites for both catalysts. Although the heat of adsorption is similar for coverage higher than 0.3, the catalyst prepared from the nitrate precursor initially gave a higher initial heat of adsorption. This decrease in the heat of CO adsorption is explained by electron withdrawal induced by the chlorine anions in the support–metal interface, resulting in a decrease in the back-donation of electrons from Ru to the π^* anti-bonding orbital. Shifts to higher wave numbers in the IR bands for CO adsorption have been ascribed to similar electronic modifications related to the presence of Cl and other electron-withdrawing ions [40,43,44]. These interactions seem to result in an enhancement of the adsorption strength of paracetamol and a decrease in the hydrogenation rate. A similar negative effect of chlorine has been reported in the hydrogenation of phenol and styrene, where the hydrogenation rates were lower over the palladium catalysts prepared from chloride salts [45].

The acidity of the catalysts, due to the chloride ion, seems to be responsible for the slight promotion of the hydrogenolysis process and for the deactivation rate; the latter is probably due to deposition of carbonaceous species on surface acid sites [36,45]. As suggested above, the observed increase in selectivity for the *trans* isomer with the RuClC catalysts is probably attributable to the modification of the tautomeric keto-enol equilibrium toward the ketone intermediate as a result of the interactions between the metal particles and the residual Cl ions. Modifications of the electronic properties of ruthenium on alumina-supported catalysts with high chlorine contents seem to account for the decrease in activity and the higher selectivities for cyclohexene during benzene hydrogenation [42].

3.2.3. *Effect of the solvent*

The catalyst supported on carbon was also selected to study the influence of the nature of the solvent on catalytic performance. Two other solvents were tested, 2-propanol (IPA) and tetrahydrofuran (THF). The initial activity increased in the order EtOH < THF < IPA (Table 1), which indicates an effect of the solvent. Moreover, as the production of the alcohols increased with the two new solvents, the formation of N-cyclohexylacetamide decreased. On the other hand, the stereoselectivity for the *trans* isomer was lower for IPA and THF than for EtOH.

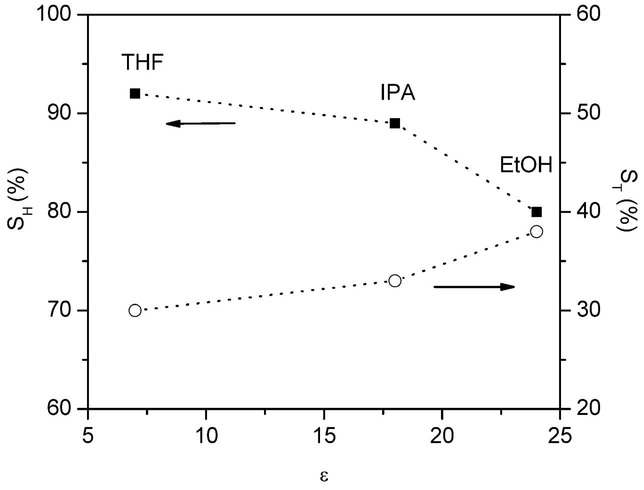


Fig. 4. Selectivity to cyclohexanol derivatives (■) and stereoselectivity to *trans* isomer (○) vs the dielectric constant of the solvents. Catalyst, RuC; temperature, 393 K; $P(H_2) = 50$ bar.

Effects of solvents have been reported for different heterogeneous catalytic processes [7,46,47]. The differences in activity and selectivity cannot be explained initially by the values of H_2 solubility, since they are very similar for the three solvents. Thus, we tried to correlate the catalytic results with the polarity of the reaction medium. Fig. 4 shows the dependence of the selectivity for acetamidocyclohexanols and the stereoselectivity for the *trans* isomer on the dielectric constant of the solvent. The activity values (Table 1) do not show a clear relationship with the dielectric constants of the solvent. However, since the carbon has acidic and basic oxygen surface groups, the more polar solvent may be adsorbed to the surface, thus reducing the adsorption of the reactant, which may explain the lower activity with EtOH. In this sense, the diffusivity of paracetamol is known to increase when surface acidic sites (oxidized carbons, hydrophilic or polar surfaces, and metal cations) are effectively blocked by water [38]. On the other hand, the selectivity for the total hydrogenation of the aromatic ring seems to decrease with solvent polarity. Moreover, the increase in selectivity for N-cyclohexylacetamide when EtOH was used could imply a greater contribution of the activation of the molecule via the substituent oxygen. This is supported by the favored formation of phenoxide in polar solvents.

Finally, the results for the RuC catalyst indicate that the lower the polarity of the solvent is, the higher is the stereoselectivity for the *cis* isomer. This can again be explained by the favored adsorption of the molecule in a planar mode as the polarity decreases or by modification of the tautomeric equilibrium keto-enol of the reaction intermediate.

4. Conclusions

We have shown that the stereoselective hydrogenation of paracetamol for 4-*trans*-acetamidocyclohexanol depends on several factors. The best results for activity and selectivity for the cyclohexanols and for the *trans* isomer were obtained with the ruthenium catalysts supported on metal oxides. The influence of the metal precursor on the carbon-supported catalyst indicates that the residual chloride slightly promotes the stereoselectivity for the *trans* isomer. However, it is detrimental to the chemo-selectivity, since larger amounts of side products are obtained, and the catalyst deactivates with time in reaction. On the other hand, the use of solvents of medium or low polarity enhances the activity but reduces the stereoselectivity. Our results suggested that the product distribution obtained in the hydrogenation of paracetamol can be controlled by selecting the appropriate catalyst and reaction conditions.

Acknowledgments

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