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A polymer supported palladium(II) β-ketoesterate complex as active and recyclable pre-catalyst for selective reduction of quinolines in water with sodium borohydride

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Dedicated to the memory of Professor Benedetto Corain

Abstract

A polymer supported palladium catalyst, obtained by copolymerization of Pd(AAEMA)$_2$ [AAEMA$^-$ = deprotonated form of 2-(acetoacetoxy)ethyl methacrylate] with ethyl methacrylate (co-monomer) and ethylene glycol dimethacrylate (cross-linker), exhibited excellent activity and selectivity for the hydrogenation of quinolines to 1,2,3,4-tetrahydroquinolines in the presence of NaBH$_4$ as hydrogen donor in water. Both the activity and selectivity could be maintained for at least seven reaction runs. No metal leaching into solution occurred during recycles. TEM analyses carried out on the catalyst showed that the active species were supported palladium nanoparticles having a mean size of 3 nm, which did not aggregate with the recycles.

1. Introduction

The hydrogenation of quinoline and its derivatives is an important area of research, since its products are valuable intermediates for the synthesis of drugs, agrochemicals, dyes, alkaloids, and many other biological active molecules [1-3]. In fact, the direct catalytic hydrogenation of readily available quinolines in order to selectively obtain 1,2,3,4-tetrahydroquinolines is preferable in terms of atom economy compared to other synthetic approaches, such as the catalytic cyclization [4,5] and the Beckman rearrangement [6]. However, the hydrogenation [7] of these N-heterocycles is a difficult task [8] due to the resonance stabilized aromatic nucleus and the fact that the product secondary amines could act as poison to most industrially common heterogeneous metal catalysts [9,10].

Extended efforts have been devoted to the selective hydrogenation of these compounds using hydrogen gas and soluble metal catalysts based on Os [11], Ir [8,12] Ru [13-15] and Rh [16,17], although they were difficult to be re-used and very often needed the presence of a co-catalyst. Also heterogeneous catalytic systems based on noble metals [18], such as Ru [19,20], Rh [21], Au [22] and Pd [23-25] have been developed, but they presented clear drawbacks, such as the need of harsh conditions (30÷60 bar of H_2, 100÷150 °C) and/or the presence of toxic organic solvents (for example: toluene or *n*-hexane). Only a limited number of heterogeneous catalysts have been found active in promoting the reduction of quinolines in water under hydrogen gas. They are: Ru nanoparticles intercalated in hectorite [26], Ir complex anchored onto a solid support [27] and Pd nanoparticles stabilized by black wattle tannin [28,29], only the latter being recyclable. Recently, with the growth of green and sustainable chemistry concepts [30], considering water not only as a

possible solvent [31] but also a reagent has attracted great attention in organic synthesis [32]. In the field of reduction, water has extensively been used for both hydrogenation and transfer hydrogenation reactions [33]. Examples of transfer hydrogenation catalytic systems active in water for promoting the selective reduction of quinolines and quinoxalines are those based on: a Ni-Al alloy [34], an Ir complex with HCOONa as the hydrogen source [35], a Pd/C and Zn mixture [36], being the majority of transfer hydrogenation catalysts active and selective only in commonly used organic solvents (alcohols, toluene, etc.) [37-44].

However, the major problem related to the recyclability of these transfer hydrogenation catalytic systems in water remains unsolved and the development of more effective, recyclable, and handle-convenient catalysts for this transformation is still highly desirable.

With the aim to set up new environmentally friendly synthetic methods to be performed under mild and sustainable conditions with high efficiency, we decided to evaluate the catalytic activity of a polymer supported palladium catalyst (in the following *Pd-pol*) for the partial hydrogenation of quinolines in water with $NaBH_4$. In order to obtain a material with a uniform distribution of the active sites, the catalyst was synthetized in an uncommon way [45], *i.e.* by co-polymerization of the metal-containing monomer $Pd(AAEMA)_2$ [$AAEMA^-$ = deprotonated form of 2-(acetoacetoxy)ethyl methacrylate] with suitable co-monomer (ethyl methacrylate) and cross-linker (ethylene glycol dimethacrylate) [46,47] (Scheme 1).
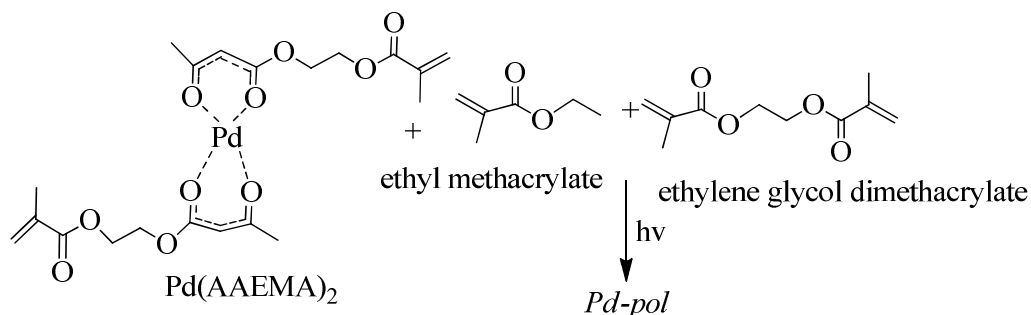
Scheme 1: synthesis of *Pd-pol*

