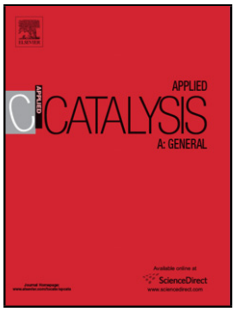

Pd/C Catalyzed selective hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of $NH_2OH \cdot HCl$: influence of the operative variables and insights on the reaction mechanism

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Pd/C Catalyzed selective hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of $NH_2OH{\cdot}HCl$: influence of the operative variables and insights on the reaction mechanism

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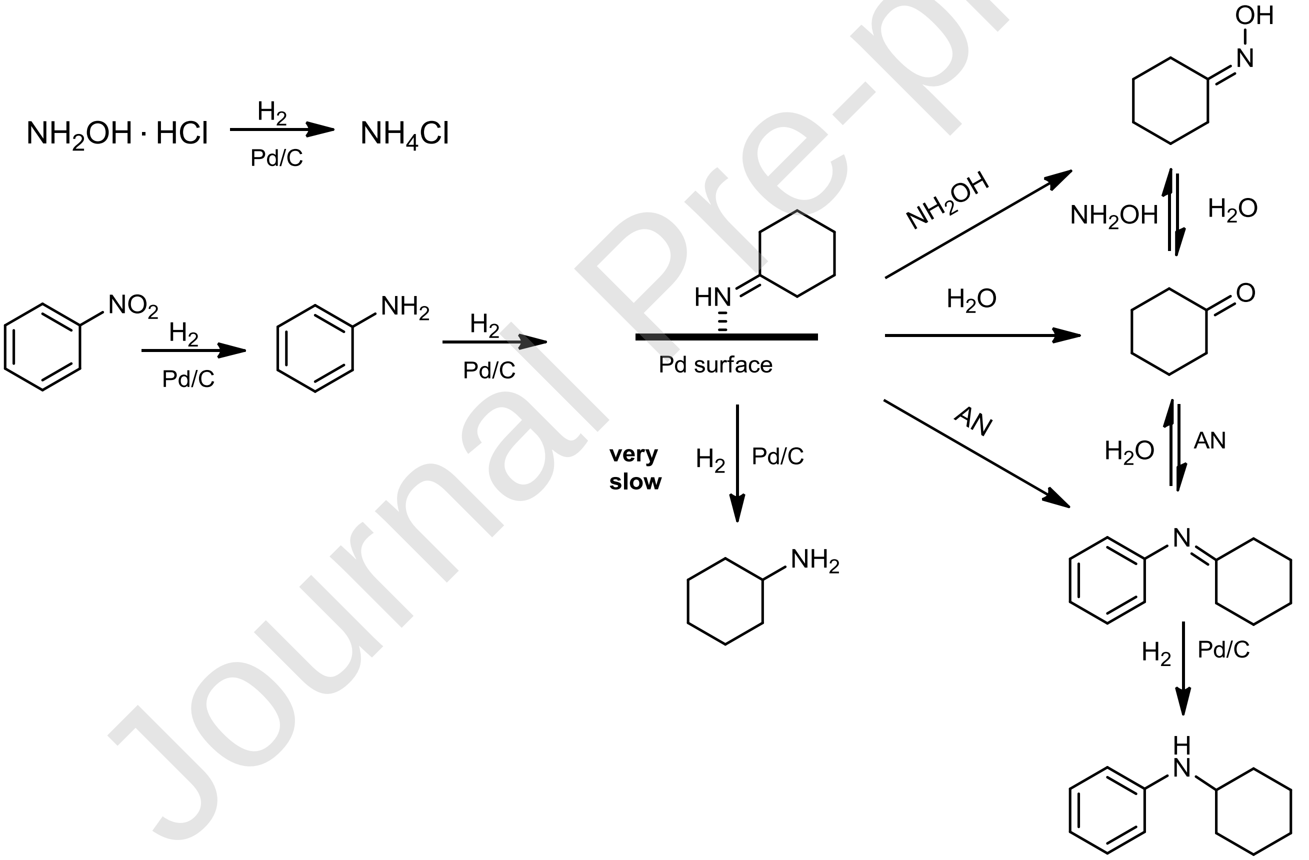
Graphical abstract



Consecutive, parallel reactions and equilibria affecting the selectivity in cyclohexanone oxime

Highlights

- Nitrobenzene hydrogenation catalyzed by Pd/C in the presence of NH_2OH HCl forms Aniline and cyclohexanone oxime.
- Catalysts based on different metal are not selective to the cyclohexanone oxime.
- The best solvent are ethers followed by dichloromethane and dimethylcarbonate
- NH_2OH HCl hydrogenates to NH_4Cl in the presence of Pd/C as a catalyst.
- Aniline in the presence of NH_2OH HCl gives cyclohexanone oxime and the presence NH_4Cl favors the selectivity to cyclohexanone oxime.
- Cyclohexanone, cyclohexanone oxime and N-cyclohexylideneaniline are in equilibrium and derive from a common imine intermediate on catalyst surface.

Abstract

We studied the influence of temperature, solvent, pressure, catalysts type on the selectivity of nitrobenzene hydrogenation to cyclohexanone oxime (COX) in the presence of NH_2OH. The best reaction conditions are: pressure 0.8 MPa, temperature 333K, solvent ethers, and catalyst Pd/C5%. Other hydrogenation metal catalysts did not give comparable results. The amount of Pd/C influences the yield in COX, which rises above to 90% at the highest load. The reaction profile shows that aniline is the reaction intermediate. Indeed, aniline as a substrate gives COX, though in lower yield than that achieved employing nitrobenzene. The NH_2OH parallel hydrogenation to NH_4Cl, influences positively the selectivity to COX. It has been observed that COX, cyclohexanone and N-cyclohexylideneaniline are in equilibrium in the reaction solution and all likely derive from nucleophilic substitutions to a common imine intermediate formed on the Pd surface, whose high activity does not need any further metal catalyst.

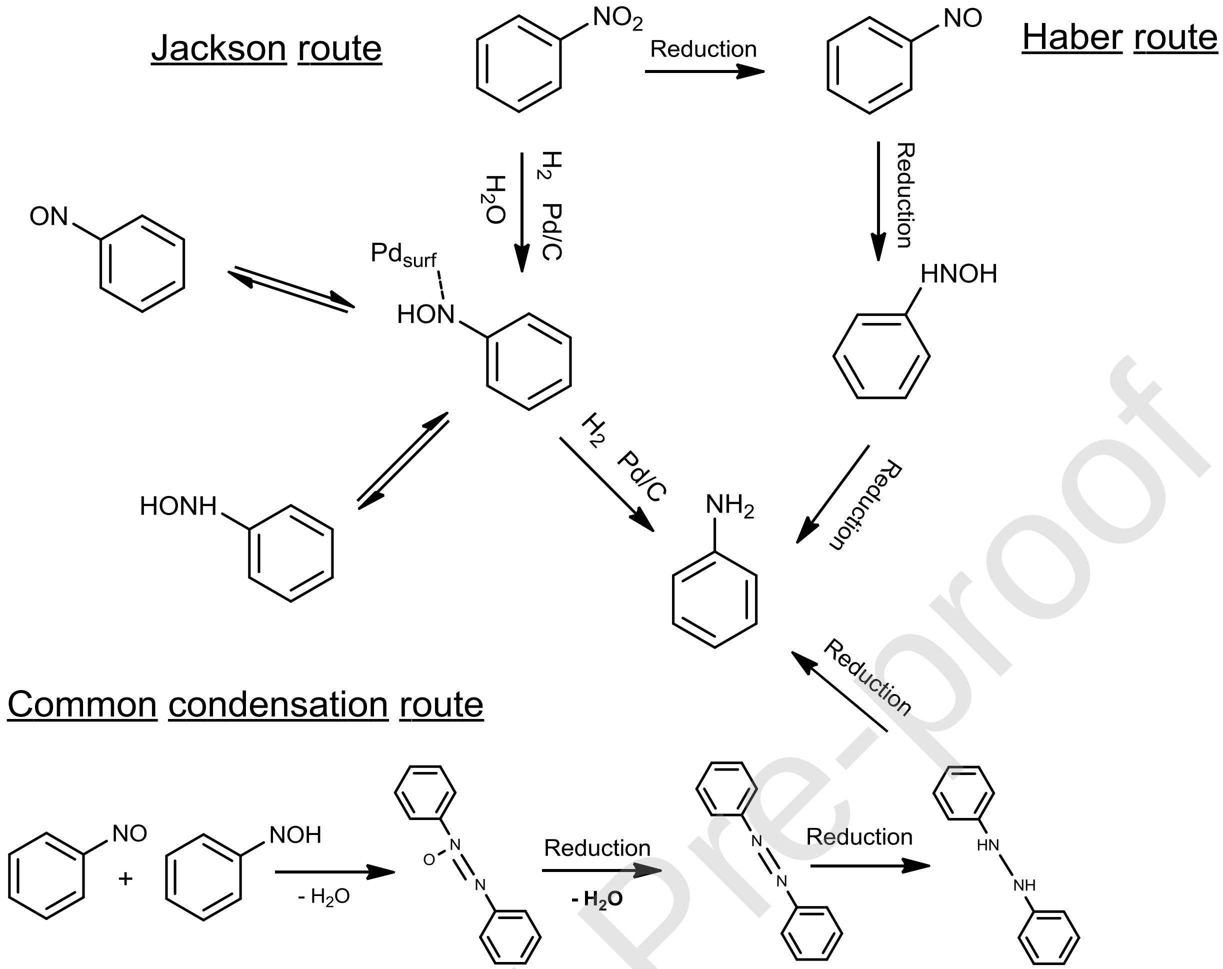
Keywords: Nitrobenzene hydrogenation, Aniline Hydrogenation, NH_2OH hydrogenation, cyclohexanone oxime, Pd catalysts.

1. Introduction

Nitrobenzene and in general nitro-aromatic compounds reductions are really important and useful reactions for several industrial processes [1]. Béchamps-Brimmeyr reductions method with Fe-$FeCl_2$ system is still used mainly for the formation of the Black Fe_3O_4 inorganic pigment as by-product of reduction of the nitrocompound [2]. Other stoichiometric reduction methods of nitrocompounds employ Zn or hydrazine for achieving high selectivity with sensitive substituents or particular synthesis two-step one pot synthesis [1, 3].