Pd-pol was successfully tested as active and recyclable catalyst in several palladium promoted reactions [48-53]. The reticular and macro porous polymeric support of *Pd-pol* is able to immobilize and stabilize palladium nanoparticles formed under reaction conditions by reduction of the pristine Pd(II) anchored complex. Furthermore, its good swellability in water renders *Pd-pol* an ideal potential catalyst for reactions carried out in water, since the migration of the reagents to the active sites would not be hampered by the solid support. In fact, *Pd-pol* was active and recyclable in the Suzuki cross coupling of arylhalides with arylboronic acids [54], the aerobic selective oxidation of benzyl alcohols [55] and the reduction of nitroarenes [56], all of them carried out in water. Moreover, *Pd-pol* was already tested in aqueous medium as catalyst for the hydrogenation of quinolines into 1,2,3,4-tetrahydroquinolines at 80°C under 10 bar H_2, resulting uncommonly recyclable at least for nine consecutive runs with high yields [57]. To the best of our knowledge, *Pd-pol* is still the second example reported to date of active palladium catalyst recyclable in aqueous solvent for the selective hydrogenation of quinolines and heteroaromatic nitrogen compounds under mild conditions using hydrogen gas, being the first reported example Pd nanoparticles on black wattle tannin [28,29]. For this reason, we decided to evaluate the catalytic activity of *Pd-pol* also in the transfer hydrogenation of quinolines in water.

Following our studies, herein we report on the ability of *Pd-pol* to efficiently catalyze the selective reduction of quinolines into tetrahydroquinolines in neat water using $NaBH_4$ as hydrogen source, thus using "safer" conditions compared to the ones previously proposed by us [57].

2. Experimental Section

2.1. General considerations

Tap water was de-ionized by ionic exchange resins (Millipore) before use. All other chemicals were purchased from commercial sources and used as received. *Pd-pol* (Pd $\%_w$ = 5.0) was synthesized according to literature procedure [53]. Palladium content in *Pd-pol* was assessed after sample

mineralization by atomic absorption spectrometry using a Perkin Elmer 3110 instrument. Catalyst mineralization prior to Pd analyses was carried out by microwave irradiation with an ETHOS E-TOUCH Milestone applicator, after addition of 12 mL HCl/HNO$_3$ (3:1, v/v) solution to each weighted sample.

GC-MS data (EI, 70 eV) were acquired on a HP 6890 instrument using a HP-5MS crosslinked 5% PH ME siloxane (30.0 m $\times$ 0.25 mm $\times$ 0.25 μm) capillary column coupled with a mass spectrometer HP 5973. The products were identified by comparison of their GC-MS or ^{1}H NMR features with those of authentic samples. Reactions were monitored by GLC or by GC-MS analyses. GLC analysis of the products was performed using a HP 6890 instrument equipped with a FID detector and a HP-1 (Crosslinked Methyl Siloxane) capillary column (60.0 m x 0.25 mm x 1.0 μm). GLC yields were assessed by using biphenyl as internal standard. Isolated yields were determined by flash column chromatography using Merck® Kieselgel 60 (230–400 mesh) silica gel. ^{1}H NMR spectra were recorded on a Bruker Avance III 700 MHz spectrometer and the signals are reported in ppm relative to tetramethylsilane (Supporting Information Section).

Transmission electron micrographs were obtained using a JEM 2010 instrument operating at 200 kV (Jeol - Oxford Instruments) equipped with a GIF100 GATAN and 1k $\times$ 1k pixel GATAN ERLANGSHEN ES 500W CCD camera. Samples were finely ground and suspended in bidistilled water with 15 minute Sonication. A few droplets of the suspension were deposited on a copper grid covered with a Formvar® film and carbon sputtered to assure optimal conductivity. The particle size distributions were obtained by TEM image analysis using the ImageJ software (freeware software: http://rsb.info.nih.gov/ij/).

Micro-FTIR spectra (neat) were recorded using a Perkin Elmer Spectrum 2000 instrument.

2.2. General procedure for catalytic transfer hydrogenation of quinolines

2.2.1. Procedure A

1.0 mmol of substrate, 37.2 mg of *Pd-pol* (Pd%$_w$ = 5.0, 0.0175 mmol of Pd) and 20.0 mmol of sodium borohydride were stirred under nitrogen at 60°C in 5 mL of double deionized water for the appropriate amount of time, using a three-necked flask equipped with a reflux condenser and a gas bubbler in order to discharge the hydrogen excess produced during reaction. The progress of the reaction was monitored by GLC. After completion of the reaction, the reaction mixture was centrifuged to separate the catalyst. The solid residue was first washed with deionized water and then with acetone and diethyl ether to remove any traces of organic material. The filtrate containing the reaction mixture was extracted with ethyl acetate (3 × 5 mL) and then dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to yield the crude product, which was then purified by flash column chromatography using silica gel and an appropriate eluent (Supporting Information) to afford the pure product. The products were characterized by GC-MS or ^{1}H NMR by comparison with authentic samples. For the assessment of the chromatographic yields, biphenyl (50.0 mg) was used as the internal standard.