Hydrogenation, however, is actually the most important and more used method of reduction in aromatic nitro-compounds [1, 4]. Among them, nitrobenzene hydrogenation to aniline is one of the most important reaction, since the latter is used as an intermediate in many fields of application, for instance, in the production of isocyanates, rubber processing chemicals, dyes and pigments, agricultural chemicals and pharmaceuticals [1]. Industrial hydrogenation methods employ several type of catalysts and engineering solutions and each one depends on its specific use [5]. For instance, supported Pt, Ni, Pd are commonly employed as catalysts in gas/solid or liquid/solid multiphase reactors, as well as in continuous or in batch operation [6].

The reduction of the nitro-group involves several steps following the well-known Haber reaction path, where nitro-group is reduced step by step to the amine together with the formation of condensation products between nitrosobenzene and phenyl hydroxyl amine (see Scheme 1) [7].



Scheme 1. Haber and Jackson Nitrobenzene reduction/hydrogenation mechanism.

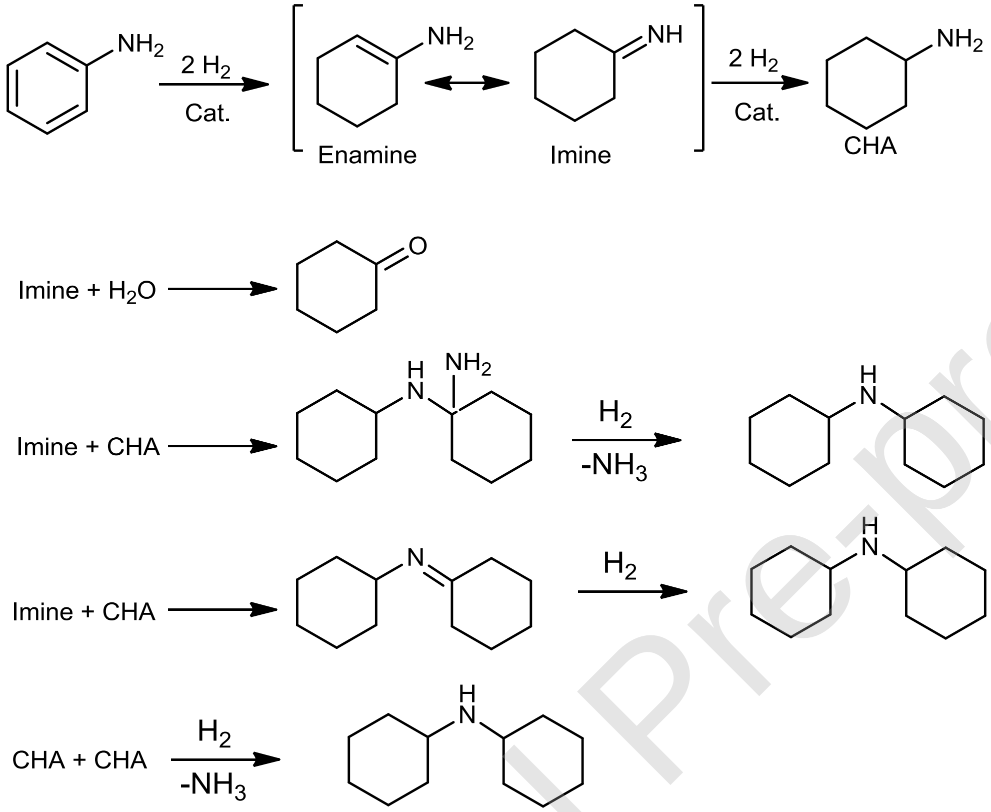
Recently, for the catalytic hydrogenation mechanism, it has been suggested a similar path, but the formation of nitrosobenzene has been related to a surface equilibrium phenyl-hydroxylamine/nitrosobenzene rather than the formation of an actual reaction intermediate (see Scheme 1 Jackson route). Condensation of nitrosobenzene and phenyl hydroxyl amine occurs in the same way of the Haber scheme [8, 9]. This has been clearly pointed out by the study of Jackson and co-workers on the kinetics of the nitrosobenzene hydrogenation, they demonstrated indeed a different reaction path for nitrosobenzene hydrogenation with respect to that of nitrobenzene [8].

Among the one-pot multi-steps processes the selective hydrogenation of nitrobenzene to 4-aminophenol is an elegant example of an industrial application, which combine a noble metal catalyzed reaction with a homogeneous acid catalysis [9-13]. Industrially, the reaction is carried out in continuous stirred tank reactor in a biphasic reaction medium, in the presence of aqueous sulfuric acid and a supported Pt catalyst. At first, nitrobenzene is hydrogenated to N-phenylhydroxylamine, and then the acid catalyses the Bamberger rearrangement of the intermediate [3, 9-13]. From an environmental point of view, the major drawback of the process is the neutralization of the sulphuric acidic phase, which causes huge corrosion concern, with the consequent increased costs [3, 9-13]. However, the use a single reactor system allows an increase of the sustainability of the process compared to other multistep ones [9].

Besides, Corma and Co-workers studied the selectivity of aromatic nitrocompounds reductions and they direct selectivity of Au/supported catalyst towards azobenzene. They recognized responsible for such a selectivity the stabilization of surface nitrosobenzene-Au species [14].

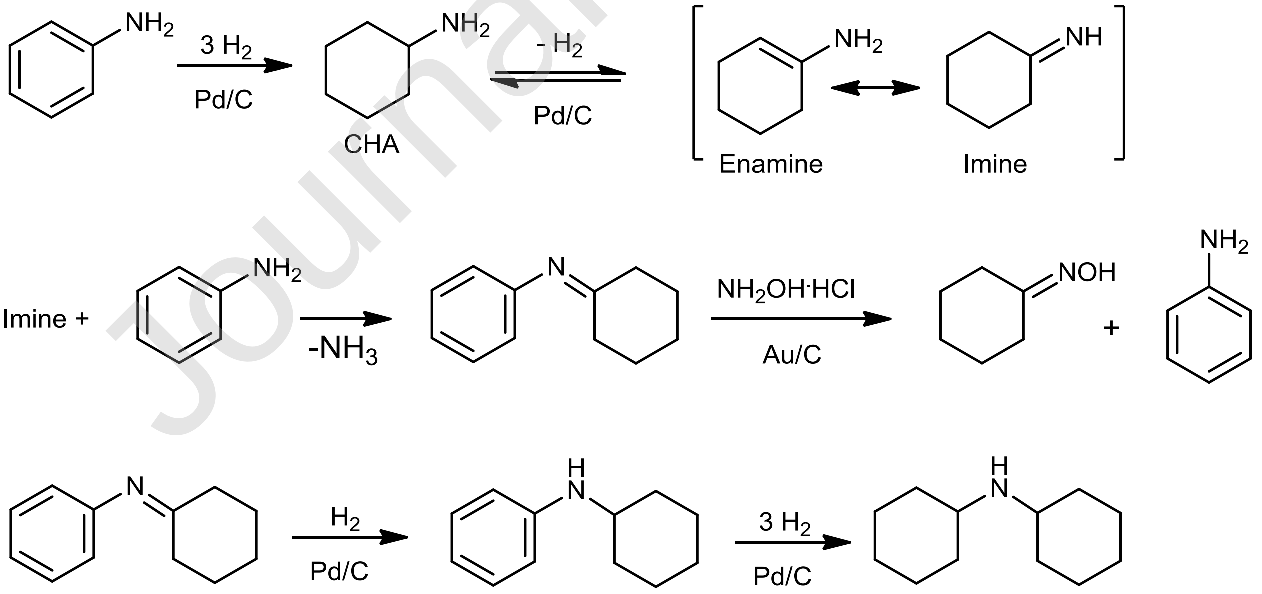
The complexity of the reaction scheme of nitrocompounds reduction allow to take into consideration (see Scheme 1) the possibility of designing catalyst or processes that gives, under particular experimental conditions, quite selectively a particular intermediate [9]. For instance, formation of azo-compounds can be achieved by combining the partial reduction of nitrobenzene condensation and dehydration in basic media [15]. Other interesting reduction methods for nitro-aromatic compounds are hydrogen transfer reactions [17-19]. For instance nitrobenzene can be easily reduced to azo, azoxy, anilines, carbamates and ureas by using CO as reductant and Pd(II) complexes as catalysts, the operating conditions will determine the selectivity to each product [17, 18]. Under similar reaction conditions in the presence of mild oxidant, nitrobenzene is, at first glance, reduced to an intermediate, which gives aniline in protic solvent, while in aprotic one the main products is isocyanate [17, 18]. The reaction gives almost selectively diphenyl urea in the presence of Pd supported catalysts in liquid biphasic conditions and aqueous NaOCHO as reductant, [20].

The further reduction of the aromatic amines and of aniline in particular, is relatively less studied compared to the hydrogenation of the nitro-aromatic compounds [21-33]. Hydrogenation of aniline to the cyclohexylamine, particularly, has been investigated from long time, and the best catalytic system is mostly Ru supported catalysts at quite high temperature and pressure (373-473K, 1-10 MPa) [22-26]. Even though, less studied than that of nitrobenzene reduction, the mechanism of this reaction has been already proposed by Greenfield in the early sixty. In this paper, the author has assumed the formation of the imine (Scheme 2) as the key intermediate, which, due to its high reactivity, undergoes facile condensation reactions with all the nucleophiles present in solution, as showed in Scheme 2 [21]. The reactivity of such an intermediate drives the selectivity toward the formation of cyclohexyl amine, di-cyclohexyl amine, and, in the presence of water, to cyclohexanone and cyclohexanol [21, 28-31]. The highly reactive imine intermediate has been never isolated in the hydrogenation medium, however, the final products observed strongly supports the goodness of such a hypothesis [21, 28-31]. Greenfield suggested also that the imine specie should be only stabilized in the adsorbed state on catalyst surface, and a direct coupling deamination of CHA can occur only at temperature higher than 200°C on Ni catalysts [21].



Scheme 2. Reaction mechanism of aniline hydrogenation suggested by Greenfield [21].