2.2.2. Procedure B

A 50 mL stainless steel autoclave equipped with a transducer for online pressure monitoring was charged, under air, of *Pd-pol* (37.2 mg, Pd%$_w$ =5.0, 0.0175 mmol of Pd), the substrate (1.0 mmol), sodium borohydride (20.0 mmol) and water (5.0 mL). The autoclave was then closed, set on a magnetic stirrer and heated to 60°C. After the minimum time needed to reach reaction completion, the autoclave was let to reach room temperature, the formed hydrogen was vented and the autoclave opened. The catalyst was recovered by filtration while the organic product was extracted with ethyl acetate (3 mL), the water phase was washed with ethyl acetate (3 × 5 mL) and the organic layers were collected and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure to yield the crude product, which was then purified by flash column chromatography using silica gel and an appropriate eluent (Supporting Information) to afford the pure product. The products were characterized by GC-MS or ^{1}H NMR by comparison with authentic samples. For the assessment of the chromatographic yields, biphenyl (50.0 mg) was used as the internal standard.

2.3. Recycling experiments

The catalyst recovered by filtration was washed with water, acetone, and diethyl ether and dried under high vacuum. The recovered catalyst was thus weighed and reused for a new cycle employing appropriate amounts of organic substrate, sodium borohydride and solvent, assuming that the palladium content remained unchanged with the recycles. Iteration of this procedure was continued for seven reuses of the catalyst.

3. Results and discussion

3.1. Catalytic hydrogenation of quinoline

To determine the optimum amount of sodium borohydride and catalyst required for the reduction of quinolines, different catalytic tests were carried out varying the temperature and amounts of $NaBH_4$ and the catalyst, using quinoline as the representative substrate (Scheme 2). The relevant results are reported in Table 1.
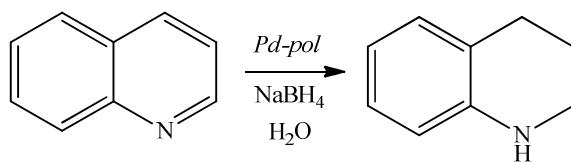
Scheme 2: reduction of quinoline catalyzed by *Pd-pol*

Table 1: Optimization of different parameters for the reduction of quinoline[a]

Entry	Amount of sodium borohydride (mmol)	Substrate/Pd (mmol/mmol)	T (°C)	t (h)[b]	Conv.[c] (%)	Selectivity[d] (%)
1	10	200	60	9	30	>99
2	10	200	80	9	37	>99
3	20	200	60	9	56	>99

4	20	100	60	9	70	>99
5	**20**	**50**	**60**	**9**	**99**	**93**
6[e]	**20**	**50**	**60**	**4**	**99**	**94**
7[f]	20	no cat	60	9	56	46
8[e,f]	20	no cat	60	9	58	54

[a] Reaction conditions: 1.0 mmol of quinoline and given amounts of $NaBH_4$ and *Pd-pol* (Pd $\%_w$ = 5.0) were stirred under nitrogen in H_2O (5.0 mL), following the procedure A (see the Experimental Section). [b] Minimum time at which the reaction stopped. [c] Determined by GLC analysis. [d] Selectivity into 1,2,3,4-tetrahydroquinoline. [e] Reaction carried out in autoclave, following the procedure B (see the Experimental Section). [f] In the absence of *Pd-pol.*

It can be seen from Table 1 that the reduction success depends on several parameters. In fact, following our procedure for the reduction of quinoline under 10 bar H_2 in aqueous medium [57], we used a Pd/substrate molar ratio equal to 1/200, registering a low conversion (30 %) after 9 hours at 60°C (entry 1). We tried to overcome this inconvenience by carrying out the reaction under the same conditions but increasing the temperature up to 80°C (entry 2), still obtaining unsuccessful results. On the base of our experience on the nitroarenes reduction in water [56], we decided to increase the molar amount of $NaBH_4$ up to twentyfold compared to the substrate, leaving the reaction temperature at 60°C and the substrate/Pd molar ratio equal to 200 (entry 3). This test allowed us to choose 20.0 mmol as the optimum amount of $NaBH_4$ and T = 60°C as the best working temperature, since under these conditions and using a Pd mol% equal to 0.5 (entry 3), the conversion was improved up to 56%, even not yet satisfactory. At this stage, we decided to increase the palladium/quinoline molar ratio up to 1/100 (entry 4) and up to 1/50 (entry 5), registering the best results in the latter case (t = 9 h, conv. = 99 %, selectivity = 93 %).

In all the above mentioned tests, the reactions were carried in a flask equipped by a condenser and a bubbler in order to discharge the excess hydrogen. Conversely, by carrying out the reduction under

the optimized conditions in a steel autoclave, the *in situ* formed hydrogen gas (scheme 3) reached a

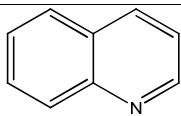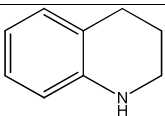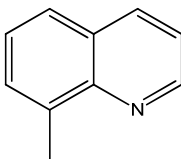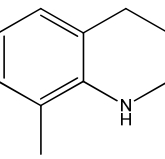pressure up to 20 bar shortening the reaction time to 4 hours (entry 6).

$$NaBH_4 + 2\,H_2O \longrightarrow 4\,H_2 + NaBO_2$$
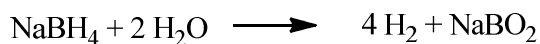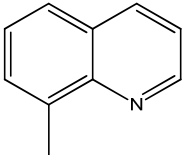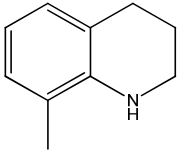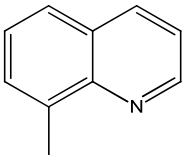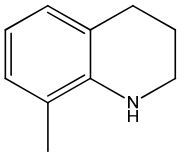
Scheme 3: metal catalyzed production of H_2 by $NaBH_4$
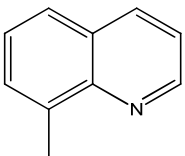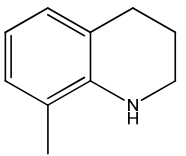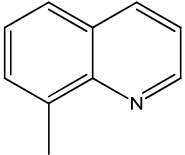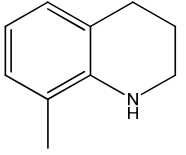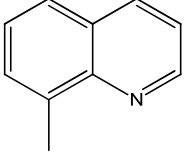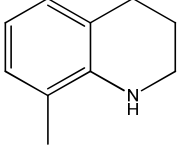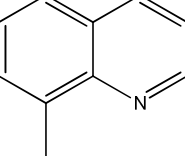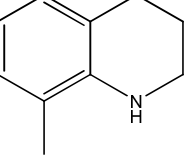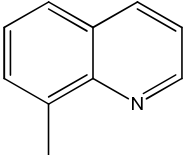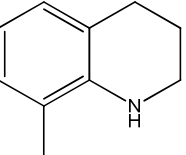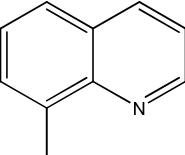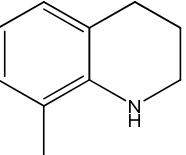
The best conditions reported in entries 5 and 6 of Table 1 (without and with the use of an autoclave,

respectively) were applied to two parallel reactions carried out in a flask and in an autoclave,

respectively, both in the absence of the palladium catalyst (entries 7 and 8). In both cases the

reduction of the model substrate did occur, being the conversion 56% (entry 7) and 58% (entry 8)

after 9 hour stirring, although the selectivity to 1,2,3,4-tetrahydroquinoline was poor (46% and

54%, respectively), being the other products dihydroquinolines and azo compounds, thus

confirming that *Pd-pol* catalyst was essential for a quantitative substrate conversion with a high

selectivity.
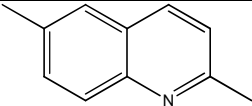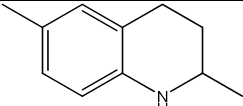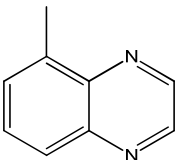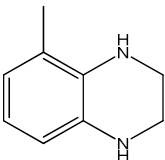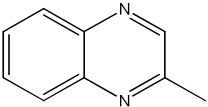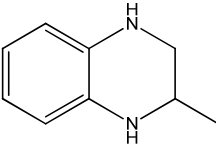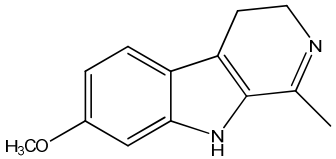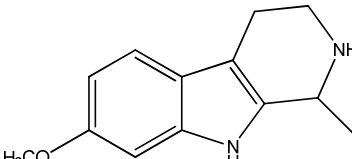
3.2. Scope of the Pd-pol catalyzed reaction

Using the optimized reaction conditions, the activity and the scope of the catalyst was explored in

the transfer hydrogenation reaction of some quinolines and quinoxalines (Table 2).

Table 2. *Pd-pol*-catalyzed transfer hydrogenation of quinolines and heteroaromatic nitrogen compounds[a]

Entry	Substrate	Product	additive	t (h)	Yield[b] (%)
1[c]			none	4	94(86)
2			none	9	33

Entry	Substrate	Product	Additive		
3[d]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	none	9	30
4[e]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	none	9	13
5	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	HCOOH (1.0 mmol)	9	31
6[f]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	$N_2H_4 \cdot H_2O$ (20.0 mmol)	9	2
7	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	KOH (1.0 mmol)	9	8
8[c]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	**none**	**5**	**(86)**
9[c,g]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	none	9	38
10[c,h]	8-methylquinoline	8-methyl-1,2,3,4-tetrahydroquinoline	none	9	2

Entry	Substrate	Product	Additive	Time (h)	Yield (%)
11[c]			none	15	(86)
12			none	9	(86)
13			none	9	(88)
14			none	9	(91)

[a] Reaction conditions: substrate (1.0 mmol), H_2O (5 mL), $NaBH_4$ (20.0 mmol), *Pd-pol* (Pd: 2 mol %), 60 °C, procedure A of the Experimental Section. [b] GLC yields using biphenyl as the internal standard. Isolated yield after column chromatography in parenthesis. [c] Reaction carried out in a steel autoclave, following the procedure B of the Experimental Section. [d] At 100 °C. [e] using CH_3OH (5 mL) as the solvent. [f] in the absence of $NaBH_4$. [g] At room temperature [h] In the absence of metal catalyst.