Cho and Park have observed a strong influence of the fluid dynamic behavior of the reactor on the selectivity of the aniline hydrogenation to cyclohexyl amine [31]. The authors suggested a non-stationary concentration of hydrogen in the reactor, which cause different rates of reactions in the various steps suggested in the Greenfield mechanism [31]. This mechanism suggests of using the reactivity of the imine intermediate towards nucleophiles; for instance, the substitution with water gives cyclohexanone, a fundamental intermediate, in the production of nylon-6 and in several fine chemistry synthesis [18, 31-33]. In fact recently, appears some patents claiming a direct route from nitrobenzene to cyclohexanone oxime by hydrogenation and direct oximation [34, 35]. In particular, Corma and coworkers have carried out the hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of hydroxyl amine hydrochloride, in multiphase systems, catalyzed by Pd and Au supported catalysts [35-36]. These authors have claimed that the presence of the two type of catalyst allows high selectivity in the cyclohexanone oxime. The highest selectivity towards the oxime is achieved in the presence of a physical mixture of the two catalysts with respect to the single catalytic system Pd/C or Au/C, moreover, the latter leads to aniline only. Finally, the bimetallic Pd-Au/C catalyst is less selective than the physical mixture of the two catalysts, as well [36]. The mechanism, suggested by the Authors (see Scheme 3), is based on the hypothesis that cyclohexyl amine is in dehydrogenative equilibrium with the cyclohexyl imine, which undergoes to the nucleophilic attack of the aniline, thus forming *N*-cyclohexylideneaniline. In turn, the latter may undergo nucleophilic attack of the hydroxylamine, or the hydrogenation to phenyl cyclohexyl amine and finally to dicyclohexyl amine. From a mechanistic point of view, the Authors have suggested the involvement of the gold catalyst in the transformation the *N*-cyclohexylideneaniline, which determines the overall selectivity to the various products [36]. In fact, the nucleophilic attack of the NH_2OH catalyzed by Au/C catalyst to the *N*-cyclohexylideneaniline lead to cyclohexanone oxime and finally its hydrolysis may give cyclohexanone if water is present [36]. Besides, Pd/C is responsible for the formation of the di-cyclohexyl amine for the sequential hydrogenation of N-cyclohexylideneaniline to N-cyclohexyl aniline, which is finally hydrogenated to the di-alkyl amine [36]. In any case, in agreement with the mechanism suggested by Greenfield, the formation of the imine intermediate is, also in this case, an important step, since its reactivity lead to the formation of the N-cyclohexylideneaniline recognized by these Authors as the actual intermediate, whose reactivity catalyzed by Au determines the high selectivity in the cyclohexanone oxime.



Scheme. 3. Mechanism of Nitrobenzene hydrogenation to cyclohexanone oxime suggested by Corma [36].

In this work, we have studied the selective hydrogenation of nitrobenzene to cyclohexanone oxime with different solvents, in the presence of various hydroxylammonium salts, and catalyzed by a commercial Pd/C catalyst. The research will focus on the influence of the operative variables (Temperature pressure and solvent type), of the amount and type of catalyst on the selectivity to the oxime and to the various byproducts. Besides, a particular attention will be reserved to the study of the likely intermediates found in traces amount in the reaction media as well as the parallel reaction of $NH_2OH \cdot HCl$ reduction whose products favors the selectivity in the cyclohexanone oxime.

2. Experimental

2.1. Materials

Nitrobenzene, aniline, cyclohexylamine, dicyclohexylamine and N-phenylcyclohexylamine (PCA) were all Aldrich products, their purity were checked by the usual methods (melting point, TLC, HPLC, GC and GC-MS) and employed without any purification, acetonitrile HPLC gradient grade was supplied by BDH, 1,4-dioxane, methanol, nitromethane, diethyl ether, dioxane, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide are ACS reagent supplied by Aldrich. N-cyclohexylideneaniline (PCNA) was synthesized by following the procedure of literature and the characterization was carried out by GC-MS, ^{1}H and ^{13}C NMR [37]. Catalysts used were commercial materials supplied by Engelhard (now Basf Catalysts): Pd/C 5% Escat 10, Pt/C 3%, Ru/C 5% Escat 40 and Rh/C 5%. Au/SBA 2% and Au/C 0.5% were gently furnished by Proff. M. Signoretto and F. Menegazzo; synthesis and characterization of these catalysts has been reported elsewhere [38, 39].

2.2. Equipment

Products were identified by gas chromatography (GC) gas chromatography coupled mass spectrometry (GC-MS) and high performance liquid chromatography (HPLC). GC and GC-MS analysis were carried out with an Agilent 7890A equipped with FID or MS detector (Agilent 5975C and a HP 5 column (I.D. 320 μm 30 m long). Helium was employed as carrier in the GC-MS analysis, while nitrogen in the GC ones, in both cases the conditions were the following: injector 523 K, detector 543 K, flow 1 mL min^{-1}, oven 333 K for 3 minutes 523 K 15 K $minute^{-1}$ and 523K for 15 minutes. In order to check the thermal stability of the products, some analysis were carried out by HPLC (Perkin Elmer 250 pump, LC 235 diode array detector and a C 8, 5 μm, 4 mm i.d. 25 cm long column) analysis were carried out with CH_3CN-H_2O as mobile phase in isocratic 70% of CH_3CN at 1 mL min^{-1}. The comparison of GC and

HPLC analysis shows a good agreement suggesting both technique gives reliable analytical data. After the test of the analytical reliability, conversion yield and selectivity are calculated by calibrations of the GC analysis obtained by standard solutions of the pure products. ^{1}H and ^{13}C NMR. were carried out in a Brucker Avance 400 II at 400MHz and 100MHz, respectively and using $CDCl_3$ as a solvent.

2.3. Catalyst characterization

Catalysts employed are commercial catalysts (except Au ones) whose characterization has been already described in previous papers [38-40].

2.4. Hydrogenation of nitrobenzene

The reactions have been carried out in several solvents (1,4-dioxane CH_3NO_2, CH_3OH, $(CH_3)_2NCHO$ and $(CH_3)_2SO$) in an AISI 316 autoclave (80 mL internal volume) equipped with a PTFE insertion (in order to avoid metal contamination), and a pressure regulator to maintain constant the reaction pressure. A circulation bath ensure a stable temperature in the range 323-353 K (± 0.5 K). Catalyst activation were preliminarily carried into the autoclave at the running temperature and pressure (0.3-2 MPa of H_2), without reagents. Blank reactions in the absence of nitrobenzene and hydroxylamine have been carried out in order to verify the stability of the solvent. Solvents employed showed no relevant products of reduction at GC analysis. A detailed description of hydrogenation apparatus has been described elsewhere [41]. In a typical experiment 20 mL of solvent with suspended the Pd/C catalyst (typically 50 mg) and $NH_2OH{\cdot}HCl$ (2.7 g), was introduced into the reactor. After that, the reactor was closed, purged before with nitrogen and then with hydrogen, pressurized at 0.2 MPa, finally heated at 323-353 K under stirring for 1 h in order to activate the catalyst. The reactor was left to stabilize at the temperature of reaction (323-353K), than the preheated solution of nitrobenzene (c.a. 2.5 mL, concentration of nitrobenzene 4 mol L^{-1}) was added to the reactor. After the addition of this solution, the computing of the reaction time starts, and the liquid phase analysis is by GC after 20 h of reaction. An electronic pressure transducer monitors hydrogen consumption, which measure the pressure drop in a reservoir at known volume.

The reaction environment, at initial stage of the reaction, is a complex mixture composed of a gas phase (mainly hydrogen and solvent), a liquid phase (solvent and nitrobenzene) and two solid phases: hydroxylamine hydrochloride and the catalyst. Both solid are not soluble (negligibly soluble) in the solvent, however, during the course of reaction the formation of water, due to nitrobenzene hydrogenation to aniline, may cause an increase of the solubility of the hydroxyl ammonium salt, or of other salts present and/or produced in the reaction vessel.

In all the experiments at the opening of the reactor, we found a solid mixture crust on the bottom of the reactor made of the catalyst and various salts, strong agitation needs for restoring the homogeneity, it is necessary to verify carefully the agitation of the system in order to avoid reproducibility problems.

Some kinetic profiles has been obtained by using a 250 mL autoclave employing 80 mL of volume under the same concentration of reagent and at 0.8 MPa of hydrogen pressure the apparatus has been detailed descripted elsewhere [41].

2.5. Determination of residual $NH_2OH{\cdot}HCl$

The residual hydroxyl ammonium salt employed in the reaction has been quantified after filtration and washing of the solid with diethyl ether. Then the salt is dissolved in water diluted, added to an almost equimolar solution of ferric sulfate, left to react for 30 minutes, and the excess of Fe (III) titrated directly with a solution of $KMnO_4$ (0.05 mol L^{-1}) [42]. The method has been checked by ionic chromatographic analysis, showing equivalent results. In some sample a residual percentage of CHA has been observed after extraction with CH_2CL_2 of the KOH basified solution to pH>12, in any case, the amount is generally lower than 1%, except in those experiments where the CHA were added in high concentration as a reagent.

3. Results and discussion

In this study, we will propose a first attempt to analyze a complex multistep multiphase reaction starting from the choice of the catalytic system, in order to verify what metals are able to hydrogenate nitrobenzene (NB) to cyclohexanone oxime (COX) in the presence of NH_2OH salts, selectively. Actually, the reaction presents a recognized intermediate, which is aniline (AN), and some compounds, recognized in the reaction media, which are candidates of being intermediate or byproducts [3, 36]. These compounds are cyclohexanone (CON), cyclohexylamine (CHA), and PCA, traces of PCNA, N,N-dicyclohexyl amine and finally as byproduct of nitro-group reduction H_2O (two moles per mole of substrate).

3.1. Choice of the catalytic system

The main results of some supported precious metal hydrogenation catalysts employed under mild conditions (333K 0.8 MPa), are reported in Tab. 1. Actually, the presence of the hydroxylamine hydrochloride is necessary for achieving a selectivity to the COX, the absence of hydroxyl amine means no selectivity to oxime (see supplementary materials). It is immediately evident the higher selectivity of the Pd/C catalyst compared with the other ones. Furthermore, it is noteworthy the lower selectivity of the Pd/Al_2O_3 catalysts, compared to that obtained by the Pd/C. Besides, other metals, under the condition investigated, are low active in the nitrobenzene hydrogenation, for instance, in the case of the Ru or Au catalysts show after 20 h of reaction 5% and 1% of nitrobenzene conversion, respectively. The reason of this behavior is likely related to the specific activity of each catalyst, however, the high activity of Pd/C in nitrobenzene hydrogenation is well known from the beginning of the studies in catalysis, while other metal are active only in more severe conditions [21-27]. As regard the selectivity in COX, only Pd shows a clear selectivity to this compound. This is related to its high activity in the hydrogenation reactions, since the formation of COX must proceed via the reduction step of aniline which is indeed a harsh substrate to be reduced [21-27].

Table. 1 Influence of the catalyst on the conversion and selectivity of nitrobenzene hydrogenation. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, hydrogen Pressure 0.8 MPa, $NH_2OH·HCl$ 30 mmol, T 333K, catalyst 50 mg, time of reaction 20h, solvent diethyl ether.

Catalyst	Conv.^{a} (%)	Select.^{a} AN (%)	Select.^{a} COX (%)	Select.^{a} CON (%)	Select.^{a} CHA (%)	Select.^{a} PCA (%)	Select.^{a} Others^b (%)
Pd/C (5%)	>99	30	64	1	1	2	2
Pd/Al_2O_3 (5%)	99	70	29	>1	>1	>1	>1
Pt/C (3%)	>99	>99	/	/	>1	>1	>1
Pt/Al_2O_3 (5%)	90	>99	/	/	>1	>1	>1
Au/C (0.5 %)	1	99^c	/	/	/	/	/
Au/SBA (2 %)	1	99^c	/	/	/	/	/
Ru/C (5%)	5	>99	/	/	/	/	/
Rh/C (5%)	10	>99	/	/	/	/	/

a) Conv. = conversion, Select. = selectivity.

b) GC-MS reveals traces of condensation products and N,N-dicyclohexylamine.

c) Traces.

We have also verified if the presence of a mixture of Pd/C and a second metal catalyst may help to improve the selectivity toward the COX. The results, reported in the supplementary materials (Tab. S2), suggest that there is no increases in COX selectivity, with a second hydrogenation catalyst. On the contrary, the addition of a second catalyst diminishes the selectivity in COX, and only the Au based ones seem to have comparable selectivity in COX with respect to that obtained with the pure Pd/C catalyst, suggesting that these materials act practically as an inert, under these reaction conditions.

3.2. Influence of solvent type, hydrogen pressure and temperature

The presence of Pd catalysts and hydroxylamine as reagent is thus the key point for obtaining COX directly from nitrobenzene hydrogenation but the second essential element is the solvent. In fact, the solvent play a fundamental role for driving selectivity toward COX, this is evident from the results of Tab.3, in which nitrobenzene is in practical quantitatively hydrogenated in all the solvent, but low or no selectivity to COX is achieved by using EtOH, acetonitrile (ACN) and toluene (Tol). The highest selectivity in COX is obtained by using THF as the solvent. The reason is not easy to explain because of the different nature of these solvents (chemical and/or physical). As can be observed in Tab. 2 there are no evident relationships between solvent dielectric constant and selectivity, even though it appears that neither polar solvent nor completely non-polar one seems to favor selectivity to COX. Other solvent parameters, such as the relative rate of nucleophilic substitution or the solvatochromic parameters does not suggest any correlation between COX selectivity and the solvent parameter itself [43]. This suggests the selectivity in COX is the result of a complex process where a cat-walk between several parallel, consecutive reactions and equilibria determines the selectivity. As a matter of fact, THF appear to be the best solvent followed by Et_2O DCM and DMC. These solvents are in any case no protic solvent and show an intermediate polarity between Tol and acetone (Act). No evidence of direct correlation between LogP$_{OW}$ (partition n-octanol/water) of the solvent and their selectivity toward COX, however the best results are obtained with solvent of intermediate hydrophilicity/hydrophobicity values (see Tab. 2) [44]. In any case, in this work we used preferentially Et_2O, because of its lower cost.

Table. 2 Influence of the solvent on conversion and selectivity. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

Solvent	LogPow	ε	Conv. (%)	Select. AN (%)	Select. COX (%)	Select. CON (%)	Select. CA (%)	Select. PCA (%)	Select. Others (%)
EtOH	-0.24	24.6	> 99	52	<1	/	/	/	47 [a]
ACN	-0.33	35.9	97	50	22	/	/	/	38 [a]
NMe	-0.35	35.9	>99	58	/	<1	/	/	41 [a]
Act	-023	20.7	<99	45	/	/	/	/	55 [a]
Tol	2.5	2.38	95	99	<1	/	<1	<1	<1 [b]
THF	0.49	7.58	> 99	24	71	<1	<1	3	1 [b]
THF/H_2O[c]	0.1	42.8	> 99	98	traces	traces	/	/	1
Et_2O	0.85	4.34	> 99	32	64	<1	<1	2	1 [b]
Et_2O[d]	0.85	4.34	> 99	64	32	<1	<1	2	1 [b]
iPr_2O	1.9	3.81	> 99	73	21	<1	<1	5	
DMC	0.23	3.07	> 99	55	40	<1	<1	3	1 [b]
DCM	1.3	8.93	> 99	40	55	<1	<1	3	1 [b]

a) Products of aniline alkylation [45].

b) Condensation products and N, N-dicyclohexylamine.

c) THF/H_2O = 1/1 wt. [46].

d) In the presence of 200 mg of molecular sieve 4A.

Tab. 3 reports the influence of hydrogen pressure and temperature on conversion and selectivity. It appears that hydrogen pressure does not influence the conversion after 20h of reaction which is quantitative, but it influences COX selectivity showing a maximum in the range of 8-10 bar (see). The reason is not evident because of the increasing of the pressure would suggest the increase of the hydrogenation rate also of the aniline, which, on the contrary, seems to be poorly affected by the pressure being CHA selectivity in the range of 0.1-1%. PCA is the only product whose selectivity raises significantly as hydrogen pressure increases thus suggesting a competition between COX and PCA formation, even though this could be only a secondary effect due to the involvement in the hydrogenation of the NH_2OH, which could be consumed faster at the higher pressure.

The influence of temperature does not affect the NB conversion, which is always quantitative, but it has an actual impact on the selectivity in COX. It is clear that the selectivity to COX reach a maximum in the range of temperature 333-343K (see also supplementary materials Fig. 4S). The hydrogenation at

323 K temperature shows a lower selectivity probably because the second step of the reaction, (AN hydrogenation) that occurs much slowly at lower temperature, and very long time of reaction appears not of practical interest for this type of processes. At the highest temperature, likely, the reaction is less selective because of an increase of the rate of side of reactions.

Table. 3 Influence of the hydrogen pressure and temperature on selectivity (quantitative NB conversion). Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, $NH_2OH{\cdot}HCl$ 30 mmol, T 323-353K, Pd/C 50 mg, time of reaction 20 h.

Entry	Pressure (Bar)	Temp. (K)	Select. AN (%)	Select. COX (%)	Select. CON (%)	Select. CHA (%)	Select. PCA (%)	Select. Others[a] (%)
1	5	333	48	49	0.1	0.1	1	<1
2	8	323	59	40	<1	<1	<1	<1
3	8	333	31	64	1	1	2	1
4	8	343	27	67	1	1	2	2
5	8	353	32	51	1	1	3	2
6	10	333	32	62	1	1	2	1
7	20	333	52	53	<1	1	3	1

a) Condensation products and N,N-dicyclohexylamine

3.3 Influence of the catalyst amount on conversion and selectivity

The reaction shows that the selectivity in COX grows as the catalyst amount increase (see Fig. 1). The explanation of this fact is not easy, but it is likely that key intermediate determining the selectivity in COX is on catalyst surface. The presence of a reactive surface intermediate derived from aniline hydrogenation explains also the increase of byproducts with catalyst amount, thus suggesting all intermediates and byproduct derive from aniline hydrogenation. This is clear, since nitrobenzene, under the reaction conditions, is readily and quantitatively hydrogenated to AN, while the hydrogenation of the AN ring is not easy. As a matter of fact, It is probably that AN has the tendency of being strongly adsorbed on catalyst surface, since stable aniline-Pd(II) complexes are well known and characterized thus justifying strong interaction between the surface Pd atoms and the AN molecule [47].

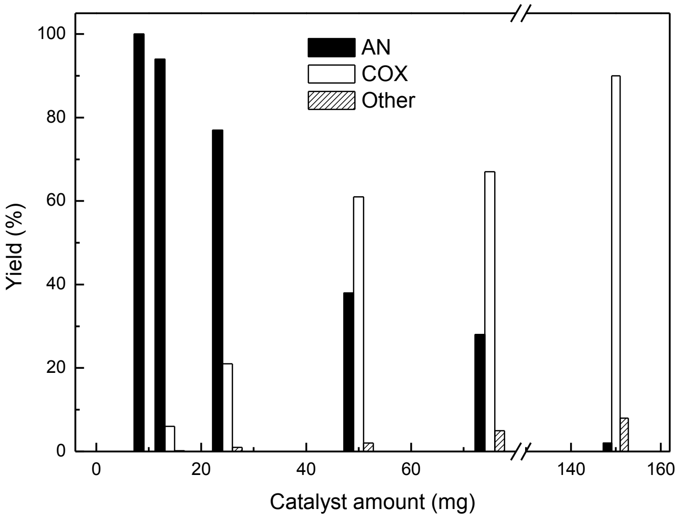


Fig. 1. Influence of the catalyst amount on the yield of aniline and cyclohexanone oxime. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

3.4 Time vs concentration profiles, hydrogen consumption and mass balance

In this study the experiments after 20 h of reaction were carried out in an 80 mL autoclave, while, the reaction profile has been obtained by using a 250 mL reactor equipped with capillary for sampling during the reaction course. The comparison of the conversion and the selectivity of the various products after 20 h of reaction obtained with the two reaction systems are similar thus suggesting a reliable comparison between the results of the two reactors. Fig. 2 shows the reaction profile of a typical experiment. This reaction profile must be considered only an attempt to represent what happen in the reaction environment, since a detailed kinetic study must take into account of the complex fluid dynamic aspect of this reaction system, which is beyond the purpose of this work. However, it appears a fast consumption of NB, during the first hours of reaction. At the end of this period, it begins the formation of COX and of other byproducts as reported in Fig. 3. It is noteworthy that when nitrobenzene is consumed, hydrogenation of aniline starts. CHA and CON are less abundant among the byproducts remaining lower than 1% of yield. Besides PCA is not abundant and we observe traces of PCNA and N,N-dicyclohexylamine after 20 h of reaction.