Differently from the reduction of quinoline (Table 1 and entry 1 of Table 2), the transfer hydrogenation of 8-methylquinoline was a tough reaction, probably due to the hyper conjugation of the methyl group in 8 position [58]. In fact, by carrying out the reaction under the optimized conditions in a flask equipped by a bubbler (procedure A of the Experimental Section), the reduction stopped after 9 hours at 33 % conversion of the substrate (entry 2, Table 2). The conversion did not increase by rising the temperature up to 100 °C (entry 3, Table 2), or by replacing water for methanol (in which the substrate is soluble, being insoluble in water) (entry 4, Table 2), or by adding a weak acid, such as HCOOH (1.0 mmol, entry 5, Table 2), in order to favor

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the pyridine nitrogen protonation [37]. The course of the reaction was even worse by replacing $NaBH_4$ for a base such as $N_2H_4\cdot H_2O$ (entry 6, Table 2) or by adding KOH (entry 7, Table 2), aiming at promoting the hydrogen transfer from the solvent to the substrate [59]. Finally, the 8-methylquinoline reduction gave good results (86% of isolated yield) after 5 hours when it was carried out at 60 °C in autoclave (entry 8, Table 2), where the *in situ* formed H_2 pressure grew up to 20 bar. Remarkably, the latter reduction stopped at 38 % of conversion after 9 h stirring in the autoclave, when it was carried out at room temperature (entry 9, Table 2). Unlike the analogous reduction of quinoline in the absence of palladium (entry 6 of Table 1), no reaction at all occurred when 8-methylquinoline and $NaBH_4$ were put together in water in a steel autoclave, letting the mixture under stirring at 60 °C for 9 hours in the absence of metal catalyst (entry 10, Table 2).

Also the transfer hydrogenation of 2,6-dimethylquinoline occurred only when the reaction was carried out in a steel autoclave (entry 11, Table 2) and needed longer time (15 h), being the latter a challenging substrate for steric hindrance reasons [60].

The water soluble 5-methylquinoxaline and 2-methylquinoxaline, important heteroaromatic nitrogen compounds used as intermediates for the synthesis of dyes, pharmaceutics and antibiotics, were smoothly converted into the corresponding 1,2,3,4-tetrahydroquinoxaline (entries 12 and 13, Table 2) under 1 atm pressure, without the use of a steel autoclave. Finally, the reduction of harmaline, another biologically important heteroaromatic nitrogen compound, successfully proceeded in 9 hours giving quantitative yield in leptaflorine (entry 14, Table 2).

3.3. Reusability of the Pd-pol catalyst

The reusability of *Pd-pol* catalyst in the transfer hydrogenation of quinoline with $NaBH_4$ in a glass flask (procedure A of the Experimental Section) was investigated. After the first use, the supported catalyst was recovered by centrifugation and reused in the next run after several washings. The recovered catalyst was successfully employed in the subsequent seven cycles with a high catalytic activity, giving the product in good yields (87-95%, Figure 1).
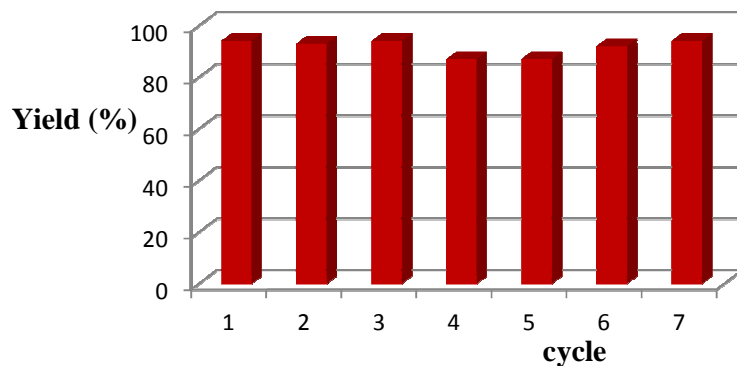
Figure 1: Recyclability of *Pd-pol* (2.0 mol% of Pd) in the transfer hydrogenation of quinoline with NaBH$_4$ in water at 60 °C (t = 9 h). Procedure A of the Experimental Section. GLC yields using biphenyl as the internal standard

Aiming at comparing the activity and selectivity of *Pd-pol* with a commercial system, we decided to investigate the performance of the Pd/C catalyst in promoting the quinoline reduction under the same conditions reported in the present work (NaBH$_4$, water, 60 °C). Pd/C showed limited recyclability (table 3), probably due to the difficulty in recovering the finely powdery catalyst. In fact, the quinoline conversion dropped to 47 % at the fourth run with Pd/C.

Table 3. commercial Pd/C catalyzed transfer hydrogenation of quinoline[a]

entry	Conv. (%)[b]	Selectivity (%)
1st run	95	98
2nd run	92	98
3rd run	71	97
4th run	47	98

[a] Reaction conditions: quinoline (1.0 mmol), H$_2$O (5 mL), NaBH$_4$ (20.0 mmol), Pd/C 10%$_w$ (Pd: 2 mol %), 60 °C, 9 h. [b] GLC conversion using biphenyl as the internal standard.

3.4. Analysis of the mother liquors

In order to verify whether the catalysis observed was truly heterogeneous or not, the reaction mixture was filtered hot at 40% of quinoline conversion, and fresh $NaBH_4$ was added to this solution. Further stirring of the filtrate under the above reaction conditions resulted in the same reaction course already observed in the reduction carried out in the absence of the metal catalyst. In addition, the samples of *Pd-pol* recovered at the end of the first run and at 40 % conversion, respectively, were mineralized and analyzed by atomic absorption spectrometry showing the same palladium content of the virgin catalyst. The same palladium amount was also found in the catalyst recovered at the end of the seventh cycle of quinoline reduction. These results rule out any possible contribution of homogeneous catalysis by leached palladium species.

3.5. TEM analyses

This study was completed with the TEM characterization of *Pd-pol* before, after the first and the seventh cycle, respectively, with the aim of ascertaining whether the reaction cycles affected the morphology and the dispersion of the palladium active species on the surface of the support.