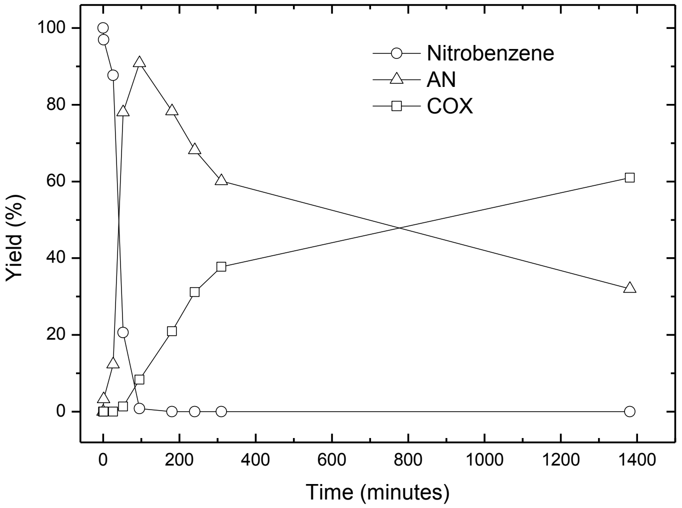


Fig. 2. Hydrogenation profile. Run conditions: reaction volume 75 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH·HCl$ 75 mmol, T 333K, Pd/C 60 mg, time of reaction 20 h.

The role of these byproducts as intermediates in COX formation could be related by their direct oximation in the presence of the hydroxylamine. In the mechanism proposed by Corma and coworkers, a dehydrogenation of CHA to cyclohexanimine occurs, starting from this suggestion, it could be useful to verify, how reactants and intermediates influence the selectivity in COX. At a first sight, as can be noticed by the reaction profile of Fig. 2, nitrobenzene looks like not relevant for the selectivity in COX, because its formation starts when nitrobenzene is practically disappeared. This behavior suggests of studying the hydrogenation of aniline, in order to verify its role, in the formation of COX, which will be reported in the next section.

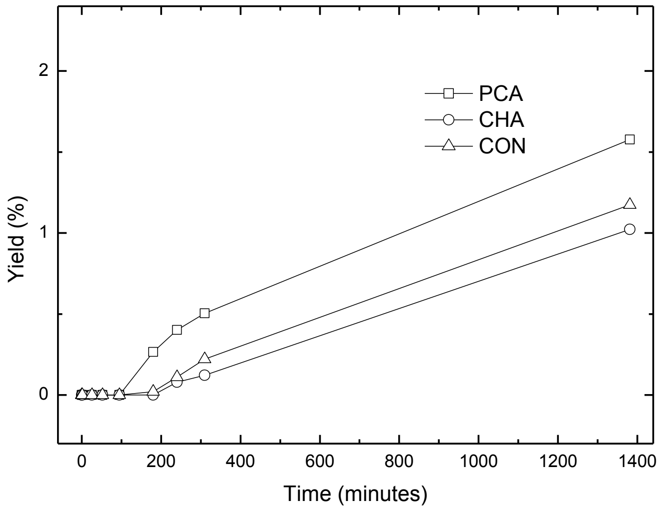


Fig. 3. Yields of low concentration products. Run conditions: reaction volume 75 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 75 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

The measure of hydrogen consumption (Fig. 4) allows to test the mass balance of H_2 by verifying if the trend is compatible with that of Fig. 2, where the consumption of nitrobenzene and the formation of the products are shown. It is noteworthy, the fast consumption of hydrogen, which follows practically a straight line, during the first 60-80 minutes. This is in agreement with the first part of the hydrogenation of nitrobenzene to aniline, whose reaction rate is fast and shows practically a linear trend. In addition, it is likely, that under this reaction conditions: with high catalyst load, multiphase system and low hydrogen pressure, diffusion phenomena may partially limits the reaction rate of nitrobenzene reduction [47]. This is in agreement with that observed by carrying out a reaction with 5 mg of catalyst where the initial hydrogen consumption rate remain practically the same of that measured with 50mg of catalyst (see supplementary materials Fig. 5S). This behavior can be ascribed to the complex reaction system, where dissolution adsorption and re-precipitation of salts occur and where it is likely that diffusion may influence hydrogen adsorption rate [48]. It is noteworthy, that also, the second part of the hydrogenation of nitrobenzene (see Fig. 6) appears as a straight line but its slope is lesser than that of the first part (Fig. 5, 0.019 mmol min^{-1} *vs.* 0.52 mmol min^{-1}, respectively). Such a behavior confirms the low activity of the catalyst in the AN hydrogenation compared with that measured for nitrobenzene. Another important point, is that the overall mass balance with all products of hydrogenation does not hold, in fact, after 70 minutes 35 mmol of hydrogen (30 mmol of hydrogen is the stoichiometric for nitrobenzene to AN) has been adsorbed, thus suggesting that there are more reactions consuming hydrogen. At first glance, the solvent reduction could have been a likely candidate, but the reaction carried out with pure solvent does not shows any hydrogen consumption (experimental section).

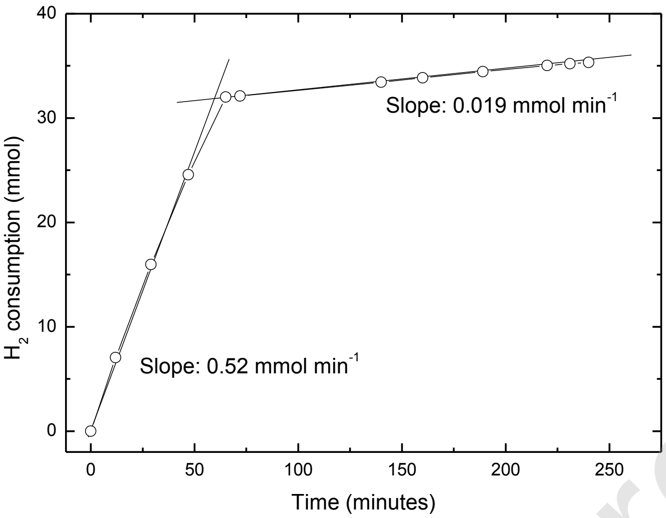


Fig. 4. Hydrogen consumption profile of nitrobenzene hydrogenation. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH \cdot HCl$ 30 mmol, T 333 K, Pd/C 50 mg.

Under such hydrogenating conditions, hydroxylamine hydrochloride, in the presence 1 mol L^{-1} of water (that is the water produced during nitrobenzene reduction), gives ammonium salt by following Scheme 4.

$$NH_2OH \cdot HCl + H_2 \xrightarrow{Pd/C} NH_4Cl + H_2O$$

Scheme 4

Fig. 5 shows a clear hydrogen consumption, thus suggesting a competitive parallel reduction of this reagent during nitrobenzene hydrogenation as well as also during the hydrogenation of the aniline and the formation of COX. The profile of hydrogen consumption is a straight line, and being this reaction rate 20 times slower than that of the NB hydrogenation, it is likely that diffusion phenomena does not influence this reaction rate. Besides, this evidence suggests that the reaction rate is not influenced by the hydroxylammonium concentration (it results as a pseudo zero order in the salt concentration) thus suggesting a strong adsorption on the catalyst surface. It is noteworthy, reactions carried out in the presence of Au catalysts do not show any hydrogen consumption in the hydrogenation of $NH_2OH{\cdot}HCl$. This intrinsic low catalytic activity of gold catalysts in the hydrogenation of this substrate, is, however, in agreement with the low activity of these catalyst also in the NB hydrogenation (see Tab.1). Taking into account the presence of precipitation-dissolution equilibria this does not allow any kinetic consideration on the reaction order because of the complexity of the system. The $NH_2OH{\cdot}HCl$ solution adsorbs after 4h, 7 mmol of hydrogen, which is in agreement with the conversion of the $NH_2OH{\cdot}HCl$ to NH_4Cl measured by titration of the solution obtained by extraction with water of the inorganic salts present into the reaction environment. The reaction rate, measured in Fig. 7, is higher than that observed in the second part of Fig. 6 (0.026 mmol min^{-1} vs 0.019 mmol min^{-1}), since it is likely that the presence of the aniline lows down kinetics and thus also that of the $NH_2OH{\cdot}HCl$ reduction.

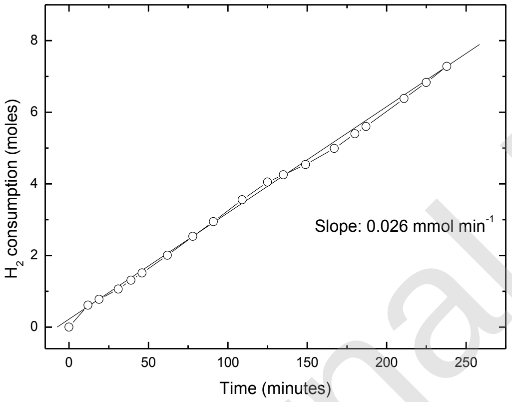


Fig. 5. H_2 consumption profile for NH_2OH hydrogenation. Run conditions: reaction volume 20 mL, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, H_2O 20 mmol, T 333K, Pd/C 50 mg.

3.5. Aniline Hydrogenation to COX

Fig. 6 reports the reaction profile of AN hydrogenation. As expected the initial reaction rate is slower than that of nitrobenzene, since AN is a harder substrate to hydrogenate [22-26]. However, after 20 h it proceeds until 47% of conversion, with a high selectivity (COX selectivity > 96%). Despite of the high selectivity in COX starting from AN, after 20h of reaction the overall yield of COX is lower (45%) with respect of what found in nitrobenzene hydrogenation (yield 62%), but the different initial condition and the course of the nitrobenzene hydrogenation may lead to a different reactivity of the system, thus determining a lower yield in COX. Indeed, the conditions of the hydrogenation of pure aniline are different with respect to what occurs at the end of nitrobenzene consumption during its reduction, because of the presence byproducts of NB and NH_2OH hydrogenation, that is water and ammonium chloride salt (Scheme 4). When we start from nitrobenzene, the presence of this parallel reaction may modify both the reaction environment and the catalyst reactivity thus inducing likely the higher final yield. On the contrary, the reaction in the presence AN shows an overall yield in COX lower even though the reaction show a higher COX selectivity. The byproducts (that is CHA, CON and PCA) are in lower concentration (traces) than that measured in NB hydrogenation, this result suggests a quite different reactivity of the system, when the starting reagent is nitrobenzene likely induced by the variable water and NH_2OH concentration.