TEM pictures of the pristine *Pd-pol* and of the catalyst recovered after the first and the seventh runs, are reported in Figures 2a, 2b and 2c, respectively. The pristine catalyst was constituted mainly by polymer-bound Pd(II) species (not visible in the TEM micrographs) [53], together with very small Pd nanoparticles with a spherical shape and a homogeneous size. Most of these Pd nanoparticles had a diameter smaller than 5 nm and were hardly recognizable since they were all grouped in clusters collecting from 6 to 10 primary nanoparticles (see enlargement of Figure 2a). Clusters were measured in diameter and the distribution is reported in Figure 2a. As it can be observed, the highest number of nanoparticle clusters had a size around 10 nm with a small number having larger size. This nanostructure reflected the way of preparation of the pre-catalyst [61]. In fact, these nanoparticles likely formed during the thermal polymerization step of the catalyst synthetic procedure [53]. The TEM image of *Pd-pol* recovered after the first run (Figure 2b) showed an evident increase in the number of primary particles homogeneously distributed throughout the

polymer. Pd nanoparticles had an average diameter from 2 nm to 4 nm, ascribable to the *in situ* NaBH$_4$ reduction of Pd(II) supported polymer. In fact, the morphological features of *Pd-pol* recovered after a run carried out under typical reaction conditions, but without substrate, were similar to those shown by the TEM image reported in Figure 2b. In this case the Pd nanoparticles were not grouped in clusters but are individually distributed (enlargement in Figure 2b). The shape of these Pd nanoparticles still was spherical without any preferential growth as already observed during the first run of the previously studied hydrogenation of quinolines under 10 bar hydrogen at 80 °C [57], where the Pd nanoparticles were slightly bigger (diameter ranging from 1.5 to 8.5 nm) compared to the present ones and showed morphology and size distribution typical for polymer stabilized Pd nanoparticles formed by reduction under gaseous H$_2$ [62].

The different nanoparticle diameter distributions observed in the two *Pd-pol* samples, the first one reduced by NaBH$_4$ and the second one reduced by 10 bar H$_2$, were presumably responsible for the slightly different catalytic activities showed by the two catalysts, being the latter less active. In fact, for example, the *Pd-pol* catalyzed reduction of 8-methylquinoline carried out in autoclave in water at 60°C with NaBH$_4$ (entry 8, Table 2) needed 5 hour stirring, while the hydrogenation of the same substrate promoted by the same batch of catalyst in H$_2$O/CH$_3$OH under 10 bar H$_2$ at 80°C took 9 hours [57]. We already noticed the effect of the reducing agent on the catalyst morphology and performance also during our previous studies on the nitroarenes reduction [56]. It is known that NaBH$_4$ acts as a reducing agent of the metal in a dual way, by providing hydrides and by generating hydrogen gas. In fact, the hydrides from sodium borohydride can displace negatively charged ligands bound to Pd(II) (the β−ketoesterato moieties in the case of *Pd-pol*, scheme 1), generating Pd-hydrides directly, which upon β-hydride elimination of H$_2$, give the reduced metal. In addition, the well-known *in situ* formed H$_2$ in water (Scheme 3) in the closeness of Pd(II) can reduce it to Pd(0) with formation of small size metal nanoparticles.

On the contrary, in the case of *Pd-pol* stirred under 10 bar H$_2$, the reduction occurs only by hydrogen gas, which has to be transported into the liquid phase and then to the *Pd-pol* structure.

Since the metal reduction proceeds more slowly compared to the one obtained in the presence of NaBH$_4$, there is enough time to form larger palladium crystallites.

On passing from the first to the seventh cycle (Figure 2c), the number of smallest size (2 nm) Pd(0) nanoparticles even increased, although some of them grew up to 18-20 nm diameter. The primary nanoparticles were still homogeneously distributed as shown in the enlargement in Figure 2c. However, the nanostructure of the catalyst was substantially maintained during the subsequent cycles and the Pd nanoparticles remained embedded into the polymer bulk. In fact, clusters of primary nanoparticles did not grow in size indicating absence of particle mobility under the reaction conditions. Interestingly, it was reported that palladium(II) centers supported onto a methacrylic resin similar to *Pd-pol* pre-catalyst, once reduced to Pd(0), gave nanoparticles, which in turn could increase their size (growth) or/and agglomerate (aggregation) with the time [62,63]. The aggregation process would decrease the catalytically active superficial area much more than the growth of a single nanoparticle. Remarkably, the Pd nanoparticles supported onto *Pd-pol* remained isolated from each other and they did not aggregate with the recycles, although a limited amount of them slightly grew up. This explains why the catalytic activity of the supported catalyst recovered after seven cycles was comparable to that of the catalyst re-used after the first run.

Numerous investigations concerning the development of the incorporation technique of metal nanoparticles into the polymer matrix have been published demonstrating the stabilization of the metal nanoparticles encapsulated into the polymer matrix [62-65]. A polymerizable Pd(II) β-ketoesterate complex is the starting monomer for the synthesis of the metal-polymer composite material *Pd-pol* [47]. This approach [45] is particularly attractive from the synthetic point of view since both the components of the composite material have ample scope for intimate contact. In order to get further insights into the Pd nanoparticle stabilization during the NaBH$_4$ assisted *Pd-pol* reduction micro-IR spectroscopy analyses of the pristine Pd-pol and of the Pd –pol recovered after 7 reduction cycles were performed. Their FT-IR spectra (Figure S1) showed the disappearance of the weak β-ketoesterate combination band signals (1602 and 1509 cm^{-1}) [46] on passing from the