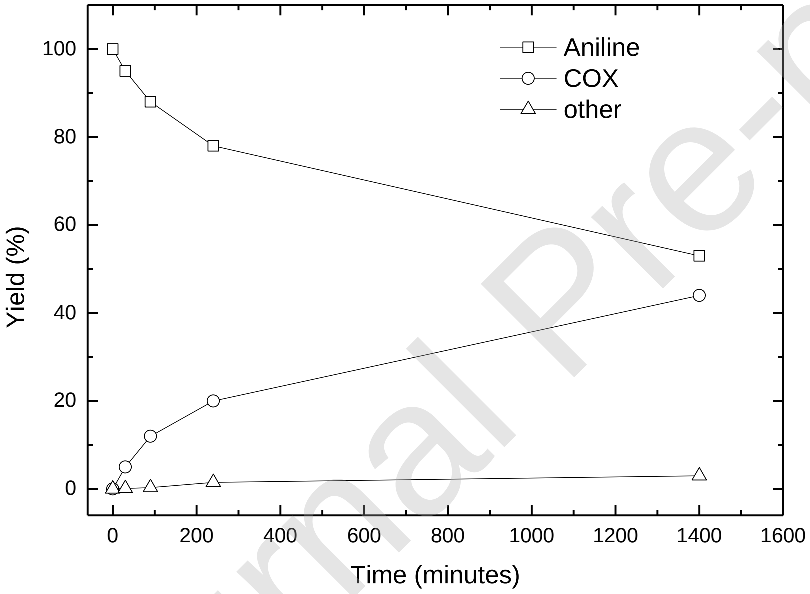
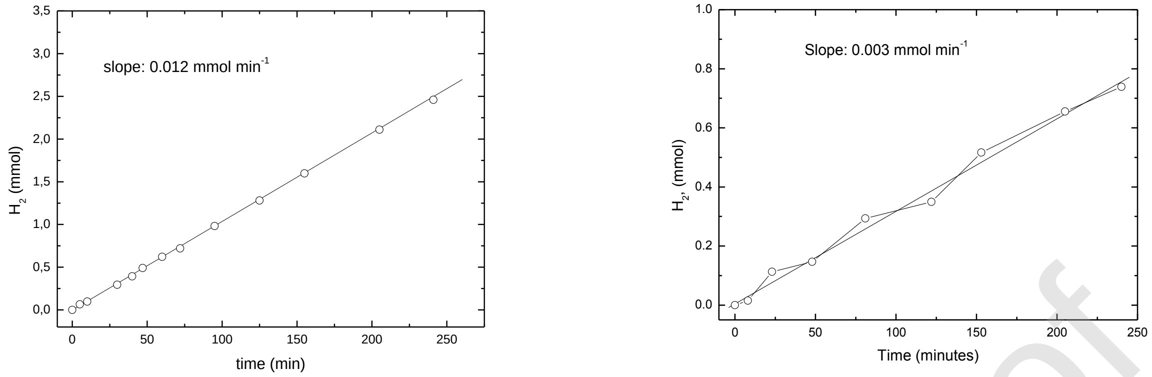


Fig. 6. Reaction profile of aniline hydrogenation. Run conditions: reaction volume 80 mL, aniline 0.5 mol L^{-1}, H_2O 20 mmol, hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 75 mmol, T 333K, Pd/C 50 mg.

Fig. 7 A shows hydrogen consumption trend for AN hydrogenation, after 240 minutes of reaction, the trend is a linear consumption of hydrogen similar to that observed in the second part of Fig. 6. The slope measured, however, is significantly lower than that of the second part of Fig. 4, (0.012 mmol min^{-1} *vs* 0.018 mmol min^{-1}) thus suggesting a strong adsorption of the AN. This is in agreement with the very low rate of hydrogen adsorption observed in Fig. 7 B (that is 0.003 mmol min^{-1}) in the absence of $NH_2OH{\cdot}HCl$.



A

B

Fig. 7. Reaction profile of hydrogen consumption for AN hydrogenation. Run conditions: reaction volume 20 mL, aniline 0.5 mol L^{-1}, H_2O 20 mmol, hydrogen Pressure 0.8 MPa, T 333K, Pd/C 50 mg. A), reaction in the presence of 30 mmol of $NH_2OH{\cdot}HCl$; B) no $NH_2OH{\cdot}HCl$.

Such an evidence confirms the strong inhibiting effect of the AN on the hydrogenation capability of the catalyst, this probably due to its tough surface adsorption coupled with a slow surface reaction kinetics. On the contrary, the presence of $NH_2OH{\cdot}HCl$ may favor the kinetics of AN reduction by diminishing the AN adsorption, and likely, increasing surface mobility of the surface Pd-H species.

The presence of CHA increases NH_2OH hydrogenation rate, as can be observed in Fig. 8 where the initial hydrogen consumption rate is almost the triple of that measured without CHA (Fig. 6, 0.026 mmol L^{-1} *vs.* Fig. 8, 0.075 mmolL^{-1}). This effect is possibly due to the basicity of the CHA, which displaces the hydroxylammonium equilibrium to NH_2OH (pKa CHA< pKa NH_3 < pKa NH_2OH < pKa AN), that easily reacts with hydrogen by the way of Pd/C catalysis [49-51]. In fact, CHA disappears from the solution because it changes to its ammonium salt, which precipitates. This is evident since the solution obtained by, washing the solid with water, filtered away the Pd/C, raised the pH of the solution with KOH at pH>12, and finally extracting the aqueous phase with CH_2Cl_2, the GC-MS analysis of such a solution shows the presence of CHA, clearly. By analyzing the profile of hydrogen consumption of Fig. 8, it is evident a non-linear trend with a decrease of the slope after 120 minutes of reaction and 10 mmol of adsorbed hydrogen. This trend suggests that the faster initial part of the reaction is due to the hydrogenation of the free NH_2OH, derived from its salt displaced by the CHA, when the reaction begin going slower it is likely due to the lower concentration of the free NH_2OH due to the precipitation of the CHA hydrochloride thus reducing the displacement of $NH_2OH{\cdot}HCl$ to free NH_2OH.

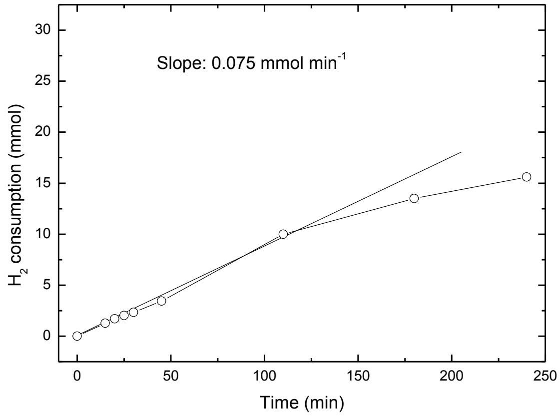


Fig. 8. H_2 consumption profile for NH_2OH hydrogenation in the presence of 0.5 mol L^{-1} CHA. Run conditions: reaction volume 20 mL, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, H_2O 20 mmol, T 333K, Pd/C 50 mg, time of reaction 4 h.

The importance of the presence of water in the reaction environment is evident by observing the results reported in Fig. 9. It shows the influence of water on the yield of COX in the AN hydrogenation. It appears, the amount of water, until 80 mmol, promotes the formation of COX, thus suggesting an influence of H_2O on NH_2OH availability. The reaction, however, occurs also in the presence of molecular sieves 5A, as H_2O scavenger, but in lower yield (about 13%), suggesting that the NH_2OH exists in solution also in the organic solvent, but the presence of small amount of water will aid the increase of NH_2OH availability. In fact, hydroxylammonium salt is sparingly soluble in organic solvent, being, on the contrary, soluble in water. The system however is really complex even when we start from aniline. The addition of 20 mmol of water (1 mol L^{-1}) to emulate that produced in the hydrogenation of nitrobenzene, is not sufficient to estimate the whole water present in the reaction media since NH_2OH is reduced in parallel giving water and ammonium salt. Furthermore, it is noteworthy, that at the higher water amount, there will be the formation of another liquid phase since 20 mL of pure diethyl ether can solubilize 13 mmol of water [52]. The calculation for these multiphase equilibria is beyond the scope of the present work but approximate values are reported in Tab S5 in the supplementary information section. In any case, the role of water is evident in Fig. 9, which shows that the increasing the amount of water until 80 mmol will cause the growth of the COX yield up to 55%. This effect is likely due to the increase of the NH_2OH concentration, which is the active specie in the COX formation. The Increase after a certain amount of water may cause a decrease of AN hydrogenation thus diminishing the overall yield in COX. This is agreement with what observed by using a mixture H_2O/THF as a solvent (see Tab. 4 entry 5) where the conversion of aniline is negligible at very high water concentration. In addition, it is necessary take into account that the NH_2OH is reduced in parallel and this cause the diminishing of the NH_2OH availability and then overall COX yield.