pristine to the used catalyst. This phenomenon is ascribable both to the loss of metal coordination by the protonated polymerized ligand, and to the reduction of the oxidation state of palladium by NaBH$_4$ with formation of nanoparticles, likely stabilized by electrostatic interactions with the oxygen atoms of the polymeric support. Similar stabilization behaviors were observed also in fluorinated copolymers containing the AAEMA$^-$ ligand [66].
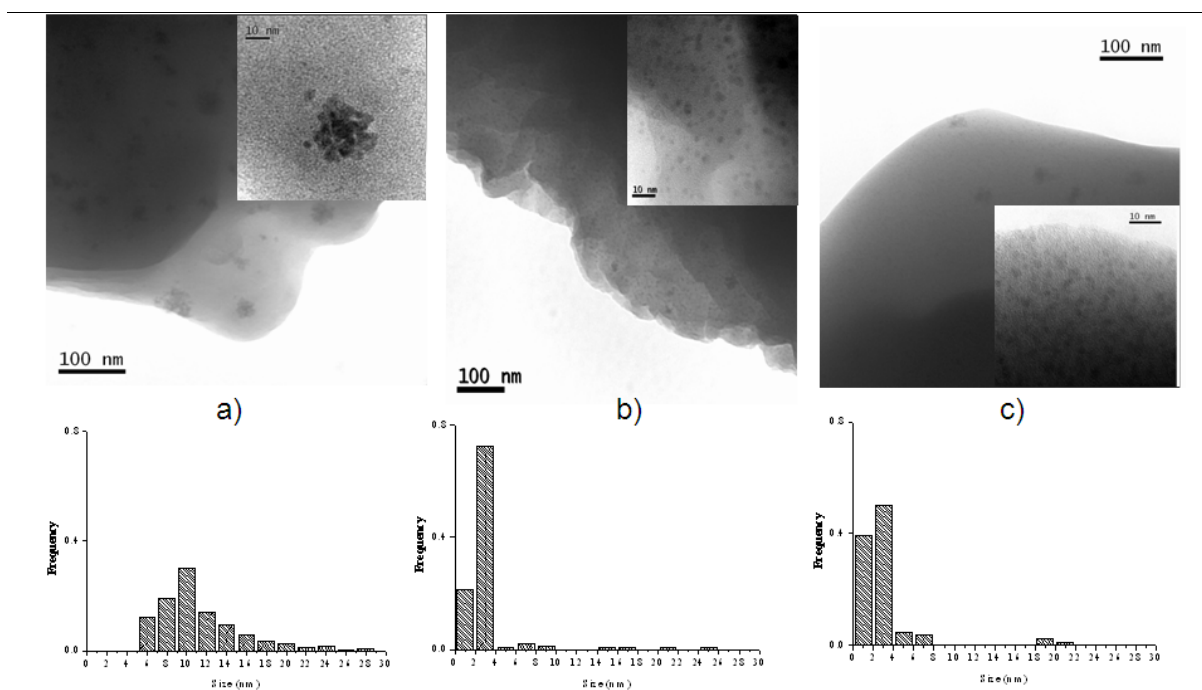

Figure 2: Transmission electron micrographs and associated size distribution of matrix polymer embedded Pd nanoparticles: (a) pristine *Pd-pol*; (b) *Pd-pol* recovered after the first run of the reduction of quinoline with NaBH$_4$; (c) *Pd-pol* recovered after the seventh run of the reduction of quinoline with NaBH$_4$

3.5. Mechanistic considerations

Pioneering studies on the reduction of quinolines, isoquinolines and quinoxalines with sodium borohydride have already been carried out using methanol as the solvent in the absence of a metal catalyst with the addition of acetic acid [67]. However, the reported reductions occurred only in the presence of electron withdrawing substituents on the aromatic ring, necessary to provide the

17

activation of the C=N bonds for the nucleophilic attack by the hydride [68], and often led to the formation of N-alkylated product [69]. In addition, the quinolines were reduced only to their corresponding 1,2-dihydroquinolines, being this method unsuitable for the formation of tetrahydroquinolines. These results are in agreement with what we observed by carrying out the reduction of quinoline with NaBH$_4$ in water in the absence of *Pd-pol* (entries 7 and 8, Table 1). Probably, the substrate was first converted into 1,2- and 1,4-dihydroquinolines, which are known to be instable [70], being rapidly oxidized by air to quinoline or decomposing by disproportionation into quinoline and tetrahydroquinoline. The proposed mechanistic pathway in the absence of metal catalyst starts with the formation of a cation (Scheme 4a) or, better, a species formed by hydrogen bond with the water solvent and the heterocycle, thus bearing a partial positive charge on nitrogen delocalized by resonance (Scheme 4b). Both species can easily be attacked by the hydride in 2 or 4 carbon position to give the dihydroquinoline products, which in turn would decompose.
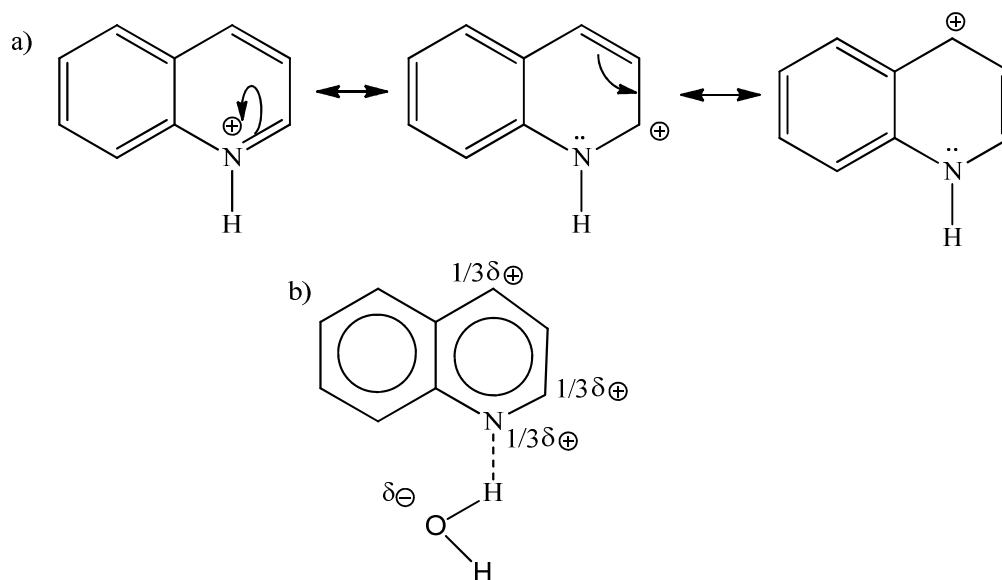
Scheme 4: a) formation of the pyridinium ion in the presence of trace acid; b) interaction between water and quinoline