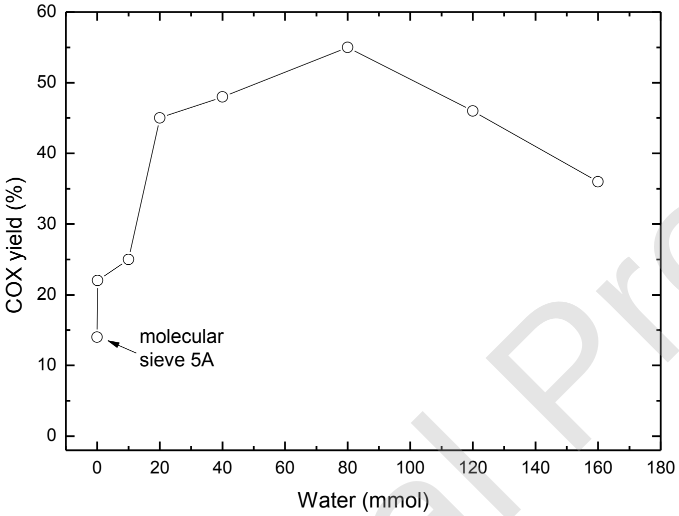


Fig. 9. Influence of H_2O on COX yield. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH·HCl$ 30 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

Further consideration must be done on the presence of the ammonium salt. In fact, its presence is not unbiased for the reactivity of the system, since it may influence all equilibria, and then, the overall COX yield. It appears from Fig. 10 that the trend of the influence of NH_4Cl amount on the COX yield have a maximum at 10 mmol (COX yield 65%). This behavior suggests that ammonium salt favor the formation of the oxime increasing the hydrogenation rate of AN. Indeed, hydrogen consumption rate reported in Fig. 11 is 0.039 mmol min^{-1}, which is higher than that measured in the presence of only $NH_2OH·HCl$ (Fig. 9 A, 0.012 mmol min^{-1}).

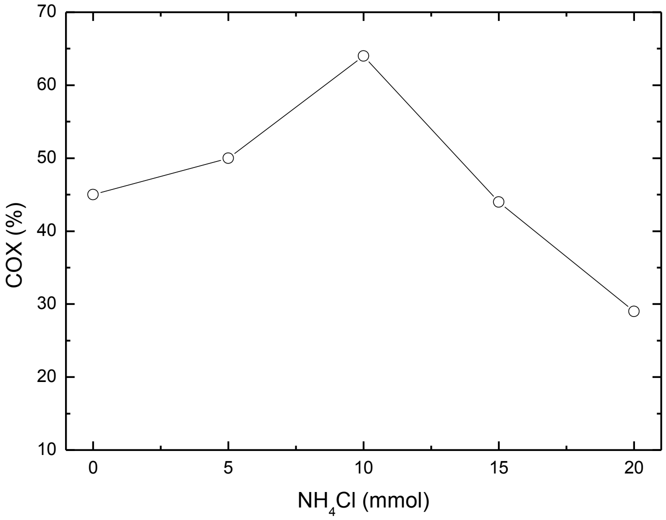


Fig. 10. Influence of NH4Cl amount on COX yield. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, H_2O 20 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

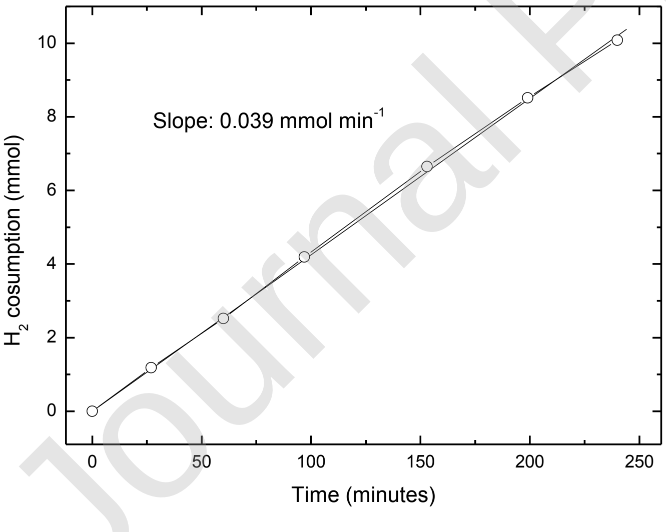


Fig. 11. Reaction profile of hydrogen consumption for AN hydrogenation in the presence of NH_4Cl. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH{\cdot}HCl$ 30 mmol, H_2O 20 mmol, NH_4Cl 10 mmol, T 333K, Pd/C 50 mg.

After this discussion, it is quite evident the first part of the reaction, that is the hydrogenation of NB to AN influences the reactivity of the system, mainly for the coproduction of water and ammonium salt, the latter deriving from the parallel reaction of $NH_2OH·HCl$ reduction. Both byproducts promote the yield in COX.

3.6. Influence of the intermediates and of the products on conversion and selectivity

As discussed in previous sections, nitrobenzene disappears quantitatively in about 60 minutes then other compounds appear in the reaction media, quantitatively the most important one is AN. Starting from this evidence we study the reactivity of AN in the presence of various solvent and the results are in Tab. 4. As expected, it appears the needs of H_2 in order to obtain the conversion of AN to COX. In fact, the reaction carried out without H_2 (see supplementary materials Tab. S3) does not show the formation of COX. It is noteworthy the high selectivity in COX observed with EtOH, Et_2O and THF as solvent. Nevertheless, the reaction does not reach high conversion, lower than 50%, except when CH_3CN is the solvent giving, however, mainly products of aniline alkylation. This low hydrogenation activity the very strong adsorption of AN on the Pd surface, thus inhibiting the reaction of hydrogenation, being the aniline surface complex stable and impeding the adsorption of hydrogen. In fact, aniline hydrogenations were generally carried at high hydrogen pressure exceeding 5 MPa [22-26]. This strong adsorption of aniline agrees with its reactivity in the absence of $NH_2OH·HCl$, it appears the conversion reaches as low as 8% and the main product is PCA and N,N-di-cyclohexylamine (see entry 6). The byproduct (CHA, CON and PCA) are in low concentrations and no other products are observed. In agreement with the experiment carried out with NB as reagent (Tab. 2), in the presence of very large amount of water (Tab. 4 entry 5) AN does not give COX or other products deriving from its reduction

Table. 4. Reactivity of AN. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, $NH_2OH·HCl$ 30 mmol, H_2 pressure 0.8 MPa, H_2O 20 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

Entry	Solvent	Conversion	Selectivity				
		(%)	COX (%)	CHA (%)	CON (%)	PCA (%)	Others (%)
1	Et_2O	47	98	0.4	0.2	1.5	0.9
2	THF	49	97	0.3	0.3	1.5	0.9
3	EtOH	12	95	traces	traces	traces	4
4[a]	CH_3CN	100	20	0.1	0.1	0.7	78
5[b]	THF/H_2O	2	/	/	/	/	100

6[c]	Et_2O	8	/	14	/	48	38

a) Other is mainly AN alkylation.
b) Reaction carried out phase in great excess of water: THF/H_2O = 1/1 wt.
c) Reaction carried out without NH_2OH.

CHA does not gives COX, neither in presence of hydrogen nor in its absence (Tab. 5 entries 1, 2). The simultaneous presence of CHA and AN does not give COX (entry 3 and 4). This confirms the strong inhibiting effect of the CHA on the formation of COX even though the role of CHA is not clear. In fact, it is important to consider that after 20 h of reaction CHA practically disappears from the reacted solution, since it is quantitatively transformed in its ammonium salt. This is confirmed by analyzing the solution obtained from the solid washed with water, where a mixtures of ammonium salts of NH_2OH, NH_3 and CHA is detected. This evidences suggests that CHA is not an intermediate but it is a byproduct deriving from AN total hydrogenation, which is not in dehydrogenative equilibrium, under this reaction condition, since its presence completely inhibits AN hydrogenation to COX or other products that could be an intermediate in COX formation such as CON.

Table. 5. Reactivity of CHA. Run conditions: reaction volume 20 mL, substrate 0.5 mol L^{-1}, $NH_2OH\cdot HCl$ 30 mmol, H_2O 20 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

Entry	substrate	P H_2 (bar)	Conversion (%)	Selectivity COX (%)	CON (%)	PCA (%)	Others (%)
1[a]	CHA	5(N_2)	1	/	/	/	100
2[a]	CHA	8	1	/	/	/	100
3[b]	CHA+AN	8	4	/	/	5	95
4[b,]	CHA+AN	5(N_2)	1	/	/	/	90

a) Other mainly products of CHA alkylations.
b) CHA/AN =1/1 conversion on aniline.

In Tab. 6 the reactivity of CON and PCNA are reported. It appears that CON reacts with $NH_2OH\cdot HCl$ quite easily since the reaction is fast being the conversion of CON after 0.5 h equal to that obtained after 20 h (conversion of 70% entries 1- 4). The selectivity is higher without any catalyst (94% in COX entry 2), this agrees with previous researches on the self-catalyzed transformation of some ketones to amides where the oximation of the ketones occur without any catalyst [53]. As expected, in agreement with what reported by Corma and co-workers PCA is poorly hydrogenated and mainly to N,N-dicyclohexylamine (entry 5) [36]. This suggests PCA is a side product and it is not an intermediate of the reaction. PCNA has been observed in solution during the reaction, only in traces amount (by a careful analysis at the GC-MS) but we have synthesized the compound and tested its reactivity. Actually, it reacts with practically all the nucleophiles giving fast substitution being AN the living group. This is evident observing that PCNA hydrolyzes to CON and AN by reacting with the water present in the solvent and/or hair moisture reaching an equilibrium after few hours (see supplementary). However, in the presence of hydrogen NH_2OH and Pd/C catalysts, PCNA gives COX in high yield (93% entry 6). In absence of hydrogen but with Pd or Au catalysts COX formation is practically equal to that observed in experiments carried out without catalysts (compare entry 7, 8, 14 and 15). This suggests the presence of the Pd/C catalyst hydrogenates AN, displaced by NH_2OH, that in turns forms COX in the presence of NH_2OH. Au based catalyst are completely ineffective (entry 12 and 13) giving the same results of that observed with no catalysts and/or hydrogen (compare entries 7, 8 and 12-15). Starting from these results, it appears there are no needs of catalysts for the nucleophilic substitution. In fact, these Au catalysts seems to be not effective in the formation of COX, in agreement with their poor hydrogenation ability already stated in Tab. 1. The hydrogenation in the presence of Pd/C of PCNA without NH_2OH shows the formation of PCA and di-cyclohexyl amine (entry 16). Entries 17 and 18 evidences the facile nucleophilic substitution of CHA towards aniline giving N,N-cyclohexylen-cyclohexylamine in the absence of Pd/C or, in the presence of the Pd catalyst, N,N-dicyclohexylamine as the result of the hydrogenation of N,N-cyclohexylen-cyclohexylamine. Comparable results have been observed with CON and COX suggesting the easy nucleophilic substitution due to CHA (see supplementary Tab. S4).

Table. 6. Reactivity of CON, PCA and PCNA. Run conditions: reaction volume 20 mL, Et_2O as a solvent, substrate 0.5 mol L^{-1}, $NH_2OH{\cdot}HCl$ 30 mmol, H_2O 20 mmol, T 333K, catalyst 50 mg.

Entry	Substrate	Catalyst	Time of	P	Conv.[a]	Selectivity				
		metal (%)	reaction (h)	H_2 (bar)	(%)	COX (%)	CHA (%)	CON (%)	PCA (%)	Others (%)
1	CON	/	20	5(N_2)	70	89	/	/	/	11
2	CON	/	0.5	5(N_2)	70	94	/	/	/	6
3	CON	Pd/C(5)	20	8	72	88	/	/	/	12
4	CON	Pd/C(5)	0.5	5(N_2)	70	91	/	/	/	9
5	PCA	Pd/C(5)	20	8	6	/	/	/	/	100[b]
6	PCNA	Pd/C(5)	20	8	>99	93	/	3	3	1
7	PCNA	Pd/C(5)	20	5(N_2)	>99	46	/	2	2	50[c]
8	PCNA	/	20	5(N_2)	>99	48	/	2	2	48[c]

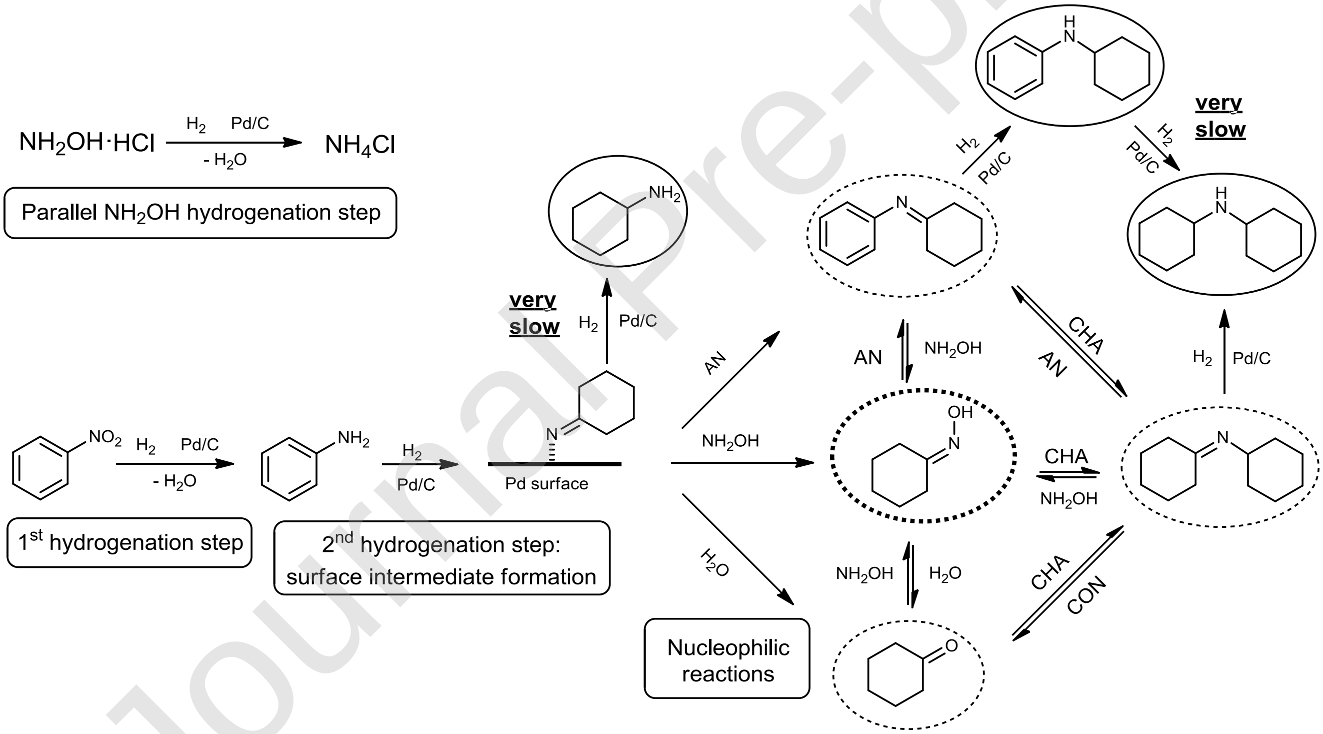
9	CON	Au/SBA(2)	0.5	5(N_2)	70	92	/	/	/	8
10	CON	Au/SBA(2)	20	5(N_2)	70	89	/	/	/	11
11	CON	Au/C (0.5)	0.5	8	70	48	/	/	/	11
12	PCNA	Au/SBA(2)	20	8	>99	47	/	2	1	50[c]
13	PCNA	Au/C (0.5)	20	8	>99		/	2	2	50[c]
14	PCNA	Au/SBA(2)	20	5(N_2)	>99	47	/	2	1	50[c]
15	PCNA	Au/C (0.5)	20	5(N_2)	>99	46	/	2	2	50[c]
16	PCNA[d]	Pd/C	20	8	98	/	/	10	72	10[b]
17	PCNA+CHA[d]	/	20	8	>99	/	/	8	/	92[e]
18	PCNA+CHA[d]	Pd/C	20	8	>99	/	8	8	4	80[f]

a) Conv. = conversion.
b) Other is mainly N, N-dicyclohexylamine.
c) Mainly AN.
d) Reaction carried without NH_2OH.
e) Mainly a mixture AN and N, N-cyclohexyliden-cyclohexane.
f) Mainly a mixture AN and N, N-dicyclohexylamine.

The above results state that the main intermediate is aniline and its hydrogenation is the key step. Besides CON and PCNA are both intermediates since the nucleophilic attack of NH_2OH to these compound gives COX. On the contrary, the addition of CHA displaces AN from PCNA, thus forming of N, N-cyclohexyliden-cyclohexane. In addition, the latter is also obtained from CON and COX (see supplementary Tab. S4) by reacting with CHA. This behavior clearly states that of CHA is a side product and not an intermediate, since no COX is obtained when CHA is present in relevant amount but only product of CHA condensation. There are no evidence of a dehydrogenative equilibrium between CHA and an imine intermediate, which in turn will react to give PCNA and finally COX since CHA reacts readily as a nucleophile with PCNA giving N, N-cyclohexyliden-cyclohexane. Also imine intermediate is not present in solution, however it is likely that such an imine intermediate is present on the Pd surface, which is finally attacked by all nucleophiles present in solution such as NH_2OH, H_2O, AN, and CHA.

3.7. Possible reaction path

Despite of the complexity of the reaction and the large number of equilibria and reactions, we can try to suggest a likely reaction path (scheme 4). All the evidences suggest the first stage is NB hydrogenation to AN. Likely, the second step is AN partial hydrogenation and formation of an imine surface intermediate, which readily reacts with all the nucleophiles present in solution giving products signed by dashed lines. The role of water is here not only the nucleophile, which allow the formation of cyclohexanone, but it favors also the multiphase equilibria that give NH_2OH thus favoring COX formation. As a matter of fact, the product that is revenue in higher amount is COX because of the higher nucleophilicity of NH_2OH compared to that of H_2O and AN [54]. In addition, all products obtained from the nucleophilic reaction are in equilibrium (molecules circled with dashed line). On the contrary, irreversible hydrogenation reactions (under the conditions investigated) occur giving the molecules circled by solid line; that is CHA, PCA and N, N-dicyclohexylamine. At the conditions investigated CHA and N, N-dicyclohexylamine are observed in low concentration (at most 1%), and the latter only after long reaction time. CHA formation is very slow and if added in a relevant amount change completely the products distribution (see Tab. 6 and supplementary materials Tab. S3). In fact, if CHA in the presence of CON, COX and DCHA easily gives nucleophilic substitution, thus forming N, N-cyclohexylen-cyclohexanamine, which is, in turn, hydrogenated to N, N-dicyclohexylamine (see supplementary Tab. S3).



Scheme 4. Proposed reaction path for the direct synthesis COX via nitrobenzene hydrogenation.

4. Conclusions

All results states the complexity of the reaction path and the large number of factors it is necessary to take into account for optimizing the yield in COX. The new insights for this process are the importance of the secondary reactions that is the reduction of $NH_2OH{\cdot}HCl$ and all nucleophiles equilibria. In fact, its reduction gives NH_4Cl and water, which, both, influences the selectivity towards COX. Aniline is the key intermediate and at first sight, its hydrogenation gives a lower yield in COX compared to that obtained using nitrobenzene as a substrate. This evidence is, however, apparent since the addition of a proper amount of water and NH_4Cl shows an increment of the yield at the level of that observed for nitrobenzene. In this way, it has been possible to recognize the role of secondary reactions, which determine the overall selectivity to COX. In fact, the nucleophilic addition to the imine surface intermediate of AN, H_2O and NH_2OH, gives PCNA, CON and COX, respectively, whose equilibria in solution displace to a higher selectivity in COX. It appears that all the nucleophilic reactions are not influenced by the presence of metal catalysts. Pd/C catalyst seems to be the best catalytic system, other supported metal catalyst does not give comparable results, and mixed catalysts gives, in any case, lower selectivity in COX. The selectivity increases as the amount of Pd/C, in agreement with the formation of a surface intermediate determining the selectivity. Besides, it suggests that the mass transfer on catalyst surface may have a role on the overall selectivity in COX, but a detailed kinetic study is beyond the scope of the present work.

The role of solvent is of paramount importance and the best results is achieved by using oxygenated non hydroxylated solvents, preferably ethers. Hydrogen pressure influences the selectivity in the range investigated 0.5-2 MPa, and the best interval of pressure is comprised between 0.8 Mpa and 1 Mpa. Temperature of reaction has been varied between 323 K and 373K and the highest selectivity has been observed in the range 333-343K.

Some experiments with the likely intermediates and byproducts of the reaction show that both CON and PCNA are intermediate while CHA and PCA are irreversible byproducts.

Author statement

All authors contributed to investigation, LR an AV had the major role on funding acquisition, LR and AV had the major role in all other aspects regarding the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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