The proposed mechanism explains the similar results obtained by carrying out the reaction in the absence of catalyst in a glass flask and in a steel autoclave, respectively (entries 7 and 8, Table 1), because the hydrogen pressure does not affect the reaction course, being dihydrogen not involved in the kinetic pathway. Indeed, the reluctance of 8-methylquinoline to be reduced by $NaBH_4$ in the absence of metal catalyst can be due to the presence of the electron donor group on the benzene ring, which would prevent the nucleophilic attack by the hydride. On the contrary, in the presence of *Pd-pol,* the dihydrogen (formed according to the reaction reported in Scheme 3) may add to the C=N double bond of the 8-methylquinoline, following an ionic pathway involving solvent assisted heterolytic hydrogen activation promoted by the basic substrate (Scheme 5). As already substantiated in similar cases [22,71], this would result in protonation of the 8-methylquinoline, followed by H-transfer from the metal to the adjacent carbon atom, as also suggested by Crabtree and Eisenstein [8] and by Sánchez-Delgado [72,73].
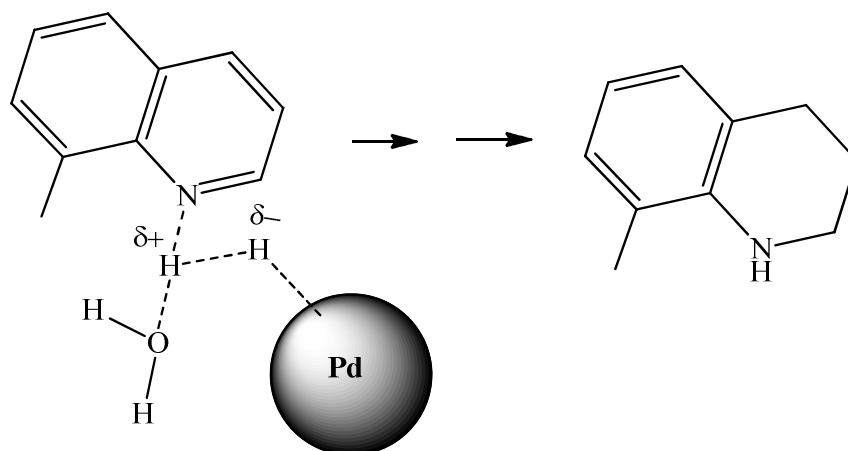
Scheme 5: plausible transition state for the hydrogenation of 8-methylquinoline with *Pd-pol* in water

When the substrate was 8-methylquinoline, the hydrogen pressure was crucial, being dihydrogen the only reducing agent involved in the kinetic pathway as the formation of 8-methyl-1,2,3,4-tetrahydroquinoline occurred only when the reaction was carried out in a steel autoclave retaining all the *in situ* formed hydrogen gas. On the other hand, the reduction of the simple quinoline in the

presence of *Pd-pol* followed both mechanistic routes depicted in Schemes 4 and 5, and the formation of 1,2,3,4-tetrahydroquinoline occurred also when the reaction was carried out in a flask discharging the produced hydrogen gas.

4. Conclusions

In conclusion, we have demonstrated that polymer supported palladium catalyst (*Pd-pol*) can promote the hydrogenation of quinolines (a class of well-known poisons for the traditional noble metal-based hydrogenation catalysts) in high yield and excellent selectivity, by using sodium borohydride and water as the hydrogen source under mild condition.

The catalyst did not change its nanostructure and could be recovered at the end of the reaction and re-cycled for at least seven times with the same activity and selectivity. TEM analyses showed that the active species are Pd nanoparticles with average size of 3 nm diameter, that do not aggregate with the re-uses and do not leach out in solution during reaction. *Pd-pol*, which is still to the best of our knowledge the second example reported to date of active palladium catalyst recyclable in aqueous solvent for the selective hydrogenation of quinolines and heteroaromatic nitrogen under hydrogen gas, is also active, selective and recyclable for the transfer hydrogenation of quinolines under safer conditions, *i.e.* by using $NaBH_4$ in water.

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